

Probabilistic Inference for Modelling of Transcription Factor Activity

Part of the PUMA project for Propagating Uncertainty in
Microarray Analysis

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Outline

- 1 Microarray Processing
 - Affymetrix GeneChip Arrays
- 2 Transcription Factors
 - ChIP-microarray and Transcription Factor Activities
 - Transcription Factor Concentrations
 - From Simple to Complex Models
 - Biological Problem
- 3 Non-linear Response Model
 - Linear Response with MLP Kernel
 - Non-linear Responses
- 4 Conclusions

Online Resources

All source code and slides are available online

- This talk available from my home page (see talks link on side).
- Project main page (with links to software)
 - <http://bioinf.manchester.ac.uk/resources/puma/>.
- Additional project homepage
 - <http://www.cs.man.ac.uk/~neill/projects/pipeline/>.

PUMA Project Outline

Noise Problems in Microarrays

- Project was motivated by the fact that microarray data is very noisy.
- The aim of the project is to:
 - Assess the level of noise in the estimated gene expression.
 - Propagate the noise through downstream analysis.
- Personnel:
 - **Investigators:** Neil Lawrence, Magnus Rattray
 - **Fellows/Post-docs:** Pei Gao (from July 1st), Marta Milo (Sheffield), Guido Sanguinetti (former post-doc Sheffield)
 - **PhD Students:** Xuejun Liu, Richard Pearson

Central Dogma

DNA → mRNA → Protein

- Every cell has the same DNA.
- Cells produce different proteins (building blocks of life).
- Level of mRNA produced is known as *gene expression*.
- Has a downstream effect on level of Protein produced.
- Gene expression is controlled by *Transcription factors*.
- Transcription factors themselves are proteins.
 - Feedbacks in these systems lead to gene networks.

Affymetrix Arrays

Photolithography and Combinatorial Chemistry

- Affymetrix arrays are a technology for measuring level of mRNA.
- PM (perfect match) probes match the gene sequence.
- MM (mismatch) probes have wrong middle base.
- MM designed to measure non-specific binding.
- Approx 10,000 probe-sets per chip.

Affymetrix Arrays

Photolithography and Combinatorial Chemistry



Figure: Affymetrix arrays for human and mouse (image from Wikimedia Commons under GFDL).

Affymetrix Arrays

Photolithography and Combinatorial Chemistry

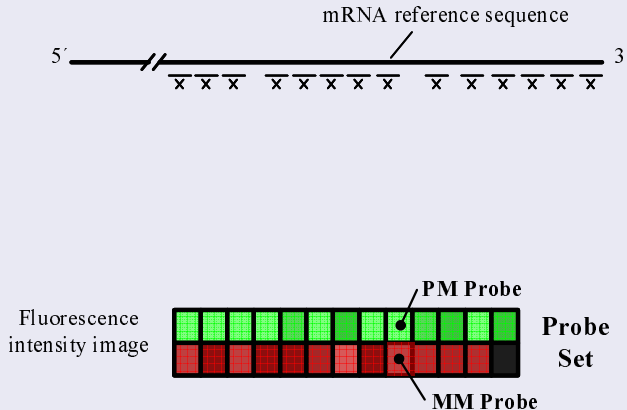


Figure: Affymetrix array schematic

Affymetrix Arrays

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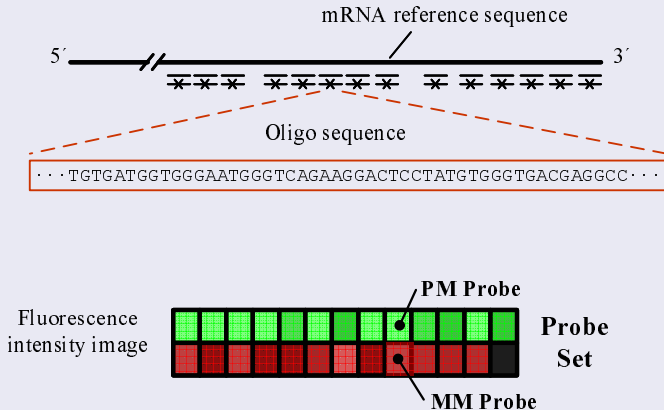


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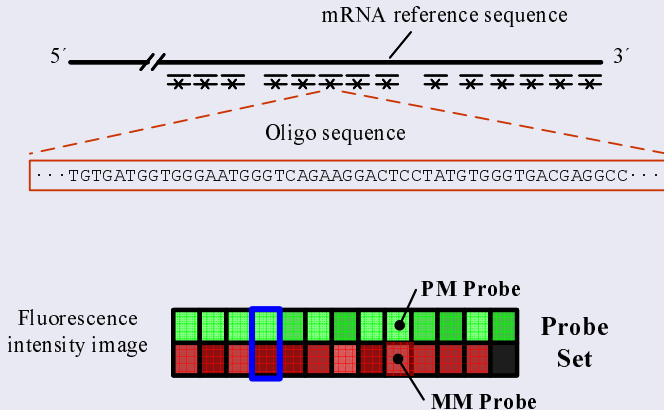


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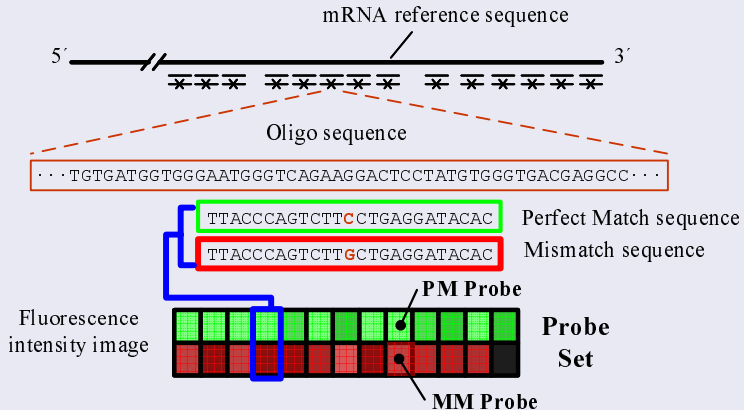


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gMOS Family of Methods

Gamma Model of Signal (Milo et al., 2003; Liu et al., 2005)

- Most methods return a single expression level estimate.
- The gMOS family of methods additionally provide confidence intervals.
- This confidence intervals can the be propagated through higher level analysis.

gMOS Family of Methods II

Gamma Model of Signal

$$m_j \sim \text{Ga}(m_j | a, b)$$

$$s_j \sim \text{Ga}(s_j | \alpha, b)$$

$$y_j = m_j + s_j$$

$$y_j \sim \text{Ga}(y_j | a + \alpha, b)$$

$$\text{Ga}(x | a, b) = \frac{b^a}{\Gamma(a)} x^{a-1} \exp(-bx)$$

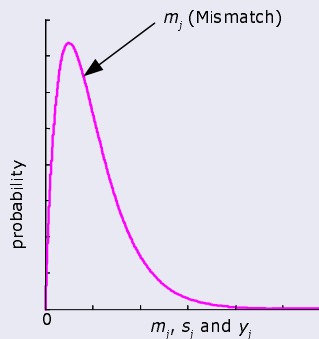


Figure: PDF of m_j , s_j and the implied distribution for y_j .

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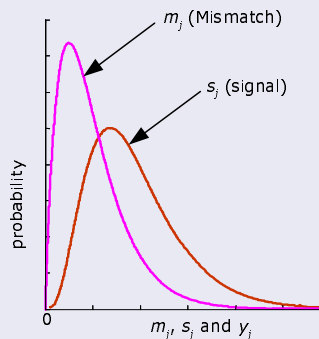


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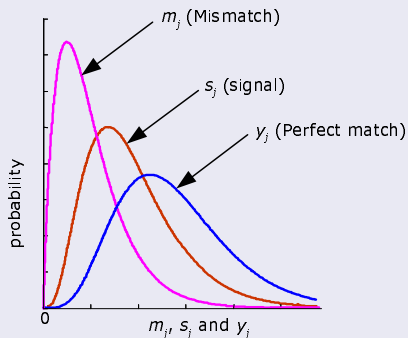


Figure: PDF of m_j , s_j and the implied distribution for y_j .

gMOS

Inferring the Signal

- Maximise likelihood with respect to α , a and b .
 - Assume independence between y_j and m_j ,

$$p(y_j, m_j) = \text{Ga}(y_j | \alpha, b) \text{Ga}(m_j | a, b).$$

- Use resulting $\hat{\alpha}$ and \hat{b} to give distribution over s_j .

$$p(s_j) = \text{Ga}(s_j | \hat{\alpha}, \hat{b}).$$

Modelling Probe Pair Affinity

mgMOS

- y_j and m_j are correlated.
- gMOS makes an independence assumption.
- Correlations arise through shared binding affinity (scale).
- Assume each probe pair has a shared scale b_j .
- Assume $b_j \sim \text{Ga}(b_j | c, d)$ and marginalise.

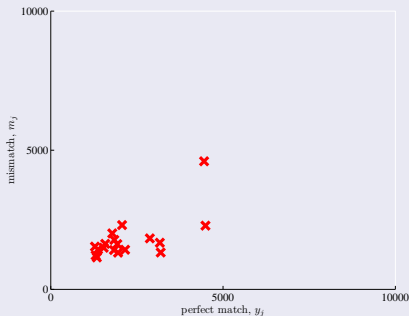


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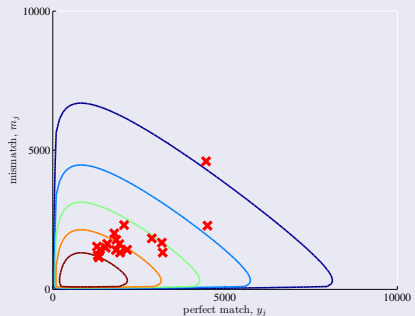


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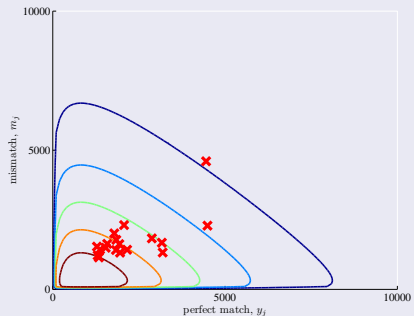


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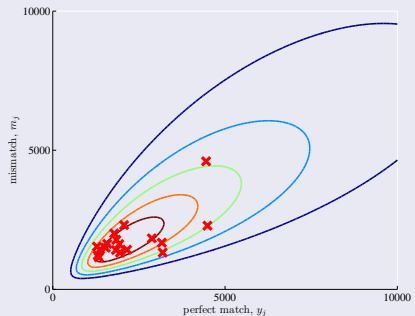


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Specific Binding to Mismatch

Mismatch Effected by Signal

- Affymetrix Latin Square Spike-In data set.
- The perfect match responds to increasing mRNA.
- But so does the mismatch.

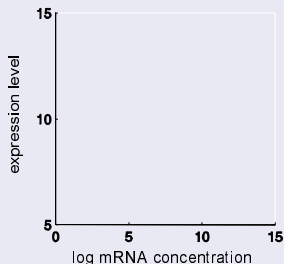


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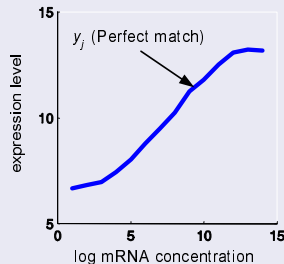


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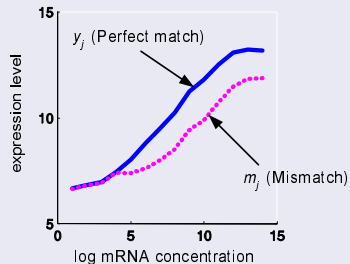


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Specific Binding and Multiple Arrays

multi-mgMOS

- Specific Binding to MM probe:

- Introduce parameter ϕ and assume

$$y_j \sim \text{Ga}(y_j | a + \alpha, b_j), \quad m_j \sim \text{Ga}(m_j | a + \phi\alpha, b_j)$$

- Log normal prior for ϕ and seek a MAP solution.
- Multiple arrays:
 - Still take $b_j \sim \text{Ga}(b_j | c, d)$ but **share c and d parameters across chips.**

Mouse Data Set

<http://www.ncbi.nlm.nih.gov/projects/geo>

Mouse back skin mRNA expression profile for Dab2 (Lin et al., 2004).

RMSE	Root Mean Square Error	
	qr-PCR	x-probe set
MAS 5.0	0.656	0.360
GCRMA	0.694	0.370
multi-mgMOS	0.601	0.233



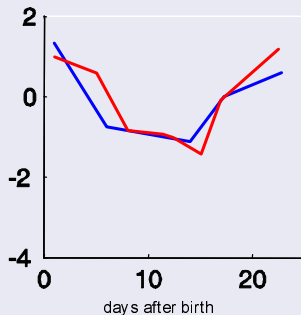
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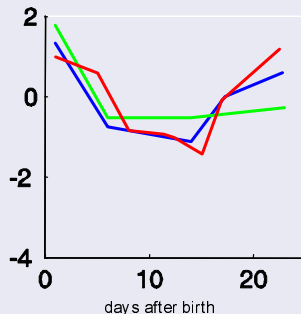
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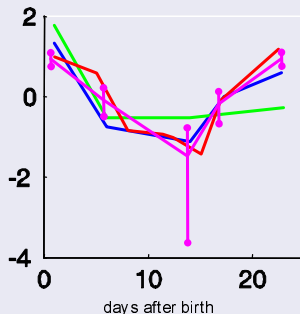
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Prediction of Dab2 Expression level from qr-PCR, MAS 5.0, GCRMA and multi-mgMOS.

Transcription Factor Activities

Inferring Activity of Transcription Factors

- Transcription factors control the expression of genes.
- Knowledge of their 'activity' is key to understanding the mechanism behind biological processes.
- Transcription factors are proteins — activity is a combination of their concentration and effect.
- The mRNA concentration of a given transcription factor may be known but:
 - Transcription factors are often lowly expressed — mRNA concentrations difficult to measure.
 - Transcription factors are often post-transcriptionally regulated.

ChIP Microarrays

Chromatine Immunoprecipitation (ChIP) Microarrays

- ChIP Microarrays tell us which TFs bind to which genes under certain conditions.
- In effect this gives a structure for the regulatory network.
- Combine this information with gene expression data to obtain transcription factor activities (TFA).

Transcription Factor Activities

Evaluating Activities of Transcription Factors

- Several approaches based on regression (Liao et al., 2003; Gao et al., 2004; Boulesteix and Strimmer, 2005; Alter and Golub, 2004)
- Assume a gene's expression is given by a linear relationship

$$\mathbf{y}_i = \mathbf{B}\mathbf{x}_i + \epsilon_i.$$

$\mathbf{y}_i \in \mathbb{R}^{T \times 1}$ is the expression profile of the i th gene,

$\mathbf{x}_i \in \{0, 1\}^{q \times 1}$ indicates which transcription factors bind to the i th gene

$\mathbf{B} \in \mathbb{R}^{T \times q}$ is the matrix of TFAs.

$$\epsilon_i \sim N(\mathbf{0}, \sigma^2 \mathbf{I})$$

- Problem: the matrix \mathbf{B} is *not* gene specific. It gives average TFA across genes.

Gene Specific TFAs

Associate TFAs to Genes (Sanguinetti et al., 2006)

- Introduce gene specific TFAs,

$$\mathbf{y}_i = \mathbf{B}_i \mathbf{x}_i + \epsilon_i.$$

- Parameter Explosion

- Assume prior distribution for \mathbf{B}_i .

$$p(\mathbf{B}) = \prod_{i=1}^N p(\mathbf{B}_i) = \prod_{i=1}^N \prod_{t=1}^T p(\mathbf{b}_{i,t})$$

$$p(\mathbf{b}_{i,t}) = N(\mathbf{b}_{i,t} | \mathbf{0}, \Sigma)$$

$\mathbf{b}_{i,t} \in \mathbb{R}^{q \times 1}$ is the vector of TFAs for each TF associated with the i th gene at time t

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Temporal Continuity of TFAs

Time Course Experiments

- Introduce concept of temporal continuity with Gaussian distribution.

$$p(\mathbf{b}_{i,t}|\mathbf{b}_{i,t-1}) = N(\mathbf{b}_{i,t}|\gamma\mathbf{b}_{i,t-1} + (1-\gamma)\boldsymbol{\mu}, (1-\gamma^2)\Sigma)$$

The temporal continuity, γ is between 0 and 1.

Temporal Continuity of TFAs II

Effect of γ

- When $\gamma = 0$ we recover

$$p(\mathbf{b}_{i,t}) = N(\mathbf{b}_{i,t} | \boldsymbol{\mu}, \Sigma)$$

which is equivalent to the original independent model.

- As $\gamma \rightarrow 1$ we recover

$$p(\mathbf{b}_{i,t} | \mathbf{b}_{i,t-1}) = \lim_{\sigma^2 \rightarrow 0} N(\mathbf{b}_{i,t} | \mathbf{b}_{i,t-1}, \sigma^2 \mathbf{I})$$

which is appropriate if the 'time points' are in fact biological replicates.

Results on TFAs

Yeast Cell Cycle Data with ChIP-on-chip 204 TFs

- Yeast cell cycle *cdc15* data set (Spellman et al., 1998).
- ChIP-on-chip from 113 TFs (Lee et al., 2002).
- 24 experimental points in time series data.
- Compare with non-specific TFAs obtained by Regression.

Results on TFAs II

Graphs of TFAs

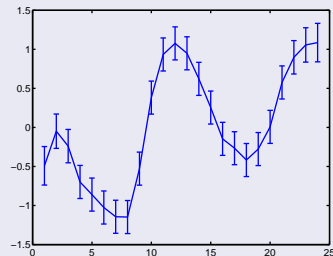
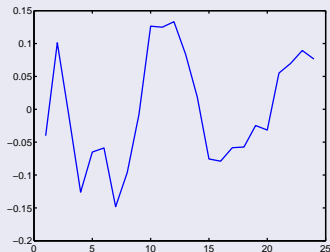


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA for average of B_i across genes.

Results on TFAs II

Graphs of TFAs

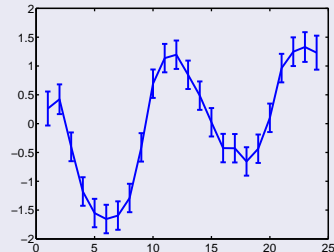
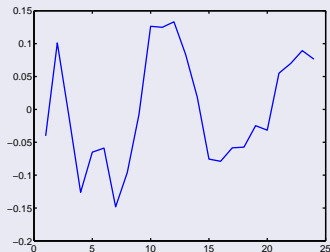


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA SCW11.

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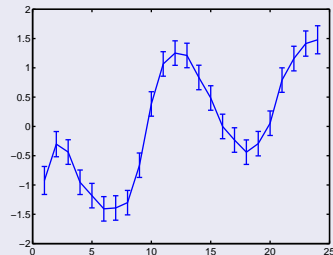
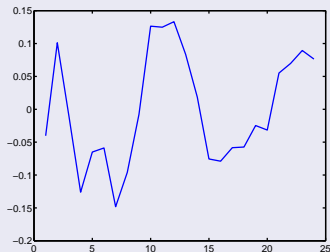


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA CTS1.

Results on TFAs II

Graphs of TFAs

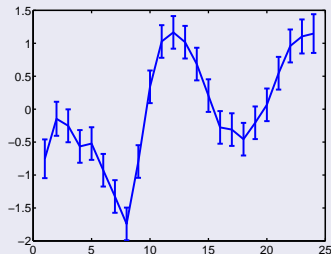
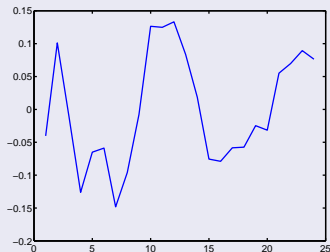


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA YER124C.

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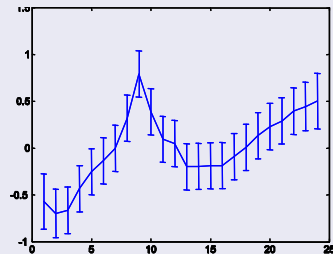
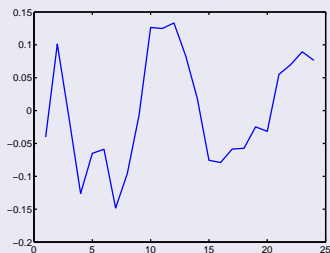


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA YKL51C.

Separation of Concentration and Effect

Splitting the Activity into Component Parts

- TFA is a combination of:
 - TF concentration.
 - TF effect.
- Model expression by splitting the two:

$$\mathbf{y}_i = (\mathbf{B} \odot \mathbf{X}) \mathbf{c}_t + \epsilon_t$$

where \odot is the Hadamard (element by element) product.

$\mathbf{B} \in \mathbb{R}^{N \times q}$ is a matrix of each TFs effect on each gene.

$\mathbf{c}_t \in \mathbb{R}^{q \times 1}$ is concentration of each TF at time t .

- Bayesian treatment of \mathbf{c} and \mathbf{B} through a variational approach.

TF Concentration Results

Concentration of ACE2

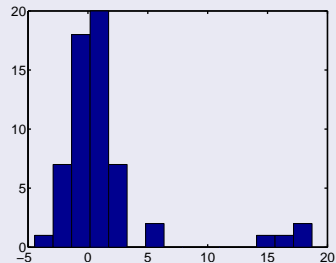
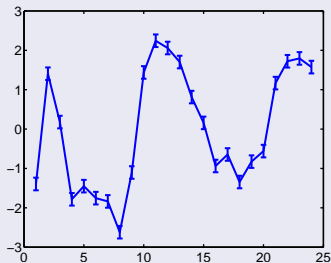


Figure: *Left:* concentration of ACE2 and *right:* effect of ACE2 on its target genes as a histogram.

TF Concentration Results II

Nice ACE2 Stories in Results

- ACE2 four most significant targets: CTS1, DSE1, DSE2, SCW11.
 - Evidence to back this up comes from biological literature.
 - CTS1 relationship is known.
 - DSE1 and DSE2 are involved in cell wall degradation causing daughter to separate from parent.
 - SCW11's function is unclear but protein is localised at cell wall.
- Negative regulation of NCE4
 - Not documented, but ACE2 terminates mitosis & NCE4 ensures DNA stability during replication

More Complex Model

Complex Models on Small Networks

- Simple linear models allow genome wide analysis of TFAs.
- We now consider a more complex model on a much smaller network.

Differential Equation Model

Inference of p53 Concentration

- p53 is an important in cancer.
- Many targets of p53 are not shared with other TFs.

Differential Equation model

- Simple linear model differential equation model recently used by Barenco et al. (2006).
- Initially inferred transcription factor concentrations using Markov Chain Monte Carlo (10^7 iterations). Now use maximum likelihood and curvature.
- 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 i th 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

Integral of Gaussian Process

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

The integral of a GP is also a 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

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

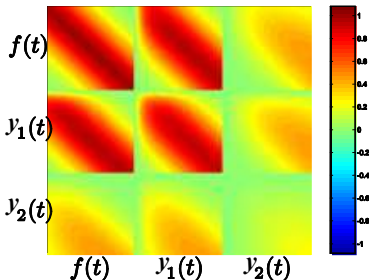
Covariance for Transcription Model

RBF 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 $x_1(t)$, $x_2(t)$ 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

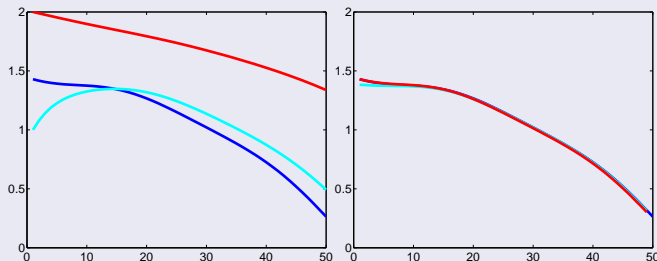


Figure: *Left:* joint samples from the transcription covariance, *blue:* $f(t)$, *cyan:* $y_1(t)$ and *red:* $y_2(t)$. *Right:* numerical solution for $f(t)$ of the differential equation from $y_1(t)$ and $y_2(t)$ (blue and cyan). True $f(t)$ included for comparison.

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

gpsimTest

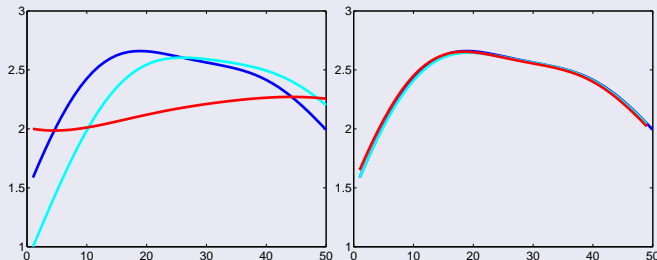


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Joint Sampling of $y(t)$ and $f(t)$ from Covariance

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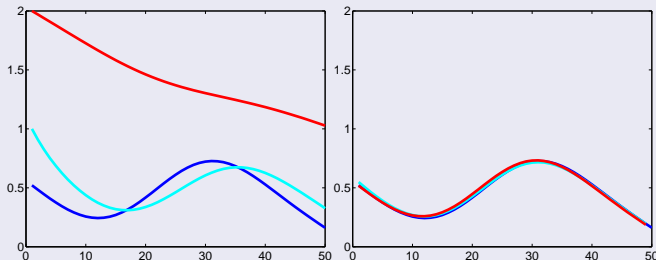


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Artificial Data

Toy Problem

- Results from an artificial data set.
- We used a 'known TFC' and derived six 'mRNA profiles'.
 - Known TFC composed of three Gaussian basis functions.
 - mRNA profiles derived analytically.
- Fourteen subsamples were taken and corrupted by noise.
- This 'data' was then used to:
 - Learn decays, sensitivities and basal transcription rates.
 - Infer a posterior distribution over the missing TFC.

Artificial Data Results

demToyProblem1

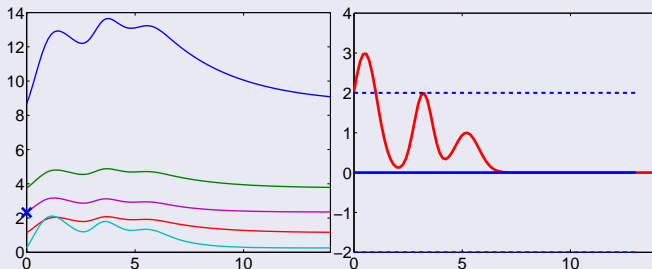


Figure: *Left:* The TFC, $f(t)$, which drives the system. *Middle:* Five gene mRNA concentration profiles each obtained by using different parameter sets $\{B_i, S_i, D_i\}_{i=1}^5$ (lines) along with noise corrupted 'data'. *Right:* The inferred TFC (with error bars).

Artificial Data Results

demToyProblem1

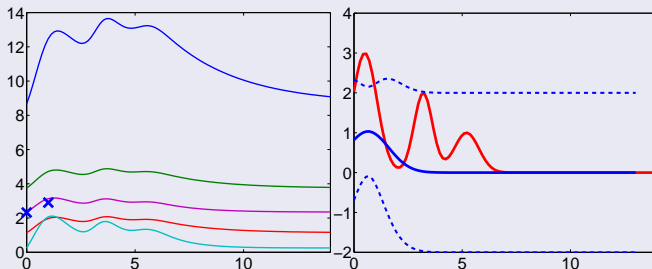


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Artificial Data Results

demToyProblem1

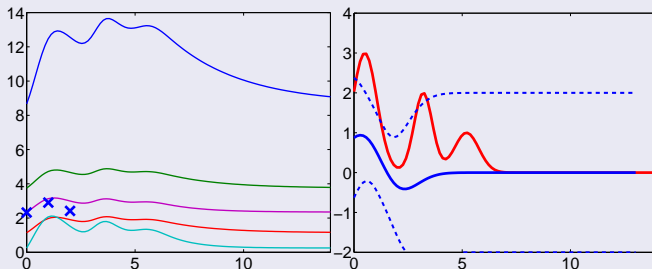


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Artificial Data Results

demToyProblem1

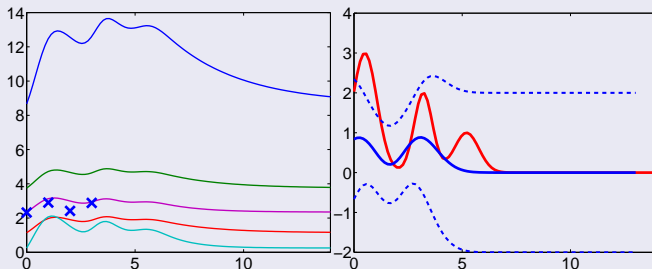


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demToyProblem1

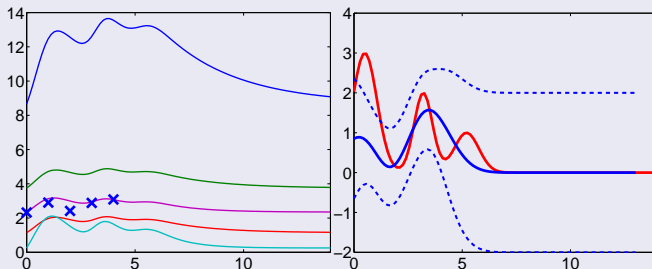


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Artificial Data Results

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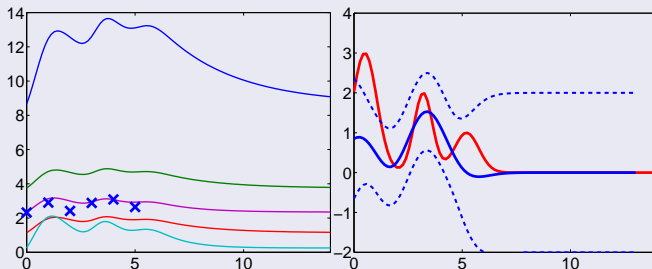


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Artificial Data Results

demToyProblem1

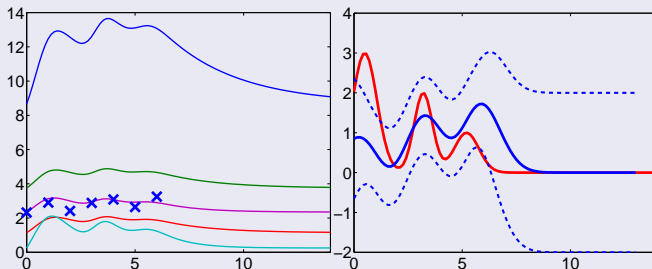


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Artificial Data Results

demToyProblem1

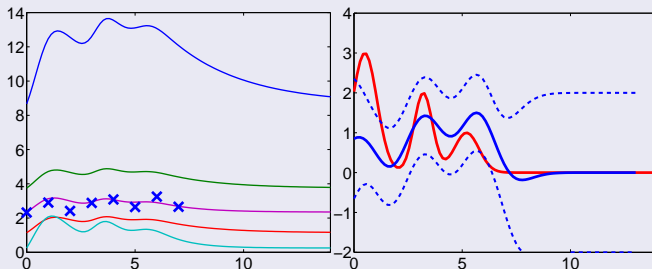


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demToyProblem1

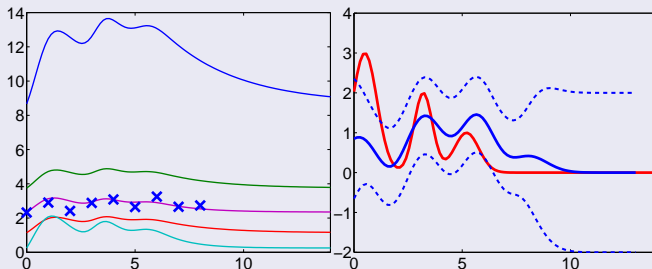


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Artificial Data Results

demToyProblem1

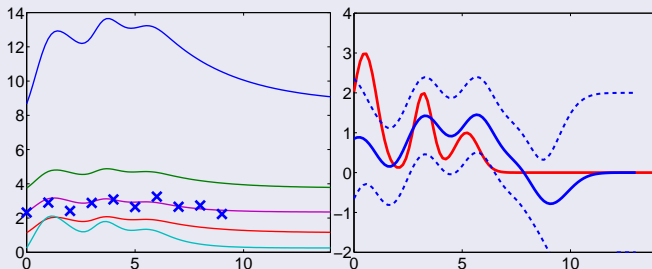


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demToyProblem1

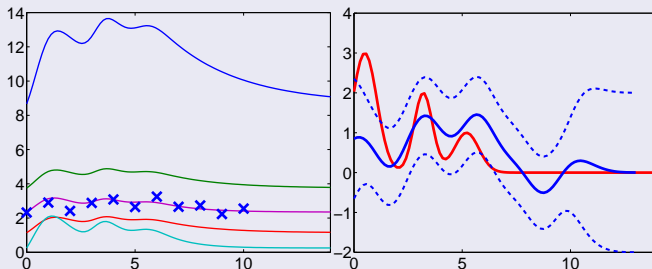


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Artificial Data Results

demToyProblem1

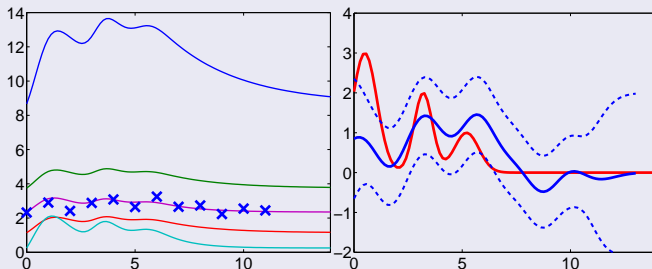


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demToyProblem1

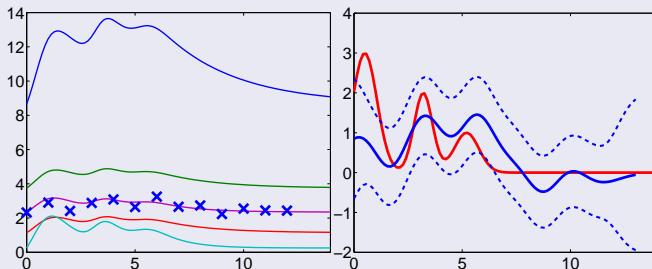


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Artificial Data Results

demToyProblem1

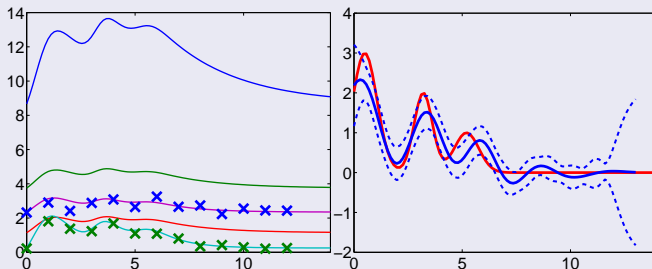


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Artificial Data Results

demToyProblem1

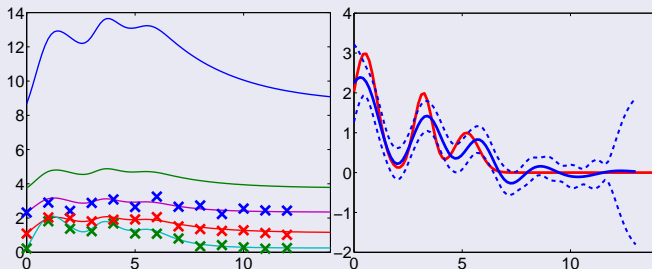


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Artificial Data Results

demToyProblem1

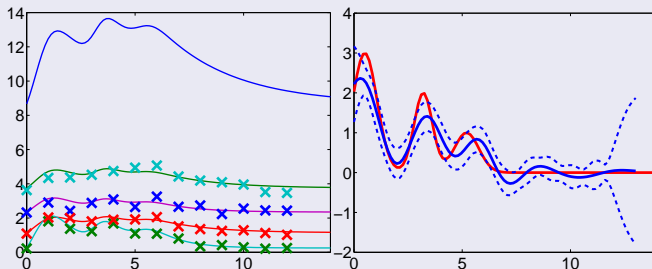


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Artificial Data Results

demToyProblem1

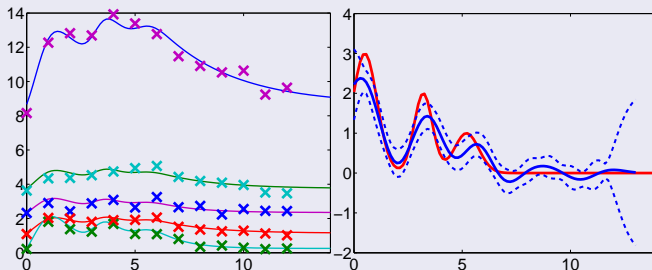


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Results

Linear System

- Recently published biological data set studied using linear response model by Barenco et al. (2006).
- Study focused on the tumour suppressor protein p53.
- mRNA abundance measured for five targets: *DDB2*, *p21*, *SESN1/hPA26*, *BIK* and *TNFRSF10b*.
- Quadratic interpolation for the mRNA production rates to obtain gradients.
- They used MCMC sampling to obtain estimates of the model parameters B_j , S_j , D_j and $f(t)$.

Linear response analysis

Experimental Setup

- We analysed data using the linear response model.
- Raw data was processed using the mmgMOS model of Liu et al. (2005) which provides variance as well as expression level.
- We present posterior distribution over TFCs.
- Results of inference on the values of the hyperparameters B_j , S_j and D_j .
 - Samples from the posterior distribution were obtained using Hybrid Monte Carlo (see e.g. Neal, 1996).

Linear Response Results

demBarenco1

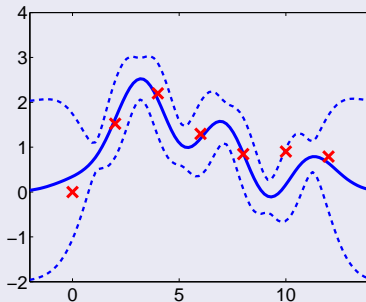


Figure: Predicted protein concentration for p53. Solid line is mean, dashed lines 95% credibility intervals. The prediction of (Barenco et al., 2006) was pointwise and is shown as crosses.

Results — Transcription Rates

Estimation of Equation Parameters demBarenco1

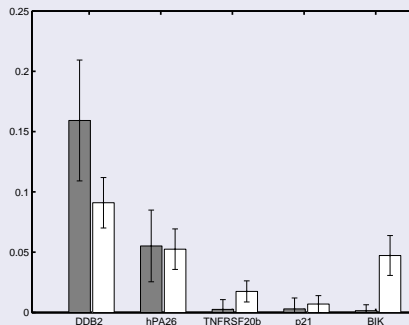


Figure: Basal transcription rates. Our results (black) compared with Barenco et al. (2006) (white).

Results — Transcription Rates

Estimation of Equation Parameters demBarenco1

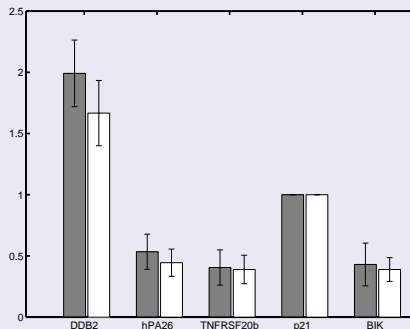


Figure: Sensitivities. Our results (black) compared with Barenco et al. (2006) (white).

Results — Transcription Rates

Estimation of Equation Parameters demBarenco1

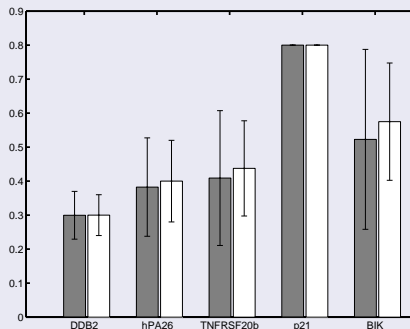


Figure: Decays. Our results (black) compared with Barenco et al. (2006) (white).

Linear Response Discussion

GP Results

- Note oscillatory behaviour, possible artifact of RBF covariance Rasmussen and Williams (see page 123 in 2006).
- Results are in good accordance with the results obtained by Barenco et al..
- Differences in estimates of the basal transcription rates probably due to:
 - different methods used for probe-level processing of the microarray data.
 - Our failure to constrain $f(0) = 0$.
- Our results take about 13 minutes to produce Barenco et al. required 10 million iterations of Monte Carlo.

Non-linear Response Model

More Realistic Response

- Transcription factor concentrations are positive, but direct samples from a GP will not be.
- Linear models don't account for saturation.
- *Solution:* model response using a positive nonlinear function.

Formalism

Non-linear Response

- Introduce a non-linearity $g(\cdot)$ parameterised by θ_j

$$\frac{dx_j}{dt} = B_j + g(f(t), \theta_j) - D_j x_j$$
$$x_j(t) = \frac{B_j}{D_j} + \exp(-D_j t) \int_0^t du g(f(u), \theta_j) \exp(D_j u) .$$

- The induced distribution of $x_j(t)$ is no longer a GP.
- Derive the functional gradient and learn a MAP solution for $f(t)$.
- Also compute Hessian so we can approximate the marginal likelihood.

Example: linear response

Using non-RBF kernels

- Start by taking $g(\cdot)$ to be linear.
- Provides 'sanity check' and allows arbitrary covariance functions.
- Avoids double numerical integral that would normally be required.

Response Results

demBarencoMap1, demBarencoMap2

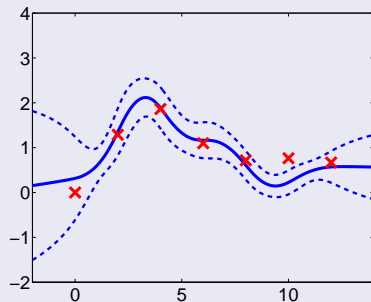
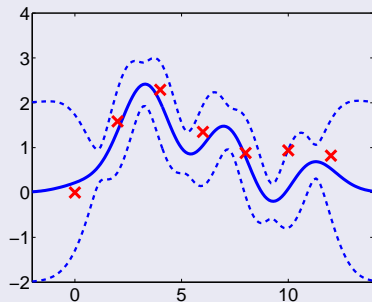


Figure: *Left:* RBF prior on f (log likelihood -101.4); *Right:* MLP prior on f (log likelihood -105.6).

Non-linear response analysis

Non-linear responses

- Exponential response model (constrains protein concentrations positive).
- $\log(1 + \exp(f))$ response model.
- $\frac{3}{1+\exp(-f)}$
- Inferred MAP solutions for the latent function f are plotted below.

exp(\cdot) Response Results

demBarencoMap3, demBarencoMap4

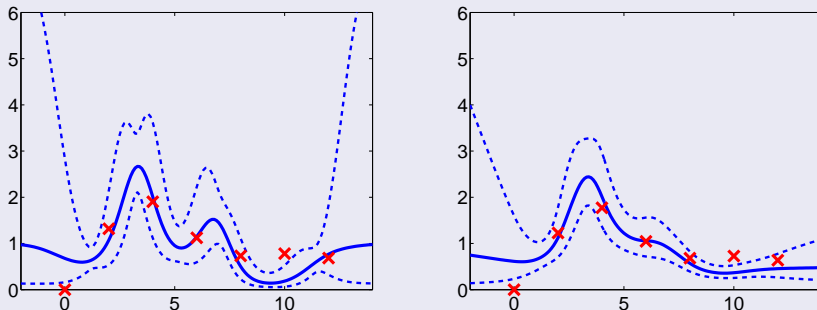


Figure: *Left:* shows results of using a squared exponential prior covariance on f (log likelihood -100.6); *Right:* shows results of using an MLP prior covariance on f (log likelihood -106.4).

$\log(1 + \exp(f))$ Response Results

demBarencoMap5, demBarencoMap6

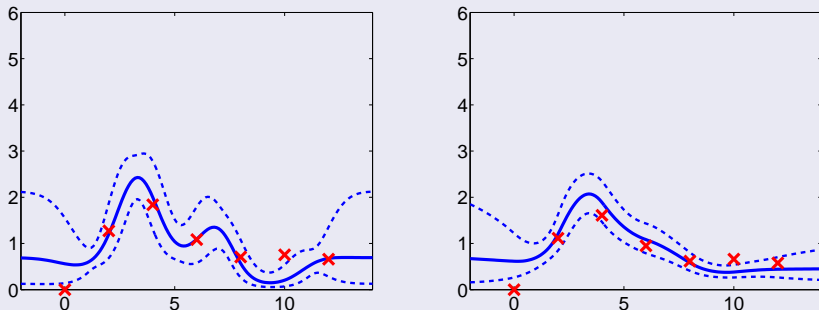


Figure: *Left:* shows results of using a squared exponential prior covariance on f (log likelihood -100.9); *Right:* shows results of using an MLP prior covariance on f (log likelihood -110.0).

$\frac{3}{1+\exp(-f)}$ Response Results

demBarencoMap7, demBarencoMap8

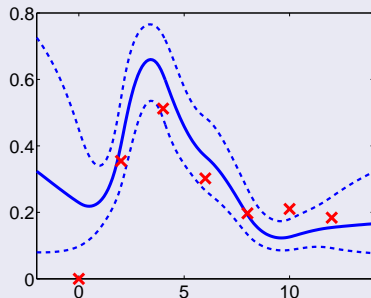
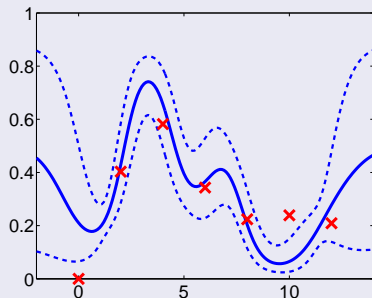


Figure: *Left:* shows results of using a squared exponential prior covariance on f (log likelihood -104.1); *Right:* shows results of using an MLP prior covariance on f (log likelihood -111.2).

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).
- Expect to extend it to systems with *multiple transcription factors*.

Summary

PUMA: Propagation of Uncertainty in Microarray Analysis

- Level of Noise in the Array can be Assesed (gMOS methods).
- Probabilistic Models can:
 - Improve selection of over-expressed genes (PPLR) — Appendix
 - Clean up gene expression profiles (NPPCA) — Appendix
- Simple (log-linear) probabilistic models can be used with network connectivity data to
 - To infer *genome wide* transcription factor activities (chipdyno).
 - To infer *genome wide* transcription factor protein 'concentrations' (chipvar).
- Gaussian processes & differential equations for complex interactions.
- And finally ...

Acknowledgements

Team:

- Principal Investigators
 - Neil Lawrence and Magnus Rattray
- gMOS family of Methods and PPLR
 - Xuejun Liu and Marta Milo
- Uncertainty Propagation through PCA
 - Marta Milo and Guido Sanguinetti
- Inference of Transcription Factor Activities
 - Guido Sanguinetti and **3 year RA Position Available!!**
- BBSRC award “Improved Processing of Microarray Data Using Probabilistic Models”.

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Differential Gene Expression

Probability of Positive Log Ratio(Liu et al., 2006)

- Differential gene expression is normally assessed with log ratios of gene expression.

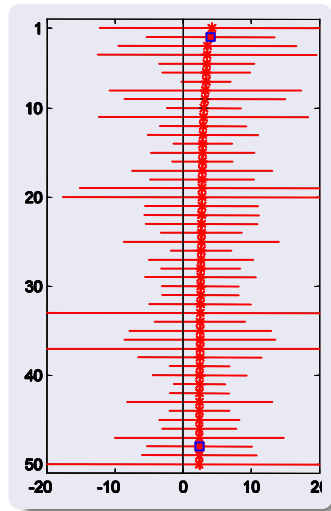
$$r_{ij} = \log \frac{s_i}{s_j}$$

- This measure is very sensitive to noise at low expression levels.
- Use variance of expression to obtain Probability of Positive Log Ratio (PPLR).

PPLR Results

Golden spike-in dataset (Choe et al., 2005)

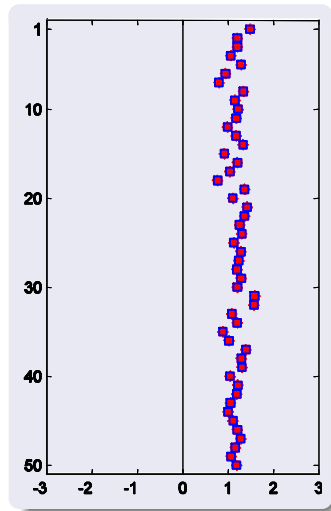
- Ranking (y-axis) against log ratio (x-axis) for.
 - **Ranking by Expected Log Ratio.**
 - Ranking by PPLR.
- Red stars indicate expected log ratio.
- Red lines indicate error bars.
- Blue squares indicates genes that were spiked-in.



PPLR Results

Golden spike-in dataset (Choe et al., 2005)

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 - Ranking by Expected Log Ratio.
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Cleaning up Profiles

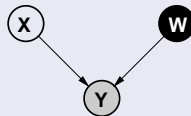
Converting Noisy Profiles to Clean

- If we can 'clean up' the profiles we can use in other methods.
- Construct a probabilistic model for the data and corruption process.
- Work with posterior distribution over cleaned up profile.
- We designed a heteroschedastic Probabilistic PCA for doing this (Sanguinetti et al., 2005).

Probabilistic PCA

Probabilistic PCA

- Define *linear-Gaussian relationship* between latent variables and data.
- Latent variable approach:
 - Define Gaussian prior over *latent space*, \mathbf{X} .
 - Integrate out *latent variables*.



$$p(\mathbf{Y}|\mathbf{X}, \mathbf{W}) = \prod_{i=1}^n N(\mathbf{y}_{i,:} | \mathbf{W}\mathbf{x}_{i,:} + \boldsymbol{\mu}, \sigma^2 \mathbf{I})$$

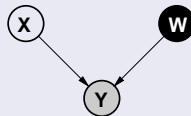
$$p(\mathbf{X}) = \prod_{i=1}^n N(\mathbf{x}_{i,:} | \mathbf{0}, \mathbf{I})$$

$$p(\mathbf{Y}|\mathbf{W}) = \prod_{i=1}^n N(\mathbf{y}_{i,:} | \boldsymbol{\mu}, \mathbf{W}\mathbf{W}^T + \sigma^2 \mathbf{I})$$

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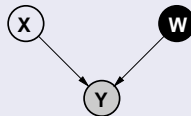
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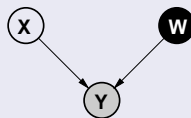
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Probabilistic PCA

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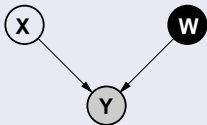
$$p(\mathbf{Y}|\mathbf{X}, \mathbf{W}) = \prod_{i=1}^n N(\mathbf{y}_{i,:} | \mathbf{W}\mathbf{x}_{i,:} + \boldsymbol{\mu}, \sigma^2 \mathbf{I})$$

$$p(\mathbf{X}) = \prod_{i=1}^n N(\mathbf{x}_{i,:} | \mathbf{0}, \mathbf{I})$$

$$p(\mathbf{Y}|\mathbf{W}) = \prod_{i=1}^n N(\mathbf{y}_{i,:} | \boldsymbol{\mu}, \mathbf{W}\mathbf{W}^T + \sigma^2 \mathbf{I})$$

Probabilistic PCA II

Probabilistic PCA Max. Likelihood Soln (Tipping and Bishop, 1999)



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Probabilistic PCA II

Probabilistic PCA Max. Likelihood Soln (Tipping and Bishop, 1999)

$$p(\mathbf{Y}|\mathbf{W}) = \prod_{i=1}^n N(\mathbf{y}_{i,:}|\boldsymbol{\mu}, \mathbf{C}), \quad \mathbf{C} = \mathbf{W}\mathbf{W}^T + \sigma^2\mathbf{I}$$

$$\log p(\mathbf{Y}|\mathbf{W}) = -\frac{n}{2} \log |\mathbf{C}| - \frac{1}{2} \text{tr}(\mathbf{C}^{-1} \tilde{\mathbf{Y}}^T \tilde{\mathbf{Y}}) + \text{const.}$$

Where $\tilde{\mathbf{Y}}$ is the matrix \mathbf{Y} with $\boldsymbol{\mu}$ removed. If \mathbf{U}_q are first q principal eigenvectors of $n^{-1} \tilde{\mathbf{Y}}^T \tilde{\mathbf{Y}}$ and the corresponding eigenvalues are Λ_q ,

$$\mathbf{W} = \mathbf{U}_q \mathbf{L} \mathbf{V}^T, \quad \mathbf{L} = (\Lambda_q - \sigma^2 \mathbf{I})^{\frac{1}{2}}$$

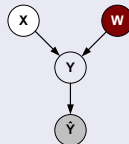
where \mathbf{V} is an arbitrary rotation matrix.

$$\boldsymbol{\mu} = n^{-1} \sum_{i=1}^n \mathbf{y}_{i,:}$$

Heteroschedastic Probabilistic PCA

Heteroschedastic PPCA

- Define *linear-Gaussian relationship* between latent variables and \mathbf{Y} .
- Define a *further* Gaussian relationship to corrupted profiles $\hat{\mathbf{Y}}$.
 - \mathbf{D}_i is a diagonal matrix of estimated variances.
- Integrate out *latent variables*.



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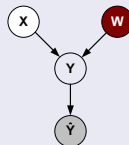
$$p(\hat{\mathbf{y}}_{i,:} | \mathbf{y}_{i,:}) = N(\hat{\mathbf{y}}_{i,:} | \mathbf{y}_{i,:}, \mathbf{D}_i)$$

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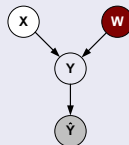
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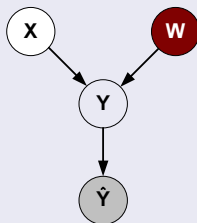
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Heteroschedastic PPCA Max. Likelihood Soln (Sanguinetti et al., 2005)



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- Can no longer solve via eigenvalue problem.
- We use an EM algorithm.
 - A major problem is the strong correlation between \mathbf{W} and $\boldsymbol{\mu}$.
 - We use some tricks to speed up convergence.
- Software available in R and MATLAB.

Heteroschedastic PPCA Results

Mouse Cochlear Dataset

- Data from a conditionally immortal cell line extracted from mouse cochlear epithelial cells.
- Twelve samples from 14 days of differentiation after extraction at E13.5 (Rivolta et al., 2002).
- Experimental setup:
 - Perform HPPCA/PCA on the data.
 - Extract 50 genes most associated with 2nd principal component
 - Cluster original profiles and reconstructed profiles.

Heteroschedastic PPCA Results

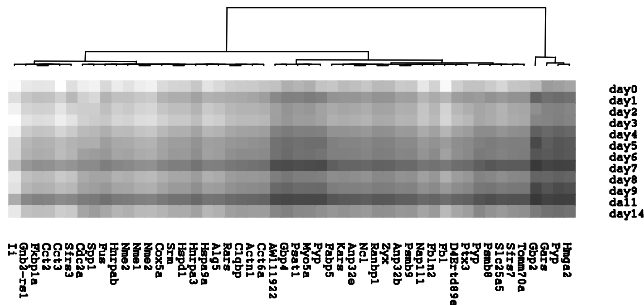


Figure: Hierarchical Clustering on Corrected Profiles.

Heteroschedastic PPCA Results

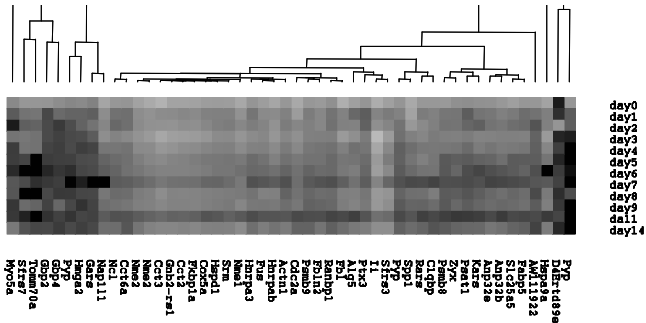


Figure: Hierarchical Clustering on Uncorrected Profiles.

Heteroschedastic PPCA Results

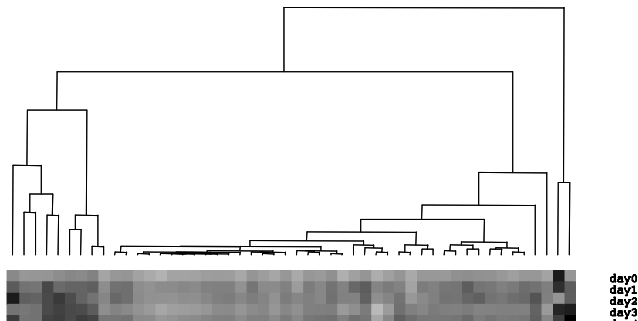


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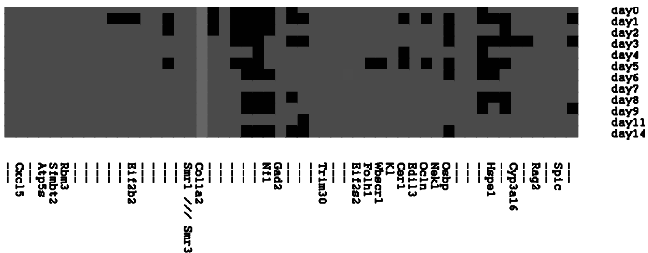


Figure: Hierarchical Clustering on genes selected by normal PCA.

Heteroschedastic PPCA Results

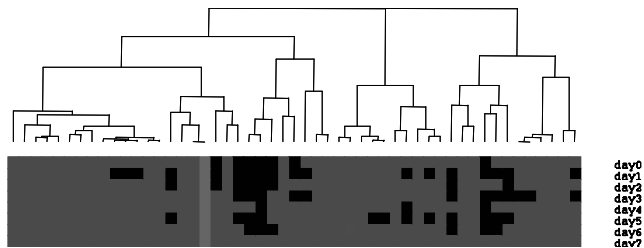


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