An Introduction to Systems Biology from a Machine Learning Perspective II

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Roadmap

Roadmap

Before ...

Quoting from Khanin *et al.*:

> *One can come up with linear (or higher order) $f(t)$ approximations on each subinterval. This will introduce additional parameters, which will be impossible to infer with any certainty given limited amount of data.*

Khanin et al. (2006)

ODE Model of Activation

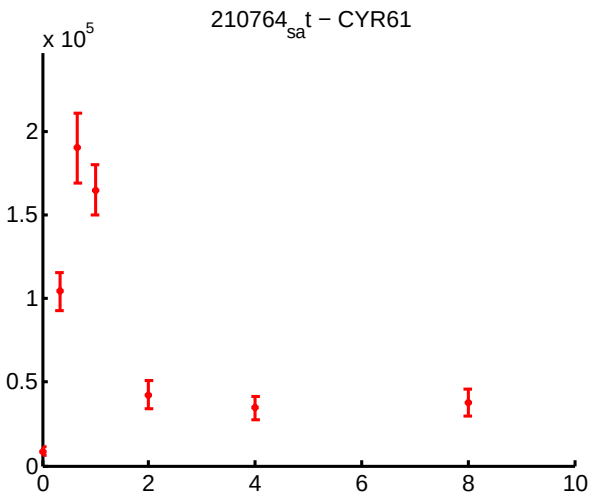
- Linear Activation Model (Barenco et al., 2006, Genome Biology)

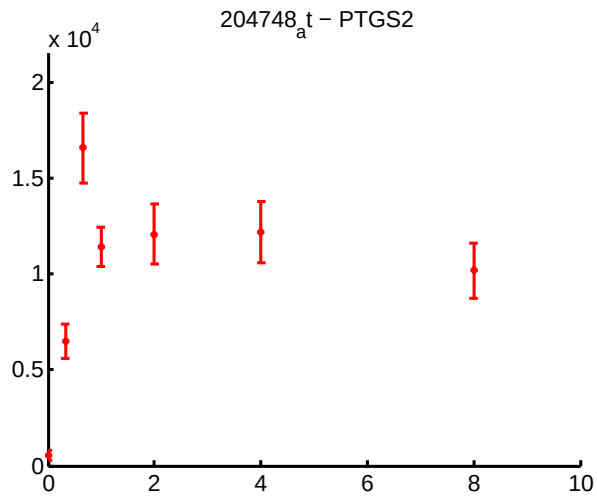
$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j f(t) - D_j x_j(t)$$

- $x_j(t)$ – concentration of gene j's mRNA
- $f(t)$ – concentration of active transcription factor
- Model parameters: baseline B_j, sensitivity S_j and decay D_j
- Application: identifying co-regulated genes (targets)
- Problem: how do we fit the model when $f(t)$ is not observed?

Why use a model-based approach?

- Co-regulated genes can differ greatly in their expression profiles





- Clustering cannot be relied on to identify co-regulated genes
- A model-based approach is required

Models of non-linear regulation

- Non-linear Activation: Michaelis-Menten Kinetics

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

used by Rogers and Girolami (2006)

- Non-linear Repression

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

used by Khanin et al., 2006, PNAS 103

Standard inference approach

- Previous approaches all use similar inference methodology:
  - Represent $f(t)$ as coarse-grained piecewise continuous function $[f_1, f_2, \ldots, f_d]$
  - Often discretize where data are collected
  - Treat f_i as additional model parameters
  - Use maximum likelihood or Bayesian MCMC to estimate $\{f_i\}$ along with other model parameters of interest
- Limitations:
  - Arbitrary choice of discretization points
  - Coarse-grain gives crude approximation to $f(t)$
  - Fine-grain leads to harder inference problem

Gaussian Processes

- Gaussian Process

$$f(t) \backsim \mathcal{GP}\left(m(t), k\left(t, t'\right)\right)$$

where

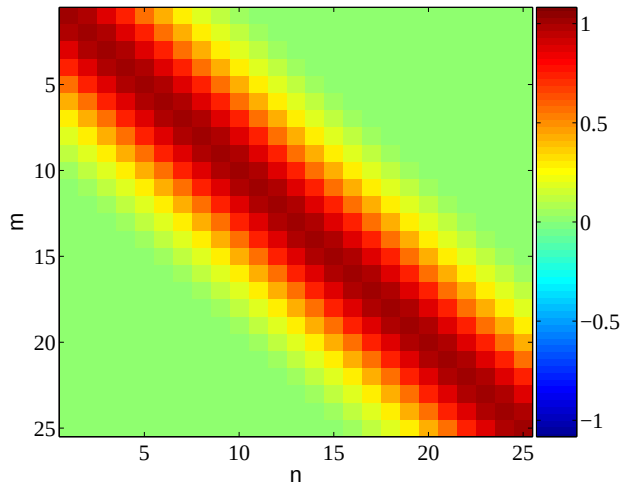
$$\begin{aligned} m(t) &= \mathbb{E}[f(t)] = \langle f(t) \rangle \\ k\left(t, t'\right) &= \mathbb{E}\left[\left(f(t) - m(t)\right)\left(f\left(t'\right) - m\left(t'\right)\right)\right] \end{aligned}$$

▸ Skip Covariance Functions

RBF Kernel Function

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

- 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.

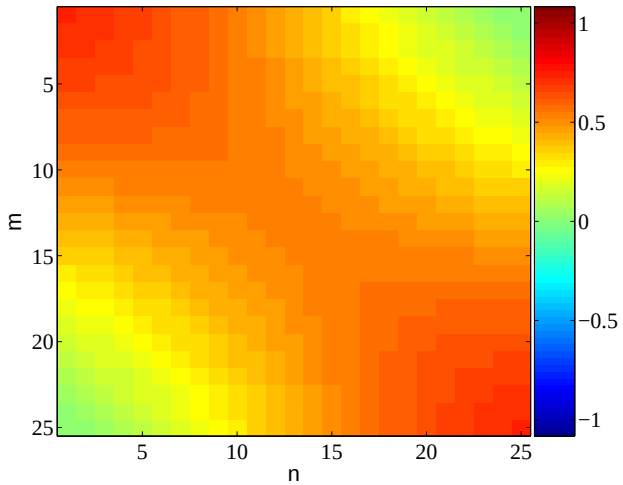


Different Covariance Functions

MLP Kernel Function

$$k\left(t, t'\right) = \alpha \sin^{-1}\left(\frac{wtt' + b}{\sqrt{wt^2 + b + 1}\sqrt{wt'^2 + b + 1}}\right)$$

- A non-stationary covariance matrix (Williams, 1997).
- Derived from a multi-layer perceptron (MLP).



Covariance Samples

`demCovFuncSample`

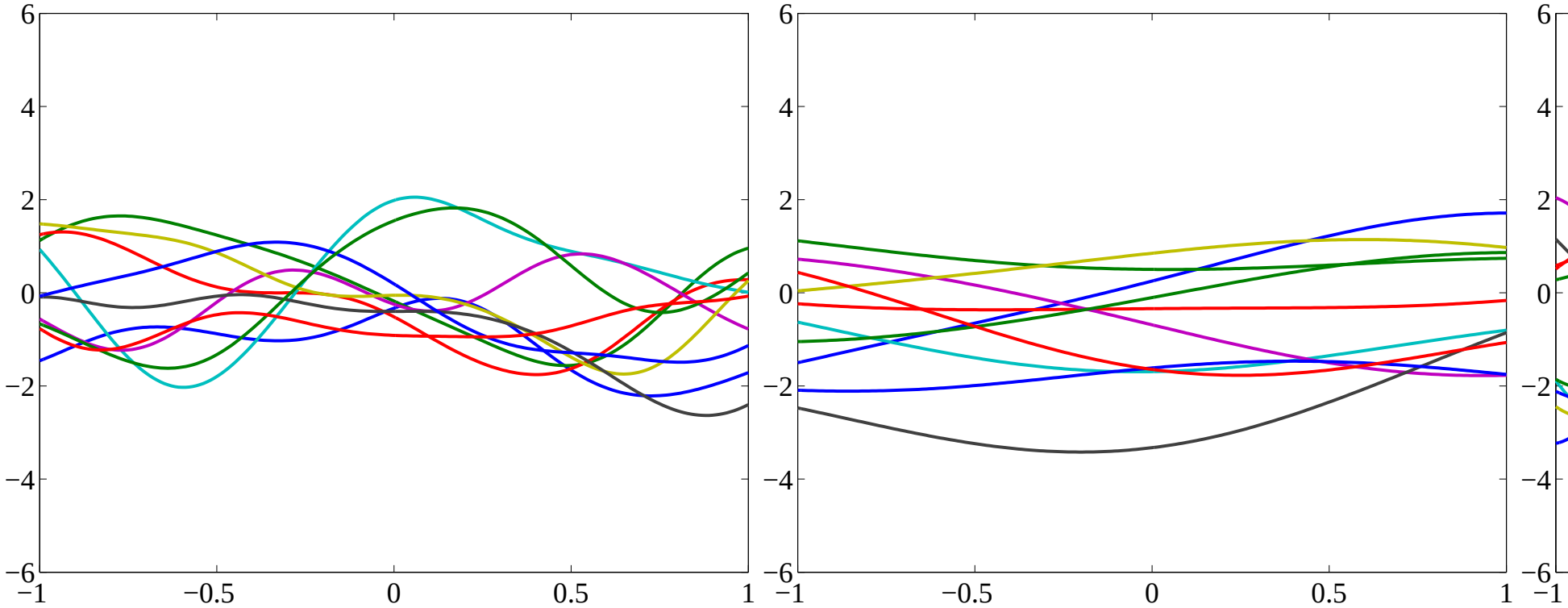


Figure: RBF kernel with $\gamma = 10^{-\frac{1}{2}}$, $\alpha = 1$ RBF kernel with $l = 1$, $\alpha = 1$ RBF kernel with $l = 0.3$, $\alpha = 4$ MLP kernel with $\alpha = 8$, $w = 100$ and $b = 100$ MLP kernel with $\alpha = 8$, $b = 0$ and $w = 100$

Linear Activation Model

Recall the linear model

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

This differential equation can be solved for $x_j(t)$ as

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

Note: This is a linear operation on $f(t)$.

If $f(t)$ is a zero mean Gaussian process then $x_i(t)$ is also a Gaussian process with mean $\frac{B_i}{D_i}$.

▸ Skip GP Properties

Two Properties of GPs

The integral of a GP is also a GP,

$$f(t) \sim N(\mathbf{0}, \mathbf{K}_{ff})$$

and

$$g(t) = \int_0^t f(u)\,\mathrm{d}u$$

then

$$g(t) \sim N(\mathbf{0}, \mathbf{K}_{gg}),$$

where

$$k_{gg}(t, t') = \int_0^t \int_0^{t'} k_{ff}(u, u')\,\mathrm{d}u\mathrm{d}u'$$

Two Properties of GPs

Product with deterministic function

Product with a deterministic function leads to another GP,

$$f(t) \sim N(\mathbf{0}, \mathbf{K}_{ff}),$$

and

$$g(t) = f(t)\, h(t)$$

where $h(t)$ is a deterministic function then,

$$g(t) \sim N(\mathbf{0}, \mathbf{K}_{gg}),$$

where

$$k_{gg}(t, t') = h(t)\, k_{ff}(t, t')\, h(t')$$

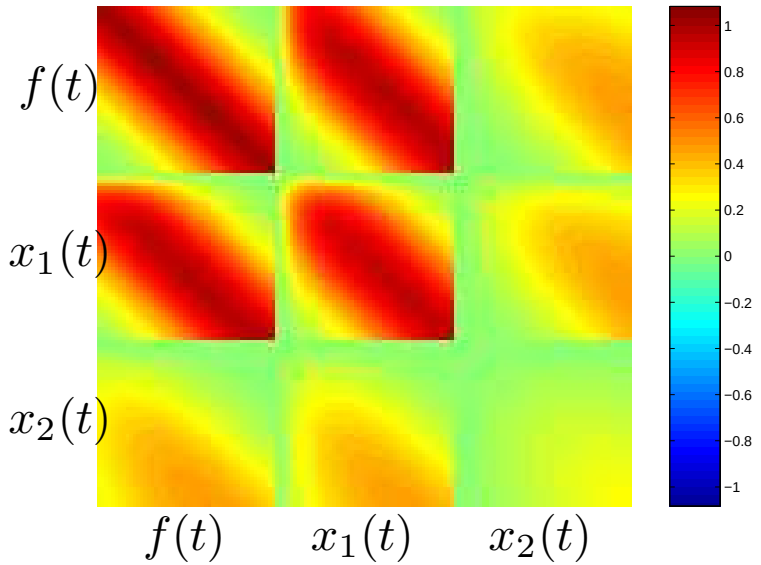
Covariance for Transcription Model

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 $x_1(t)$, $x_2(t)$ and $f(t)$.
  - Here:

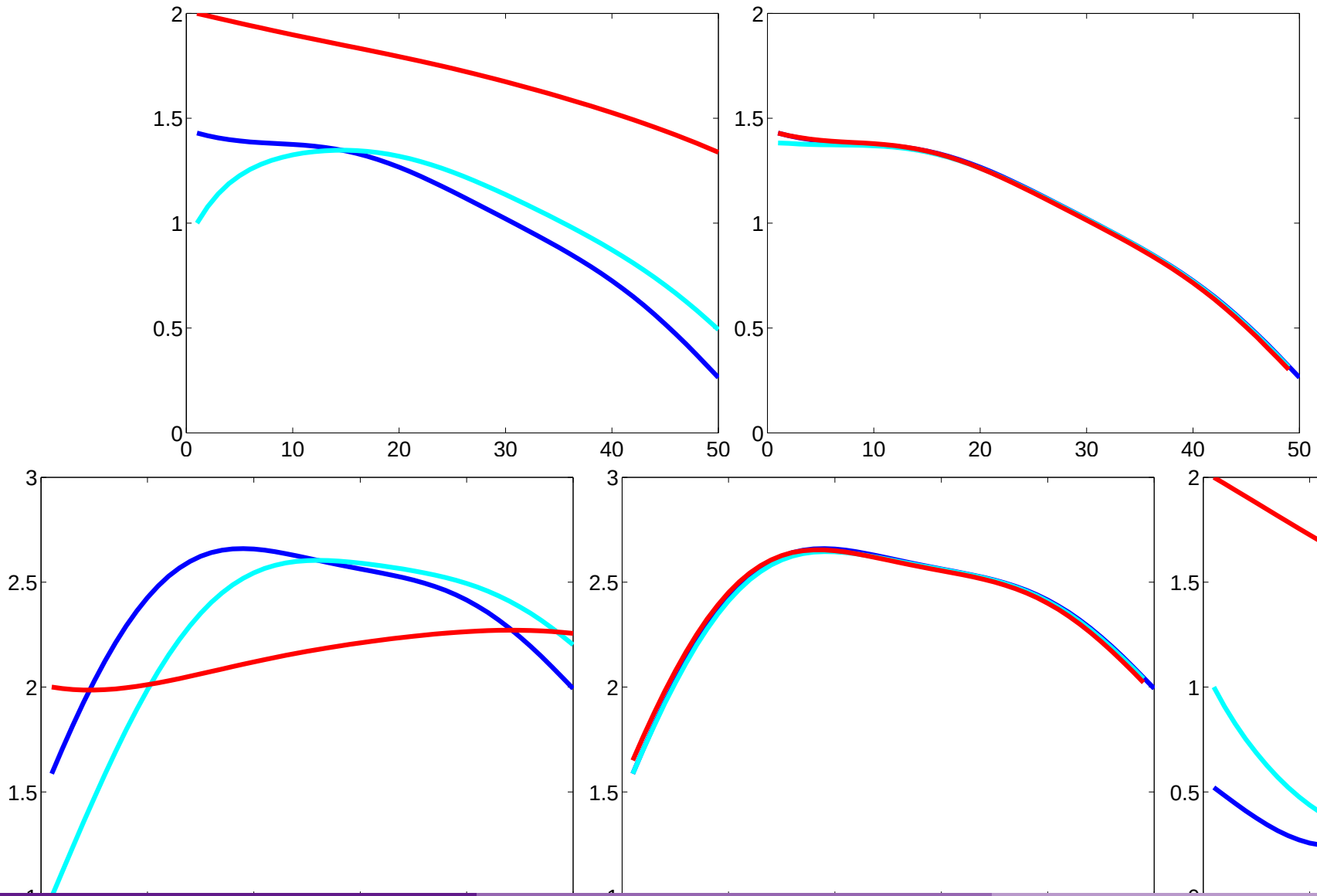
D_1	S_1	D_2	S_2
5	5	0.5	0.5



▸ Skip SIM Samples

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

`gpsimTest`



Covariance Function

Any linear opearation of a GP $\Longrightarrow$ Related GP

$$f(t) \backsim \mathcal{GP}\left(0, k_{ff}\left(t, t'\right)\right) \Longrightarrow x_j(t) \backsim \mathcal{GP}\left(\frac{B_j}{D_j}, k_{xx}\left(t, t'\right)\right)$$

Hence, the cross-covariances between the genes is

$$k_{x_i,x_j}\left(t, t'\right) = S_i S_j \int_0^t \int_0^{t'} e^{-D_i(t-u)-D_j(t'-u')} k_{f,f}\left(t, t'\right) \mathrm{d}u\mathrm{d}u' \ .$$

Cross-covariances between $x_j(t)$ and $f(t)$ is

$$k_{x_j,f}\left(t, t'\right) = \int_0^t e^{-D_i(t-u)} k_{f,f}\left(t, t'\right) \mathrm{d}u \ .$$

Prediction of the transcription factor concentration $f(t)$

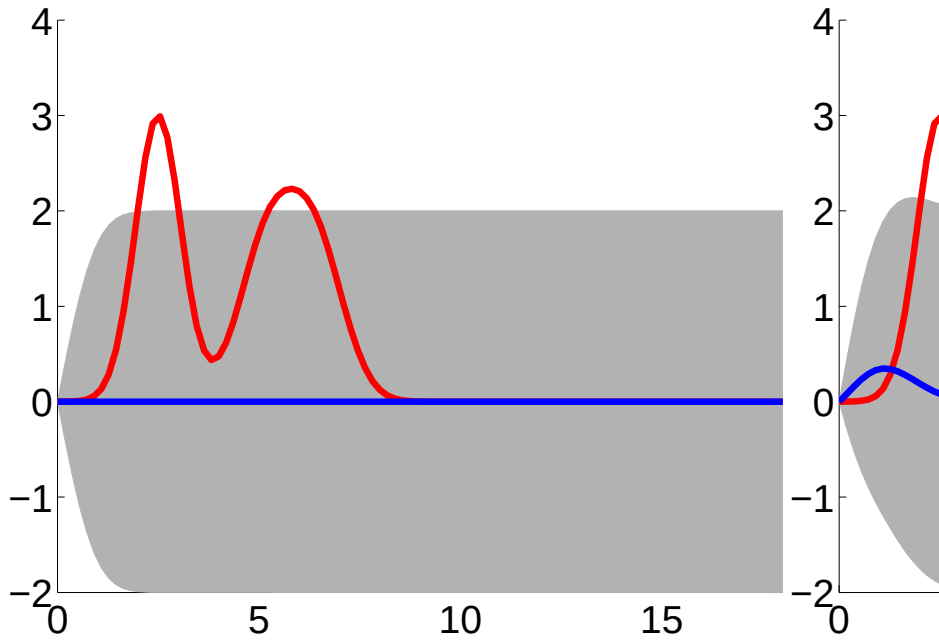
Under the linear model, we have

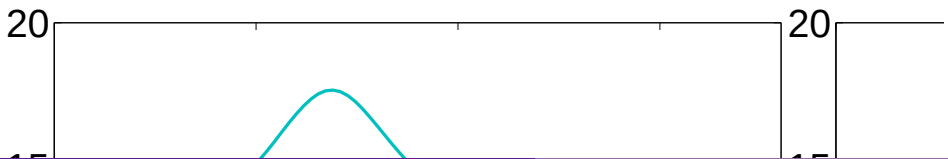
$$\begin{bmatrix} f \\ \mathbf{x} \end{bmatrix} \sim \mathcal{N}\left(\begin{bmatrix} 0 \\ \frac{\mathbf{B}}{\mathbf{D}} \end{bmatrix}, \begin{bmatrix} K_{ff} & K_{f\mathbf{x}} \\ K_{\mathbf{x}f} & K_{\mathbf{xx}} \end{bmatrix}\right)$$

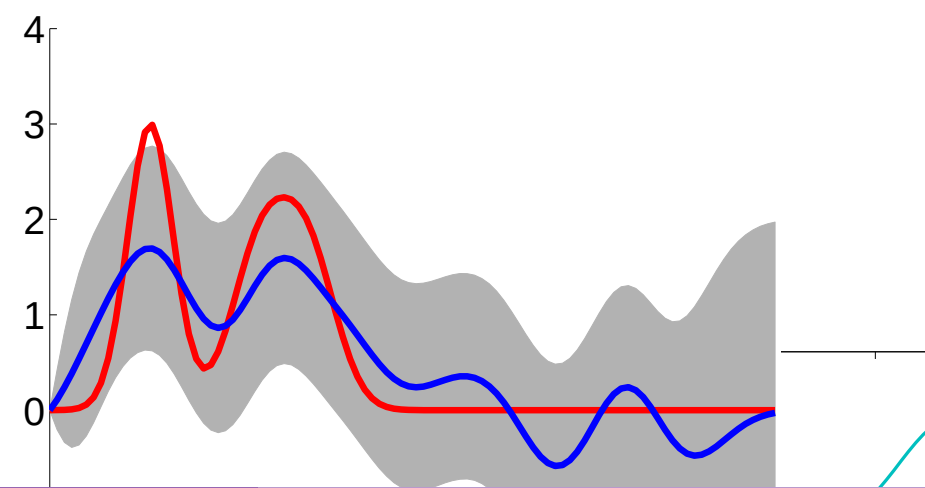
Standard GP Regression yields the mean and covariance function of the predicted process as

$$\begin{aligned} \langle f \rangle_{post} &= K_{f\mathbf{x}} K_{\mathbf{xx}}^{-1} \left(\mathbf{x} - \frac{\mathbf{B}}{\mathbf{D}}\right) \\ K_{ff}^{post} &= K_{ff} - K_{f\mathbf{x}} K_{\mathbf{xx}}^{-1} K_{\mathbf{x}f} \end{aligned}$$

Artificial Example: Inferring $f(t)$







Parameter Estimation for the Linear Model

A likelihood function for the model parameters $\theta = \{B_j, S_j, D_j\}_{j=1}^{N}$ and GP length scale l is obtained by *integrating out* the latent function $f(t)$

$$L(\theta, l) = \int \left(\prod_j p(x_j|\theta, f(t)) \right) p(f(t)|l) \, \mathrm{d}f(t)$$

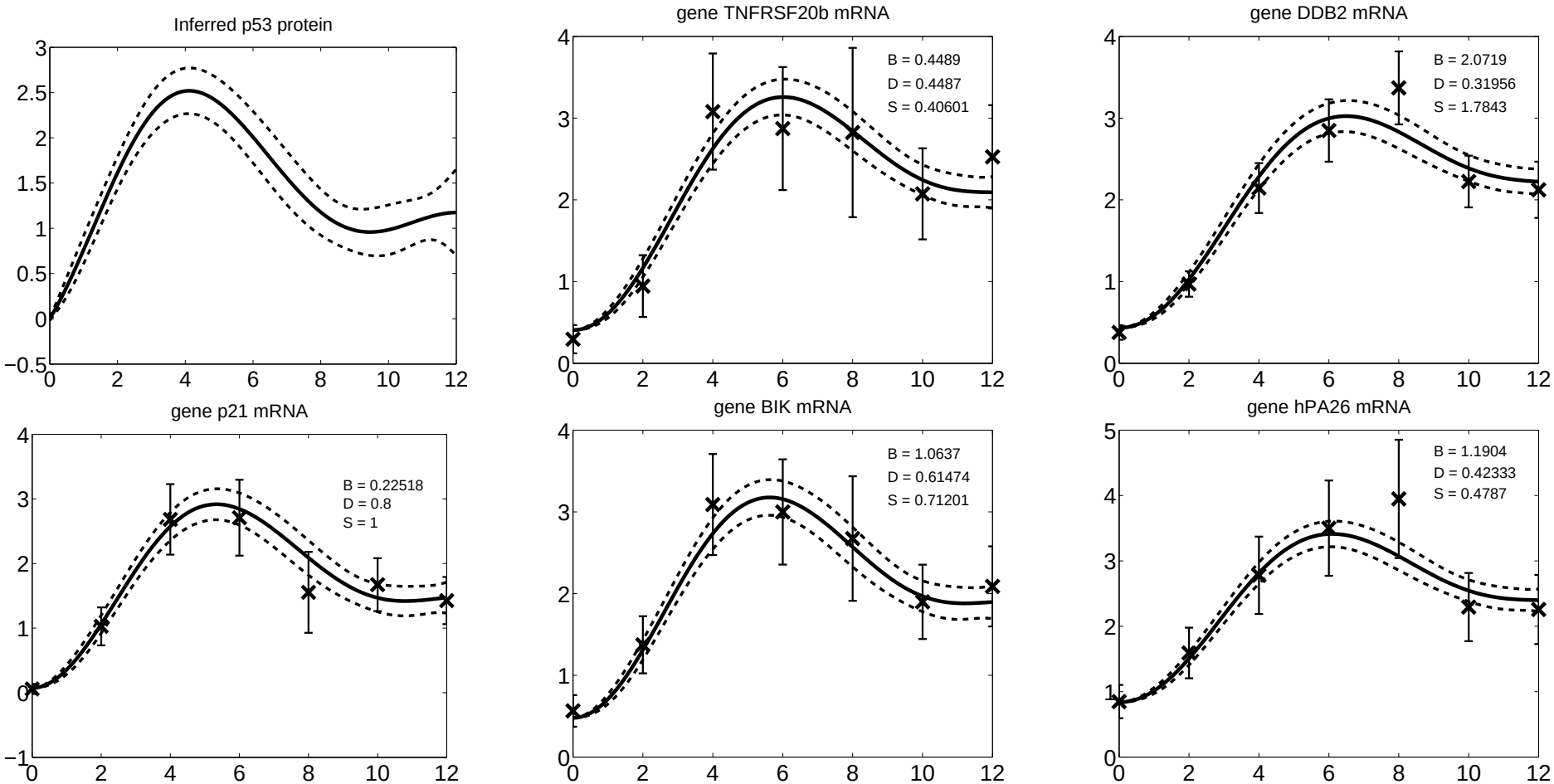
Under the GP model, the log marginal likelihood is then given by

$$\log L(\theta, l) = -\frac{1}{2} x^T \left(K + \sigma_n^2 \mathtt{I} \right)^{-1} x - \frac{1}{2} \log \left| K + \sigma_n^2 \mathtt{I} \right| - \frac{n}{2} \log 2\pi$$

Maximise to find model parameters.

p53 (RBF covariance)

Pei Gao

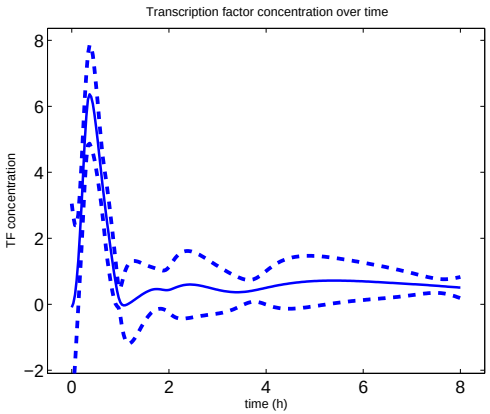


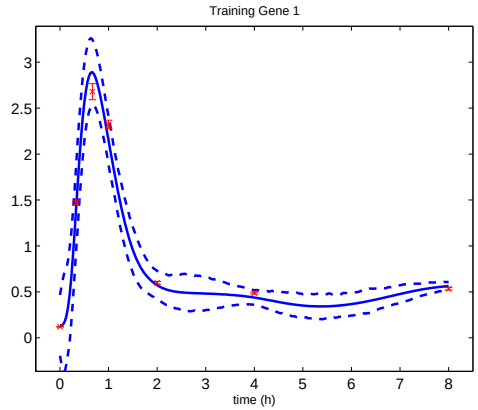
Ranking with ERK Signalling

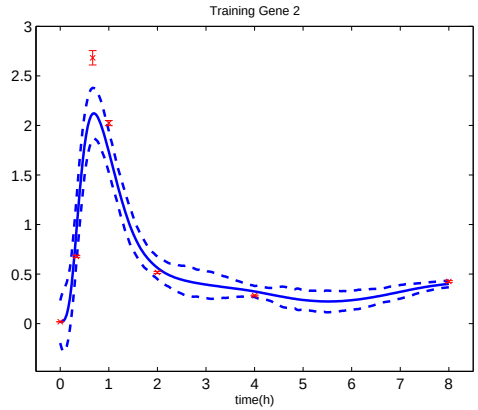
- Target Ranking for Elk-1.
- Elk-1 is phosphorylated by ERK from the EGF signalling pathway.
- Predict concentration of Elk-1 from known targets.
- Rank other targets of Elk-1.

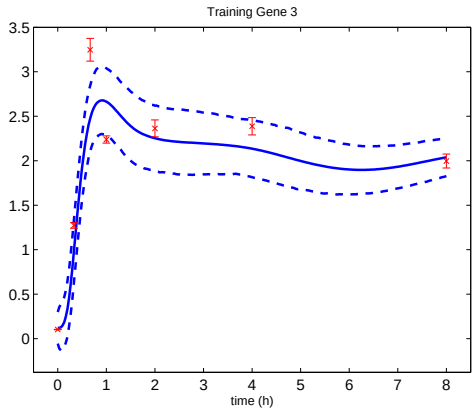
Elk-1 (MLP covariance)

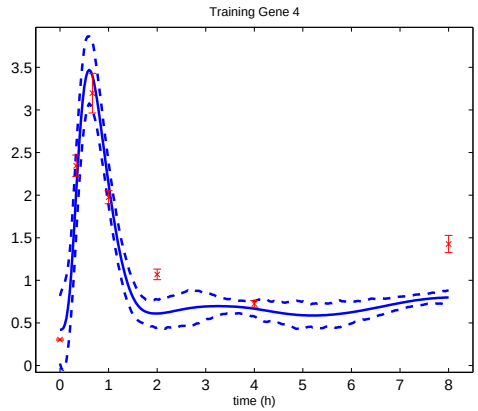
Jennifer Withers

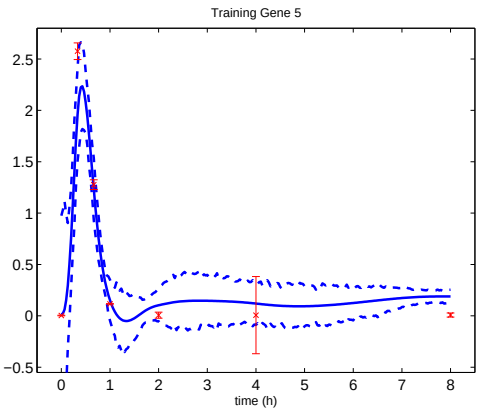






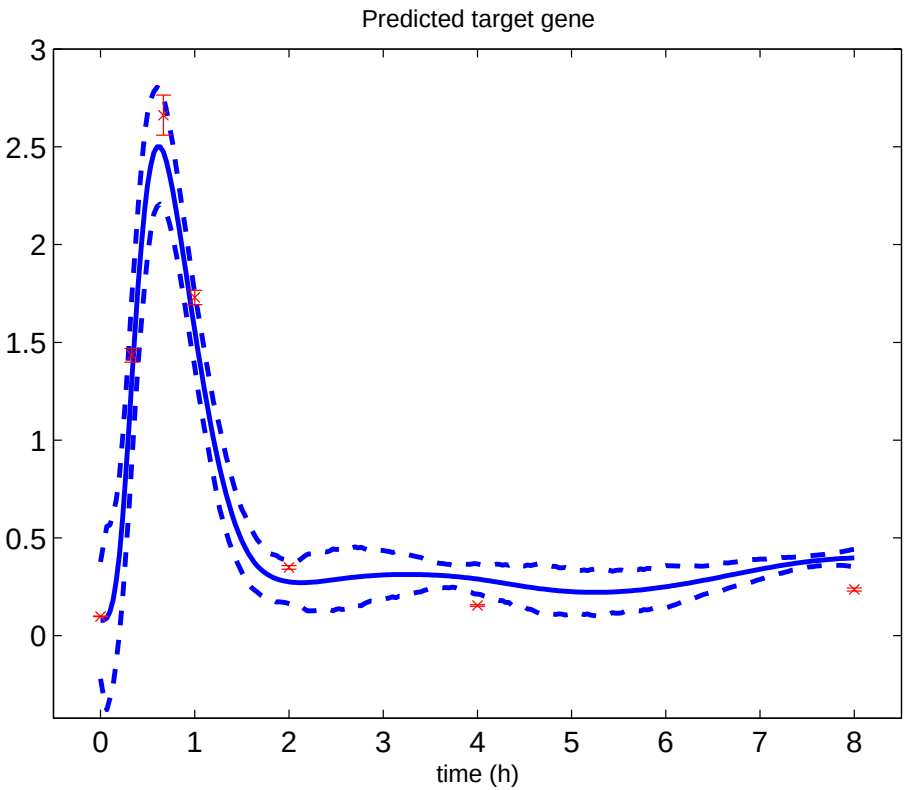


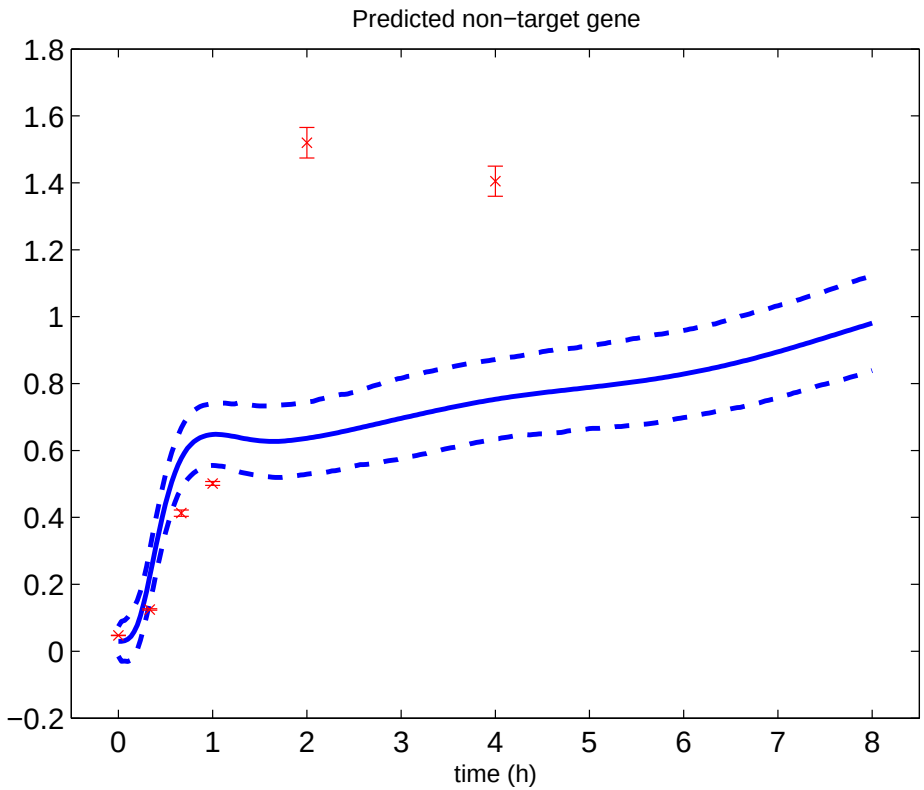




Elk-1 target selection

Fitted model used to rank potential targets of Elk-1





Roadmap

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

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

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

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

Covariance for Translation/Transcription Model

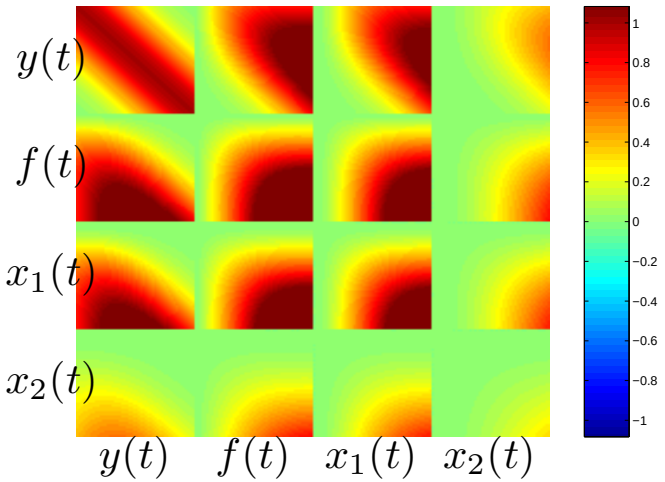
RBF covariance function for $y(t)$

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

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

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

δ	D_1	S_1	D_2	S_2
0.1	5	5	0.5	0.5



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

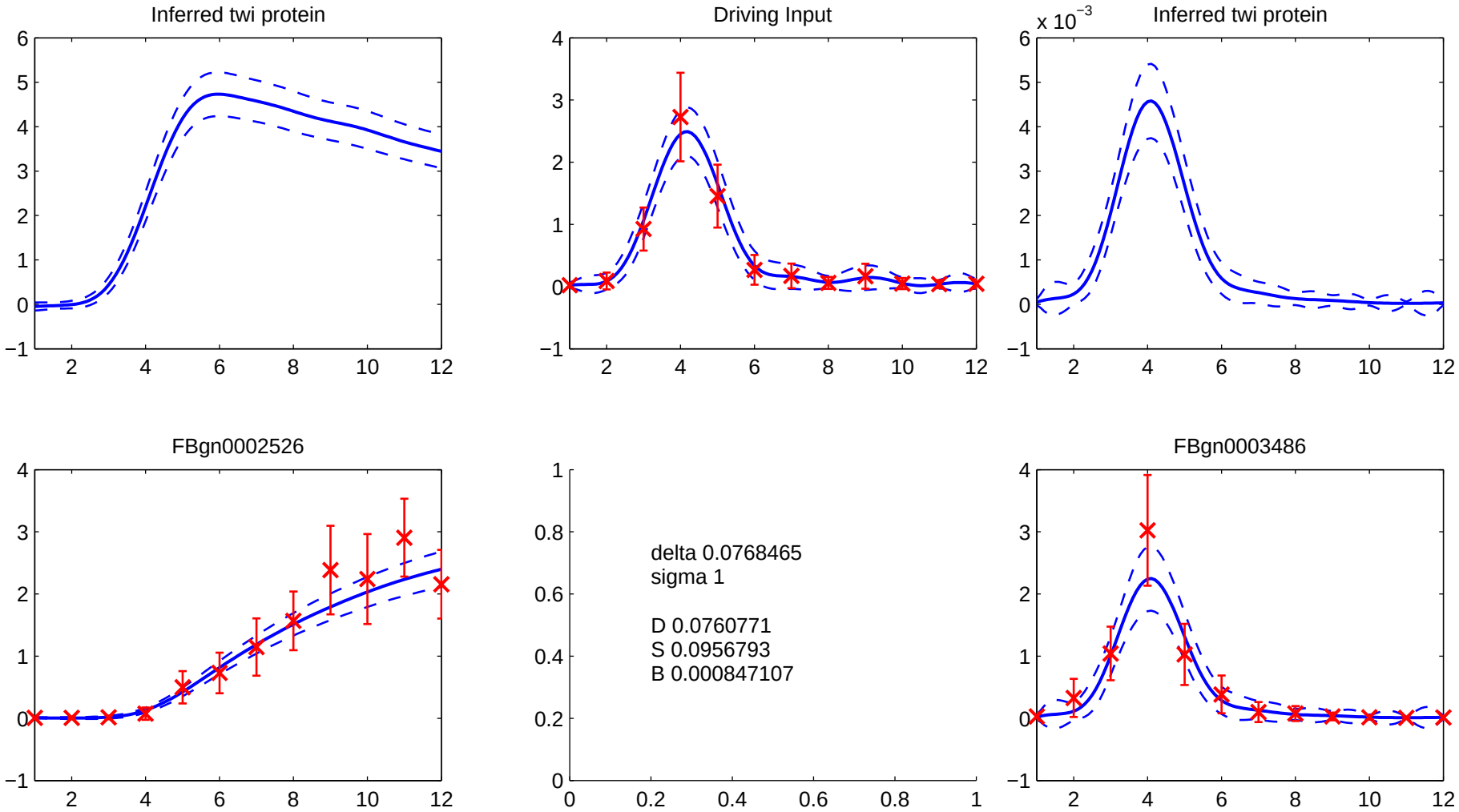


Figure: Model for flybase gene identity FBgn0002526034861120630005531007352573028 6

Results of Ranking

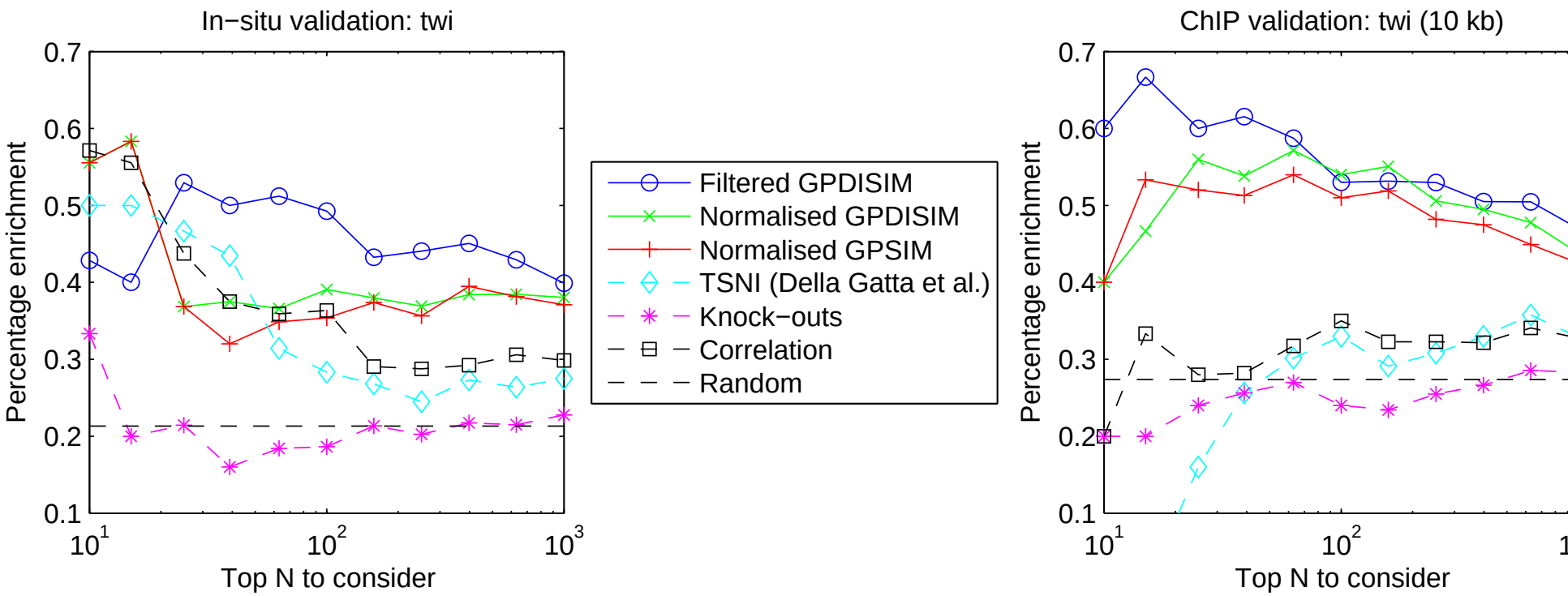


Figure: Percentage enrichment for top N targets for relevant terms in *Drosophila* in situsChIP-chip confirmed targets.

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.

Roadmap

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,

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

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

following function $\psi(\mathbf{f})$ as:

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

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,

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

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 *I*

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

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

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

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

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

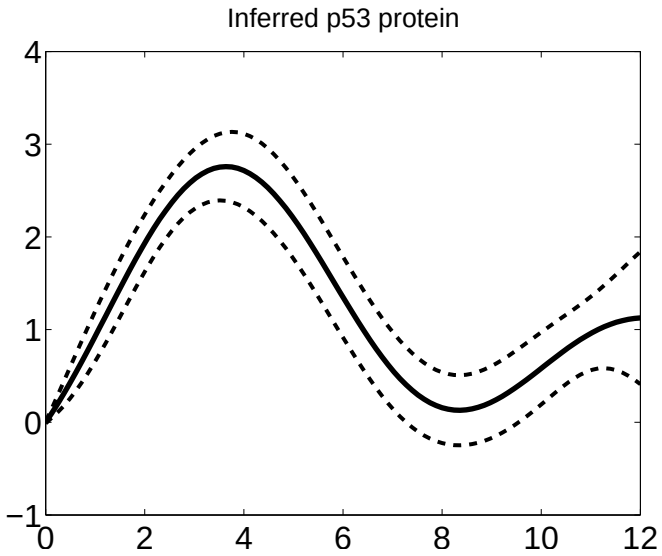
Michaelis-Menten Kinetics

Pei Gao

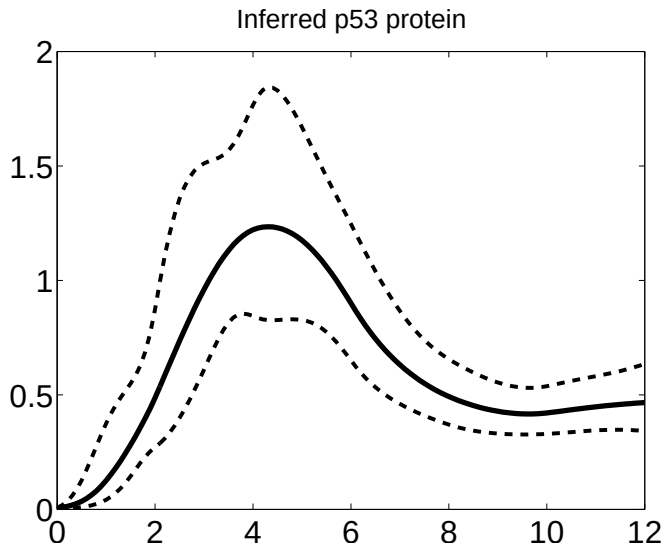
- The Michaelis-Menten activation model uses the following non-linearity

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

where we are using a GP $f\left(t\right)$ to model the log of the TF activity.



(a)



(b)

Valdiation of Laplace Approximation

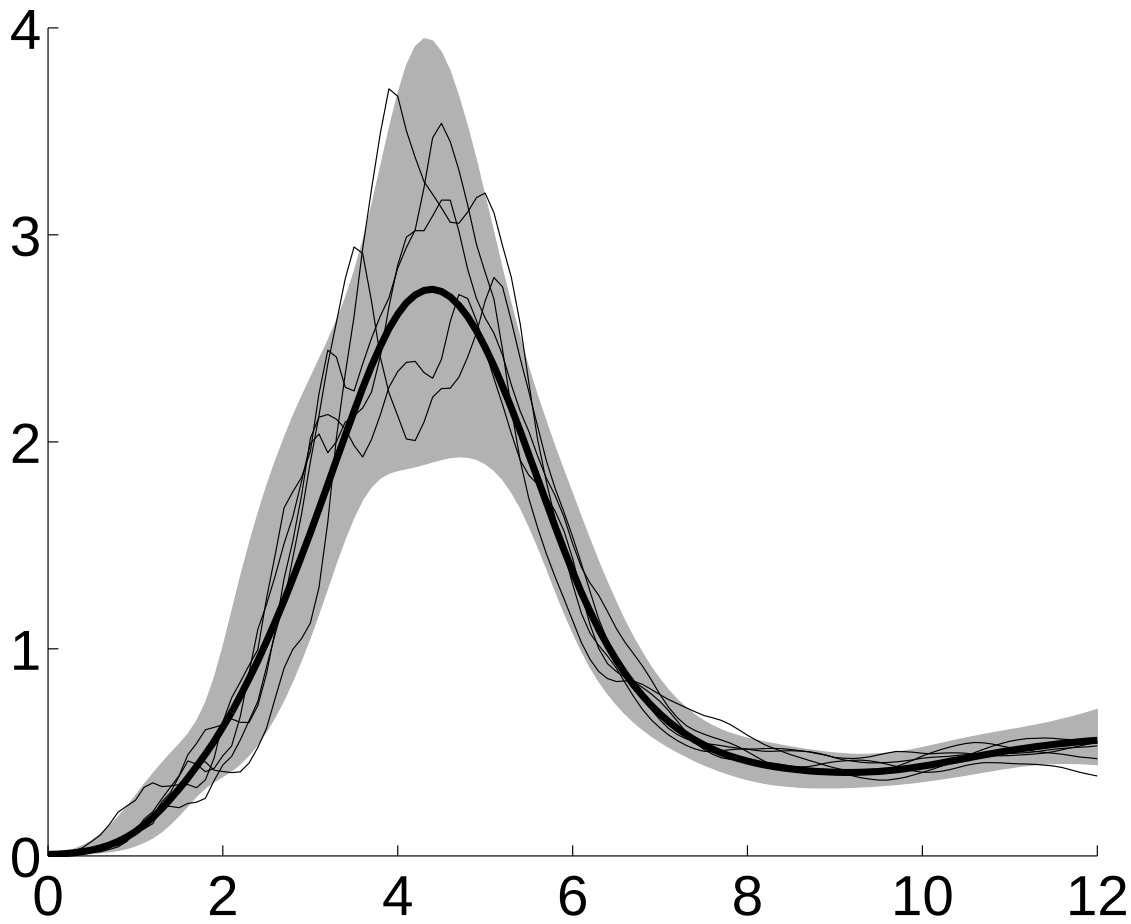


Figure: Laplace approximation error bars along with samples from the true posterior distribution.

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, $x_i(t)$, that solves the ODE in Eq. 1 can be approximated by

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

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

Khanin et al. (2006) Results Reminder

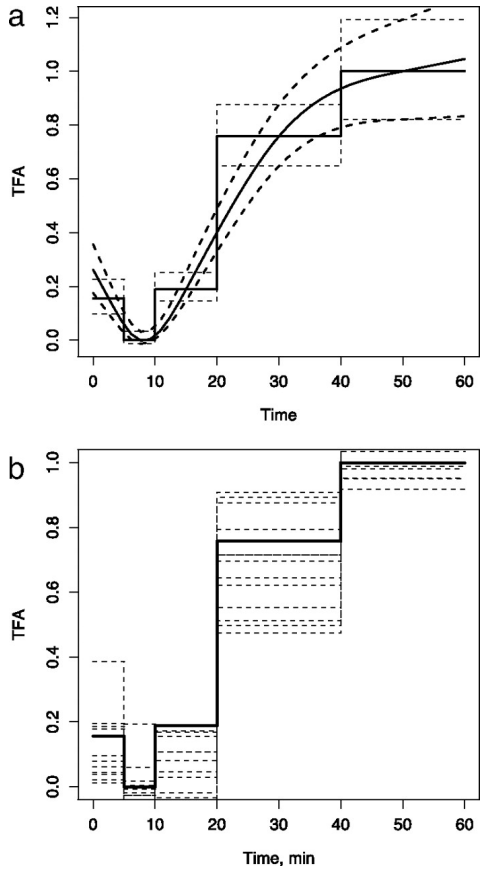


Figure: Fig. 2 from Khanin et al. (2006): Reconstructed activity level of master repressor LexA, following a UV dose of 40 J/m2.

Their Results

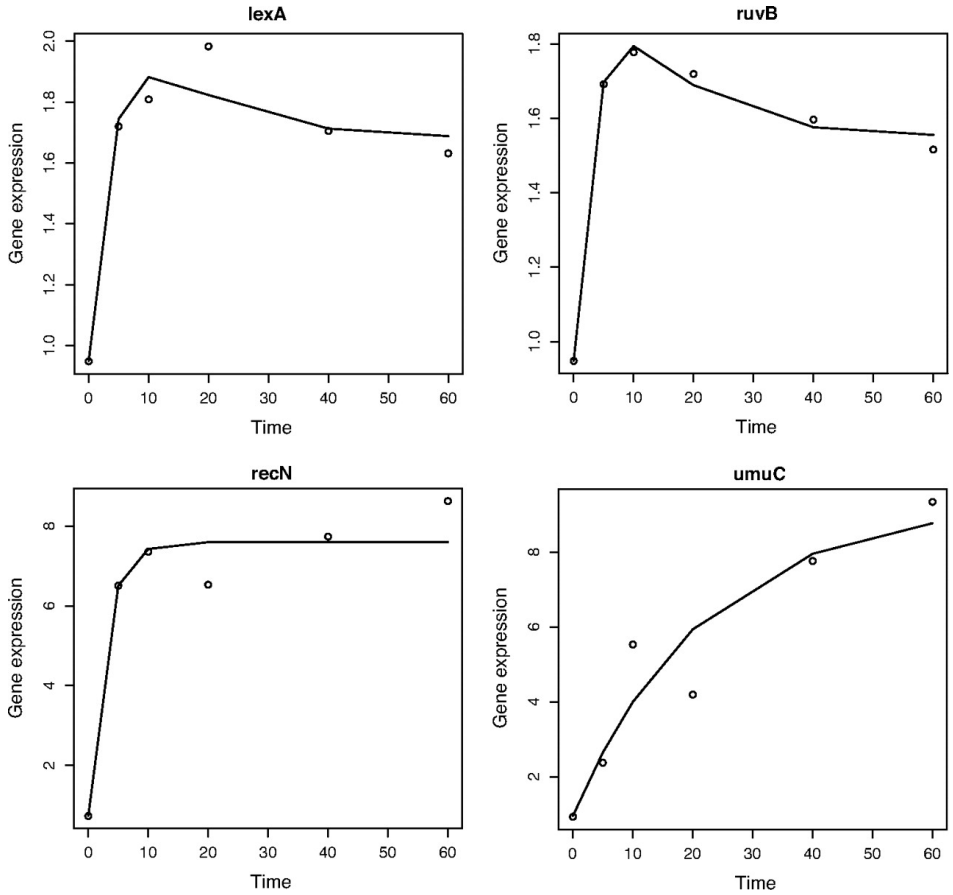


Figure: Fig. 3 from Khanin et al. (2006): Reconstructed profiles for four genes in the LexA SIM.

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

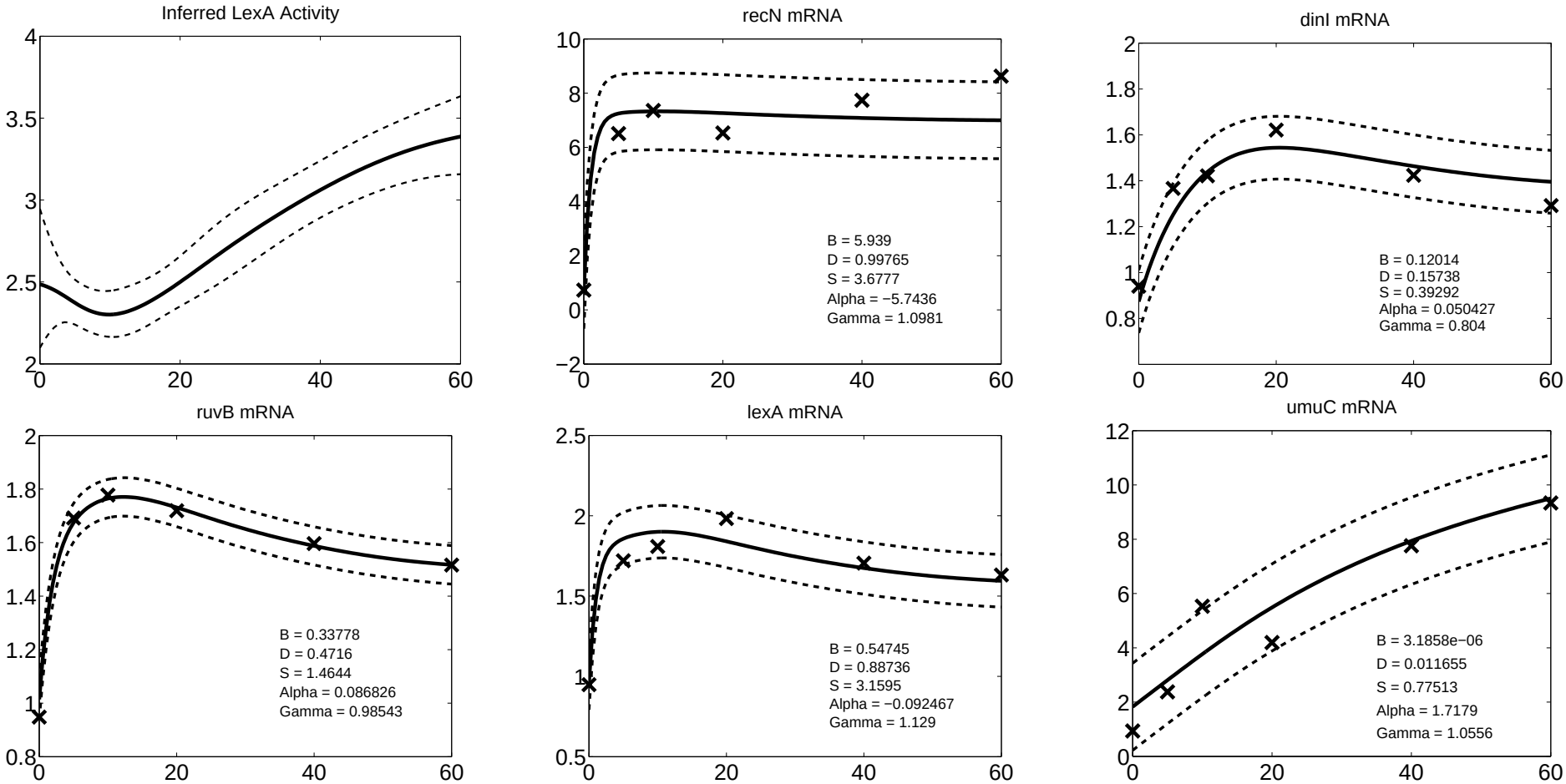


Figure: Our results using an MLP kernel. To apear at ECCB08 Gao et al. (2008).

Use Samples to Represent Posterior

Michalis Titsias

- Sample in Gaussian processes

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

- Likelihood relates GP to data through

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

- 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

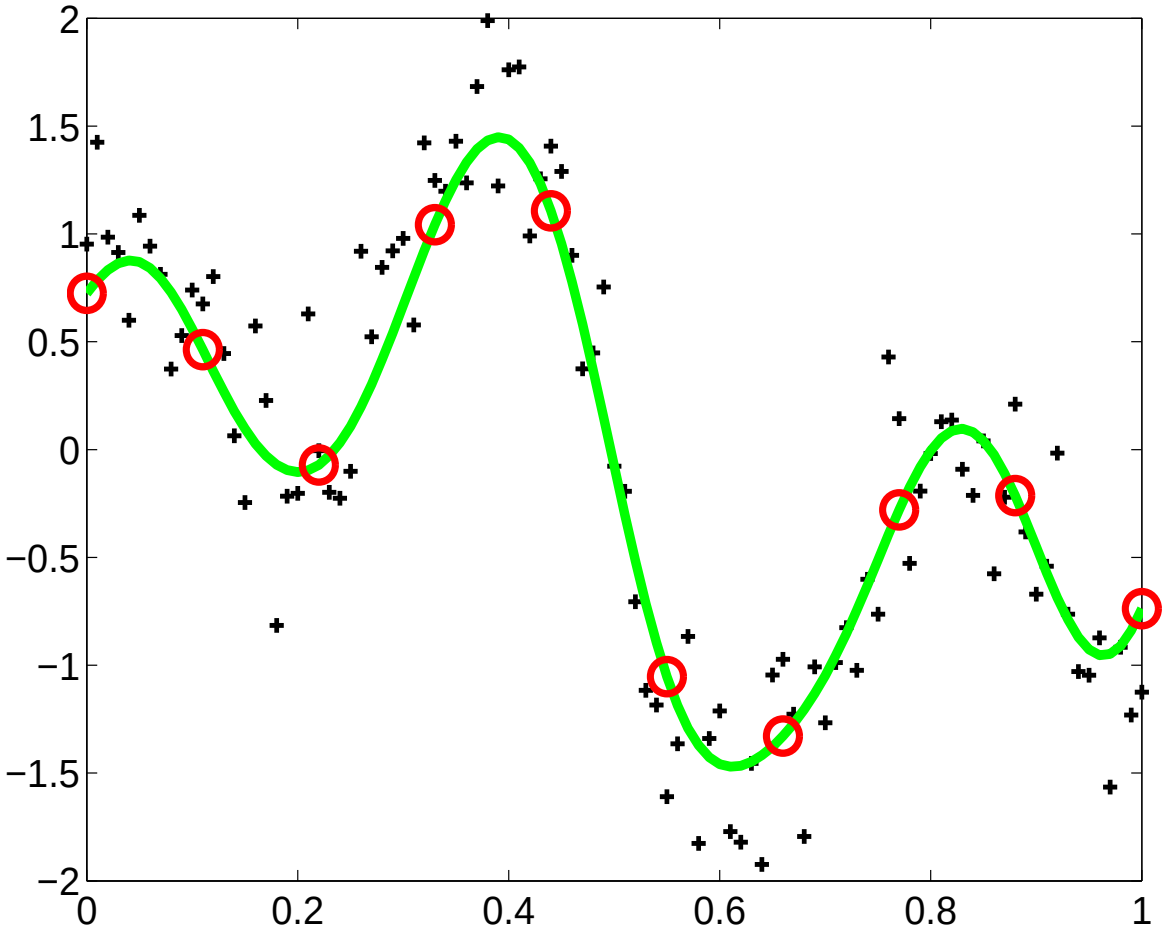
- Separate the points in $\mathbf{f}$ into two groups:
  - few control points $\mathbf{f}_c$
  - and the large majority of the remaining points $\mathbf{f}_\rho = \mathbf{f} \setminus \mathbf{f}_c$
- Sample the control points $\mathbf{f}_c$ using a proposal $q\left(\mathbf{f}_c^{(t+1)}|\mathbf{f}_c^{(t)}\right)$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

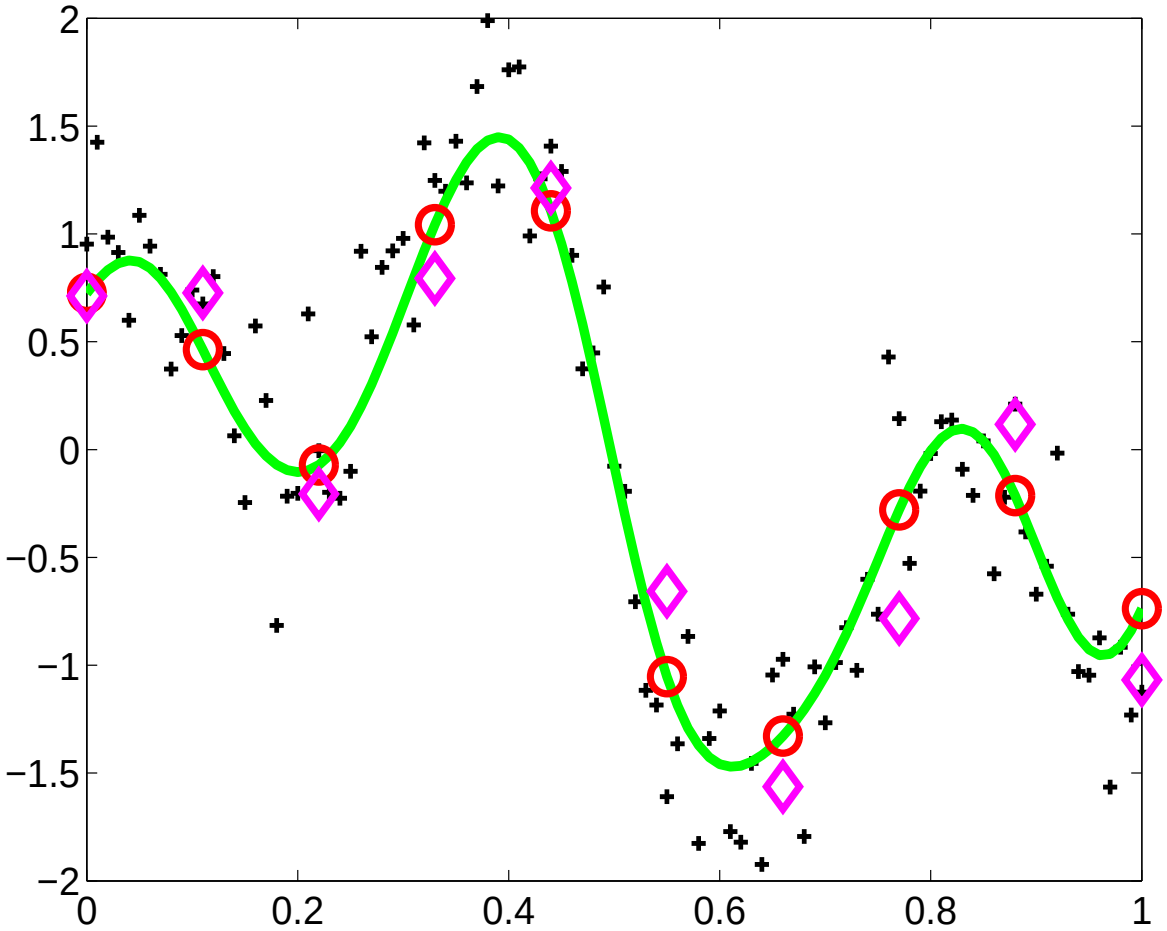
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



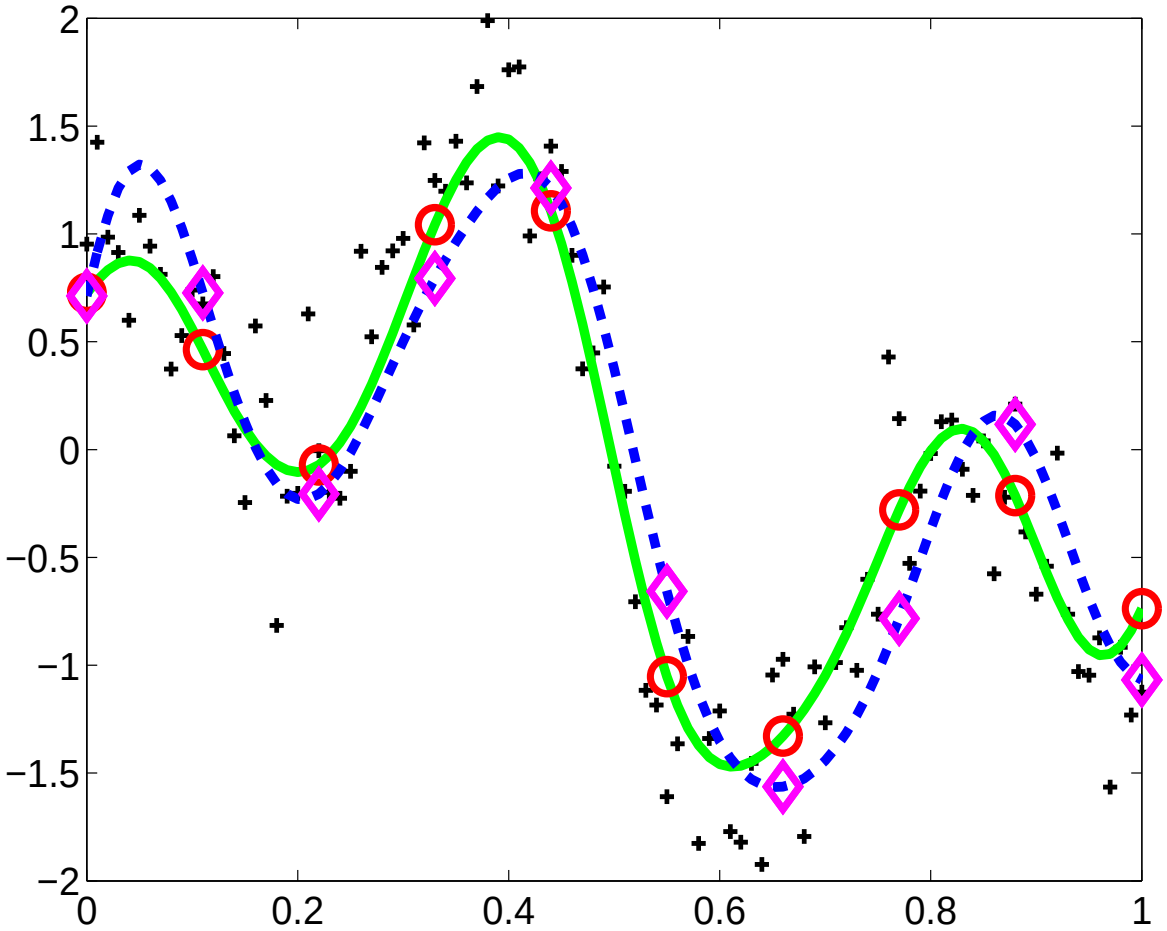
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



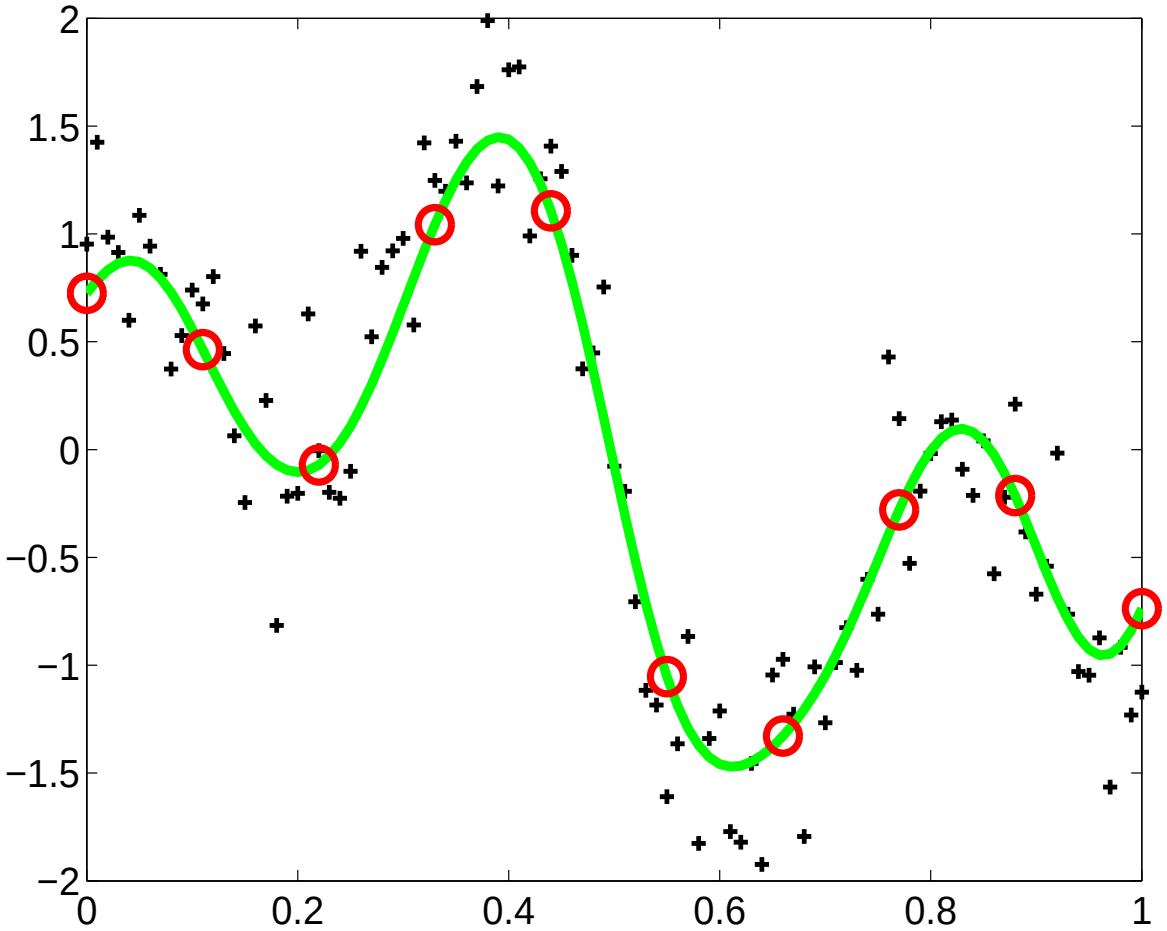
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



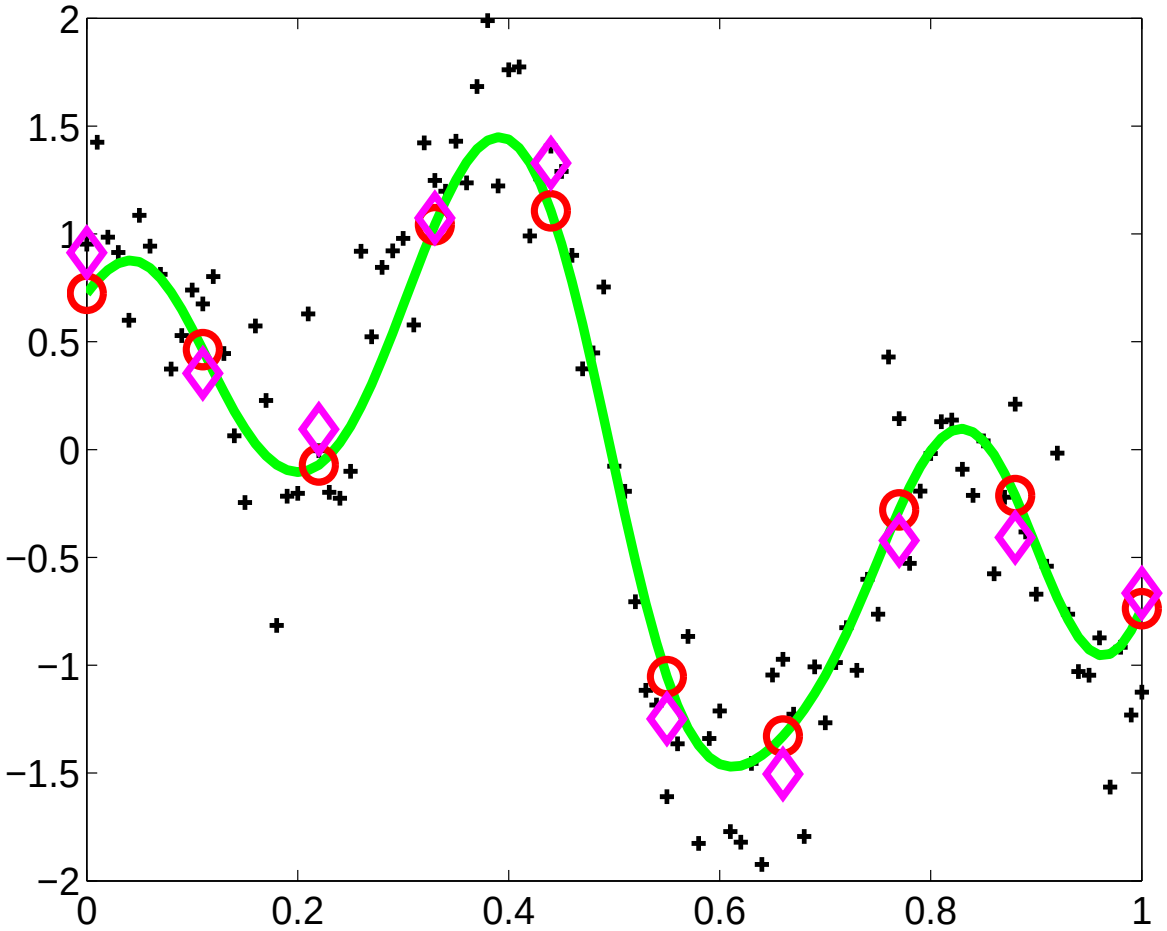
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



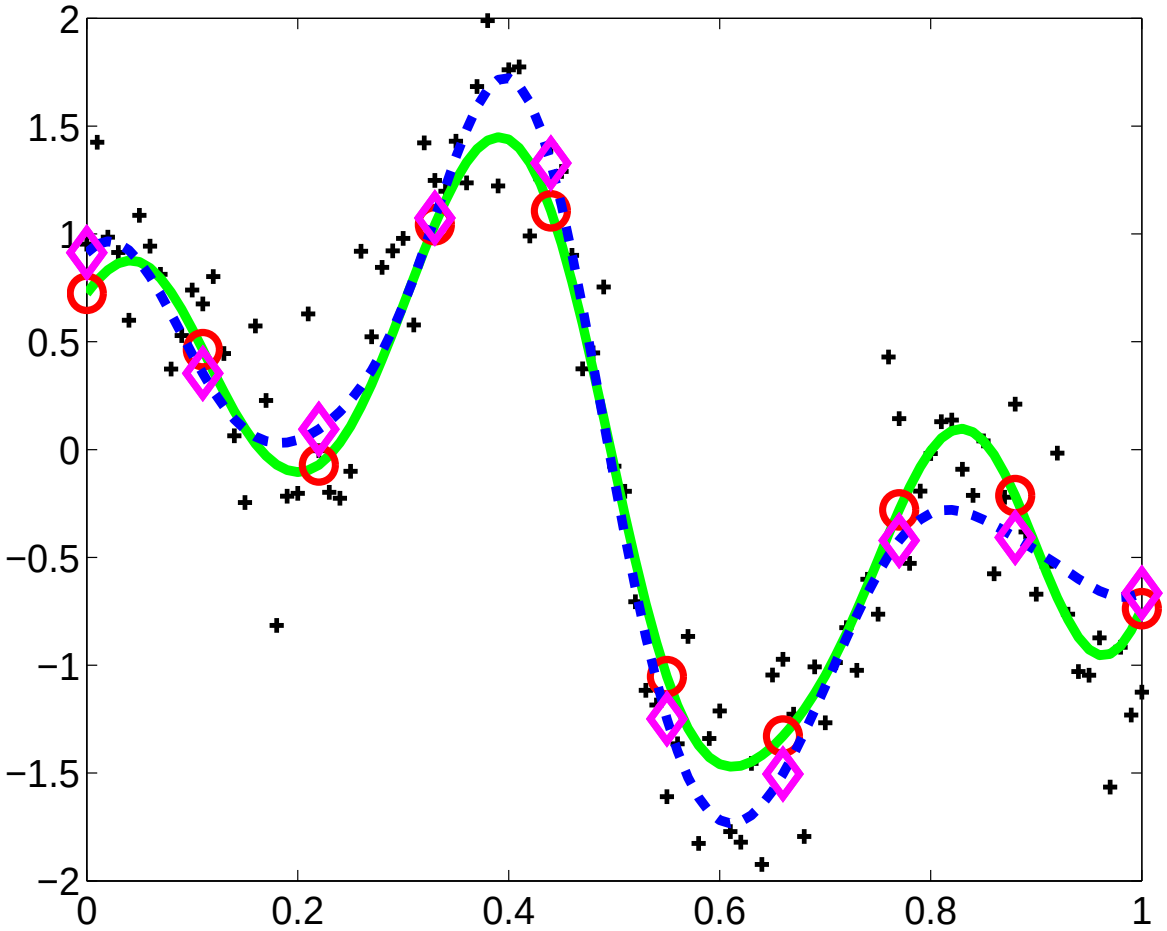
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



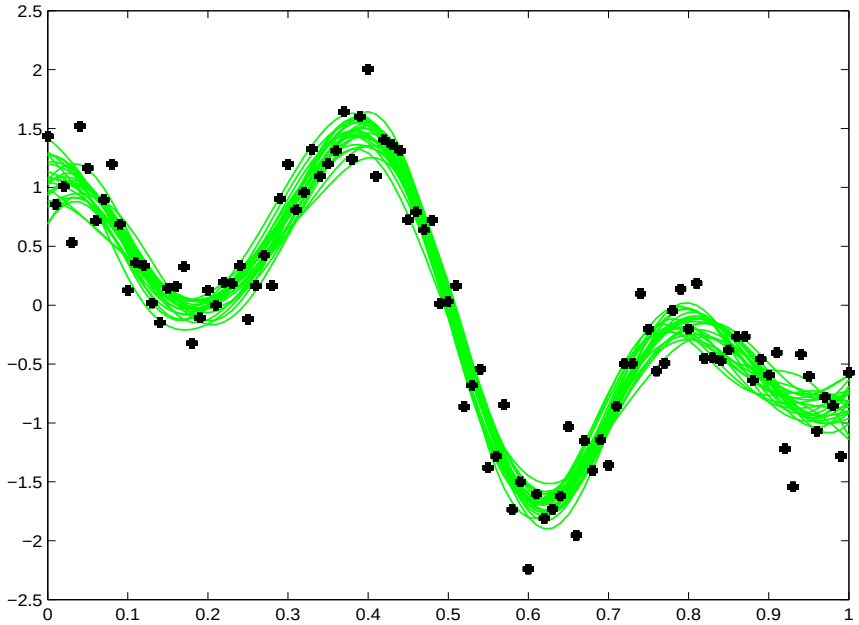
Sampling using control points: Regression-Examples

Sample 121 points using 10 control points



Sampling using control points

Few samples drawn during MCMC



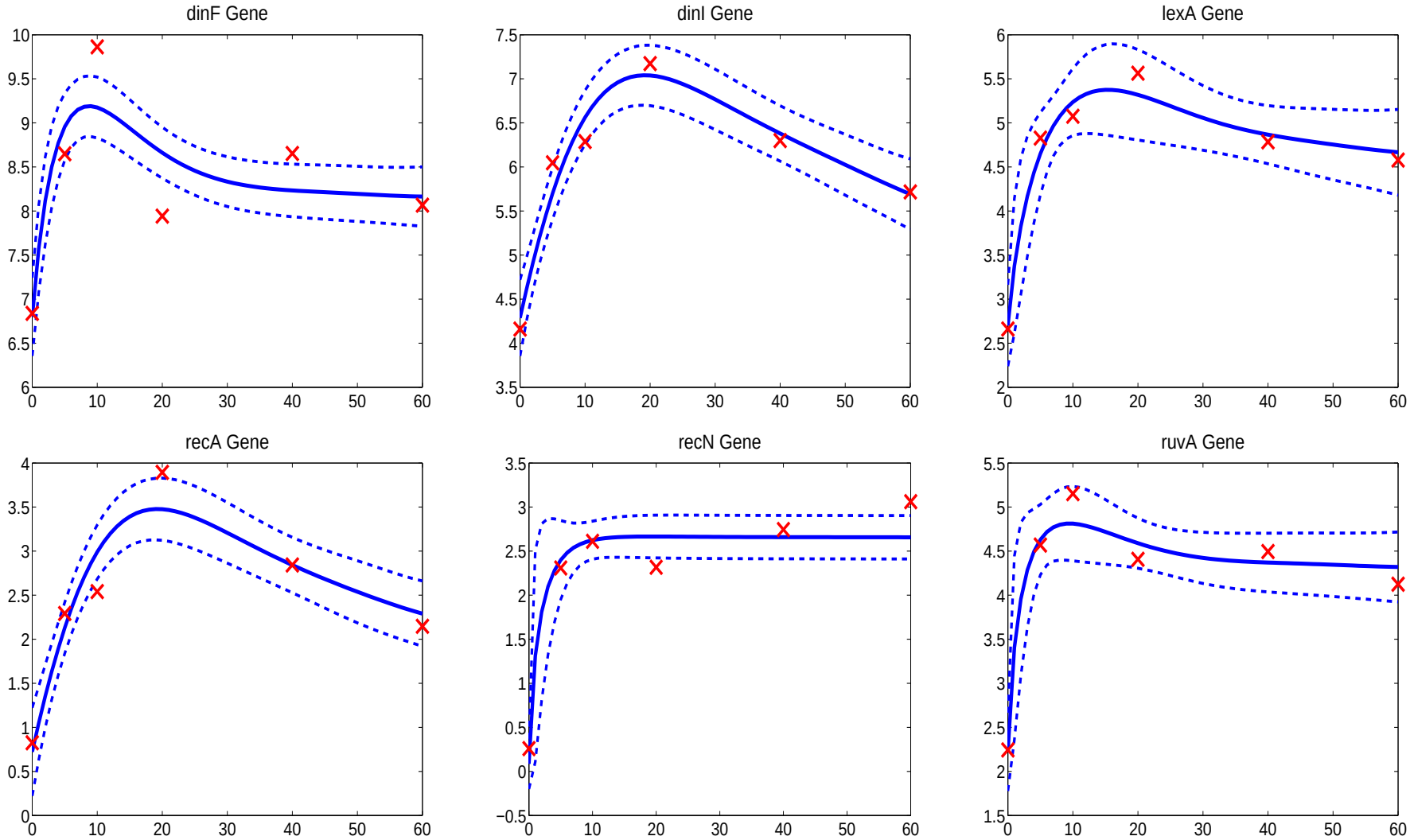
Results on SOS System

- Again consider the Michaelis-Menten kinetic equation

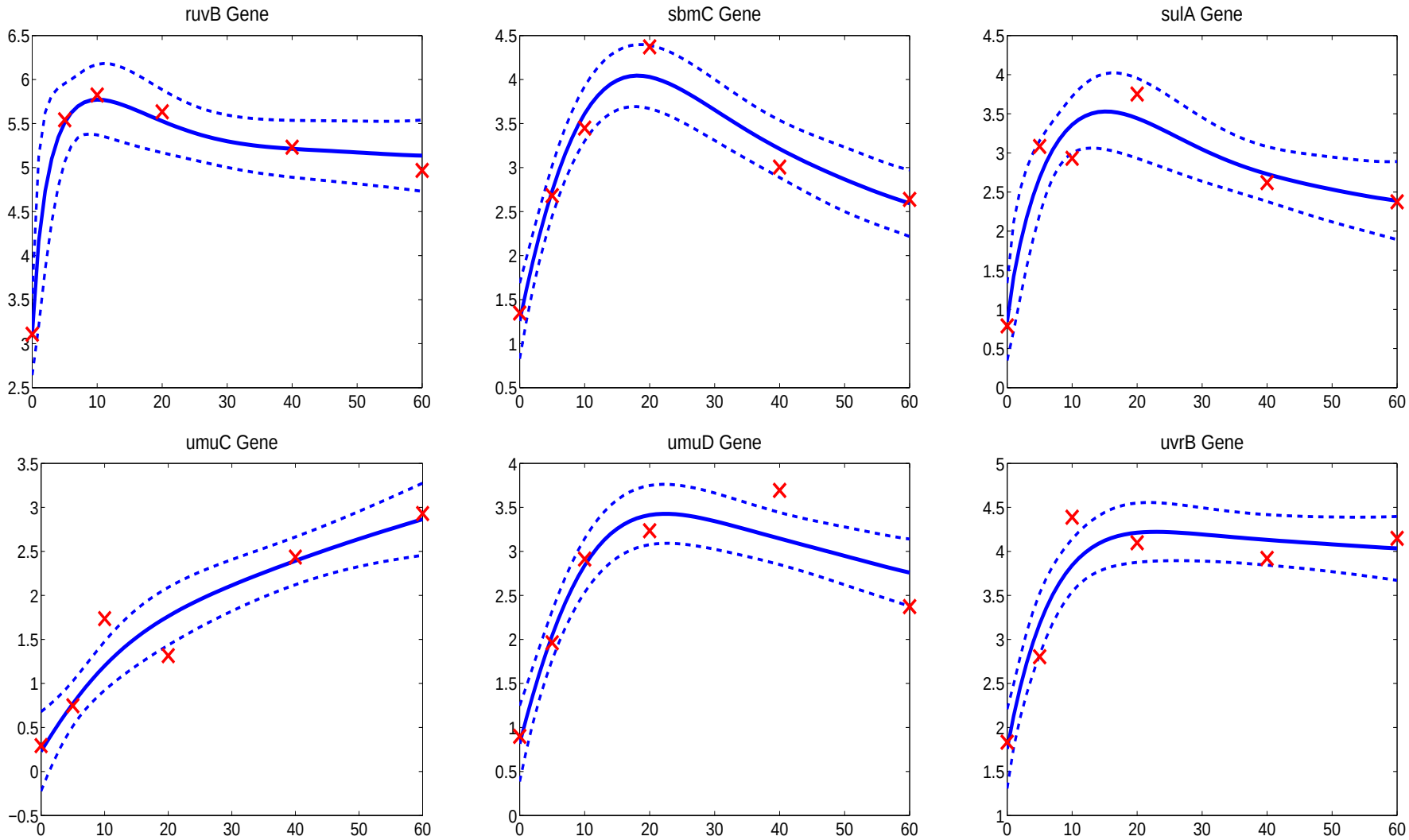
$$\frac{\mathrm{d}x_j(t)}{\mathrm{d}t} = B_j + S_j \frac{1}{\exp(f(t)) + \gamma_j} - D_j x_j(t)$$

- We have 14 genes (5 kinetic parameters each)
- Gene expressions are available for $T = 6$ time slots
- TF ($\mathbf{f}$) 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 $\mathbf{f}$ after burn in was between $15\% - 25\%$

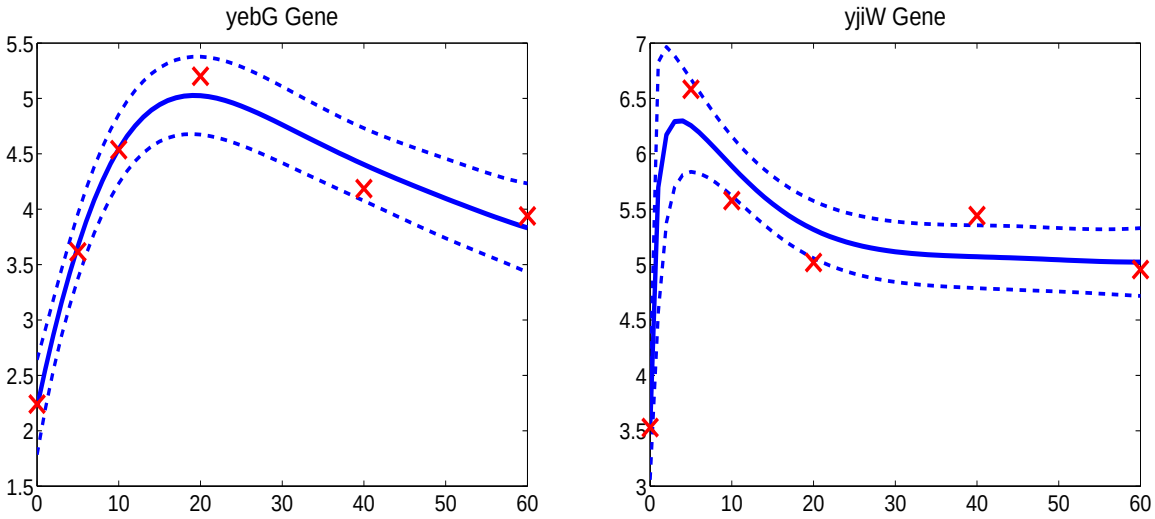
Results in E.coli data: Predicted gene expressions



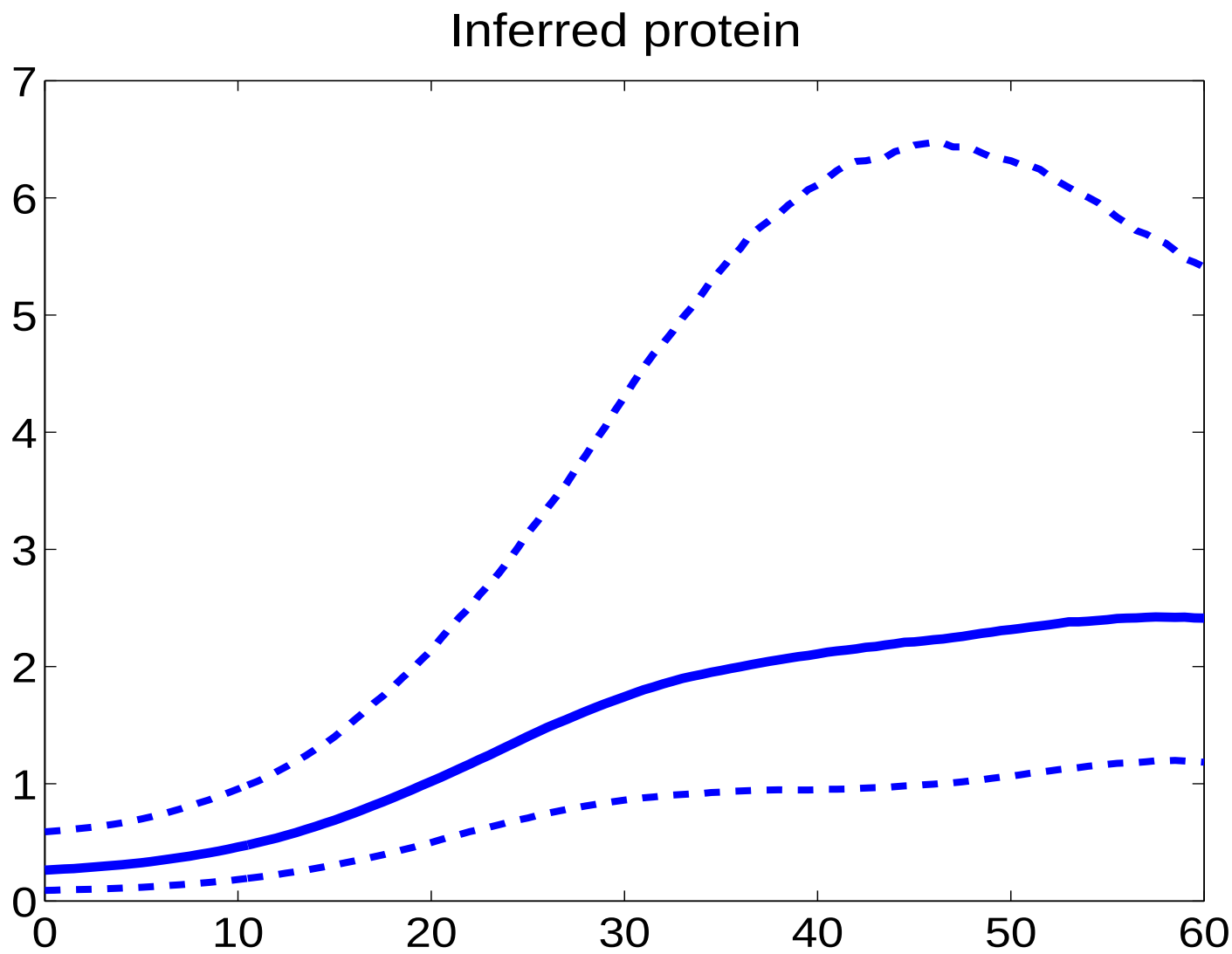
Results in E.coli data: Predicted gene expressions



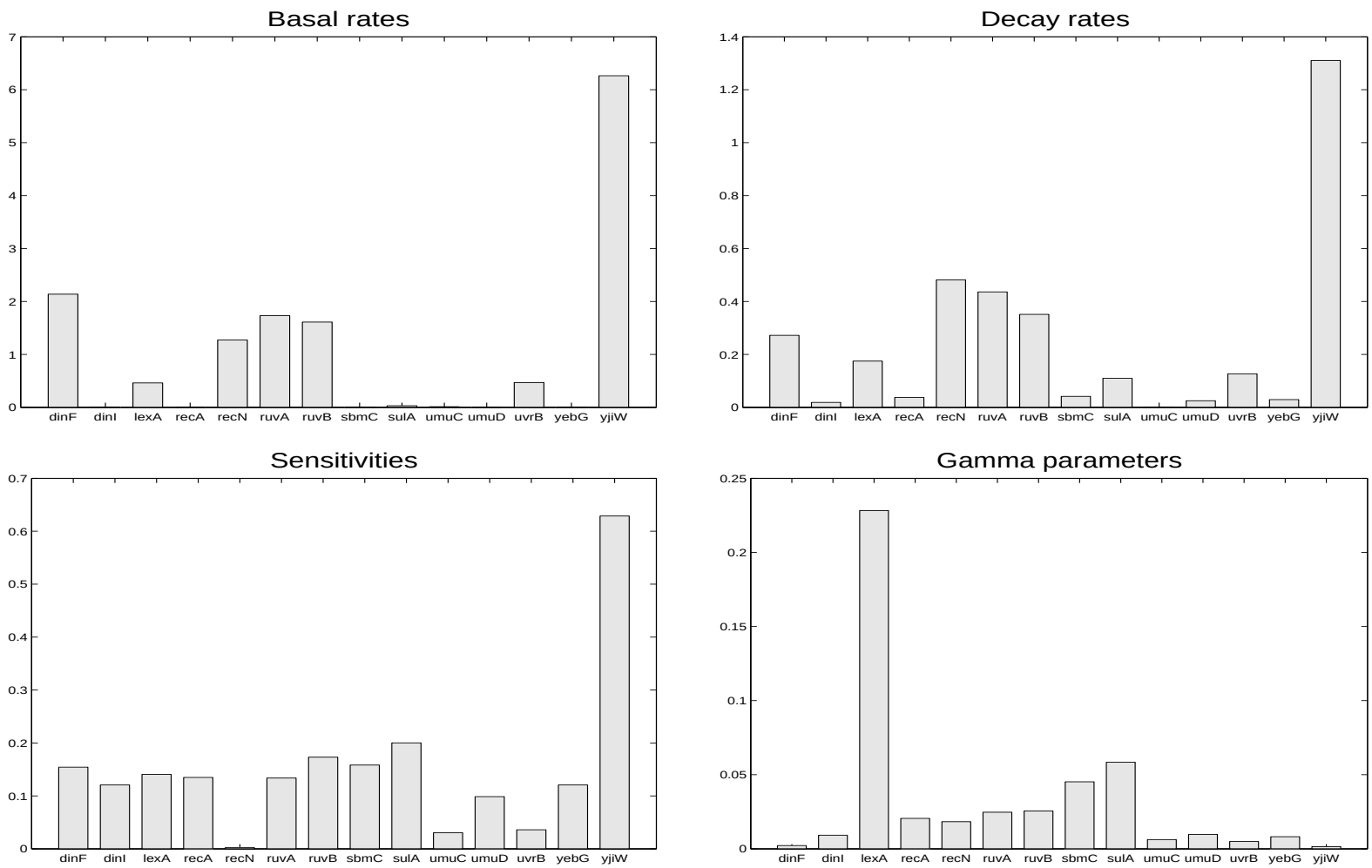
Results in E.coli data: Predicted gene expressions



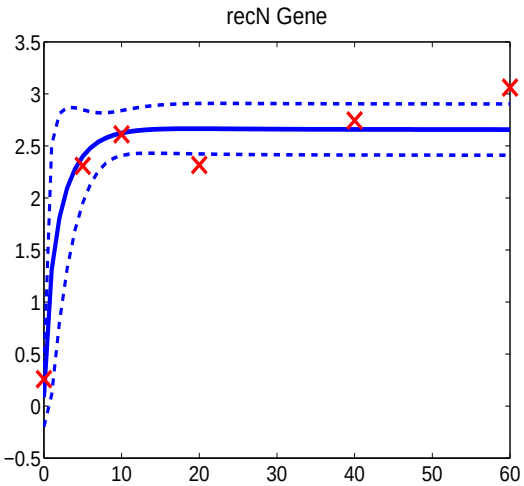
Results in E.coli data: Protein concentration

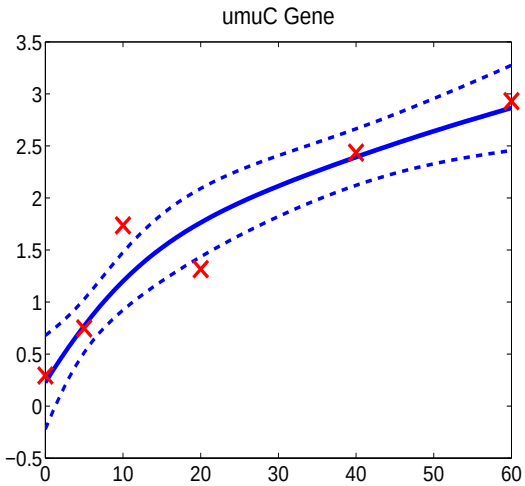


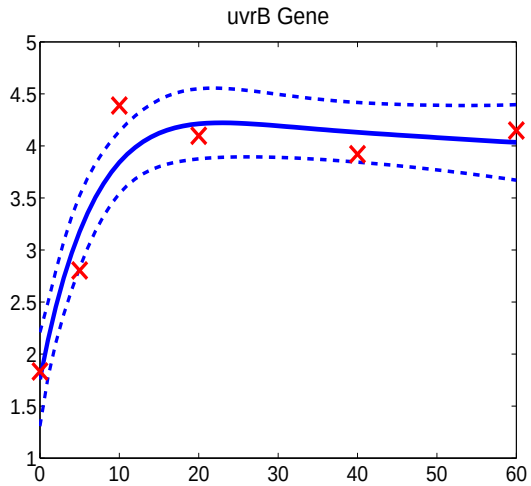
Results in E.coli data: Kinetic parameters

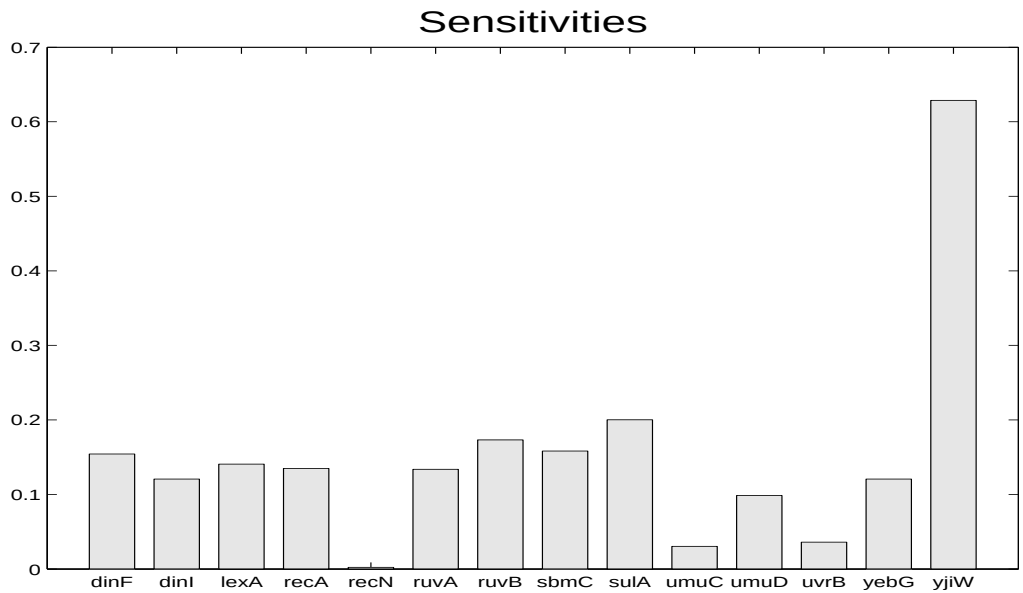


Results in E.coli data: Genes with low sensitivity value

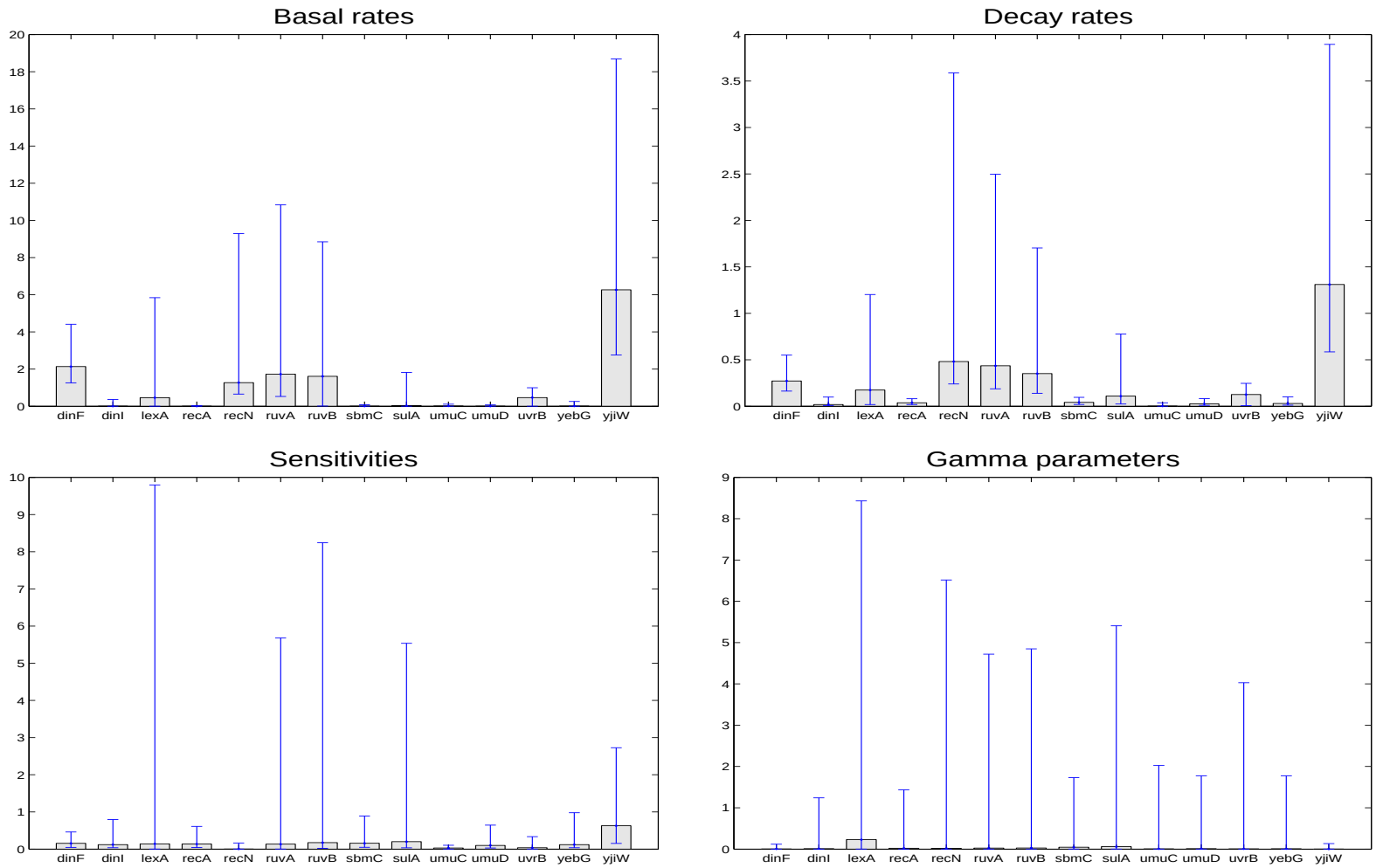








Results in E.coli data: Confidence intervals for the kinetic parameters



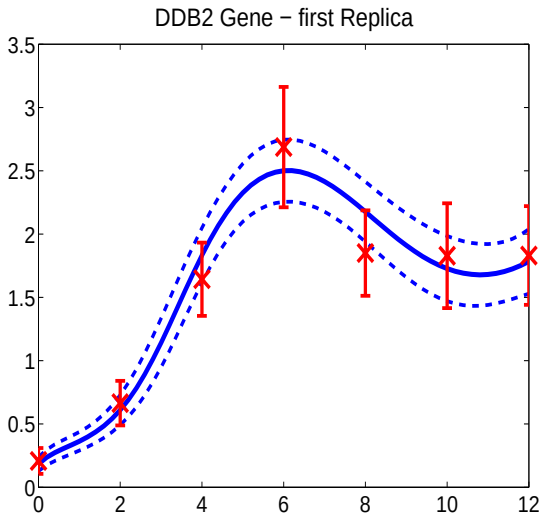
p53 System Again

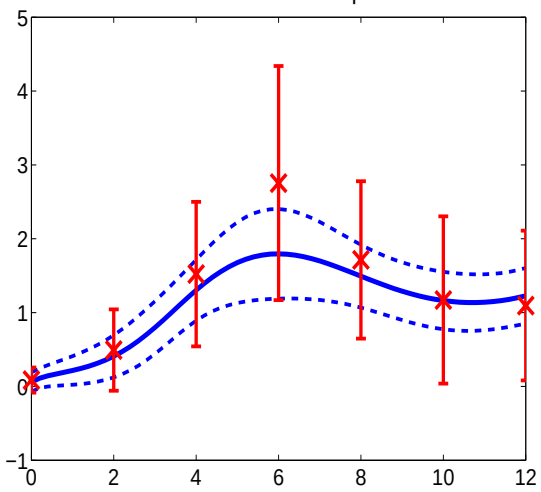
- One transcription factor (p53) that acts as an activator. We consider the Michaelis-Menten kinetic equation

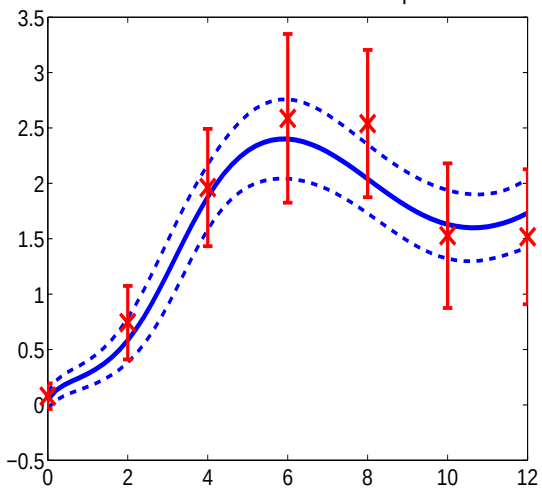
$$\frac{\mathrm{d}x_j(t)}{dt} = B_j + S_j \frac{\exp(f(t))}{\exp(f(t)) + \gamma_j} - D_j x_j(t)$$

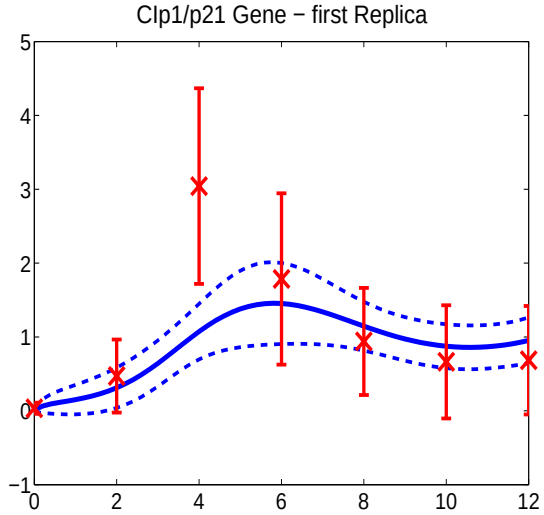
- We have 5 genes
- Gene expressions are available for $T = 7$ times and there are 3 replicas of the time series data
- TF ($\mathbf{f}$) is discretized using 121 points
- MCMC details:
  - 7 control points are used (placed in a equally spaced grid)
  - Running time 4/5 hours for 2 million sampling iterations plus burn in
  - Acceptance rate for $\mathbf{f}$ after burn in was between $15\% - 25\%$

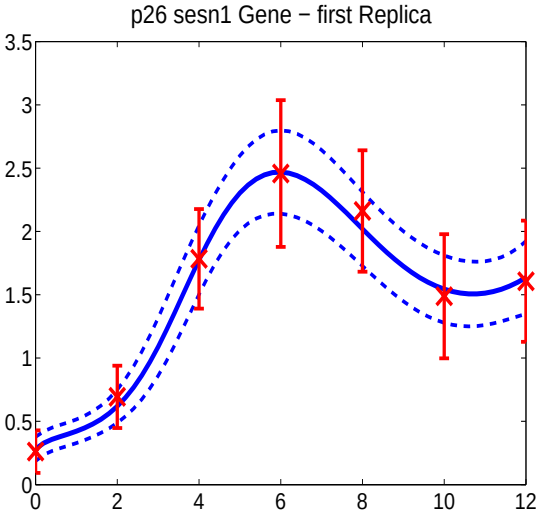
Data used by Barenco et al. (2006): Predicted gene expressions for the 1st replica



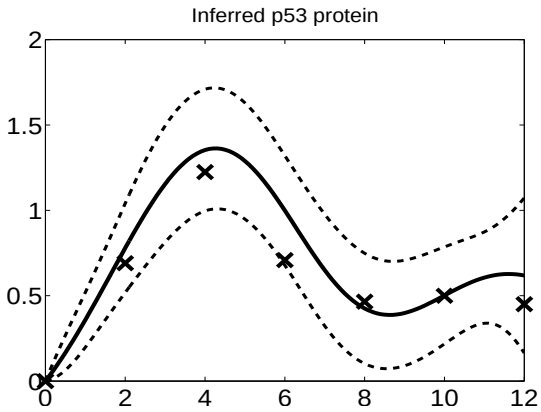


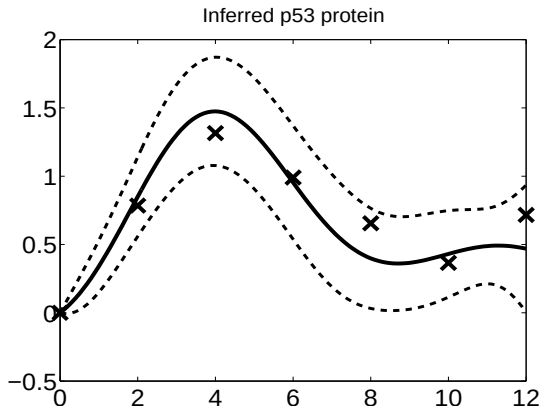


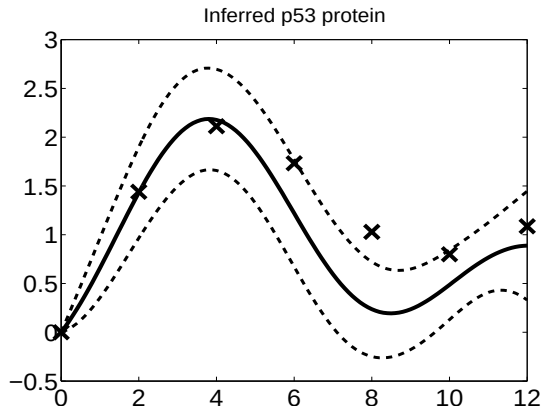




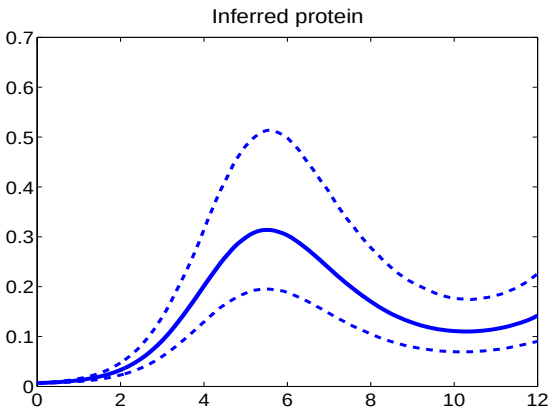
Data used by Barenco et al. (2006): Protein concentrations

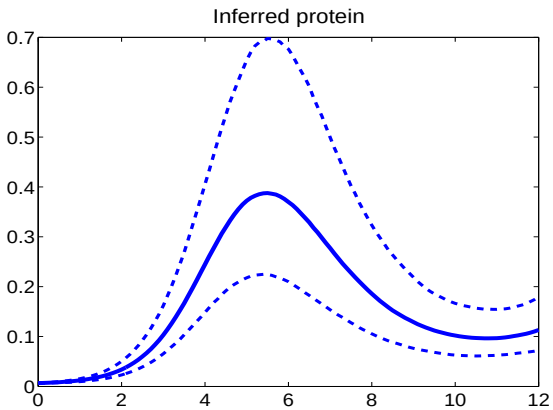


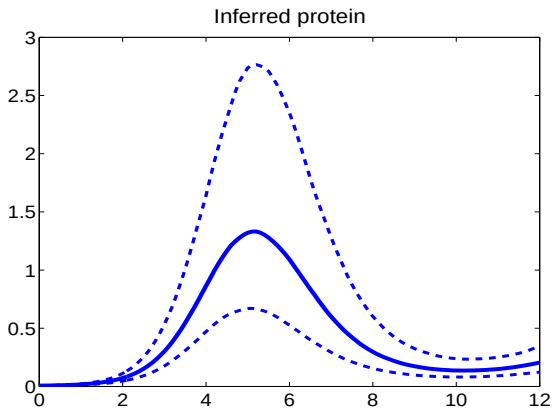




Linear model (Barenco et al. predictions are shown as crosses)

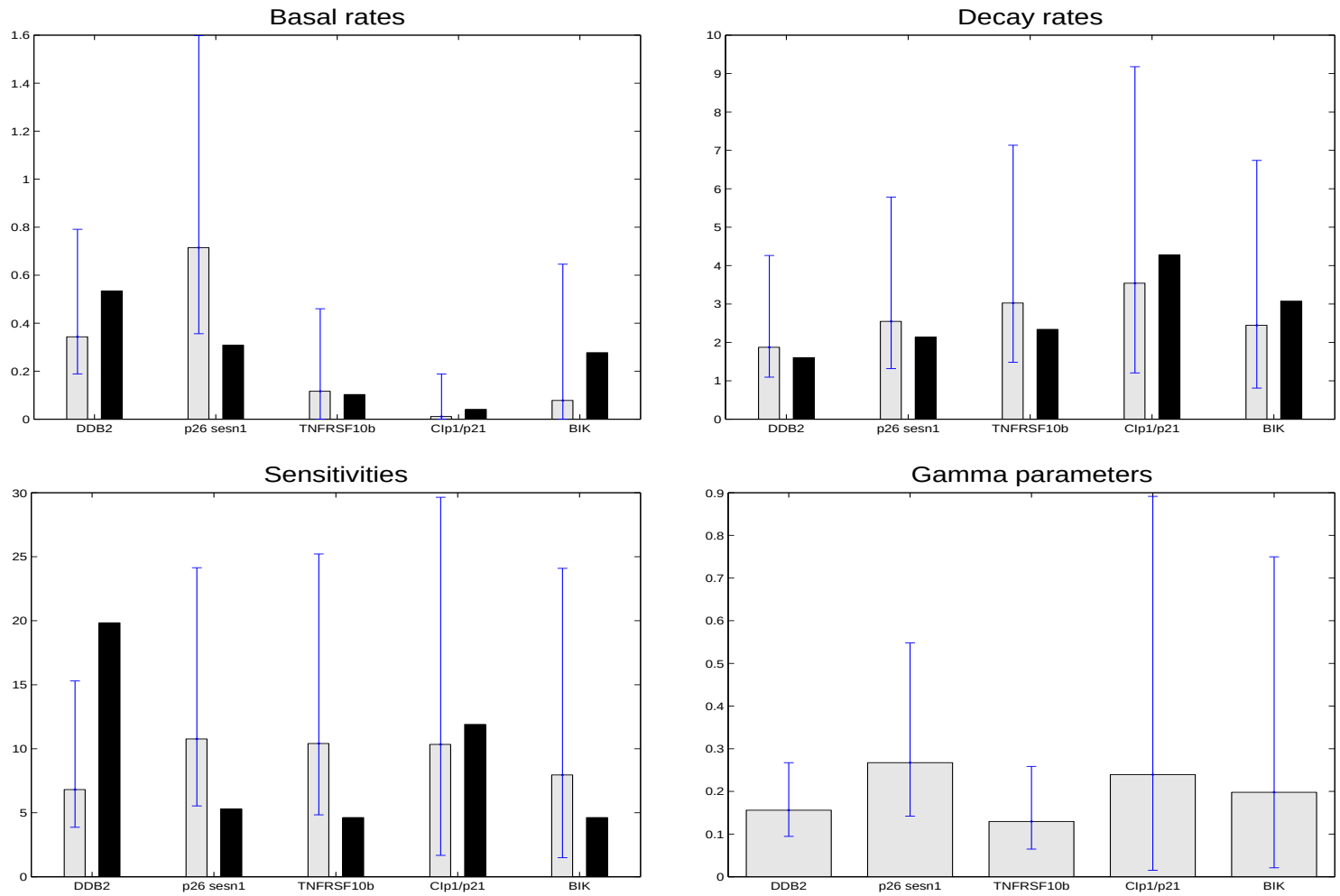






Nonlinear (Michaelis-Menten kinetic equation)

p53 Data Kinetic parameters



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

Roadmap

Discussion and Future Work

- Integration of probabilistic inference with mechanistic models.
- These results are small simple systems.
- Ongoing work:
  - Scaling up to larger systems
  - Applications to other types of system, *e.g.* non-steady-state metabolomics, spatial systems etc.
  - Improved approximations.
  - Stochastic differential equations

Outline

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- Raya Khanin and Ernst Wit of the University of Glasgow and the University of Lancaster (*E. coli* repressor system).

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