

Latent Force Models with Gaussian Processes

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- 1 Introduction
- 2 Gaussian Process Review
- 3 Covariance Functions
- 4 Convolutions and Computational Complexity
- 5 Non-linear Response Models
- 6 Cascaded Differential Equations
- 7 Discussion and Future Work

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Dimensionality Reduction I

- Linear relationship between the data, $\mathbf{X} \in \Re^{N \times d}$, and a reduced dimensional representation, $\mathbf{F} \in \Re^{N \times q}$, where $q \ll d$.

$$\mathbf{X} = \mathbf{F}\mathbf{W} + \epsilon,$$

$$\epsilon \sim \mathcal{N}(\mathbf{0}, \Sigma)$$

- Integrate out $\mathbf{F}$, optimize with respect to $\mathbf{W}$.
- For temporal data and a particular Gaussian prior in the latent space: Kalman filter/smoother.
- More generally consider a Gaussian process (GP) prior,

$$p(\mathbf{F}|\mathbf{t}) = \prod_{i=1}^q \mathcal{N}(\mathbf{f}_{:,i} | \mathbf{0}, \mathbf{K}_{\mathbf{f}_{:,i}, \mathbf{f}_{:,i}}).$$

- Given the covariance functions for $\{f_i(t)\}$ the implied covariance functions for $\{x_i(t)\}$ — semi-parametric latent factor model (Teh et al., 2005).
- Kalman filter/smoothing approach has been preferred
 - ▶ linear computational complexity in N .
 - ▶ Advances in sparse approximations have made the general GP framework practical. (Snelson and Ghahramani, 2006; Quiñero Candela and Rasmussen, 2005, also imminent work by Titsias).

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Zero mean Gaussian distribution

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

$$N(\mathbf{f}|\mu, \mathbf{K}) = \frac{1}{(2\pi)^{\frac{N}{2}} |\mathbf{K}|^{\frac{1}{2}}} \exp\left(-\frac{(\mathbf{f} - \mu)^T \mathbf{K}^{-1} (\mathbf{f} - \mu)}{2}\right).$$

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

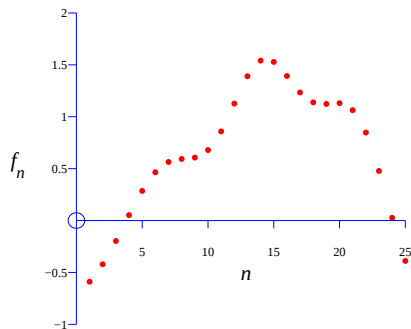
$$N(\mathbf{f}|\mathbf{0}, \mathbf{K}) = \frac{1}{(2\pi)^{\frac{N}{2}} |\mathbf{K}|^{\frac{1}{2}}} \exp\left(-\frac{\mathbf{f}^T \mathbf{K}^{-1} \mathbf{f}}{2}\right).$$

Multi-variate Gaussians

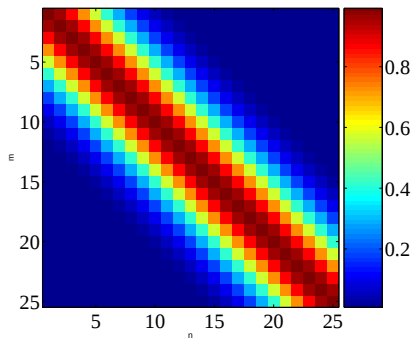
- We will consider a Gaussian with a particular structure of covariance matrix.
- Generate a single sample from this 25 dimensional Gaussian distribution, $\mathbf{f} = [f_1, f_2 \dots f_{25}]$.
- We will plot these points against their index.

Gaussian Distribution Sample

demGPSample



(a)



(b)

Figure: (a) 25 instantiations of a function, f_n , (b) colormap of covariance matrix.

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*.
- Let's focus on the joint distribution of two points from the 25.

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Prediction of f_2 from f_1

demGPCov2D([1 2])

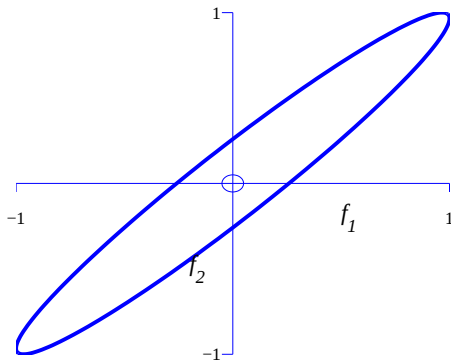


Figure: Covariance for $\begin{bmatrix} f_1 \\ f_2 \end{bmatrix}$ is $\mathbf{K}_{12} = \begin{bmatrix} 1 & 0.966 \\ 0.966 & 1 \end{bmatrix}$.

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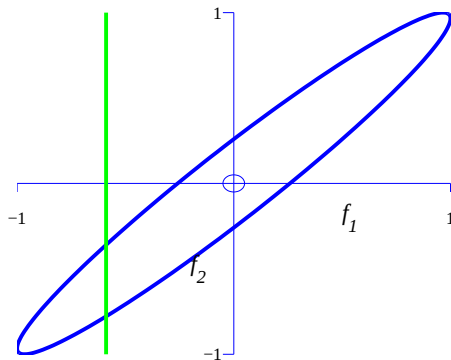


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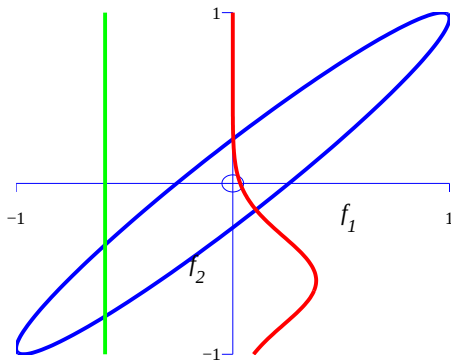


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Prediction of f_5 from f_1

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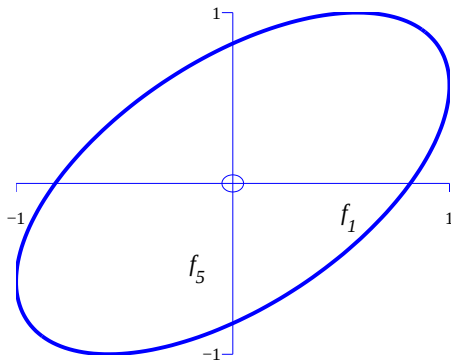


Figure: Covariance for $\begin{bmatrix} f_1 \\ f_5 \end{bmatrix}$ is $\mathbf{K}_{15} = \begin{bmatrix} 1 & 0.574 \\ 0.574 & 1 \end{bmatrix}$.

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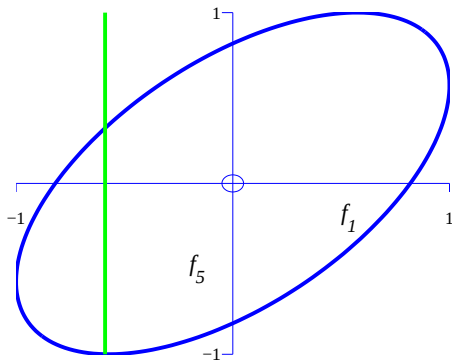


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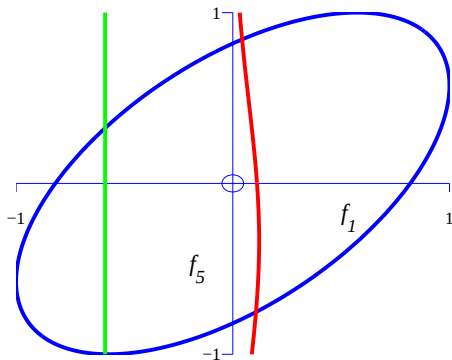


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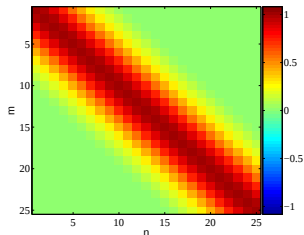
Covariance Functions

Where did this covariance matrix come from?

RBF Kernel Function

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

- 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 known as a kernel.



demCovFuncSample

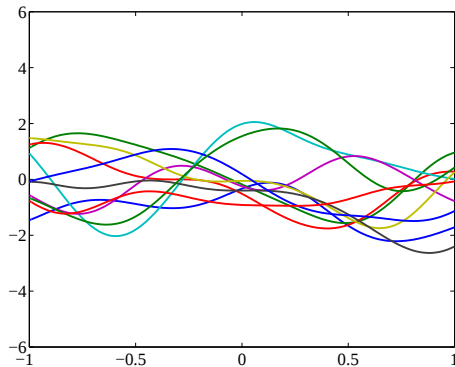


Figure: RBF kernel with $l = 10^{-\frac{1}{2}}$, $\alpha = 1$

demCovFuncSample

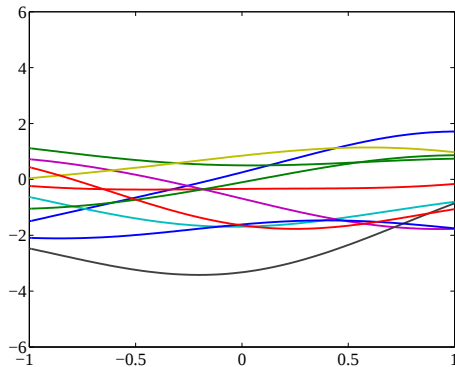


Figure: RBF kernel with $l = 1$, $\alpha = 1$

demCovFuncSample

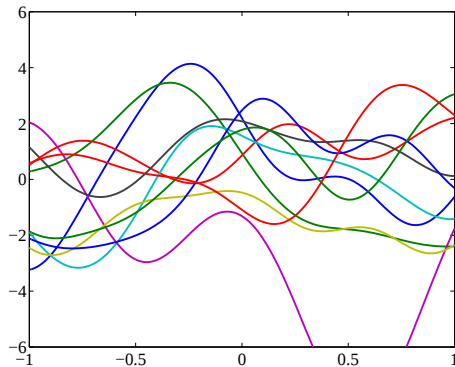


Figure: RBF kernel with $l = 0.3$, $\alpha = 4$

Gaussian Process Regression

demRegression

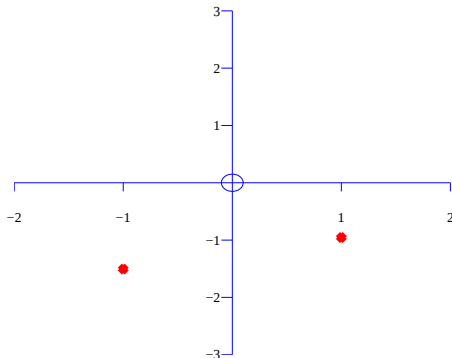


Figure: Examples include WiFi localization, C14 calibration curve.

Gaussian Process Regression

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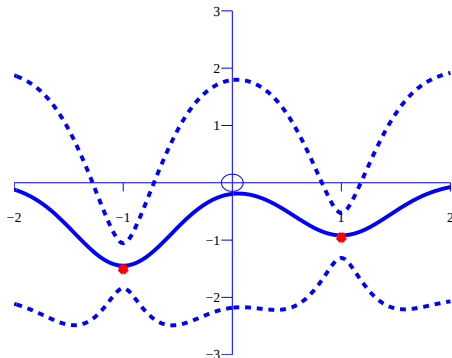


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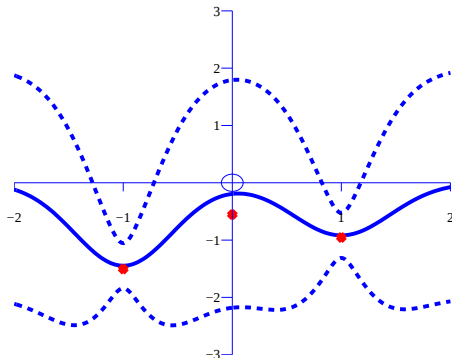


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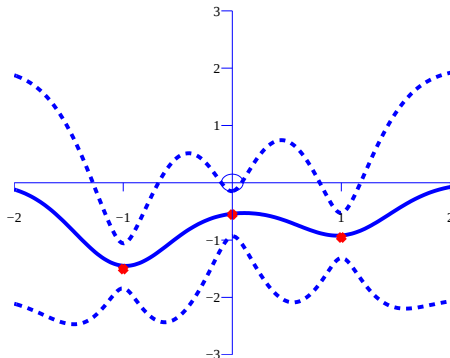


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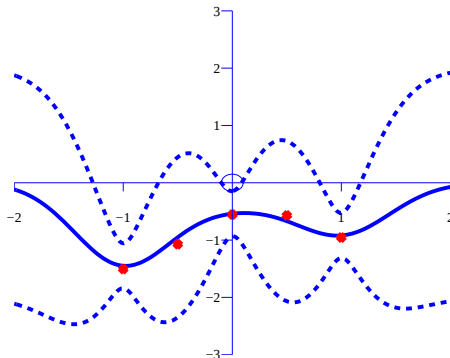


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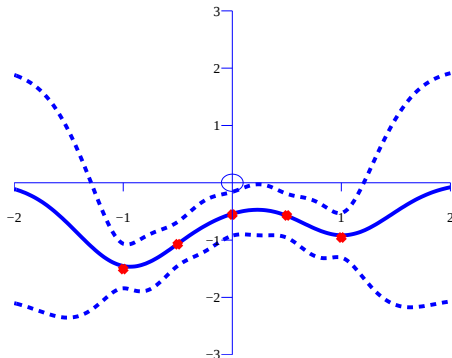


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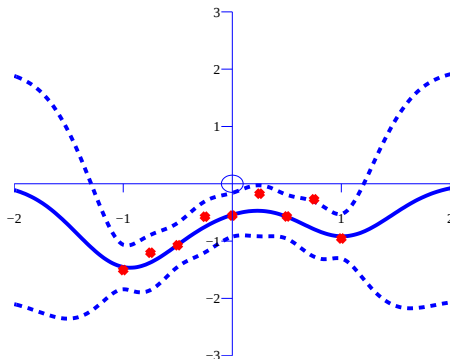


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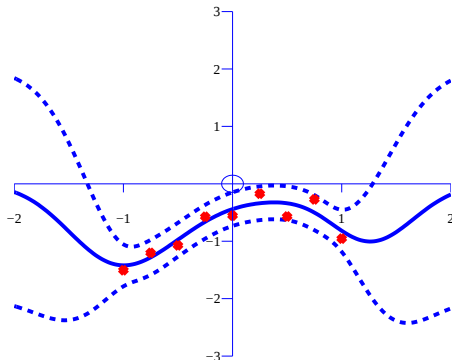
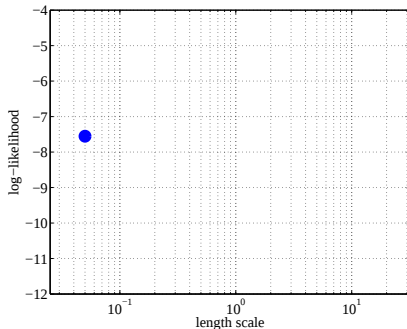
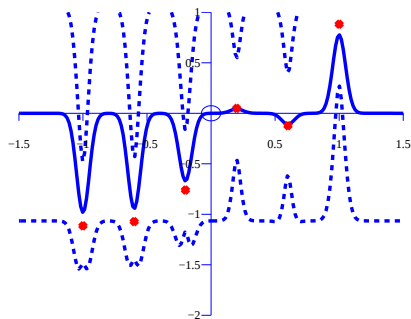


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Learning Kernel Parameters

Can we determine length scales and noise levels from the data?

demOptimiseKern

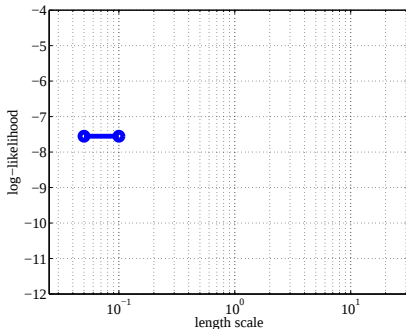
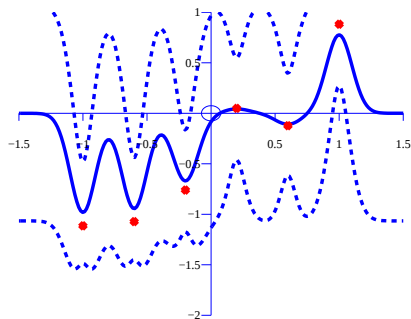


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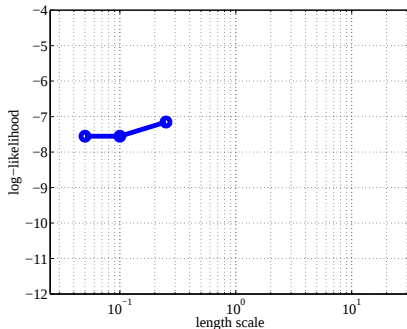
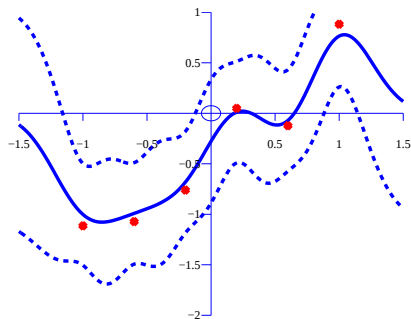


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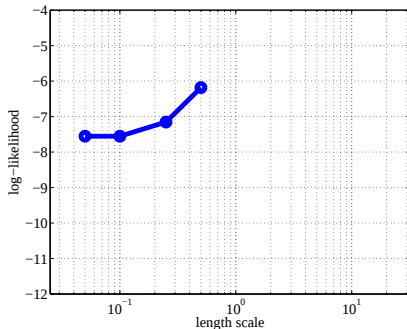
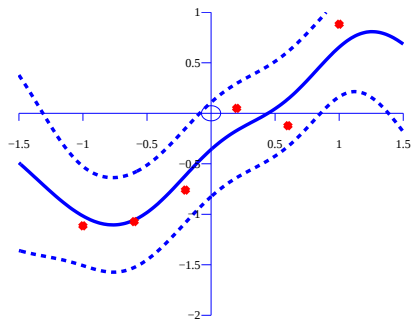


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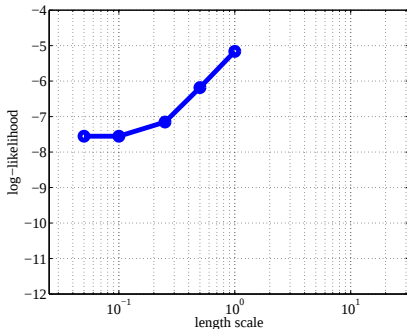
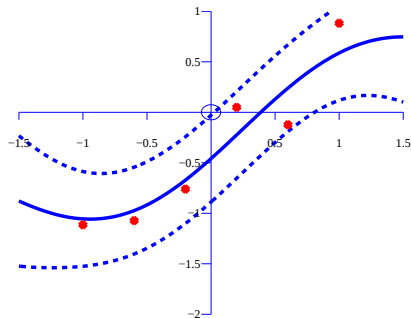


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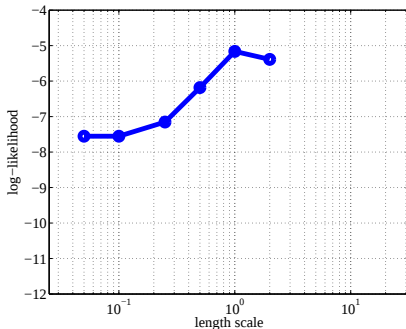
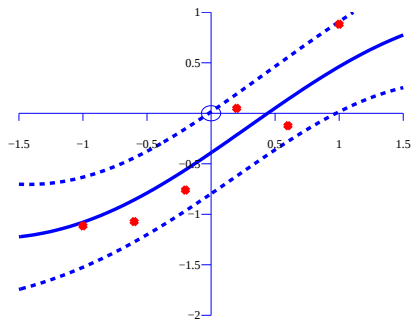


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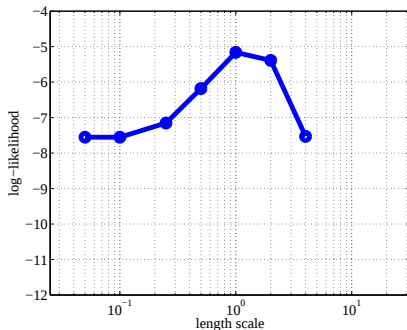
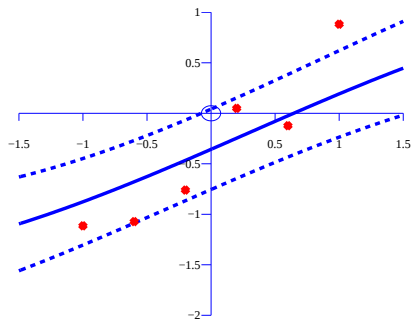


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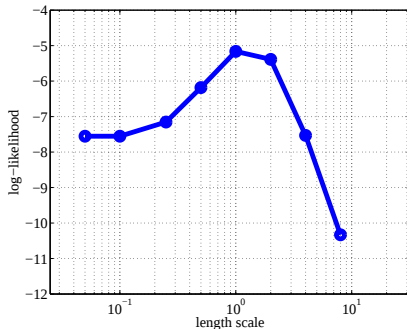
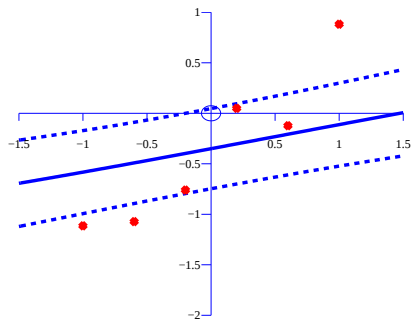


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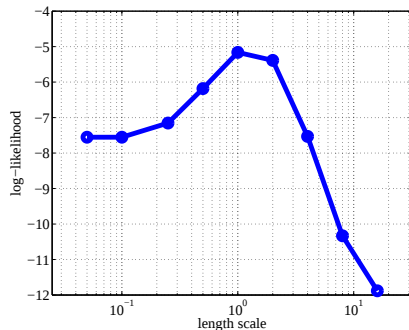
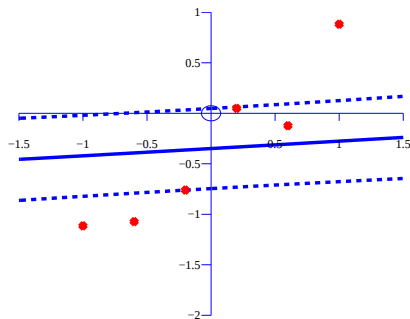


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- These models rely on the latent variables to provide the dynamic information.
- We now introduce a further dynamical system with a *mechanistic* inspiration.
- Physical Interpretation:
 - ▶ the latent functions, $f_i(t)$ are q forces.
 - ▶ We observe the displacement of d springs to the forces.,
 - ▶ Interpret system as the force balance equation, $\mathbf{X}\mathbf{D} = \mathbf{F}\mathbf{S} + \epsilon$.
 - ▶ Forces act, e.g. through levers — a matrix of sensitivities, $\mathbf{S} \in \mathbb{R}^{q \times d}$.
 - ▶ Diagonal matrix of spring constants, $\mathbf{D} \in \mathbb{R}^{d \times d}$.
 - ▶ Original System: $\mathbf{W} = \mathbf{S}\mathbf{D}^{-1}$.

- Add a damper and give the system mass.

$$\mathbf{F}\mathbf{S} = \ddot{\mathbf{X}}\mathbf{M} + \dot{\mathbf{X}}\mathbf{C} + \mathbf{X}\mathbf{D} + \epsilon.$$

- Now have a second order mechanical system.
- It will exhibit inertia and resonance.
- There are many systems that can also be represented by differential equations.
 - ▶ When being forced by latent function(s), $\{f_i(t)\}_{i=1}^q$, we call this a *latent force model*.

- For Gaussian process we can compute the covariance matrices for the output displacements.
- For one displace the model is

$$m_k \ddot{x}_k(t) + c_k \dot{x}_k(t) + d_k x_k(t) = b_k + \sum_{i=0}^M s_{ik} f_i(t), \quad (1)$$

where, m_k is the k th diagonal element from $\mathbf{M}$ and similarly for c_k and d_k . s_{ik} is the i , k th element of $\mathbf{S}$.

- Model the latent forces as q independent, GPs with RBF covariances

$$k_{f_i f_l}(t, t') = \exp\left(-\frac{(t - t')^2}{\sigma_i^2}\right) \delta_{il}.$$

Covariance for ODE Model

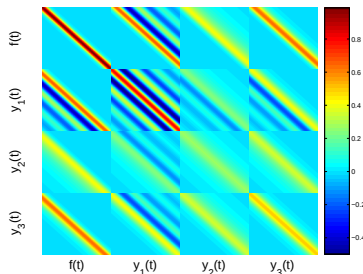
- RBF Kernel function for $f(t)$

$$x_j(t) = \frac{1}{m_j \omega_j} \sum_{i=1}^q S_{ji} \exp(-\alpha_j t) \int_0^t f_i(u) \exp(\alpha_j u) \sin(\omega_j(t-u)) du$$

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

Damping ratios:

ζ_1	ζ_2	ζ_3
0.125	2	1



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

- demLfmSample

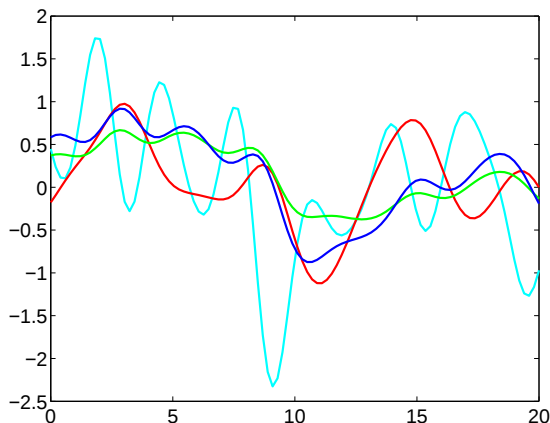


Figure: Joint samples from the ODE covariance, *cyan*: $f(t)$, *red*: $x_1(t)$ (underdamped) and *green*: $x_2(t)$ (overdamped) and *blue*: $x_3(t)$ (critically damped).

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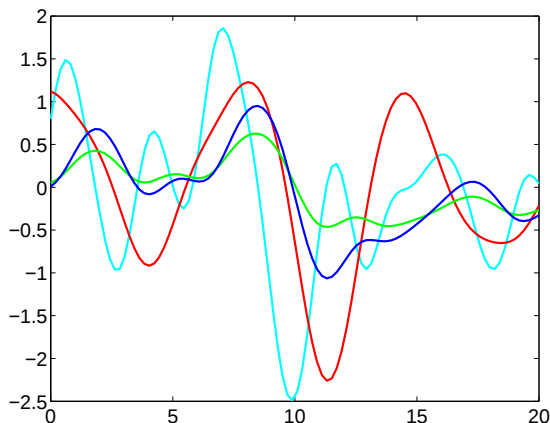


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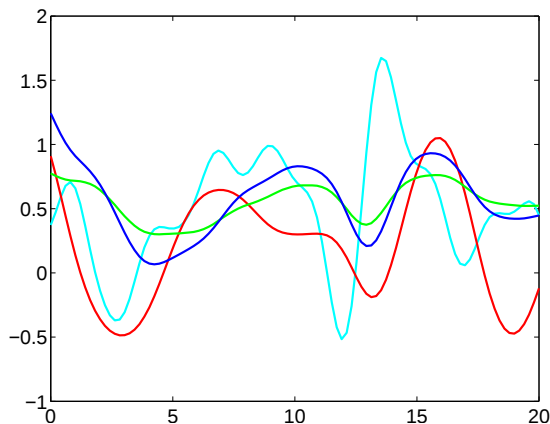


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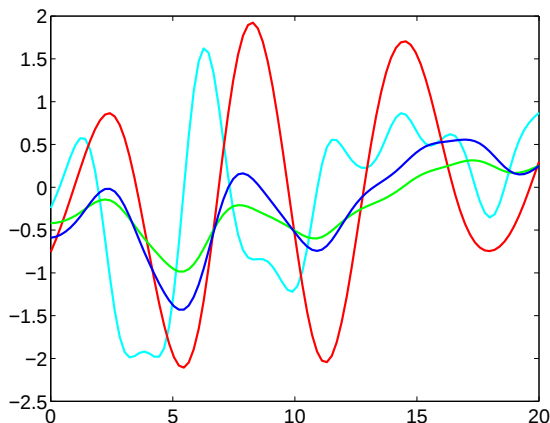


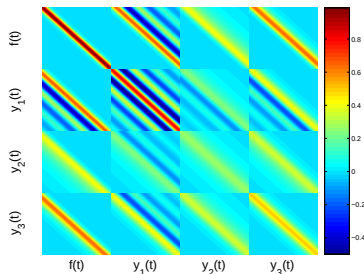
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Example: Transcriptional Regulation

- First Order Differential Equation

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

- Can be used as a model of gene transcription: Barenco et al., 2006; Gao et al., 2008.
- $x_j(t)$ – 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?

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- Problem: how do we fit the model when $f(t)$ is not observed?

Example: Transcriptional Regulation

- First Order Differential Equation

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

- Can be used as a model of gene transcription: Barenco et al., 2006; Gao et al., 2008.
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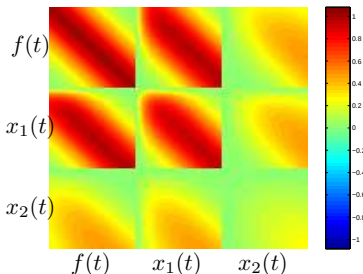
RBF covariance function for $f(t)$

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

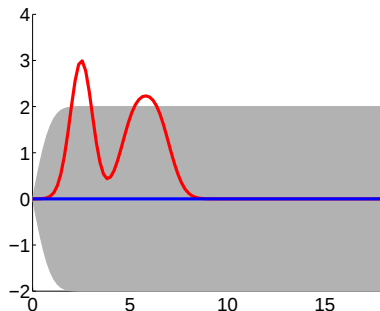
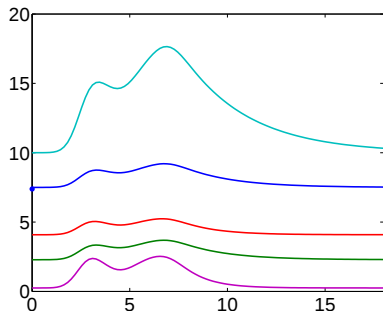
- Joint distribution for $x_1(t)$, $x_2(t)$ and $f(t)$.

► Here:

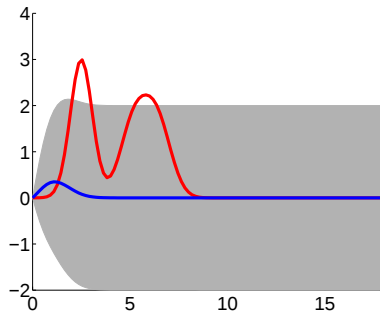
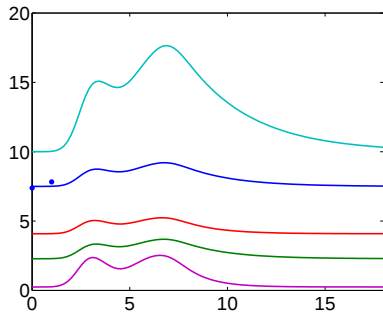
D_1	S_1	D_2	S_2
5	5	0.5	0.5



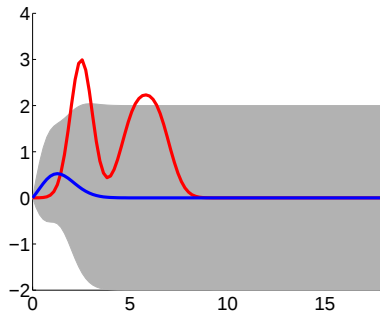
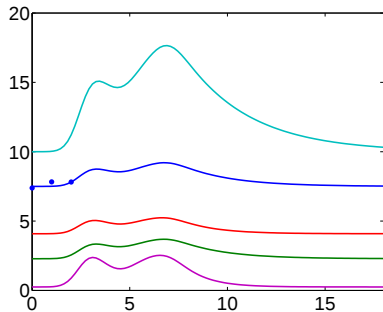
Artificial Example: Inferring $f(t)$



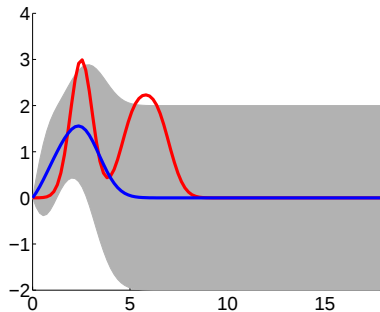
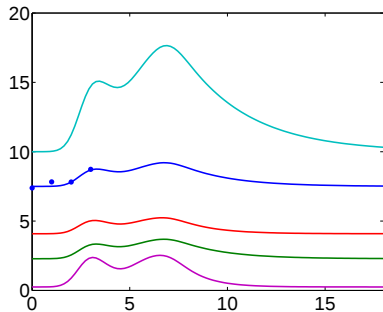
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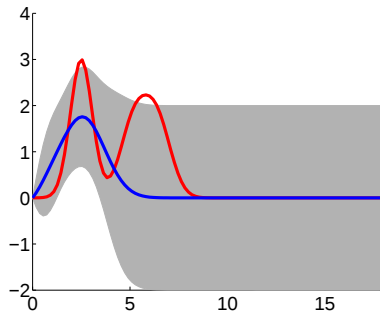
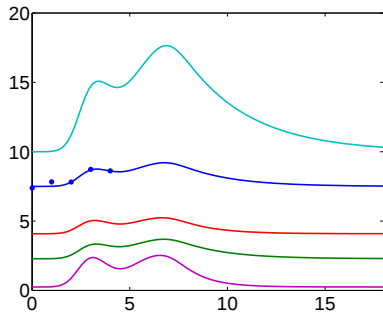
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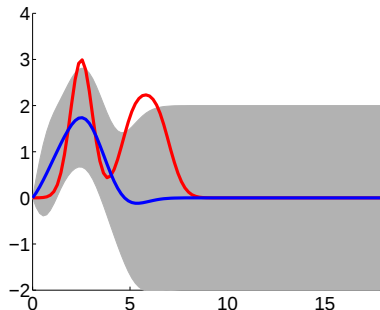
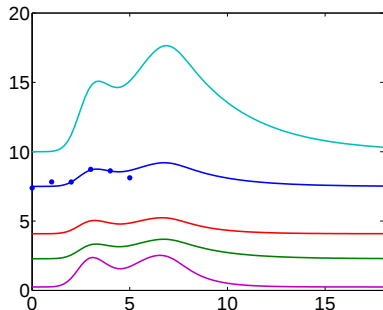
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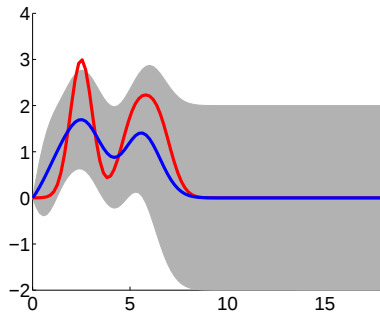
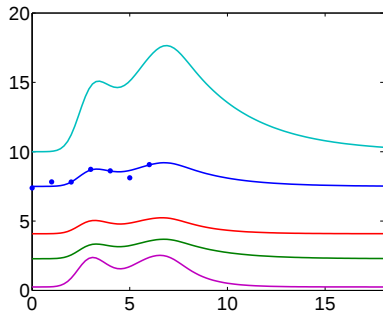
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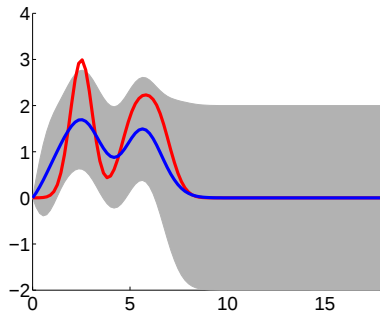
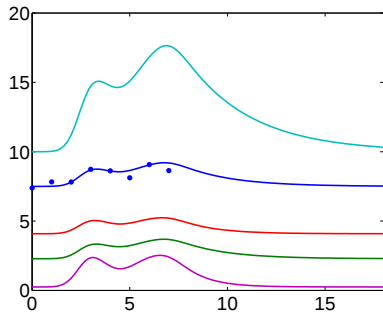
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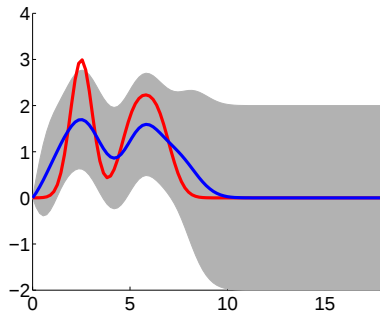
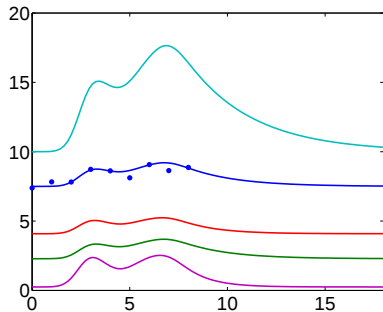
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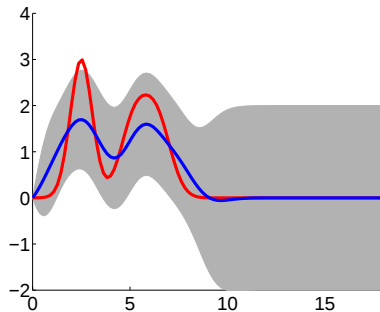
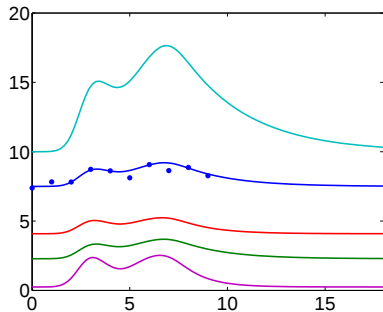
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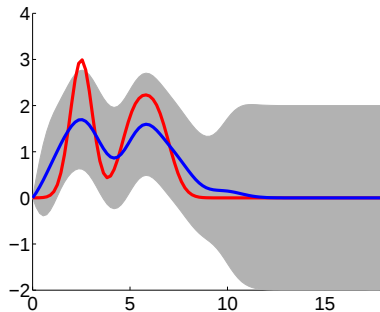
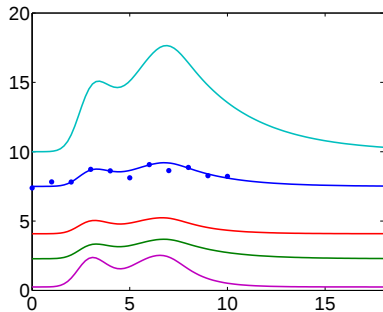
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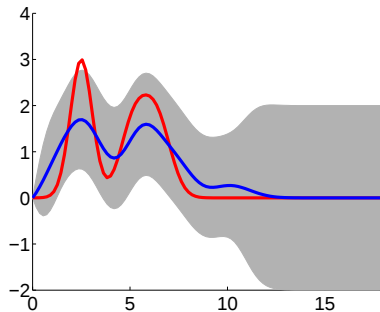
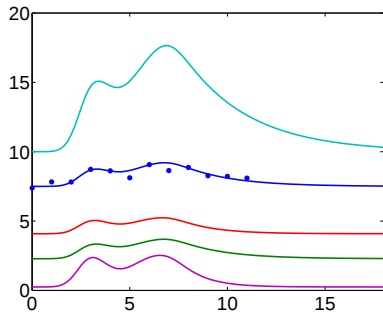
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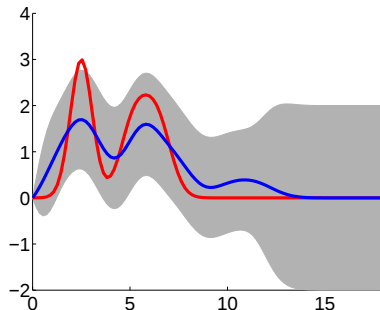
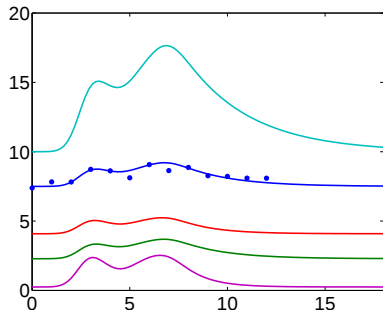
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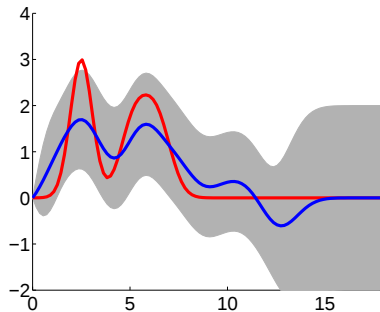
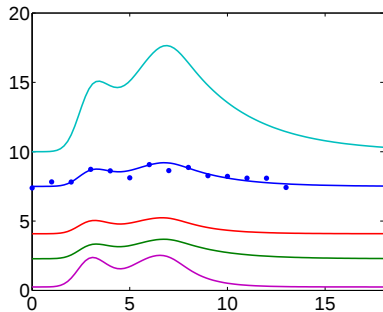
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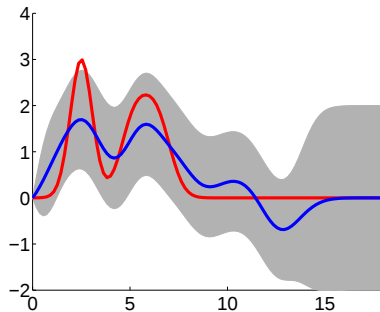
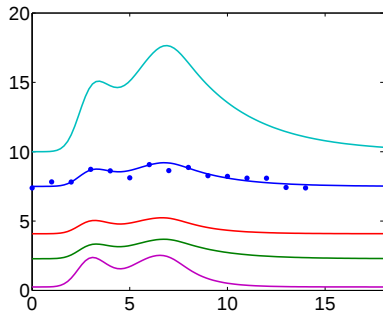
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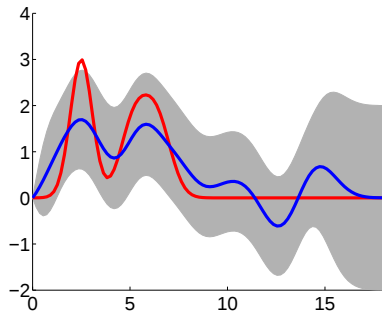
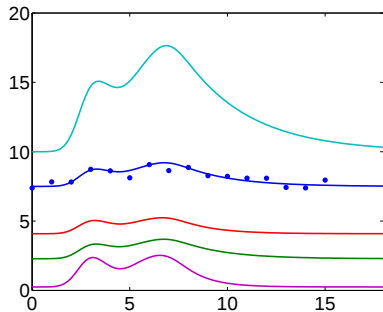
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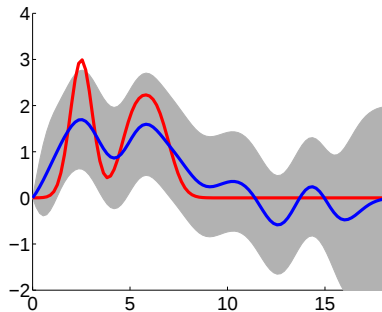
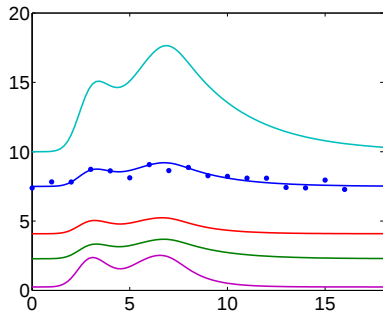
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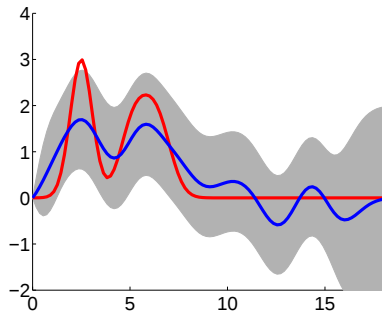
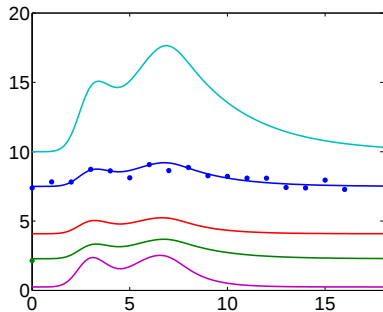
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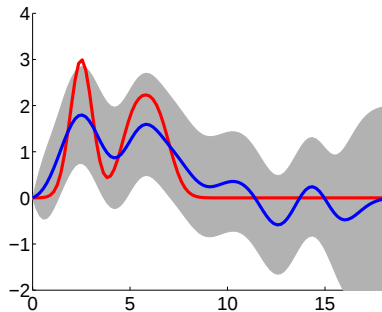
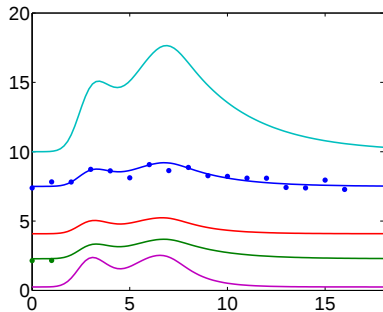
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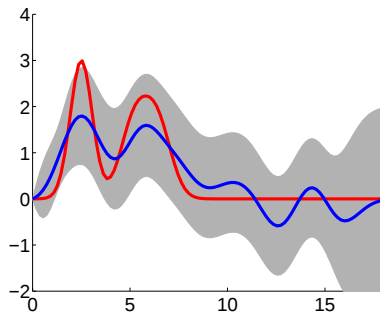
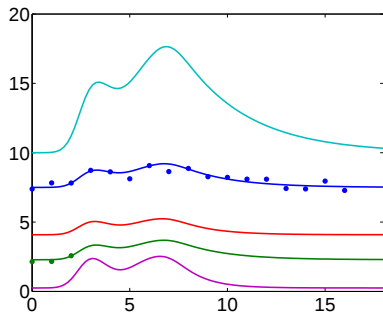
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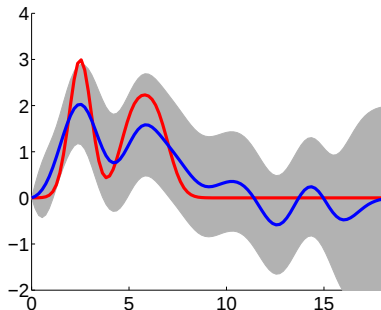
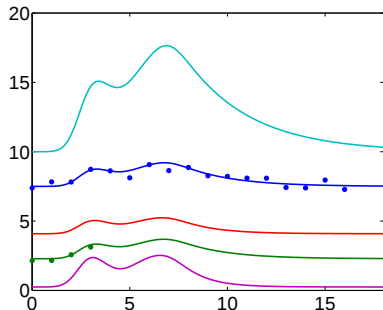
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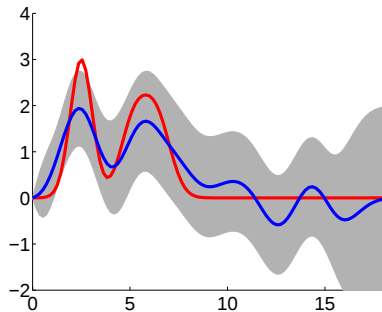
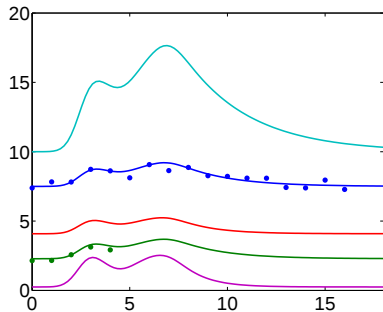
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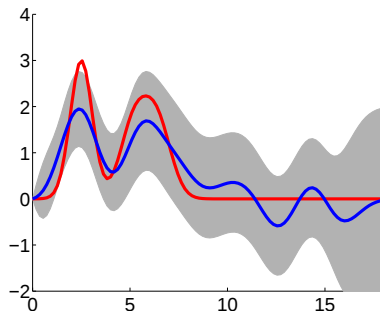
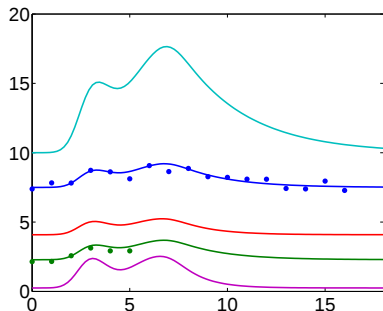
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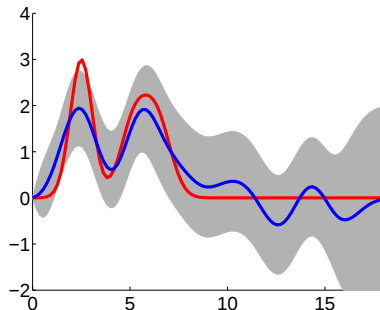
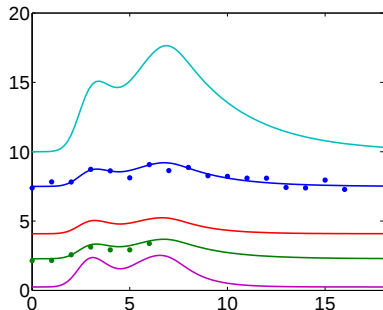
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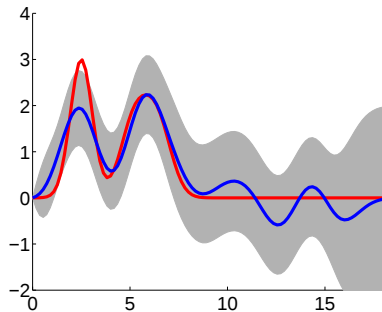
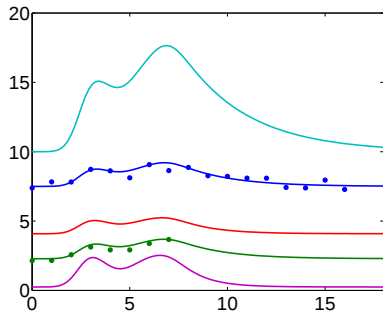
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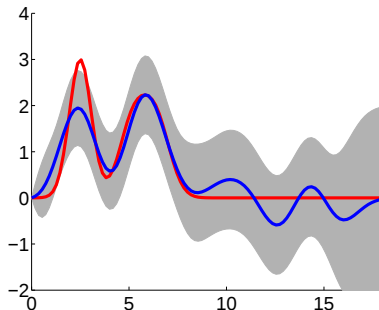
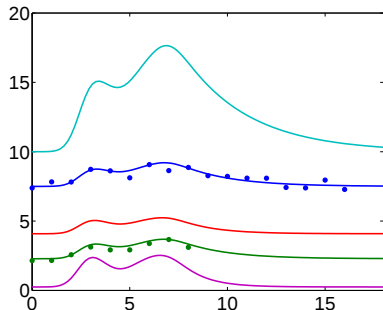
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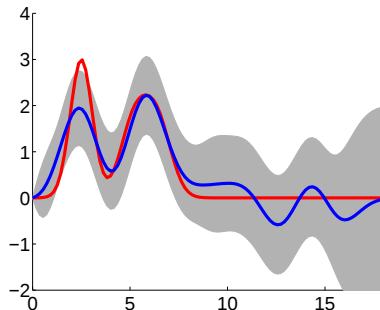
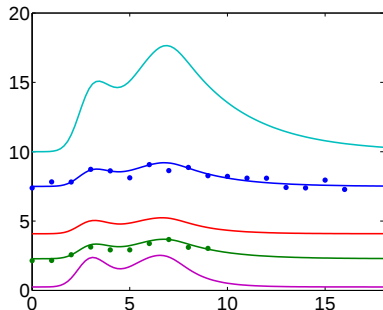
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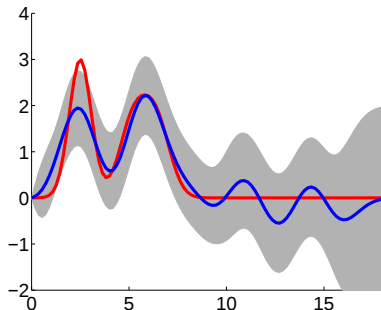
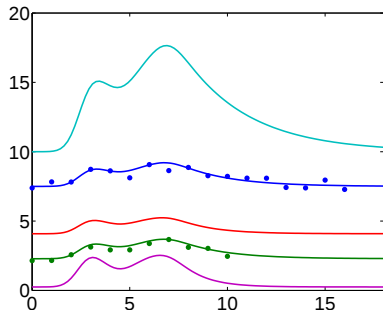
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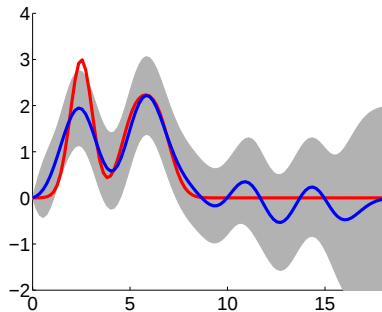
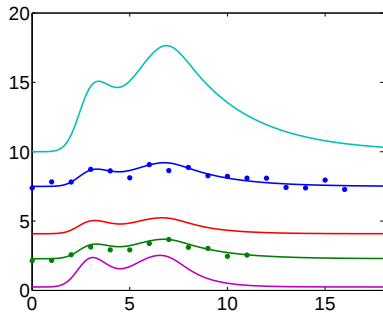
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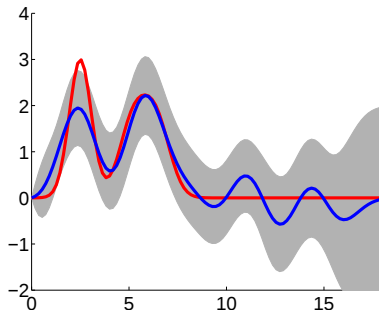
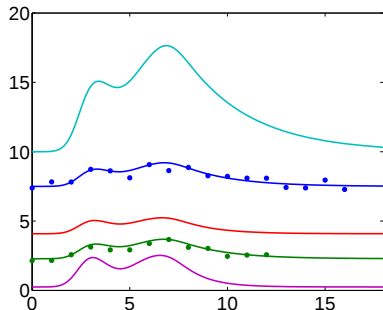
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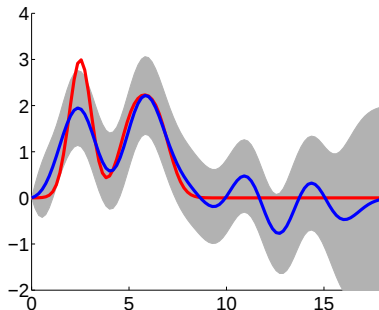
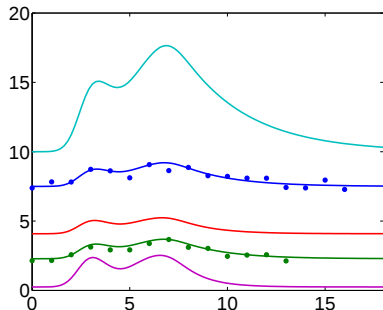
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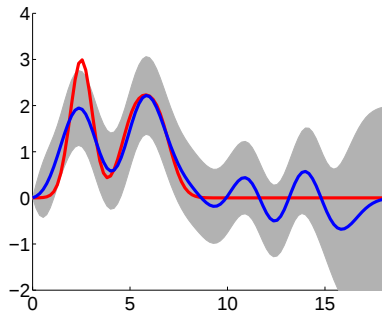
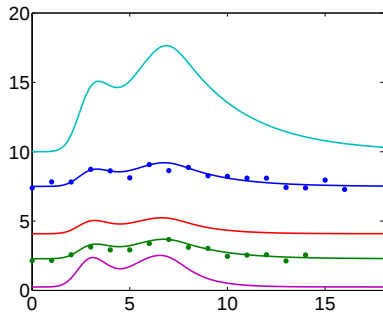
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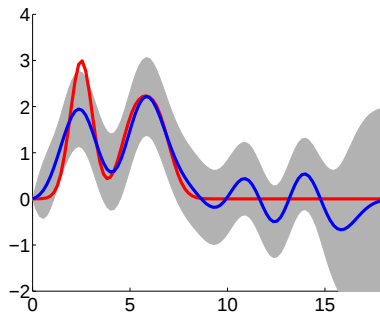
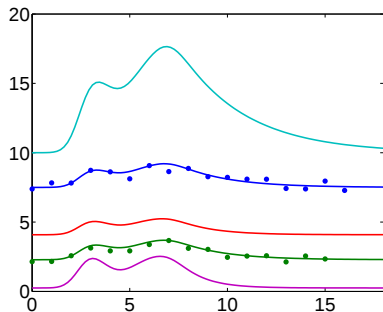
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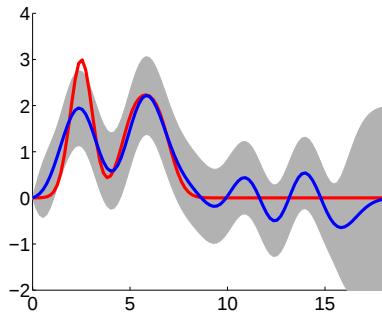
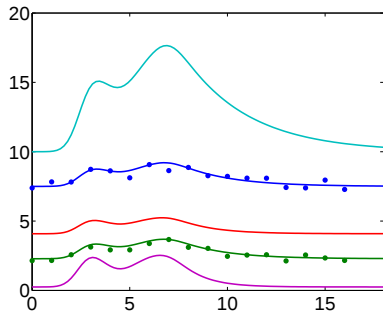
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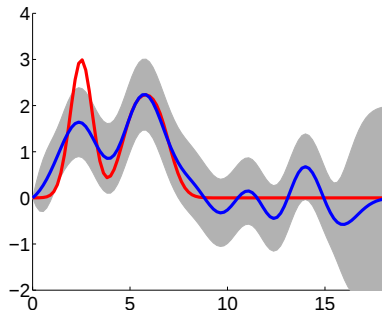
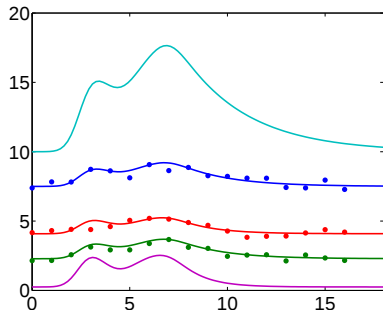
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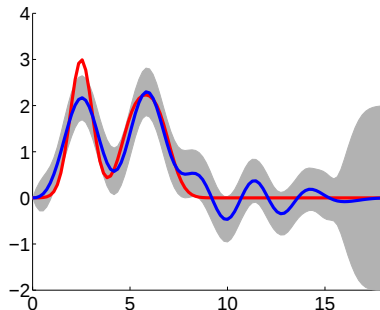
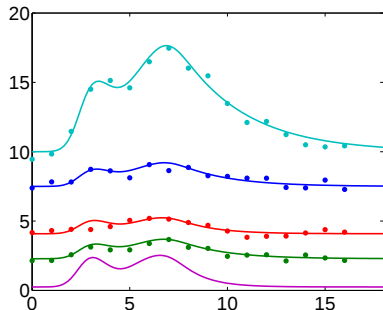
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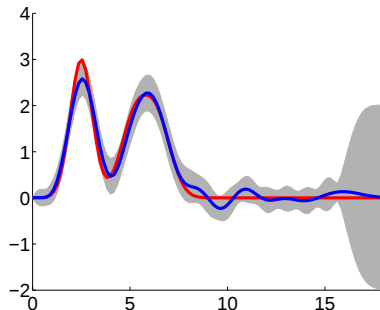
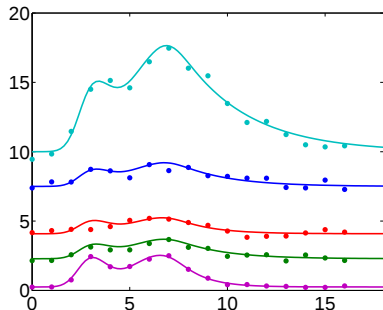
Artificial Example: Inferring $f(t)$



Artificial Example: Inferring $f(t)$



Artificial Example: Inferring $f(t)$



- Responsible for Repairing DNA damage
- Activates DNA Repair proteins
- Pauses the Cell Cycle (prevents replication of damage DNA)
- Initiates *apoptosis* (cell death) in the case where damage can't be repaired.
- Large scale feedback loop with NF- κ B.

p53 DNA Damage Repair

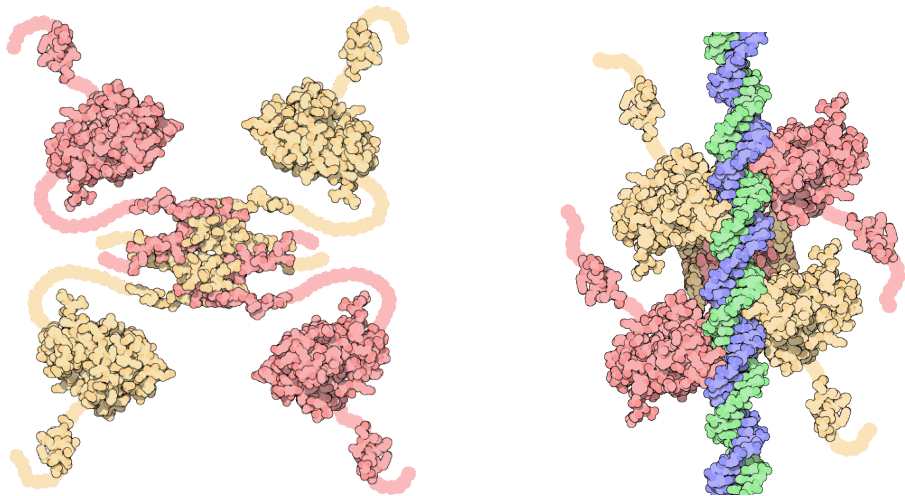


Figure: p53. *Left* unbound, *Right* bound to DNA. Images by David S. Goodsell from <http://www.rcsb.org/> (see the “Molecule of the Month” feature).

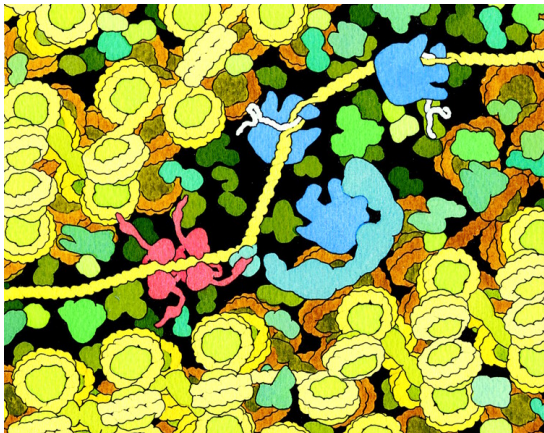


Figure: Repair of DNA damage by p53. Image from Goodsell (1999).

Modelling Assumption

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

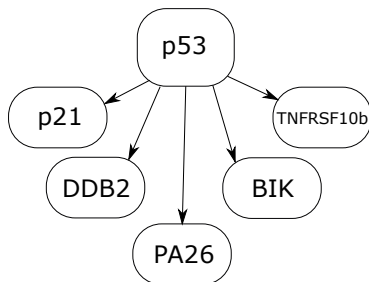
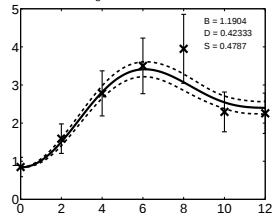
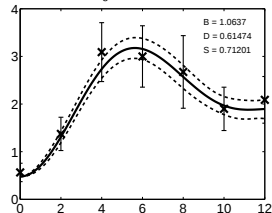
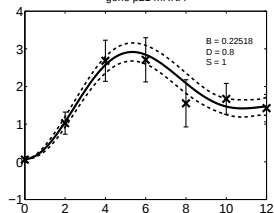
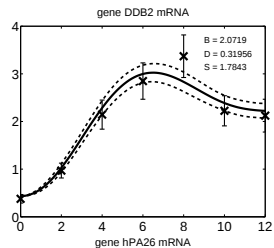
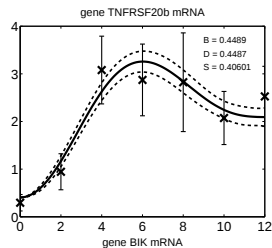
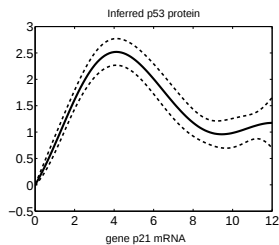
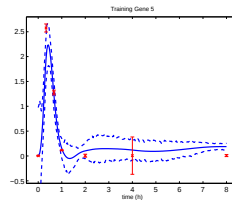
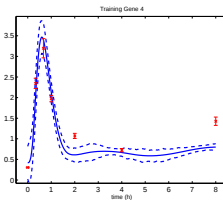
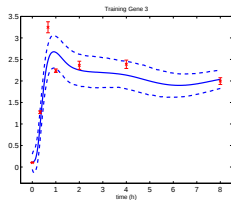
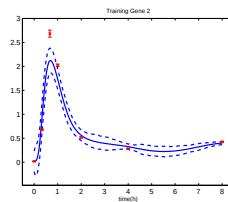
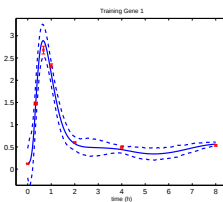
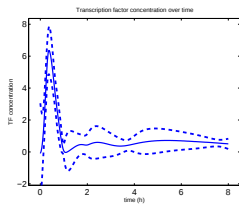


Figure: p53 SIM network motif as modelled by Barenco et al. 2006.

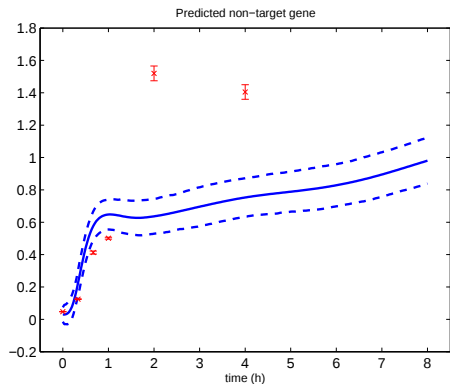
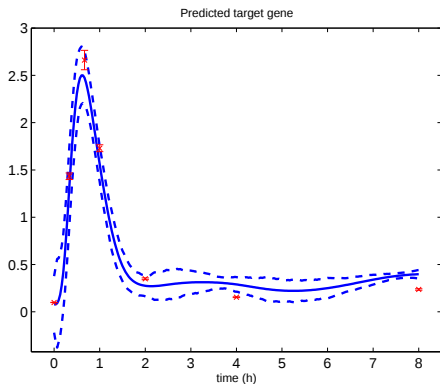


- Target Ranking for Elk-1.
- Elk-1 is phosphorylated by ERK from the EGF signalling pathway.
- Predict concentration of Elk-1 from known targets.
- Rank other targets of Elk-1.



Elk-1 target selection

Fitted model used to rank potential targets of Elk-1



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Mauricio Alvarez

- Solutions to these differential equations is normally as a convolution.

$$x_i(t) = \int f(u) k_i(u - t) du + h_i(t)$$

$$x_i(t) = \int_0^t f(u) g_i(u) du + h_i(t)$$

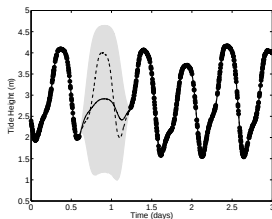
- Convolution Processes (Higdon, 2002; Boyle and Freaan, 2005).
- Convolutions lead to $N \times d$ size covariance matrices $O(N^3 d^3)$ complexity, $O(N^2 d^2)$ storage.
- Model is conditionally independent over $\{x_i(t)\}_{i=1}^d$ given $f(t)$.

Mauricio Alvarez

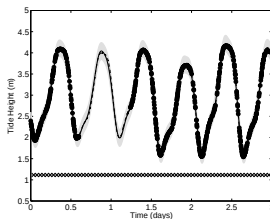
- Can assume conditional independence given $\{f(t_i)\}_{i=1}^k$. (Álvarez and Lawrence, 2009)
 - ▶ Result is very similar to PITC approximation (Quiñonero Candela and Rasmussen, 2005).
 - ▶ Reduces to $O(N^3 dk^2)$ complexity, $O(N^2 dk)$ storage.
 - ▶ Can also do a FITC style approximation (Snelson and Ghahramani, 2006).
 - ▶ Reduces to $O(Ndk^2)$ complexity, $O(Ndk)$ storage.

Mauricio Alvarez

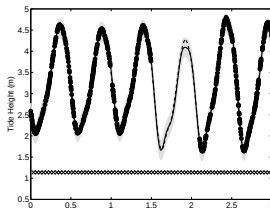
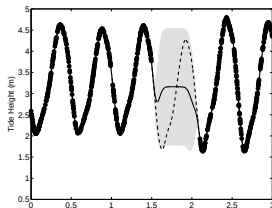
- Network of tide height sensors in the solent — tide heights are correlated.
- Data kindly provided by Alex Rogers (see Rogers et al., 2008).
- $d = 3$ and $N = 1000$ of the 4320 for the training set.
- Simulate sensor failure by knocking out one sensor for a given time.
- For the other two sensors we used all 1000 training observations.
- Take $k = 100$.



(a) Bramblemet Independent



(b) Bramblemet PITC



Mauricio Alvarez

- Jura dataset — concentrations of several heavy metals.
- Prediction 259 data, validation 100 data points.
- Predict *primary variables* (cadmium and copper) at prediction locations in conjunction with some *secondary variables* (nickel and zinc for cadmium; lead, nickel and zinc for copper) (Goovaerts, 1997, p. 248,249).

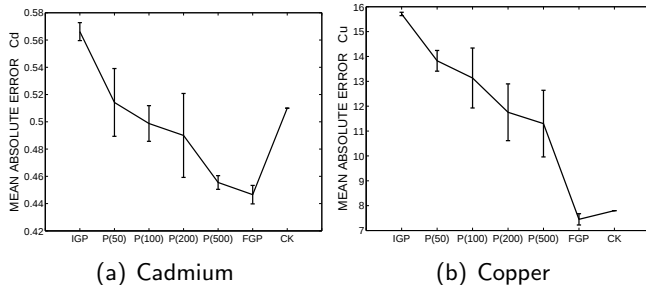


Figure: Mean absolute error. IGP stands for independent GP, $P(M)$ stands for PITC with M inducing values, FGP stands for full GP and CK stands for ordinary co-kriging.

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Models of non-linear regulation

- Non-linear Activation: Michaelis-Menten Kinetics

$$\frac{dx_i(t)}{dt} = B_i + \frac{S_i f(t)}{\gamma_i + f(t)} - D_i x_i(t)$$

used by Rogers and Girolami (2006)

- Non-linear Repression

$$\frac{dx_i(t)}{dt} = B_i + \frac{S_i}{\gamma_i + f(t)} - D_i x_i(t)$$

used by Khanin et al., 2006, PNAS 103

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$$\frac{dx_i(t)}{dt} = B_i + \frac{S_i}{\gamma_i + f(t)} - D_i x_i(t)$$

used by Khanin et al., 2006, PNAS 103

MAP Laplace Approximation

Consider the following modification to the model,

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

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

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

Use Laplace's method (Laplace, 1774),

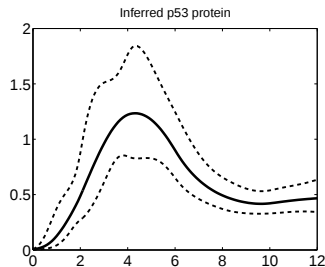
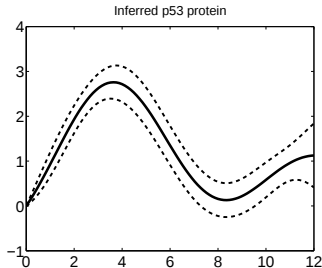
$$p(\mathbf{f} | \mathbf{x}) = N(\hat{\mathbf{f}}, \mathbf{A}^{-1}) \propto \exp\left(-\frac{1}{2} (\mathbf{f} - \hat{\mathbf{f}})^T \mathbf{A} (\mathbf{f} - \hat{\mathbf{f}})\right)$$

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

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

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

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



(a)

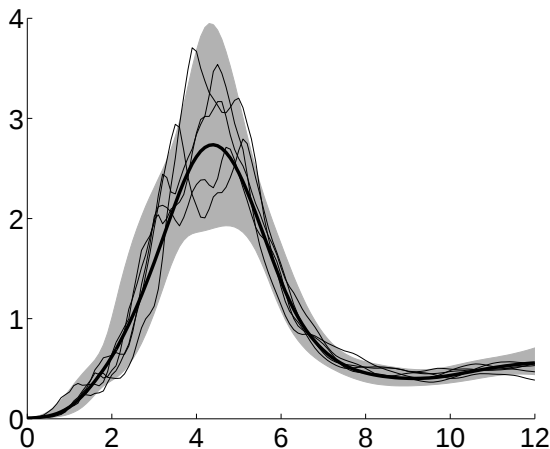


Figure: Laplace approximation error bars along with samples from the true posterior distribution.

- Sample in Gaussian processes

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

- Likelihood relates GP to data through

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

- We use *control points* for fast sampling. (Titsias et al., 2009)

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 $q(\mathbf{f}_c^{(t+1)} | \mathbf{f}_c^{(t)})$
- Sample the remaining points $\mathbf{f}_\rho$ using the conditional GP prior $p(\mathbf{f}_\rho^{(t+1)} | \mathbf{f}_c^{(t+1)})$
- The whole proposal is

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

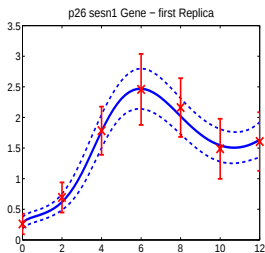
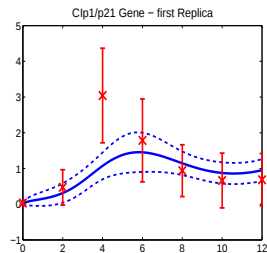
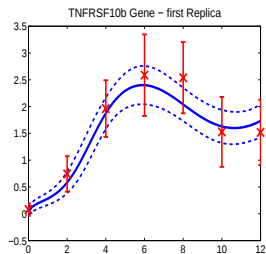
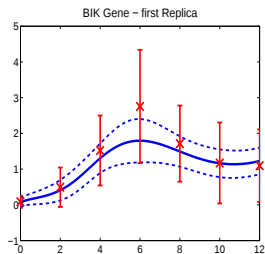
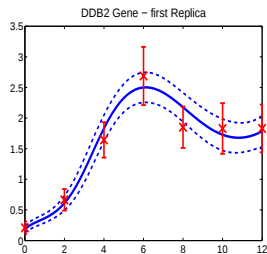
- Its like sampling from the prior $p(\mathbf{f})$ but imposing random walk behaviour through the control points.

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

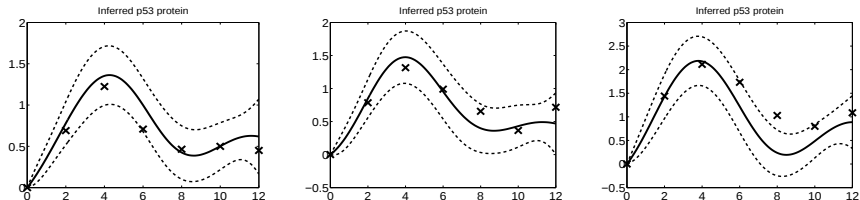
$$\frac{dx_j(t)}{dt} = B_j + S_j \frac{\exp(f(t))}{\exp(f(t)) + \gamma_j} - D_j x_j(t)$$

- 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%

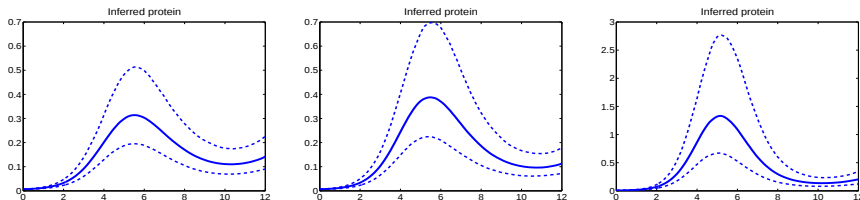
Data used by Barenco et al. (2006): Predicted gene expressions for the 1st replica



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

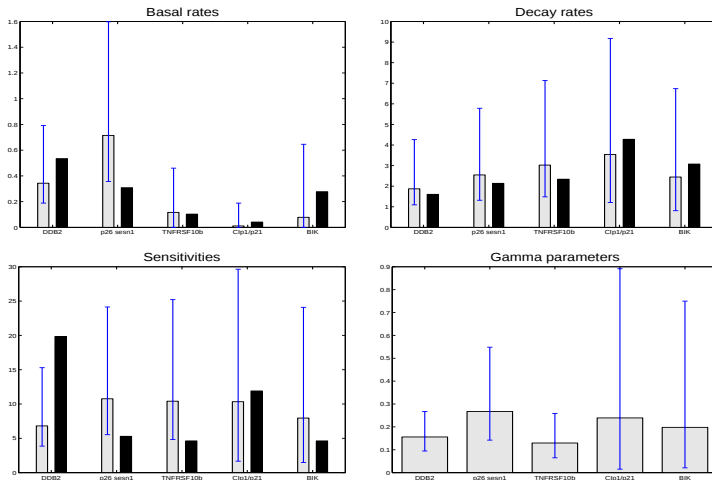


Linear model (Barenco et al. predictions are shown as crosses)



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

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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.

Data from Furlong Lab in EMBL Heidelberg.

- Describe mesoderm development.

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

$$\begin{aligned}\frac{df(t)}{dt} &= \sigma y(t) - \delta f(t) \\ \frac{dx_j(t)}{dt} &= B_j + S_j f(t) - D_j x_j(t)\end{aligned}$$

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

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

Covariance for Translation/Transcription Model

RBF covariance function for $y(t)$

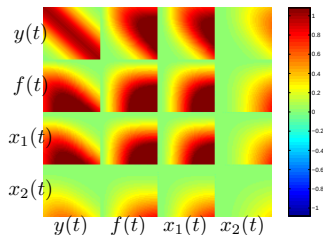
$$f(t) = \sigma \exp(-\delta t) \int_0^t y(u) \exp(\delta u) du$$

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

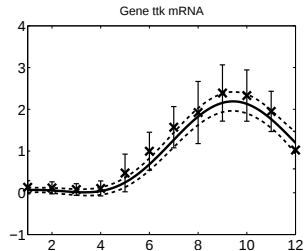
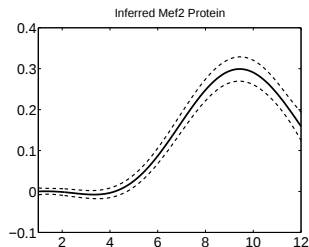
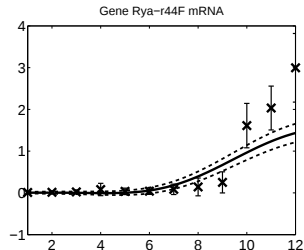
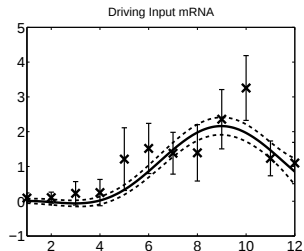
- Joint distribution for $x_1(t)$, $x_2(t)$, $f(t)$ and $y(t)$.

- Here:

δ	D_1	S_1	D_2	S_2
0.1	5	5	0.5	0.5



Results for Mef2 using the Cascade model



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- 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

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- Charles Girardot and Eileen Furlong of EMBL in Heidelberg (mesoderm development in *D. Melanogaster*).
- Martino Barenco and Mike Hubank at the Institute of Child Health in UCL (p53 pathway).

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