Statistical Inference in Systems Biology through Gaussian Processes and Ordinary Differential Equations

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University of Warwick
LICSB Workshop

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Outline

1. Introduction
2. Gaussian Process Inference for Linear Activation
3. Cascaded Differential Equations
4. Discussion and Future Work
5. Acknowledgements

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Talk Outline

- Models of Transcriptional Regulation
- Gaussian Processes
- Inference for Linear Activation
- Non-linear Response Models
- Cascaded Differential Equations

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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?

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Outline

Zero mean Gaussian distribution

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

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

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

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

Sampling a Function

Multi-variate Gaussians

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

demGPSample

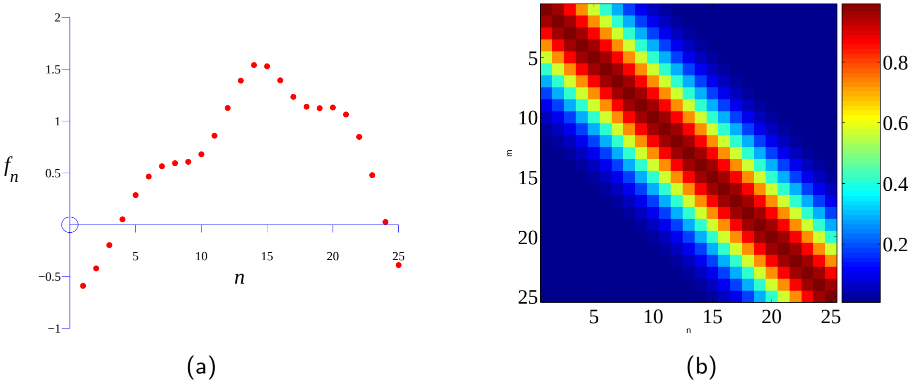

Figure: (a) 25 instantiations of a function, f_n, (b) colormap of covariance matrix.

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

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Prediction of f_2 from f_1

`demGPCov2D([1 2])`

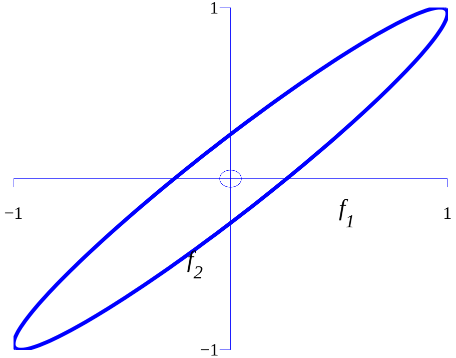

Figure: Covariance for $\begin{bmatrix} f_1 \\ f_2 \end{bmatrix}$ is $\mathbf{K}_{12} = \begin{bmatrix} 1 & 0.966 \\ 0.966 & 1 \end{bmatrix}$.

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demGPCov2D([1 2])
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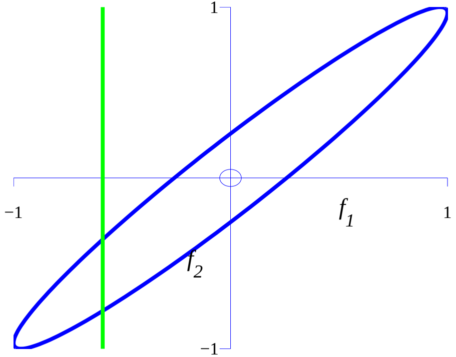

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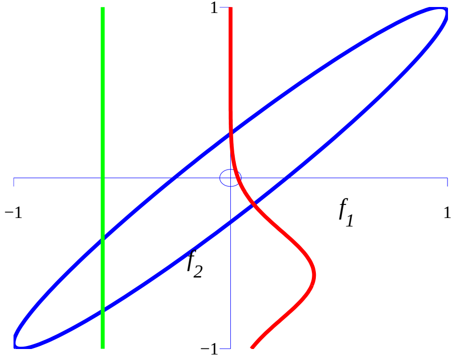

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Prediction of f_5 from f_1

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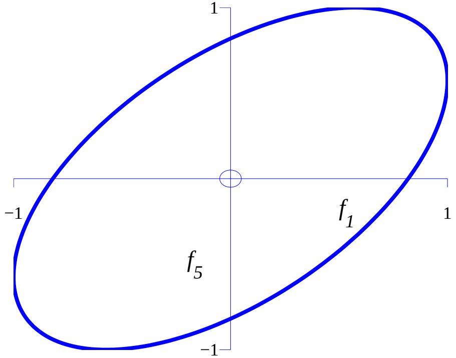

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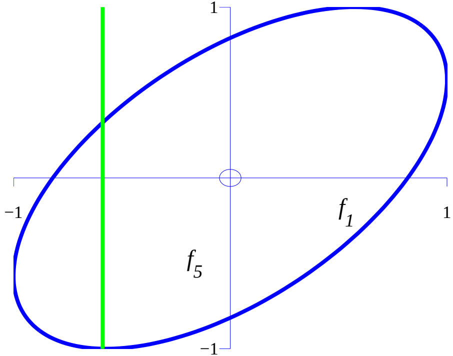

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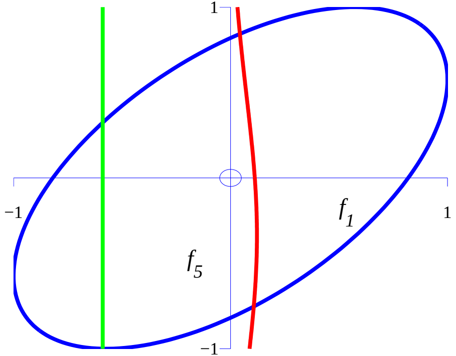

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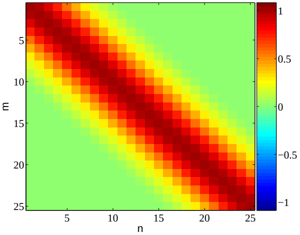
RBF Kernel Function

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

- 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.



Covariance Samples

`demCovFuncSample`

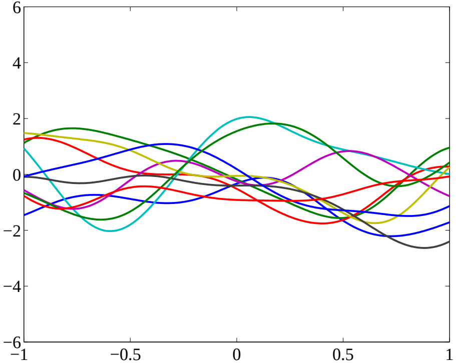


Figure: RBF kernel with $l = 10^{-\frac{1}{2}}$, $\alpha = 1$

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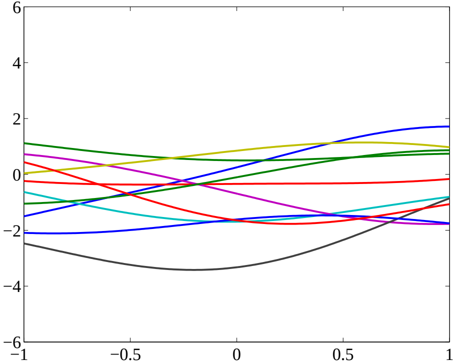

Figure: RBF kernel with $l = 1$, $\alpha = 1$

`demCovFuncSample`

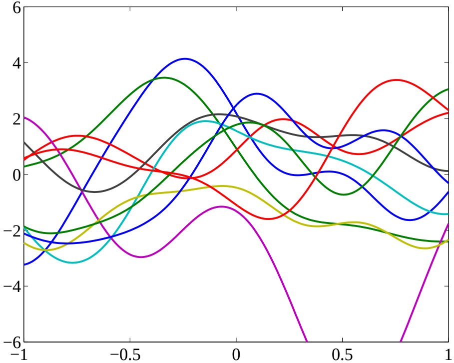

Figure: RBF kernel with $l = 0.3$, $\alpha = 4$

Gaussian Process Regression

demRegression

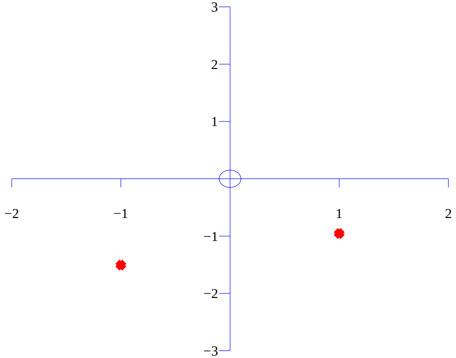

Figure: Examples include WiFi localization, C14 callibration curve.

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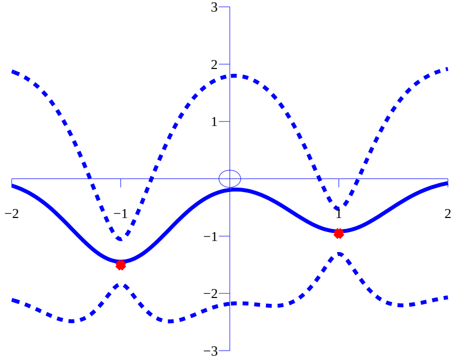

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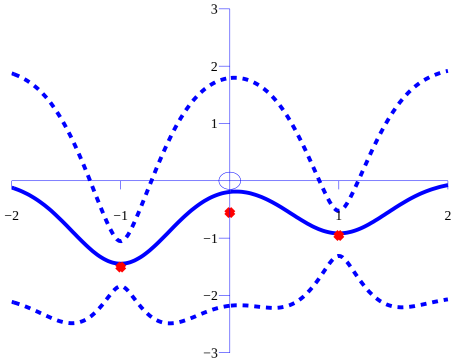

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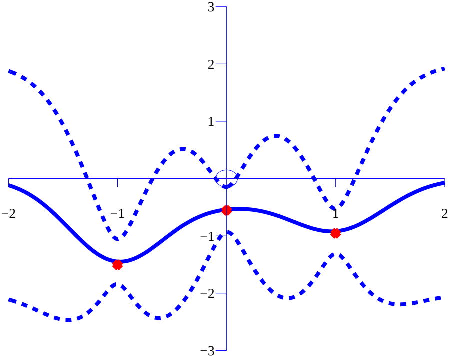

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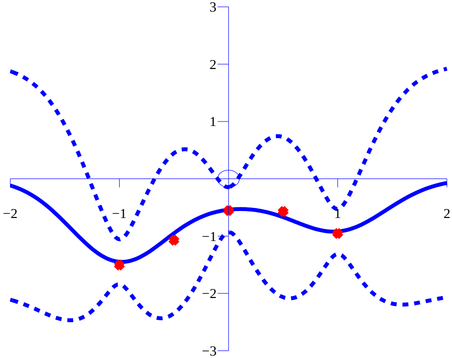

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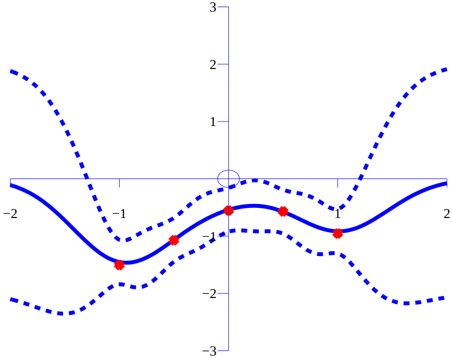

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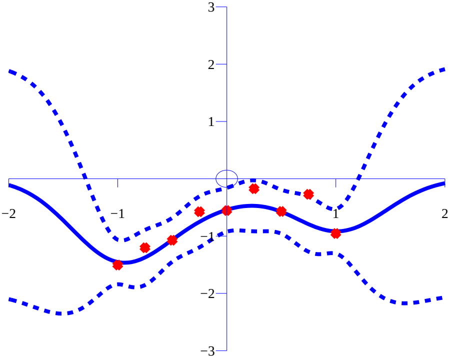

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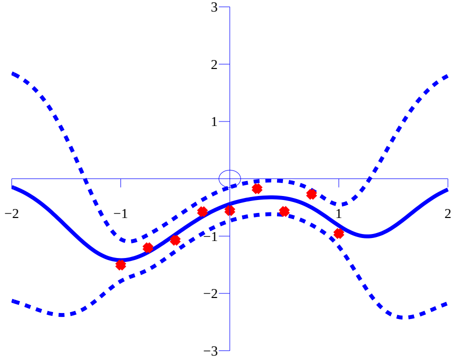

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Learning Kernel Parameters

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

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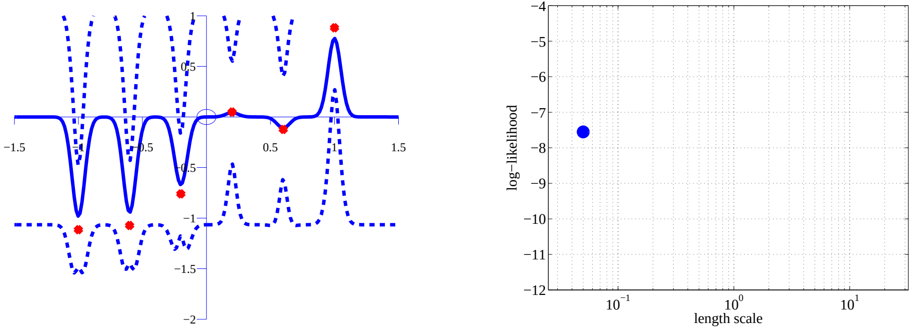

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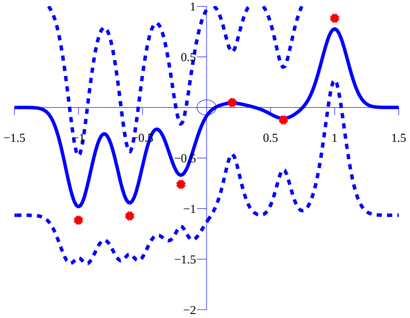

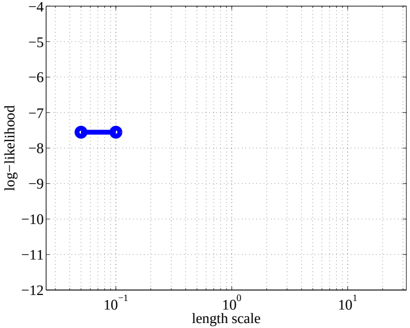

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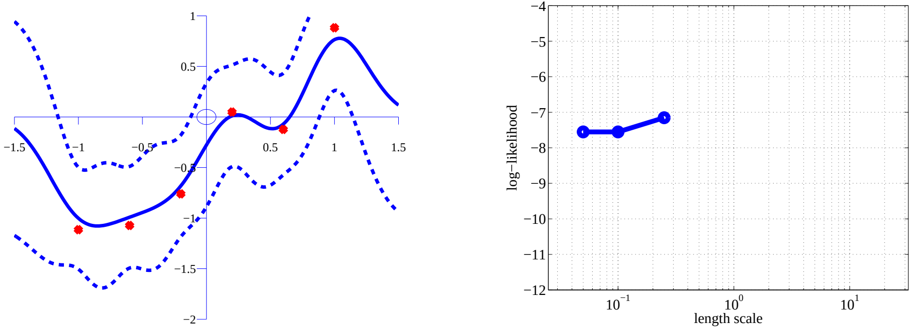

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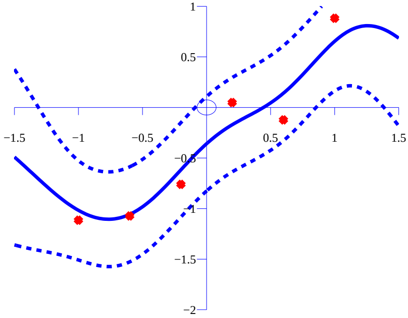

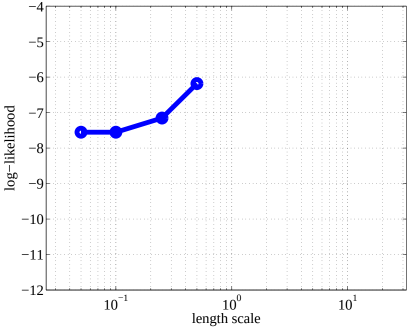

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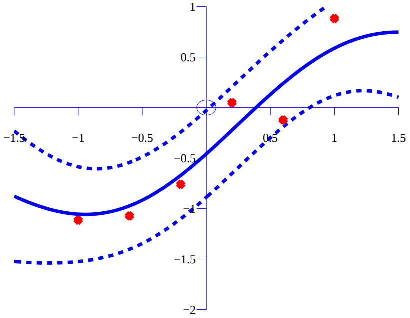

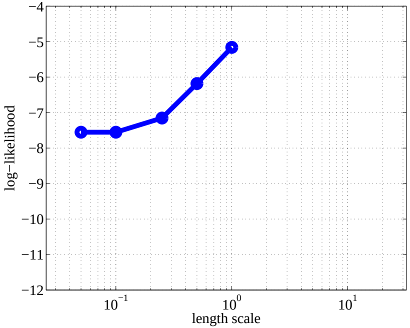

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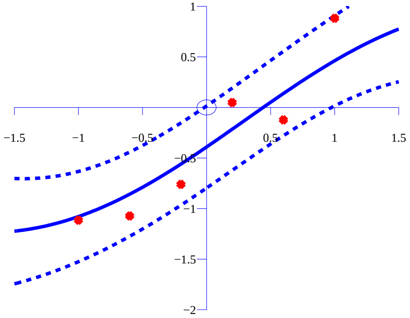

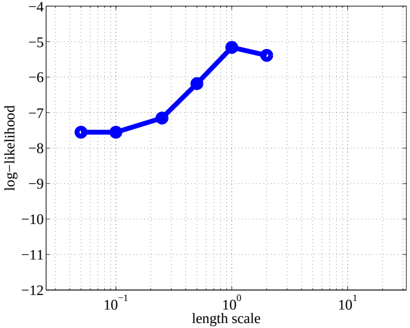

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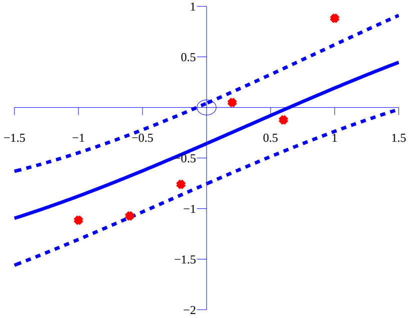

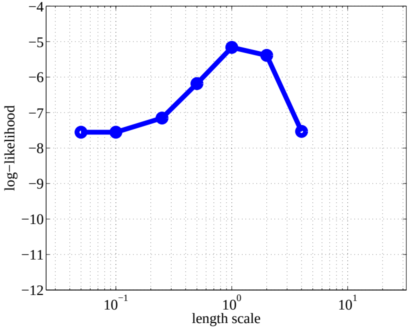

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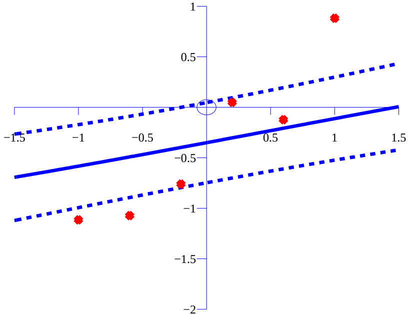

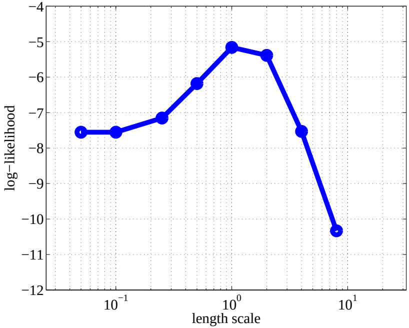

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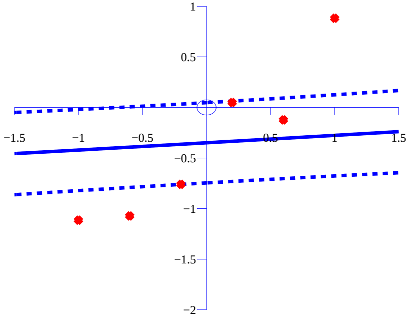

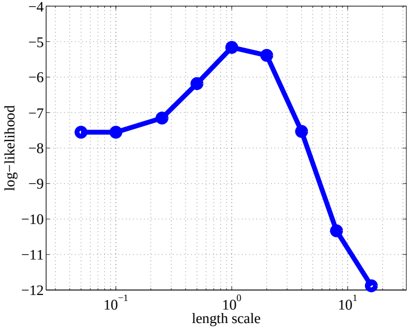

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Linear Activation Model

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 $f(t)$.

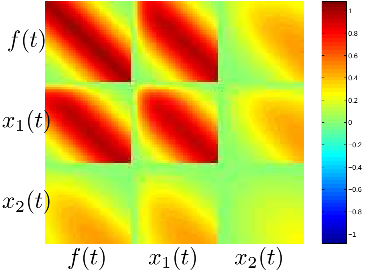
If $f(t)$ is a zero mean Gaussian process then $x_i(t)$ is also a Gaussian process with mean $\frac{B_i}{D_i}$.

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`

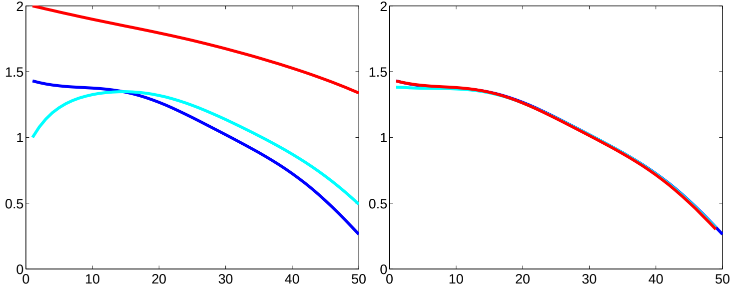


Figure: *Left*: joint samples from the transcription covariance, *blue*: $f(t)$, *cyan*: $x_1(t)$ and *red*: $x_2(t)$. *Right*: numerical solution for $f(t)$ of the differential equation from $x_1(t)$ and $x_2(t)$ (blue and cyan). True $f(t)$ included for comparison.

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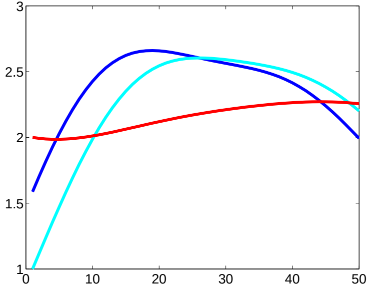

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Joint Sampling of $x(t)$ and $f(t)$ from Covariance

`gpsimTest`

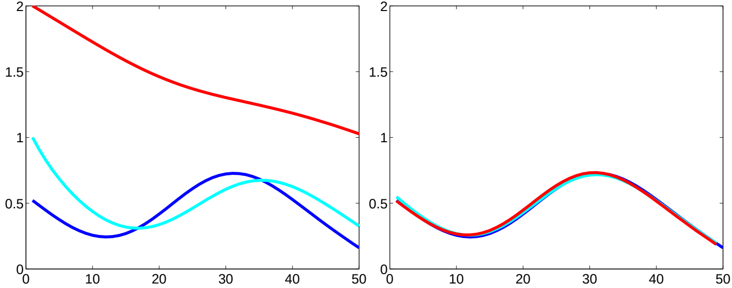
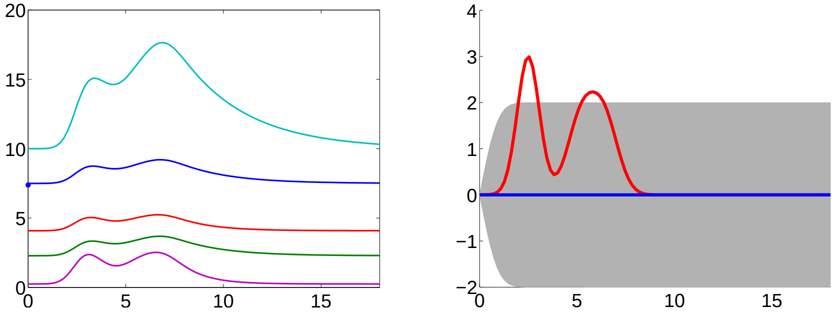


Figure: *Left*: joint samples from the transcription covariance, *blue*: $f(t)$, *cyan*: $x_1(t)$ and *red*: $x_2(t)$. *Right*: numerical solution for $f(t)$ of the differential equation from $x_1(t)$ and $x_2(t)$ (blue and cyan). True $f(t)$ included for comparison.

Artificial Example: Inferring $f(t)$



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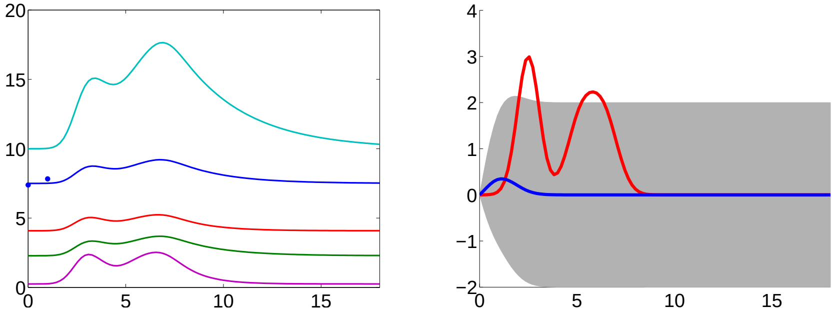

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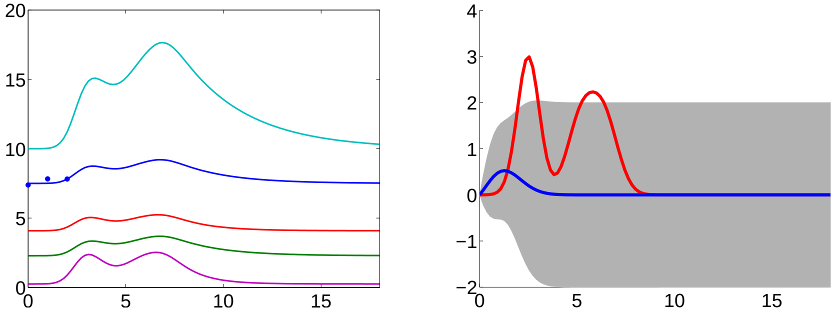

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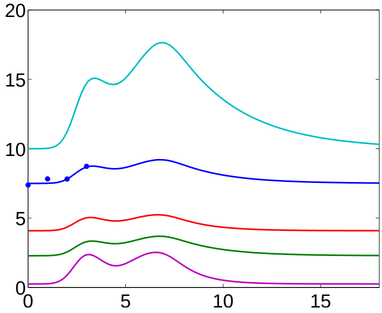

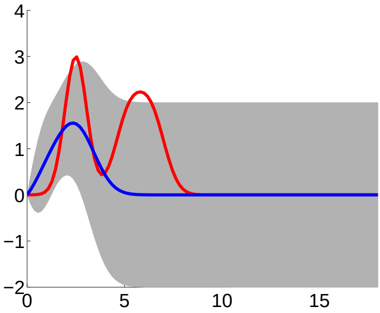

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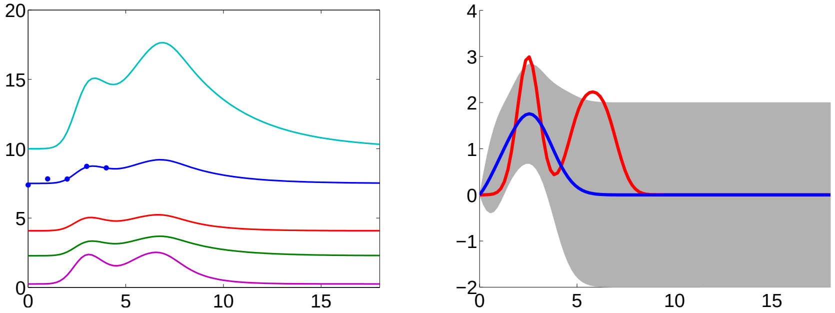

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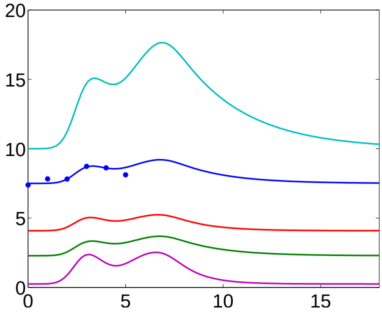

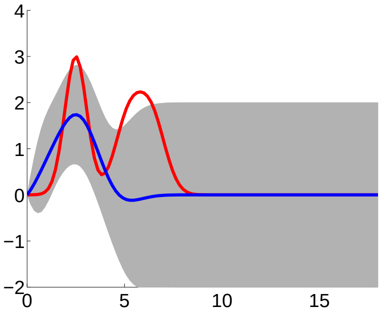

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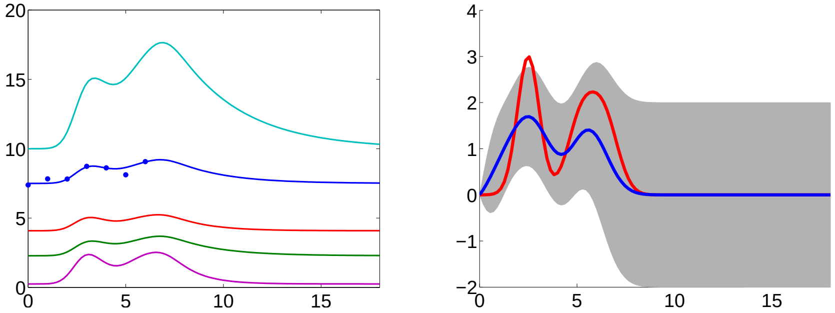

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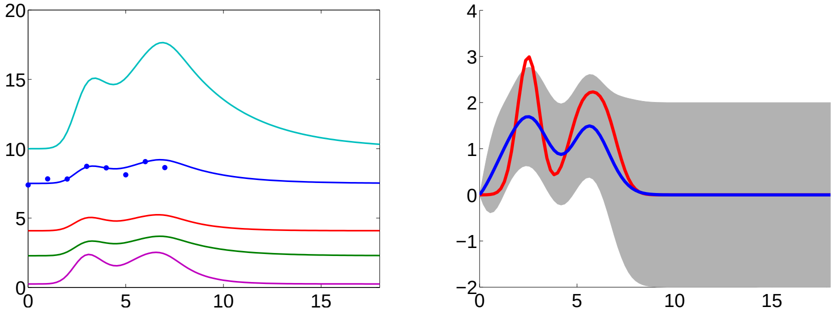

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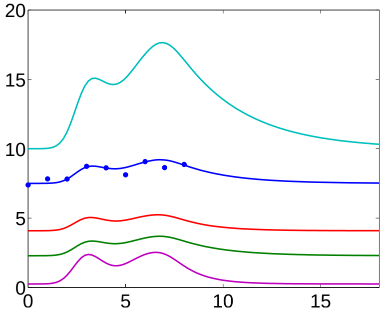

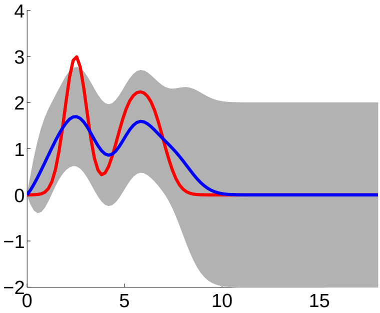

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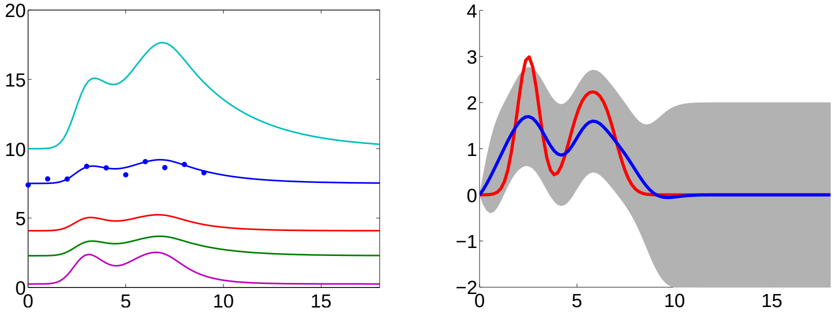

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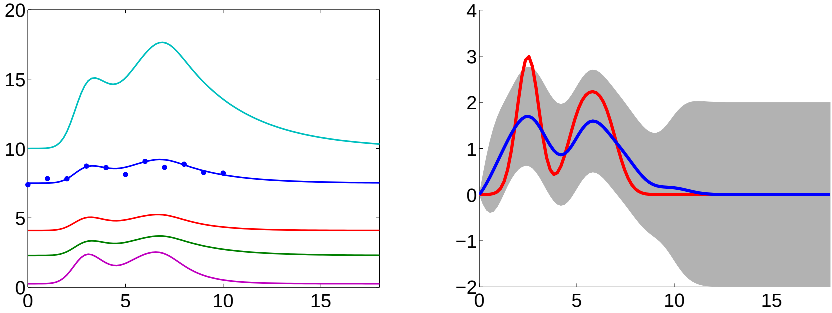

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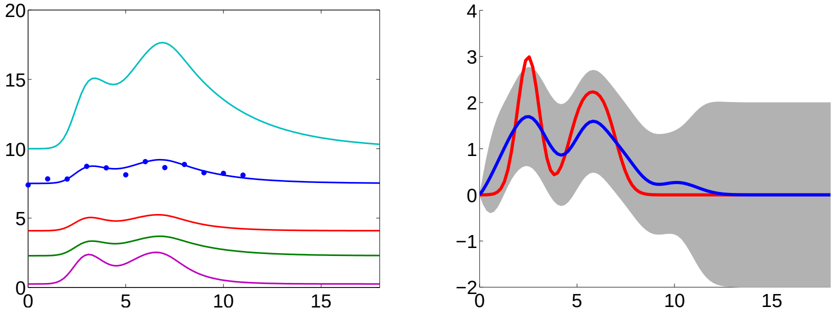

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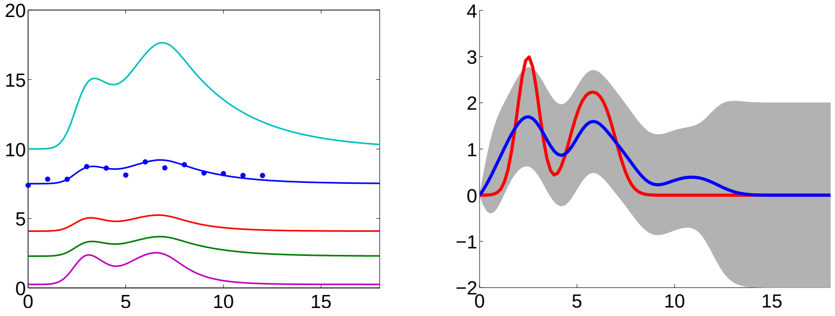

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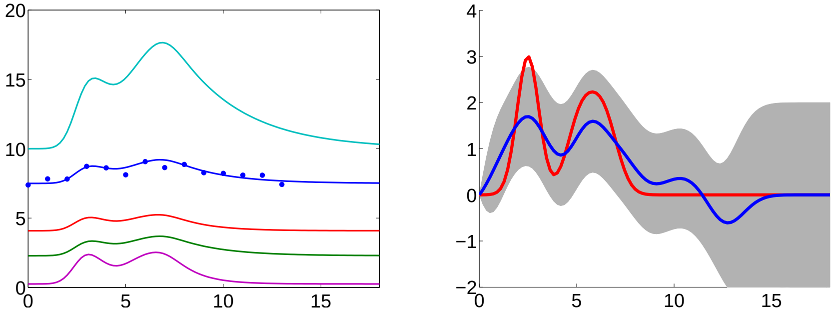

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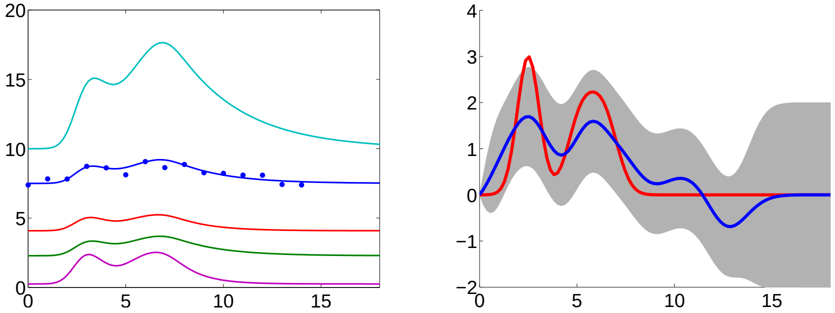

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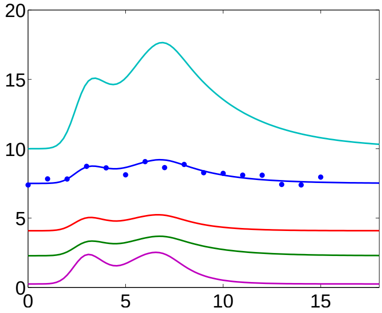

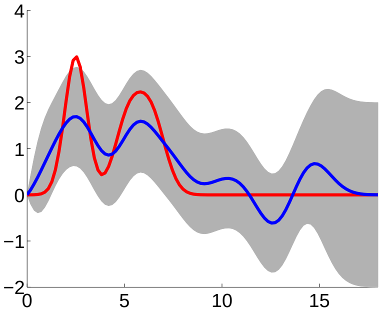

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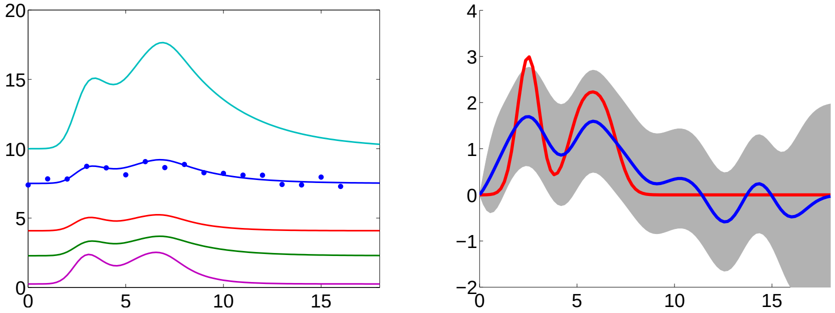

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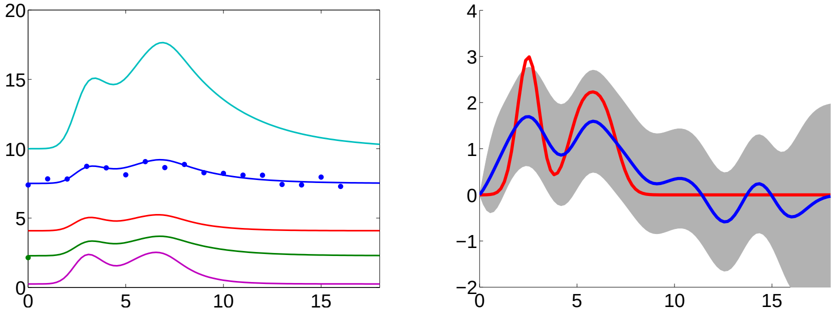

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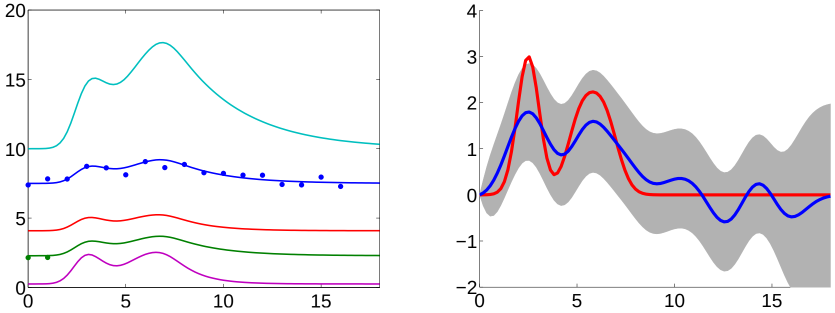

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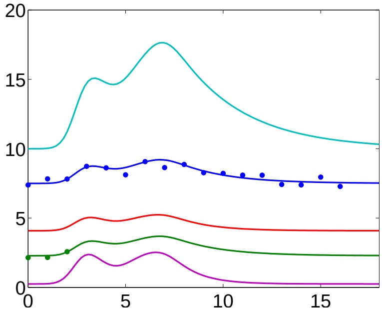

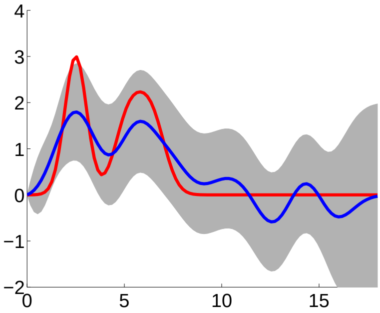

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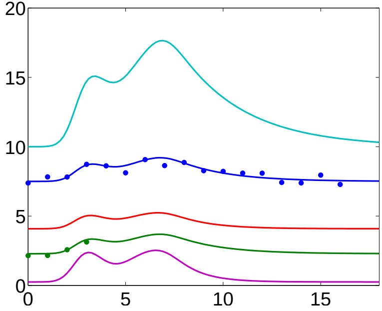

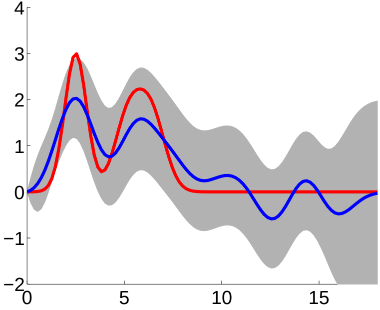

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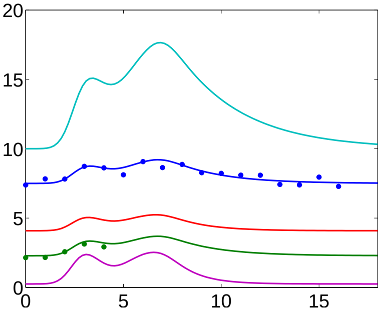

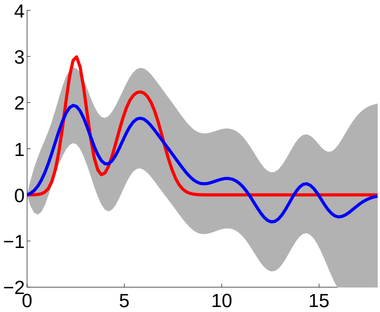

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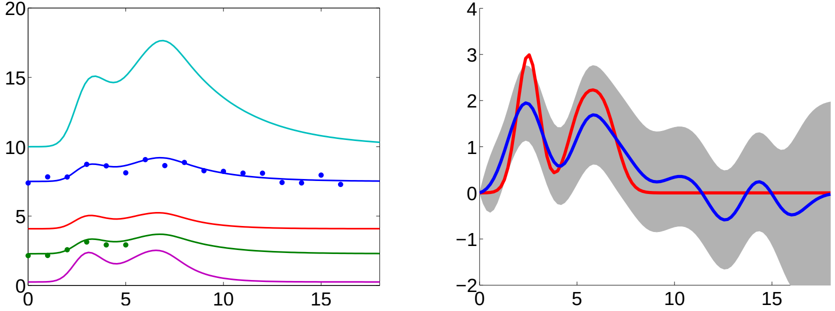

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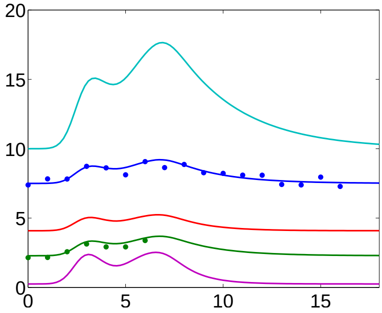

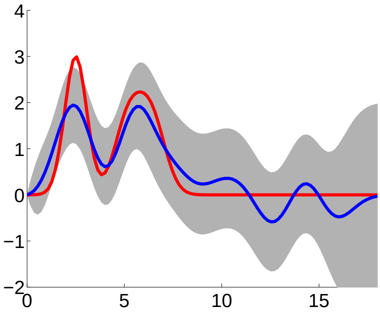

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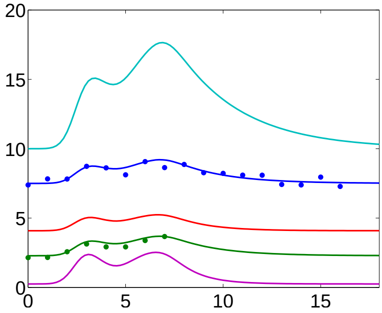

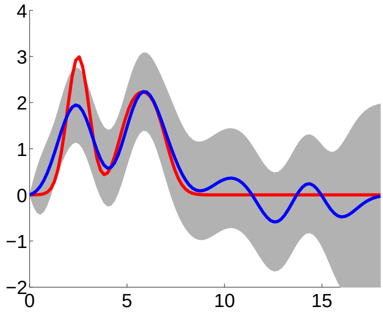

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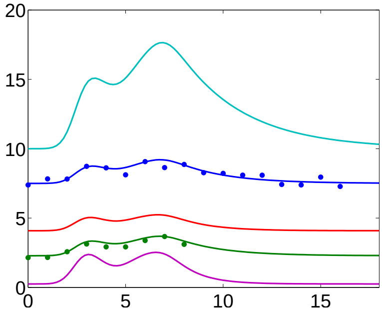

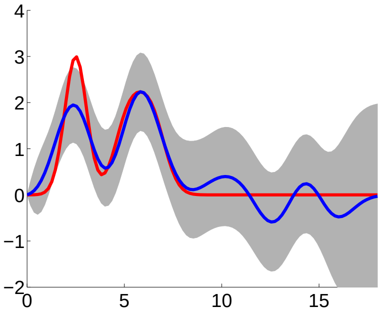

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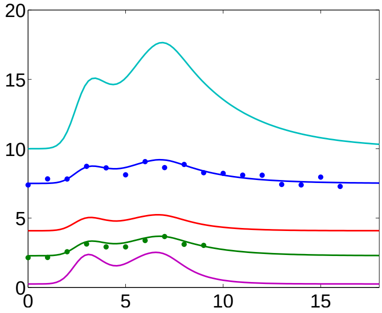

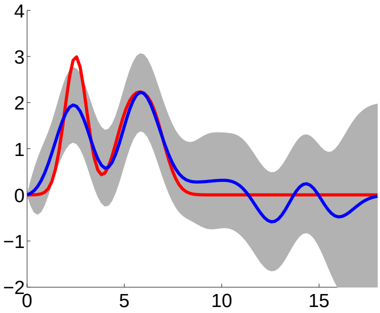

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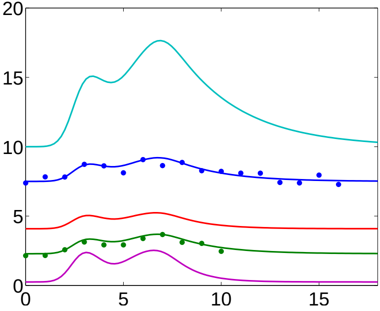

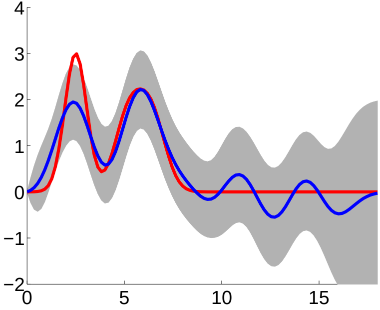

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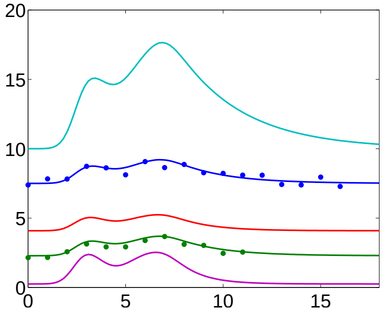

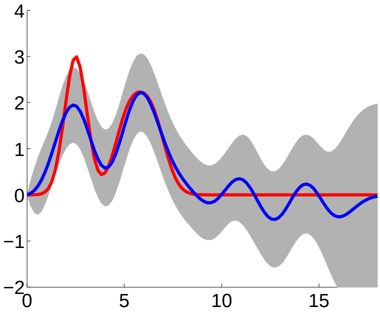

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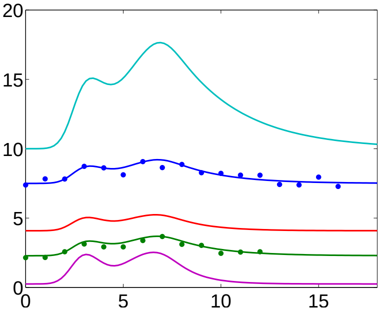

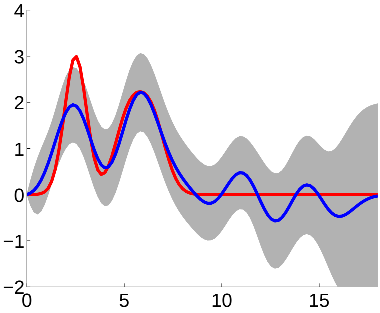

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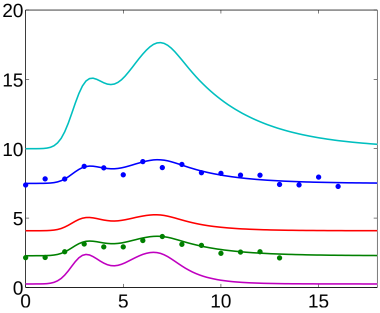

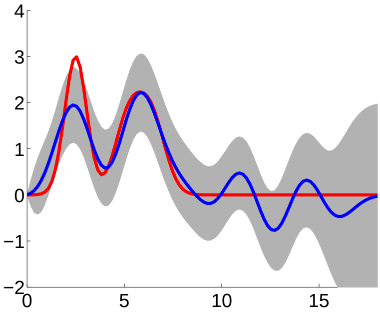

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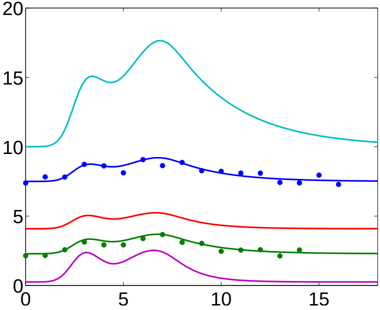

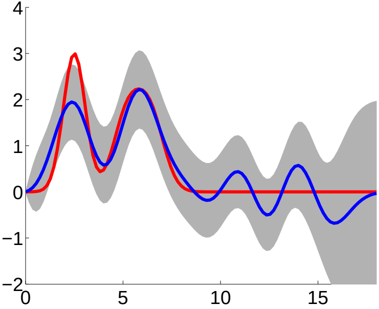

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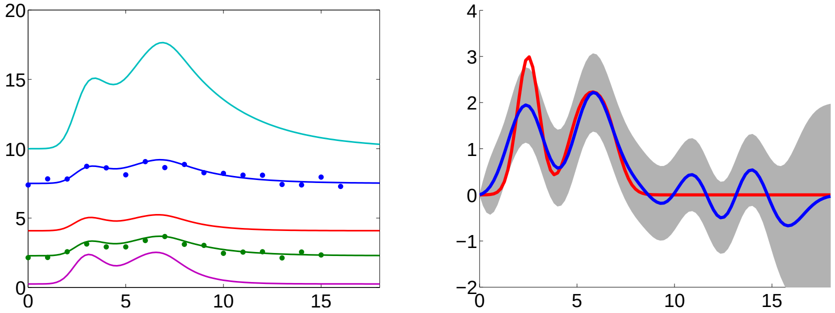

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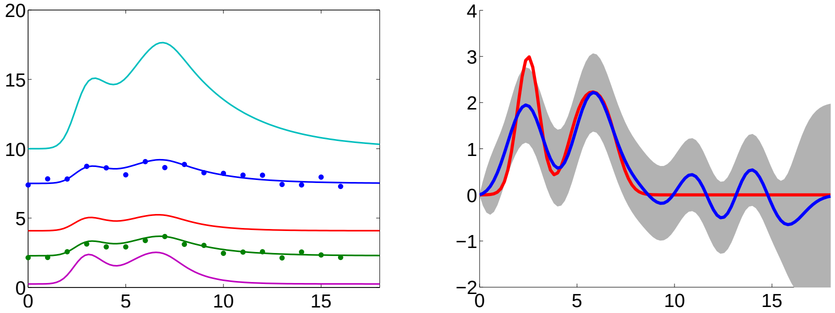

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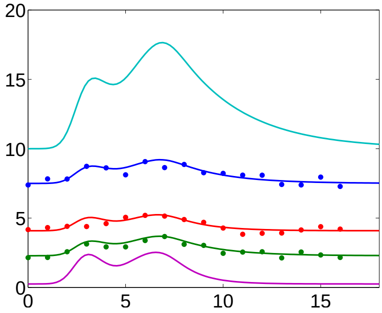

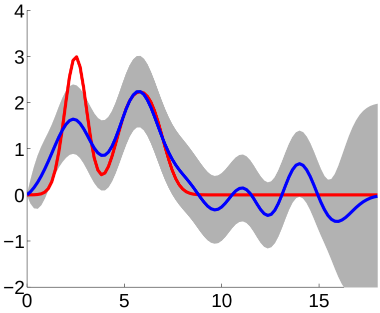

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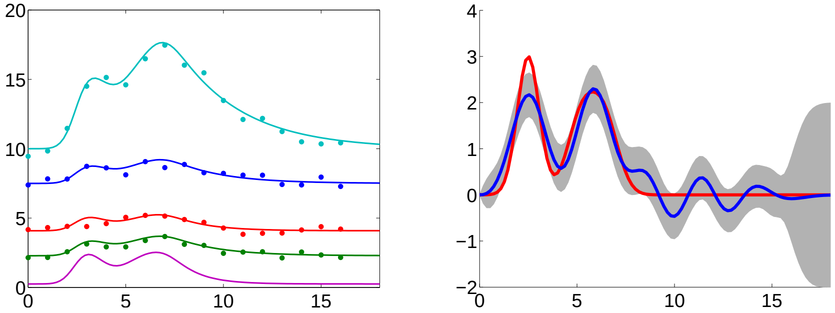

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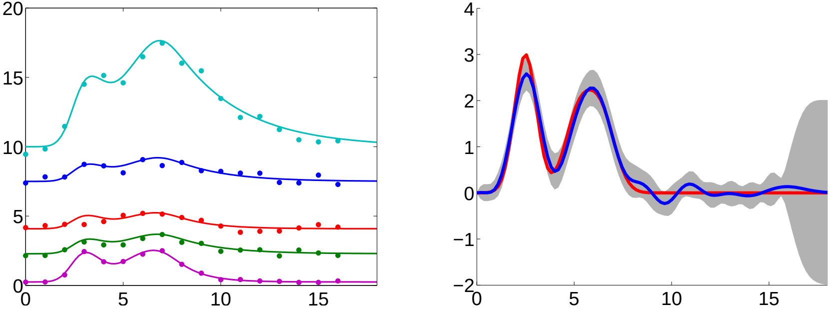
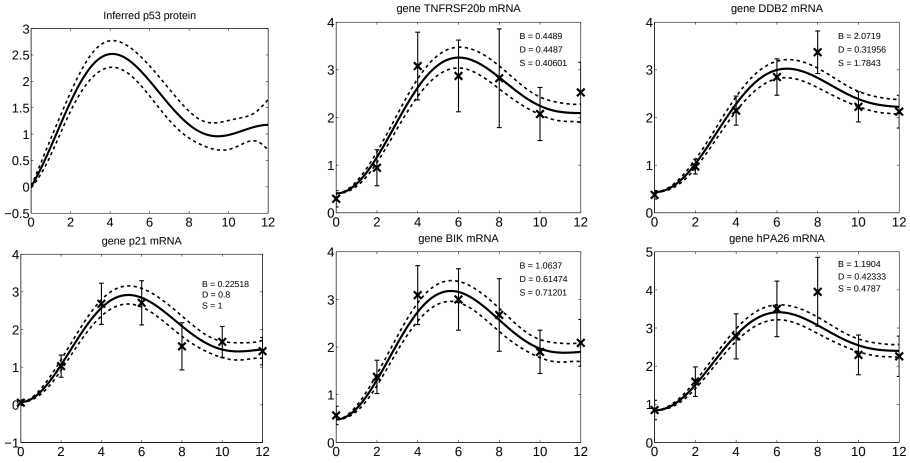


p53 (RBF covariance)

Pei Gao

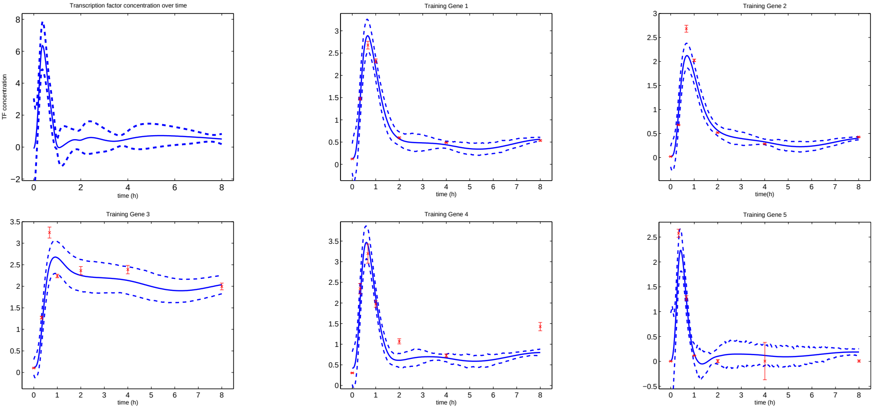


Ranking with ERK Signalling

- 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.

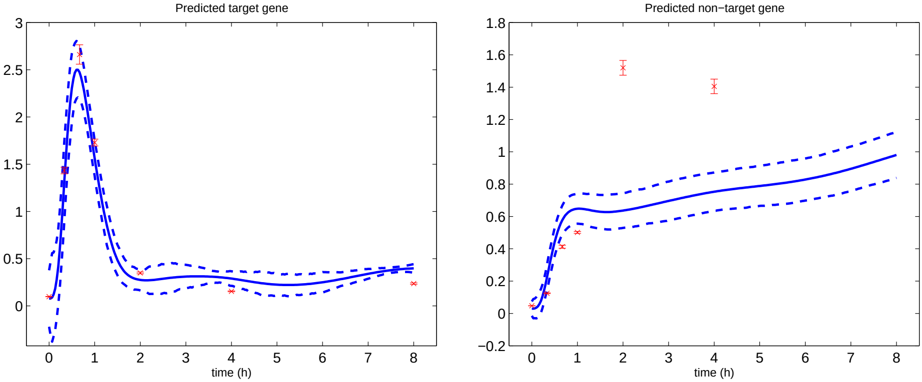
Elk-1 (MLP covariance)

Jennifer Withers



Elk-1 target selection

Fitted model used to rank potential targets of Elk-1



Outline

1. Introduction
2. Gaussian Process Inference for Linear Activation
3. Cascaded Differential Equations
4. Discussion and Future Work
5. Acknowledgements

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.

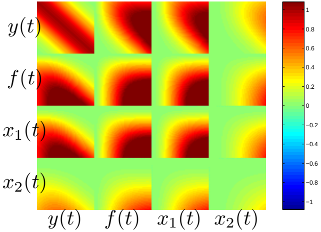
Covariance for Translation/Transcription Model

RBF covariance function for $y(t)$

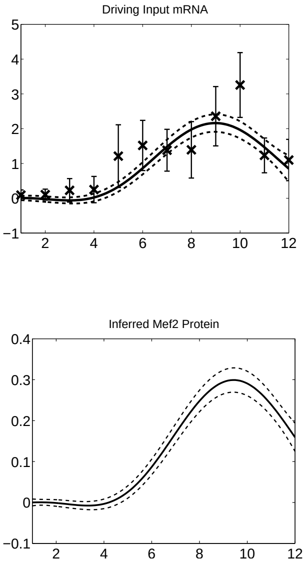
$$
\begin{aligned}
f(t) &= \sigma \exp(-\delta t) \int_0^t y(u) \exp(\delta u)\, \mathrm{d}u \\
x_i(t) &= \frac{B_i}{D_i} + S_i \exp(-D_i t) \int_0^t f(u) \exp(D_i u)\, \mathrm{d}u.
\end{aligned}
$$

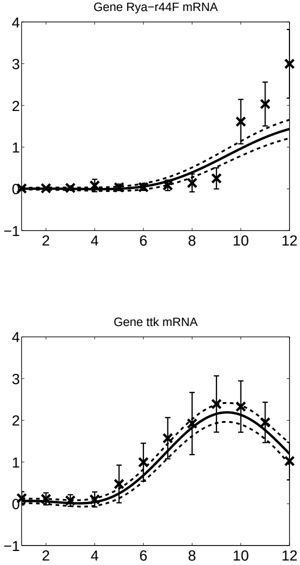
- Joint distribution for $x_1(t)$, $x_2(t)$, $f(t)$ and $y(t)$.
- Here:

δ	D_1	S_1	D_2	S_2
0.1	5	5	0.5	0.5



Results for Mef2 using the Cascade model





Outline

Discussion and Future Work

- Integration of probabilistic inference with mechanistic models.
- These results are small simple systems (we skipped non-linear).
- 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

Acknowledgements

- Investigators: Neil Lawrence and Magnus Rattray
- Researchers: Peo Gao, Antti Honkela, Michalis Titsias and Jennifer Withers
- 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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References I

M. Barenco, D. Tomescu, D. Brewer, R. Callard, J. Stark, and M. Hubank. Ranked prediction of p53 targets using hidden variable dynamic modeling. *Genome Biology*, 7(3):R25, 2006. [PDF].