Modelling Transcriptional Regulation with Gaussian processes

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7th November 2007

Outline

Online Resources

- All source code and slides are available online
  - This talk available from my home page (see talks link on side).
  - MATLAB examples in the 'oxford' toolbox (vrs 0.13).
    - `http://www.cs.man.ac.uk/~neill/oxford/`.
  - And the 'gpsim' toolbox (vrs 0.1).
    - `http://www.cs.man.ac.uk/~neill/gpsim/`.
  - MATLAB commands used for examples given in `typewriter font`.

Introduction to Gaussian Processes

- TFAs can be seen as *latent chemical species*.
- In Magnus' talk we saw how they can be modelled with Kalman filters.
- Gaussian processes (GPs) are probabilistic models for functions.
  [O'Hagan, 1978, 1992, Rasmussen and Williams, 2006]
- GPs allow inference about functions in the presence of uncertainty.

Defining a Distribution over Functions

- Gaussian Process
  - What is meant by a distribution over functions?
  - Functions are infinite dimensional objects:
    - Defining a distribution over functions seems non-sensical.

- Gaussian Distribution
  - Start with a standard Gaussian distribution.
  - Consider the distribution over a fixed number of instantiations of the function.
  - A multi-variate Gaussian distribution is defined by a mean and a covariance matrix.
  - We consider the special case where the mean is zero,

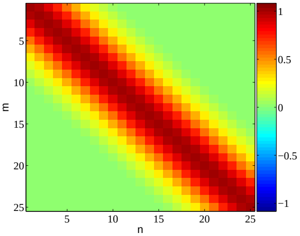
$$N(\mathbf{f}|\mathbf{0}, \mathbf{K}) = \frac{1}{(2\pi)^{\frac{N}{2}} |\mathbf{K}|^{\frac{1}{2}}} \exp\left(-\frac{\mathbf{f}^{\mathrm{T}}\mathbf{K}^{-1}\mathbf{f}}{2}\right).$$

Covariance Functions

- RBF Kernel Function

$$k(\mathbf{x}_m, \mathbf{x}_n) = \alpha \exp\left(-\frac{\left|\left|\mathbf{x}_m - \mathbf{x}_n\right|\right|^2}{2l^2}\right)$$

- Covariance matrix is built using the *inputs* to the function $\mathbf{x}_n$.
  - For the example above it was based on Euclidean distance.
  - The covariance function is also know as a kernel.



Covariance Samples

- `demCovFuncSample`

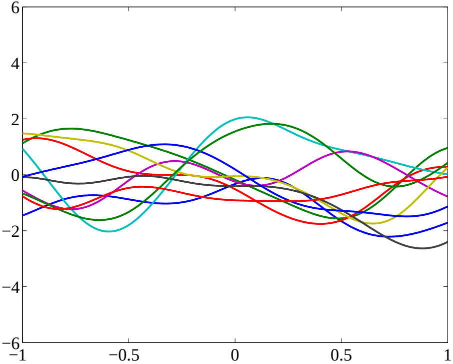


Figure: RBF kernel with $\gamma = 10$, $\alpha = 1$

- `demCovFuncSample`

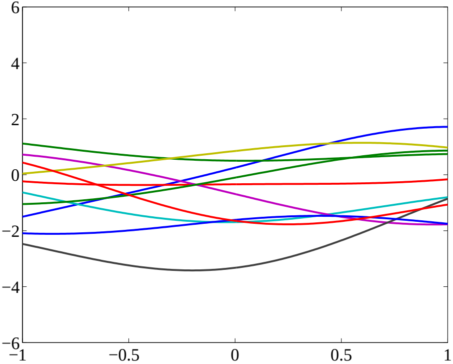


Figure: RBF kernel with $l = 1$, $\alpha = 1$

Covariance Samples

- `demCovFuncSample`

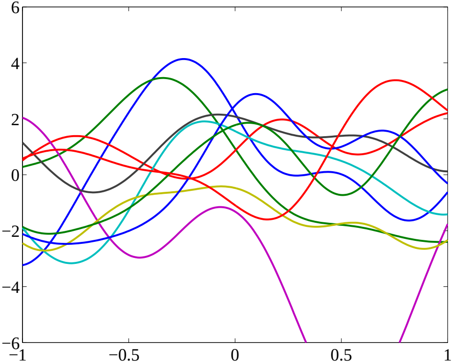


Figure: RBF kernel with $l = 0.3$, $\alpha = 4$

Covariance Samples

- `demCovFuncSample`

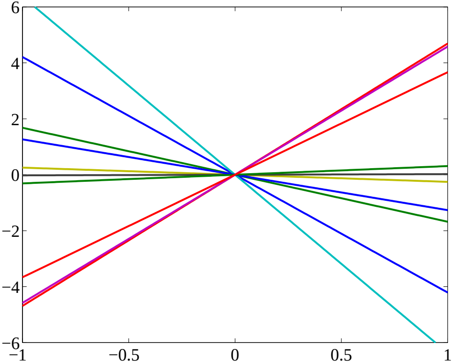


Figure: linear kernel with $\alpha = 16$

Covariance Samples

- `demCovFuncSample`

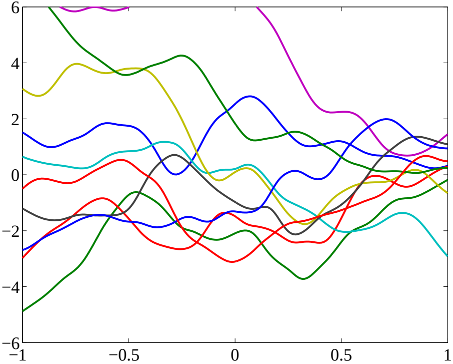


Figure: MLP kernel with $\alpha = 8$, $w = 100$ and $b = 100$

Covariance Samples

- `demCovFuncSample`

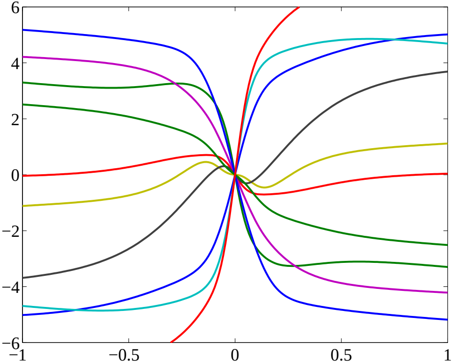


Figure: MLP kernel with $\alpha = 8$, $b = 0$ and $w = 100$

Covariance Samples

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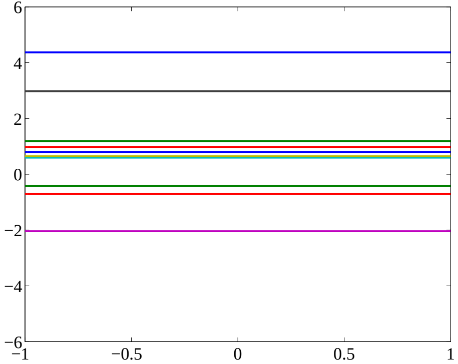


Figure: bias kernel with $\alpha = 1$ and

Covariance Samples

- `demCovFuncSample`

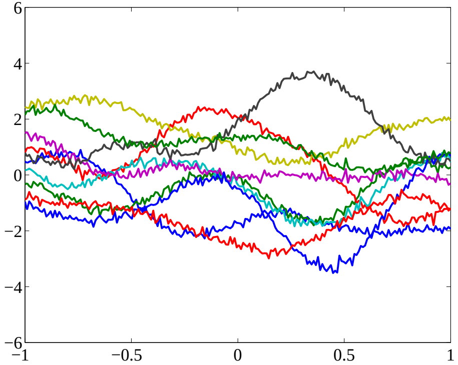


Figure: summed combination of: RBF kernel, $\alpha = 1$, $l = 0.3$; bias kernel, α =1; and white noise kernel, $\beta = 100$

Gaussian Process Regression

- `demRegression`

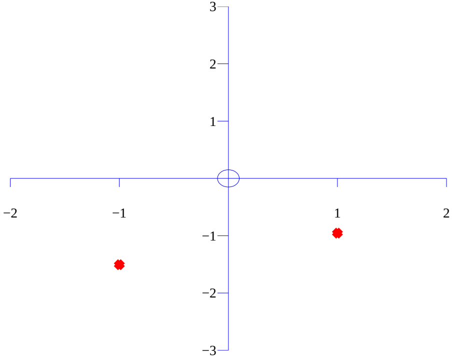
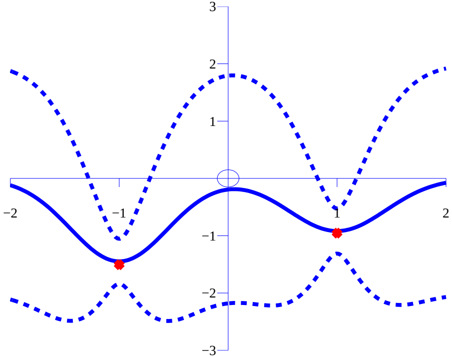


Figure: Examples include WiFi localization, C14 callibration curve.

Gaussian Process Regression

- `demRegression`



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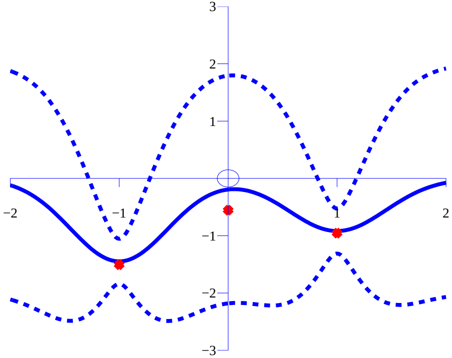

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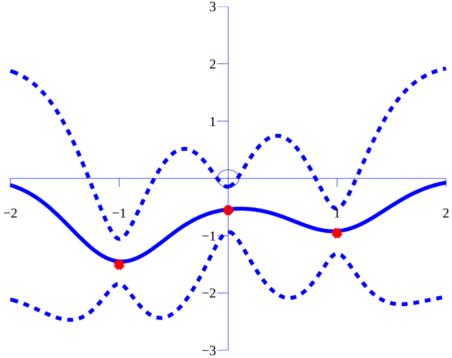

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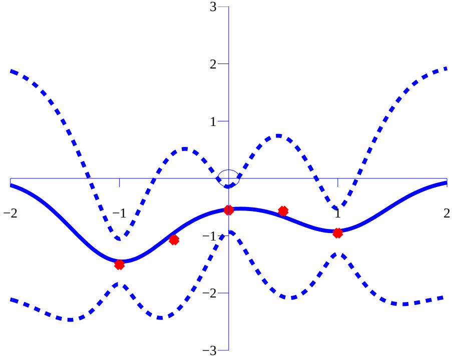

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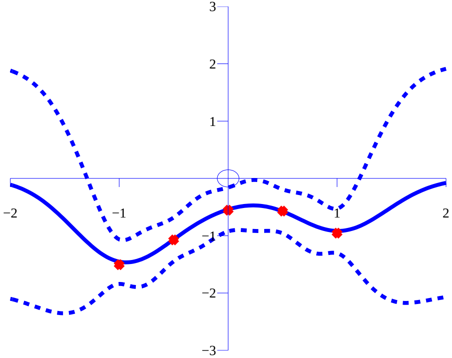

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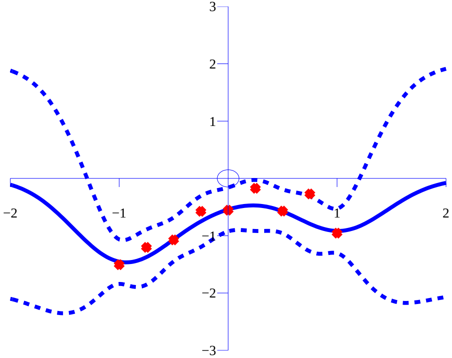

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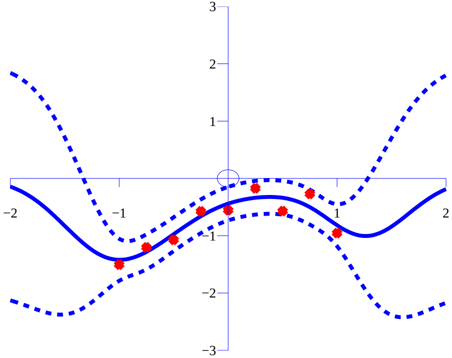


Figure: Examples include WiFi localization, C14 callibration curve.

Application

- A missing chemical species (e.g. transcription factor).
- Aim: infer its value with Gaussian processes.
- Differential Equation model
  - Simple linear model differential equation model recently used by Barenco et al. [2006].
  - We repeat their experiments with Gaussian processes.

Simple Linear Model

- Linear model of regulation

$$\frac{dy_i(t)}{dt} = B_i + S_i f(t) - D_i y_i(t)$$

- where:

$y_i(t)$	—	expression of the ith gene at time t.
$f(t)$	—	concentration of the transcription factor at time t.
D_i	—	gene's decay rate.
B_i	—	basal transcription rate.
S_i	—	sensitivity to the transcription factor.

Equation Solution

- Solve via Laplace Transforms
  - Solution to the equation:

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

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

Two Properties of GPs

The integral of a GP is also a GP,

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

and

$$g(t) = \int_0^t f(u)\, du$$

then

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

where

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

Two Properties of GPs

Product with deterministic function, if we have

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

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

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

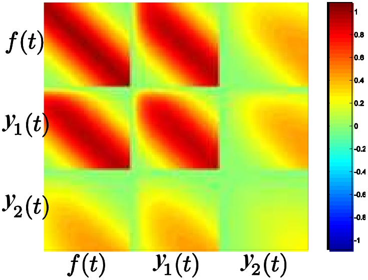
Covariance for Transcription Model

- RBF Kernel function for $f(t)$

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

- Joint distribution for $y_1(t)$, $y_2(t)$ and $f(t)$.
  - Here:

D_1	S_1	D_2	S_2
5	5	0.5	0.5



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

- `gpsimTest`

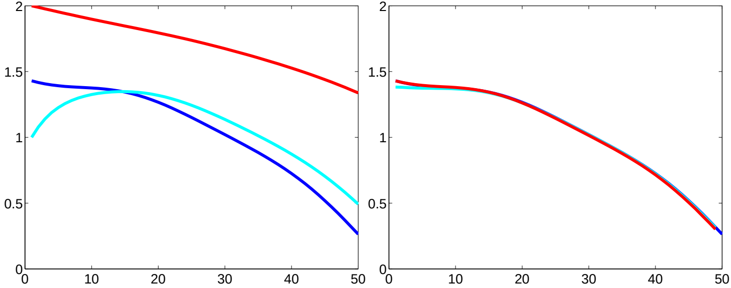


Figure: *Left*: joint samples from the transcription covariance, *blue*: $f(t)$, *cyan*: $y_1(t)$ and *red*: $y_2(t)$. *Right*: numerical solution for $f(t)$ of the differential equation from $y_1(t)$ and $y_2(t)$ (blue and cyan). True $f(t)$ included for comparison.

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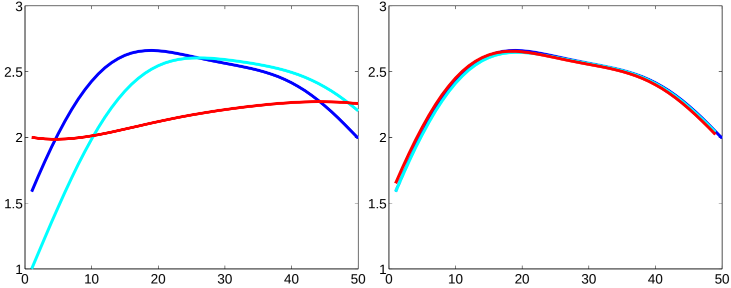

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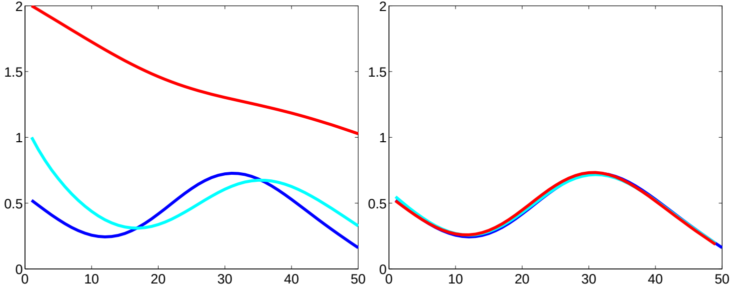

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Results — Drosophila

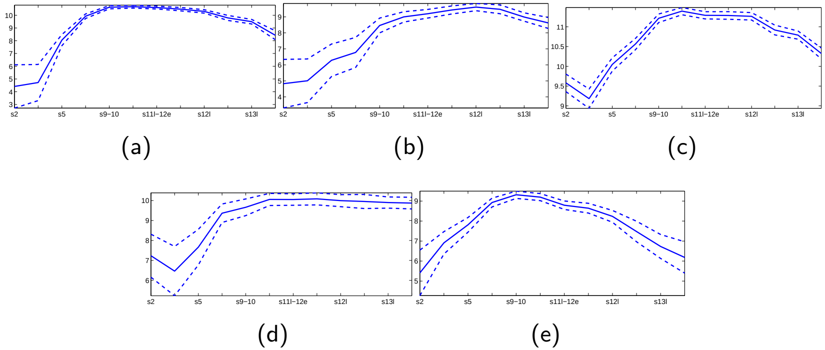
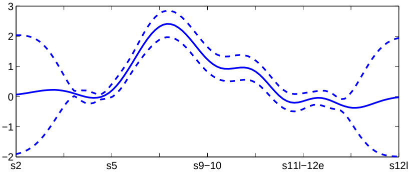
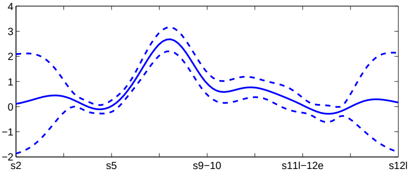


Figure: mRNA expression levels for target genes. (a) pannier, (b) hibris, (c) CG12744, (d) CG10516 (e) CG31368 .

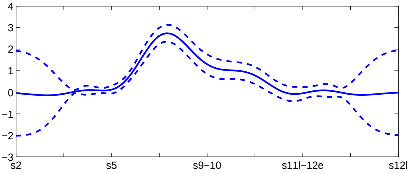
Results — Drosophila



(a)



(b)



(c)

Figure: Inferred Transcription Factor Activities

Results — Transcription Rates

- Estimation of Equation Parameters `demBarenco1`

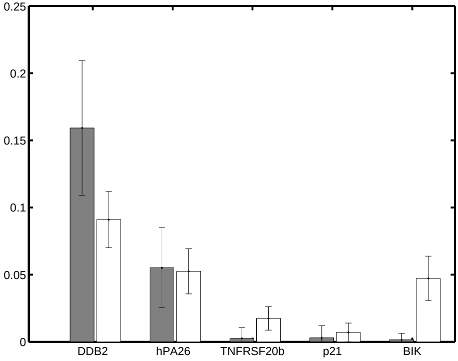


Figure: Basal transcription rates. Our results (black) compared with Barenco et al. [2006] (white).

Results — Transcription Rates

- Estimation of Equation Parameters `demBarenco1`

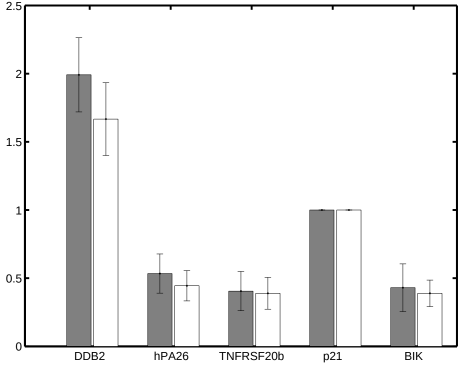


Figure: Sensitivities. Our results (black) compared with Barenco et al. [2006] (white).

Results — Transcription Rates

- Estimation of Equation Parameters `demBarenco1`

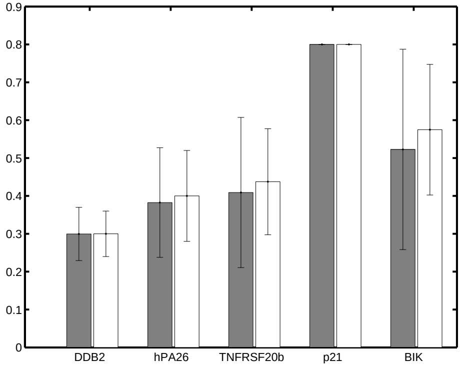
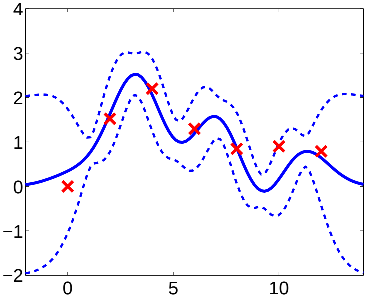


Figure: Decays. Our results (black) compared with Barenco et al. [2006] (white).

Results — Protein Concentration

- Prediction with error bars of protein concentration: $p(\mathbf{f}|\mathbf{y}_1, \mathbf{y}_2, \mathbf{y}_3, \mathbf{y}_4, \mathbf{y}_5)$



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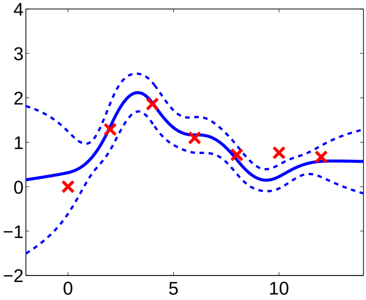
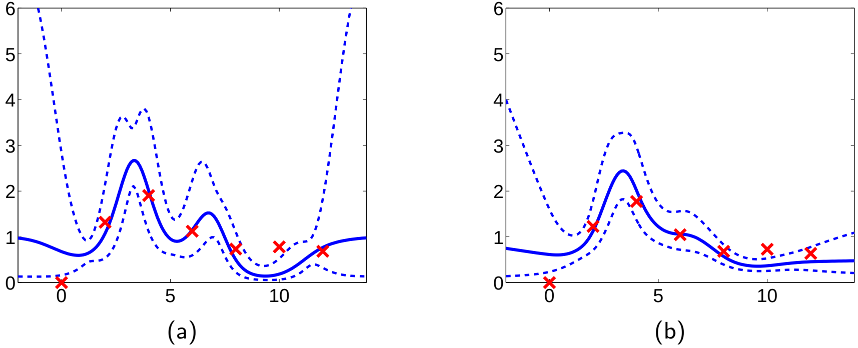


(b)

Figure: (a) RBF covariance function (b) MLP covariance function. Also included are results from Barenco et al. [2006] as crosses.

Results — Log Space

- GP predictions in log space.



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Results — $\log(1 + \exp(x))$ Constrained

- GP predictions in log space.

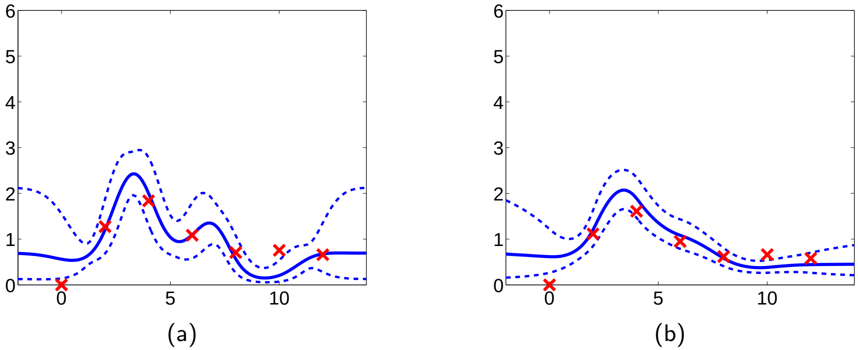

Figure: (a) RBF covariance function (b) MLP covariance function. Also included are results from Barenco et al. [2006] as crosses.

Results — Sigmoid

- GP predictions in log space.

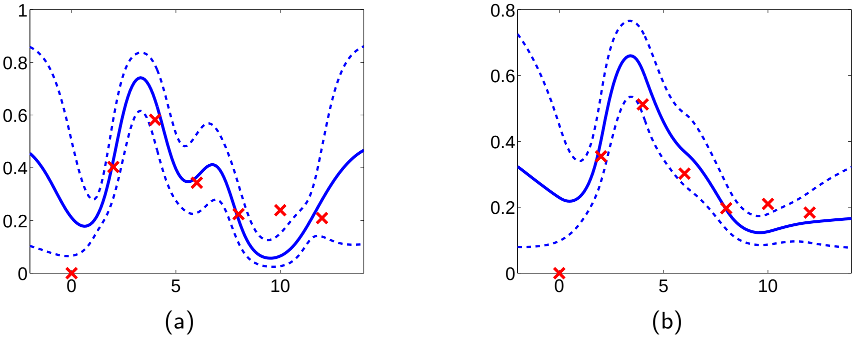

Figure: (a) RBF covariance function (b) MLP covariance function. Also included are results from Barenco et al. [2006] as crosses.

Transcription Model Summary

- Progress so far and Future work
  - Elegant solution of a problem with indirect observations.
  - Already extended to non-linear response equations (using Laplace approximation).
  - Extending to systems with *multiple transcription factors* (Pei Gao).
  - Validating with Markov chain Monte-Carlo (Michalis Titsias).
  - Sensitivities which change over time (Antti Honkela)

References

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A. O'Hagan. Curve fitting and optimal design for prediction. *Journal of the Royal Statistical Society, B*, 40:1–42, 1978.

A. O'Hagan. Some Bayesian numerical analysis. In J. M. Bernardo, J. O. Berger, A. P. Dawid, and A. F. M. Smith, editors, *Bayesian Statistics 4*, pages 345–363, Valencia, 1992. Oxford University Press.

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