PUMA: Propagation of Uncertainty in Microarray Analysis

Low Level and High Level Processing of Microarrays with Probabilistic Models

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University of Manchester

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Outline

1. Microarray Processing
   - Affymetrix GeneChip Arrays
   - Detecting Differential Gene Expression with PPLR
   - Tidying up Profiles with Probabilistic PCA
2. Transcription Factors
   - ChIP-microarray and Transcription Factor Activities
   - Transcription Factor Concentrations
   - From Simple to Complex Models
3. 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.man.ac.uk/resources/puma/.
- Additional project homepage
  - http://www.dcs.shef.ac.uk/~neil/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 (Sheffield), Magnus Rattray (Manchester)
  - **Fellows/Post-docs**: Marta Milo (Sheffield), Guido Sanguinetti (Sheffield)
  - **PhD Students**: Xuejun Liu (Manchester), Richard Pearson (Manchester)

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

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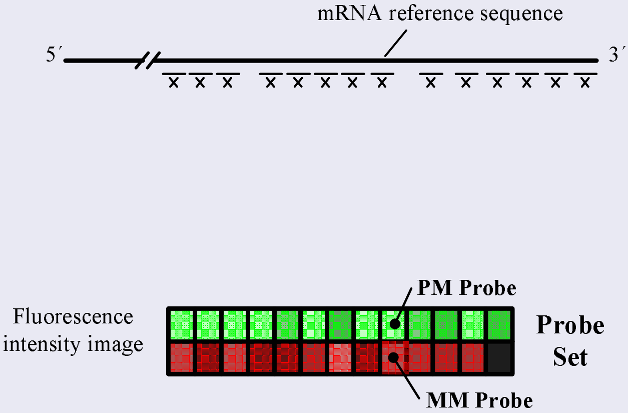
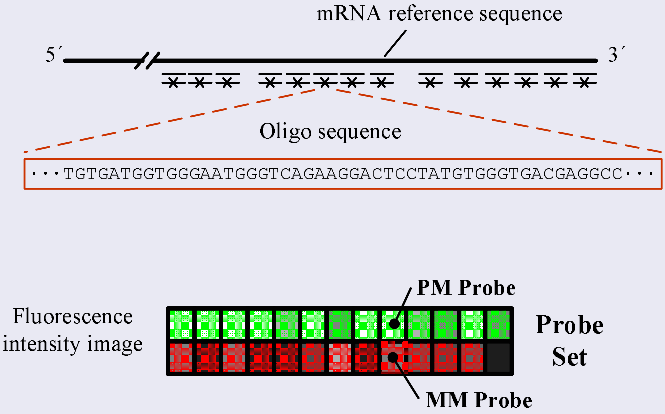


Figure: Affymetrix array schematic

Affymetrix Arrays

Photolithography and Combinatorial Chemistry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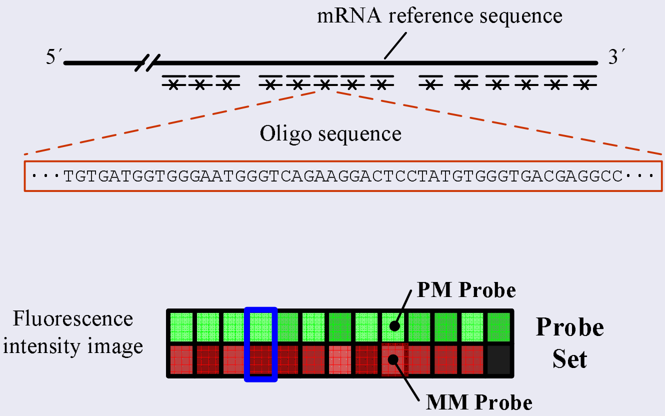
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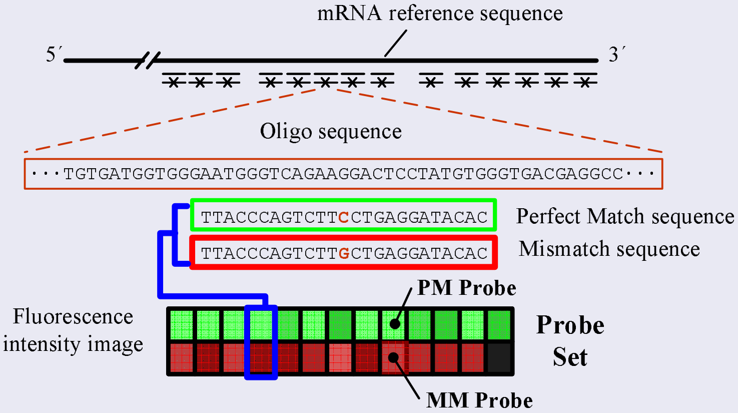
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gMOS Family of Methods

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

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

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

$$y_j = m_j + s_j$$

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

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

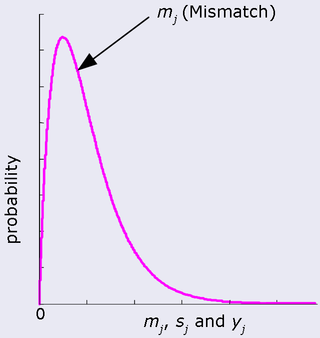

Figure: PDF of m_j, s_j and the implied distribution for y_j.

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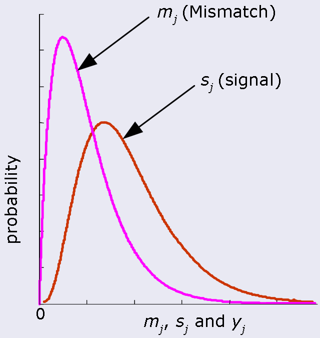

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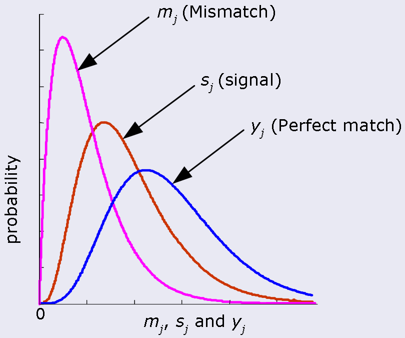

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gMOS

Inferring the Signal

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

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

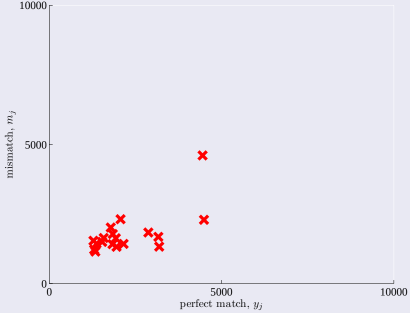
- Use resulting $\hat{\alpha}$ and $\hat{b}$ to give distribution over s_j.

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

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 $b_j \sim \mathrm{Ga}\left(b_j | c, d\right)$ and marginalise.



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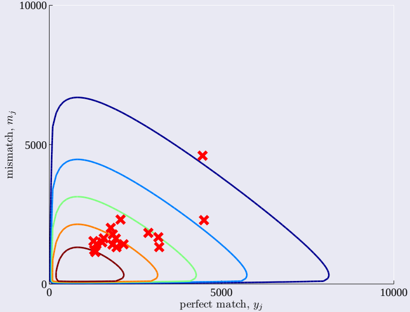

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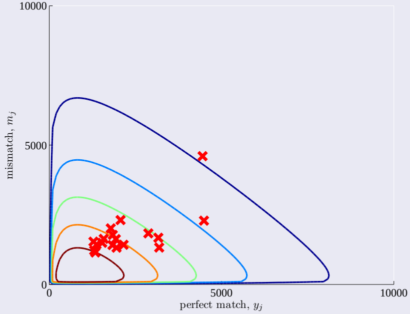

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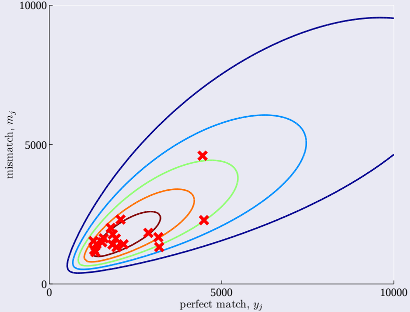

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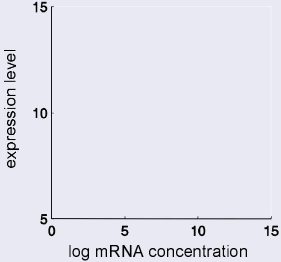
Specific Binding to Mismatch

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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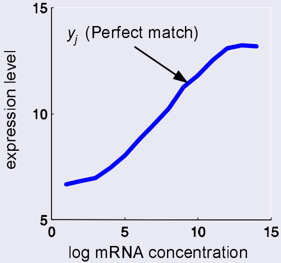

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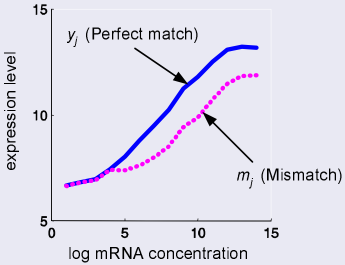

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Specific Binding and Multiple Arrays

multi-mgMOS

- Specific Binding to MM probe:
  - Introduce parameter ϕ and assume

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

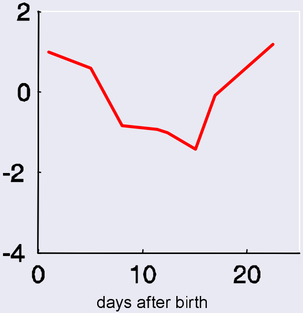
  - Log normal prior for ϕ and seek a MAP solution.
- Multiple arrays:
  - Still take $b_j \sim \text{Ga}\left(b_j|c, d\right)$ but **share c and d parameters across chips.**

Mouse Data Set

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

Mouse back skin mRNA expression profile for Dab2 [Lin et al., 2004].

	Root Mean Square Error	
RMSE	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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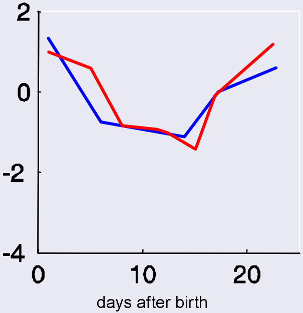

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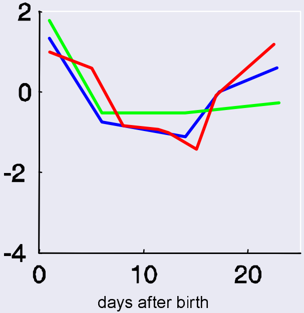

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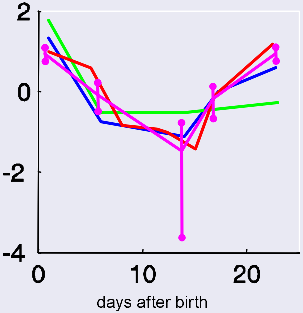

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Differential Gene Expression

Probability of Positive Log Ratio[Liu et al., 2006]

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

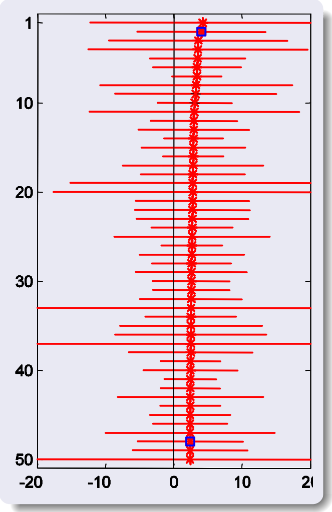
$$r_{ij} = \log \frac{s_i}{s_j}$$

- This measure is very sensitive to noise at low expresion 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.



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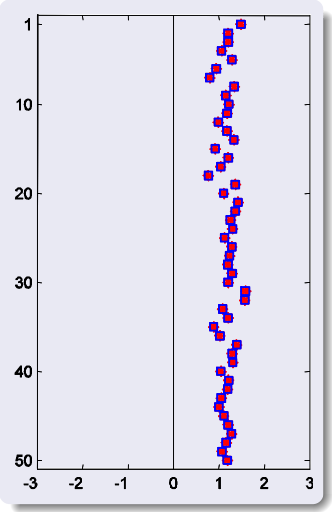


Cleaning up Profiles

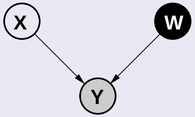
Converting Noisy Profiles to Clean

- 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*, **X**.
  - Integrate out *latent variables*.



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

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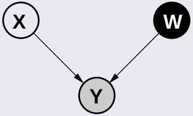

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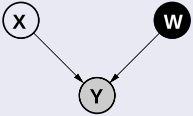

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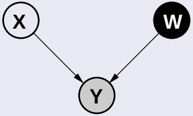

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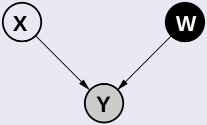
Probabilistic PCA II

Probabilistic PCA Max. Likelihood Soln [Tipping and Bishop, 1999]



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

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

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

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

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.
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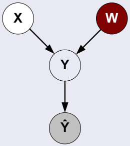

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$$p\left(\hat{\mathbf{y}}_{i,:}|\mathbf{y}_{i,:}\right) = N\left(\hat{\mathbf{y}}_{i,:}|\mathbf{y}_{i,:},\mathbf{D}_{i}\right)$$

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

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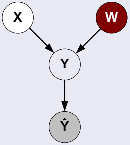


$$p\left(\mathbf{Y}|\mathbf{X},\mathbf{W}\right) = \prod_{i=1}^{n} N\left(\mathbf{y}_{i,:}|\mathbf{W}\mathbf{x}_{i,:}+\boldsymbol{\mu},\sigma^2\mathbf{I}\right)$$

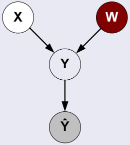
$$p\left(\hat{\mathbf{y}}_{i,:}|\mathbf{y}_{i,:}\right) = N\left(\hat{\mathbf{y}}_{i,:}|\mathbf{y}_{i,:},\mathbf{D}_i\right)$$

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

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*.



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

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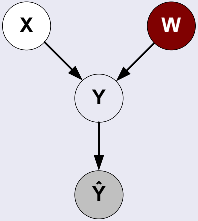
Heteroschedastic PPCA II

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 **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 imortal cell lin extracted from mouse cochlear epitheleal cells.
- Twelve samples from 14 days of differentiation after extration 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

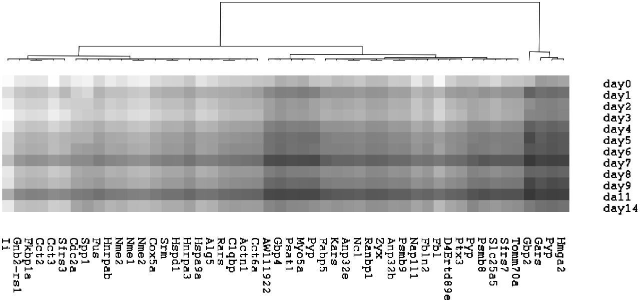


Figure: Hierarchical Clustering on Corrected Profiles.

Heteroschedastic PPCA Results

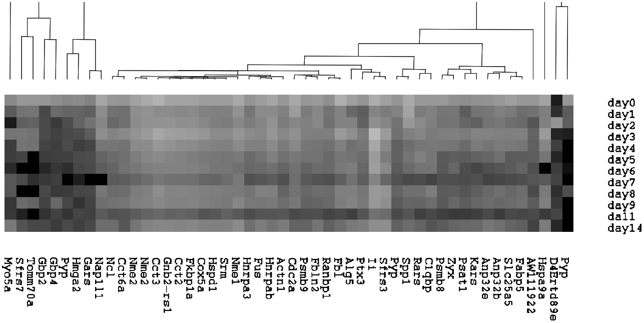
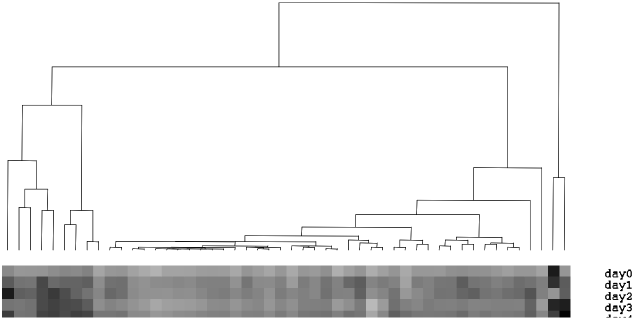


Figure: Hierarchical Clustering on Uncorrected Profiles.

Heteroschedastic PPCA Results



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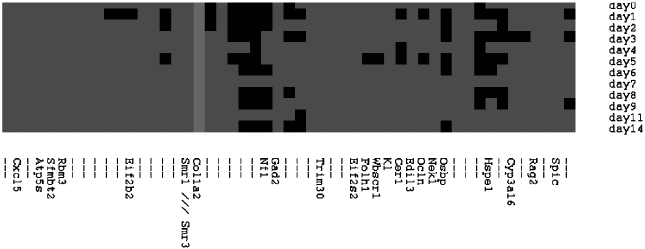
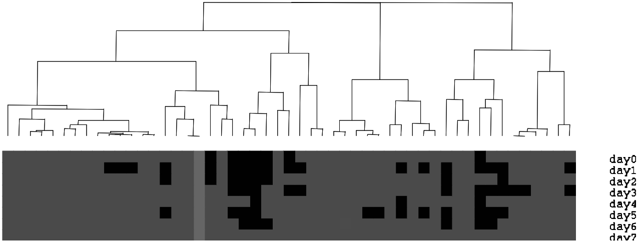


Figure: Hierarchical Clustering on genes selected by normal PCA.

Heteroschedastic PPCA Results



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Transcription Factor Activities

Inferring Activitiy 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 expresion is given by a linear relationship

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

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

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

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

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

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

Gene Specific TFAs

Associate TFAs to Genes [Sanguinetti et al., 2006]

- Intoduce gene specific TFAs,

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

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

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

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

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

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Temporal Continuity of TFAs

Time Course Experiments

- Introduce concept of temporal conitiuity with Gaussian distribution.

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

The temporal continuity, γ is between 0 and 1.

Temporal Continuity of TFAs II

Effect of γ

- When $\gamma = 0$ we recover

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

  which is equivalent to the original independent model.
- As $\gamma \rightarrow 1$ we recover

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

  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

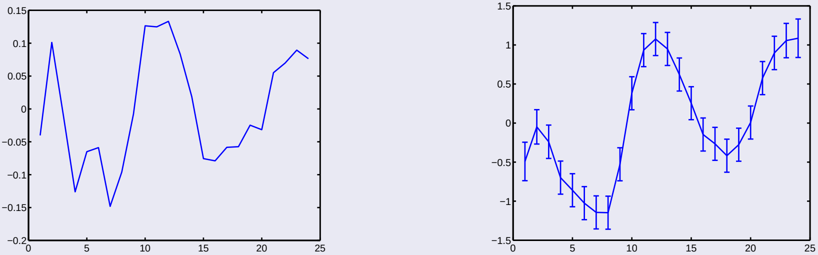


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA for averge of $\mathbf{B}_i$ across genes.

Results on TFAs II

Graphs of TFAs

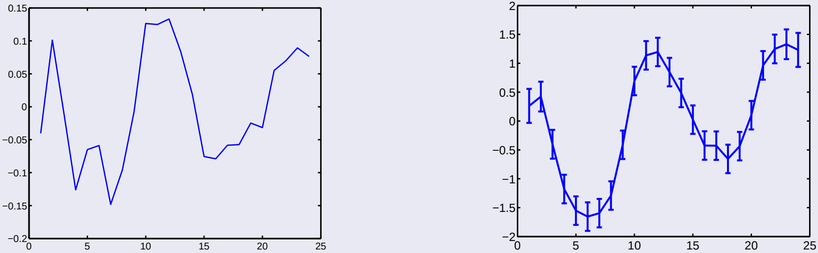


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA SCW11.

Results on TFAs II

Graphs of TFAs

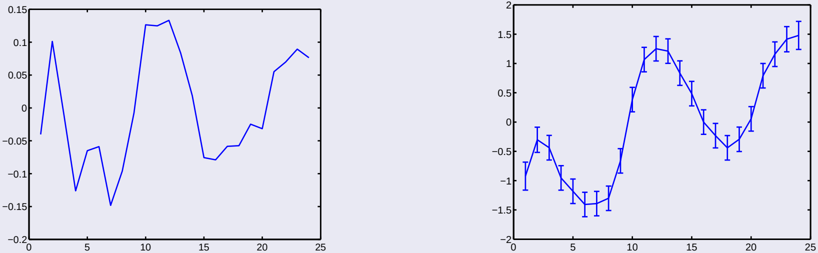


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA CTS1.

Results on TFAs II

Graphs of TFAs

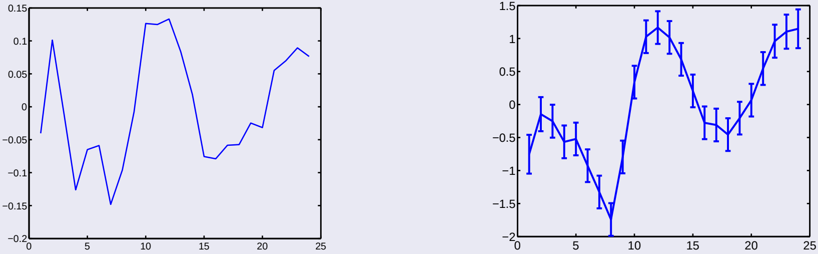


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA YER124C.

Results on TFAs II

Graphs of TFAs

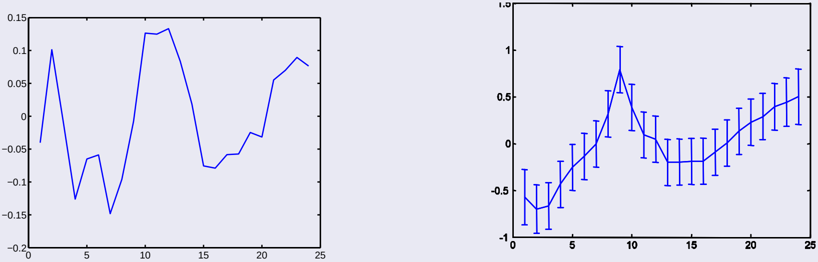


Figure: TFAs of ACE2 from the Spellman data. *Left:* TFA obtained by regression *Right:* gene specific TFA YKL51C.

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:

$$\mathbf{y}_i = \left(\mathbf{B} \odot \mathbf{X}\right) \mathbf{c}_t + \boldsymbol{\epsilon}_t$$

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

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

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

- Bayesian treatment of **c** and **B** through a variational approach.

TF Concentration Results

Concentration of ACE2

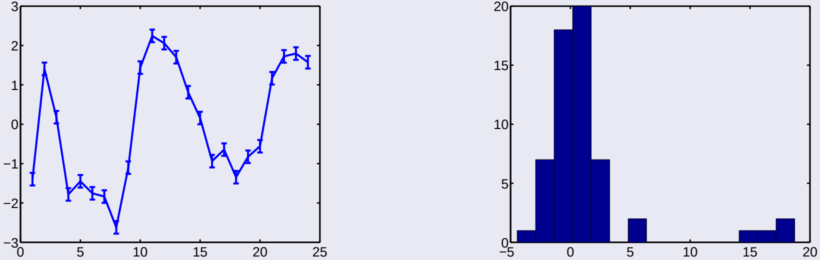


Figure: *Left:* concentration of ACE2 and *right*: effect of ACE2 on its target genes as a histogram.

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 CO data base.
  - CTS1 relationship is known.
  - DSE1 and DSE2 are involved in cell wall degradation causing daughter to seperate 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.
- Consider more complex model in the simple p53 network.

Differential Equation model

- Simple linear model differential equation model recently used by Barenco et al. [2006].
- They inferred transcription factor concentrations using Markov Chain Monte Carlo (10^7 iterations).
- We repeat their experiments with Gaussian processes.

Simple Linear Model

Linear model of regulation

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

where:

$y_i\left(t\right)$ — expression of the ith gene at time t.

$f\left(t\right)$ — 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:

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

If $f\left(t\right)$ is a zero mean Gaussian process then $y_i\left(t\right)$ 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

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

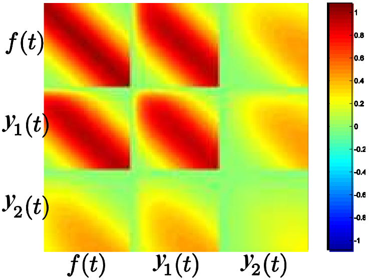
Covariance for Transcription Model

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

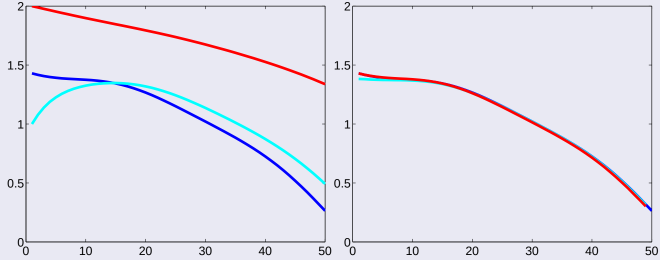


Figure: *Left*: joint samples from the transcription covariance, *blue*: $f(t)$, *cyan*: $y_1(t)$ and *red*: $y_2(t)$. *Right*: numerical solution for $f(t)$ of the differential equation from $y_1(t)$ and $y_2(t)$ (blue and cyan). True $f(t)$ included for comparison.

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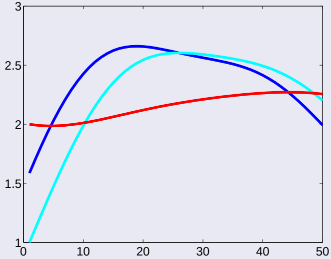

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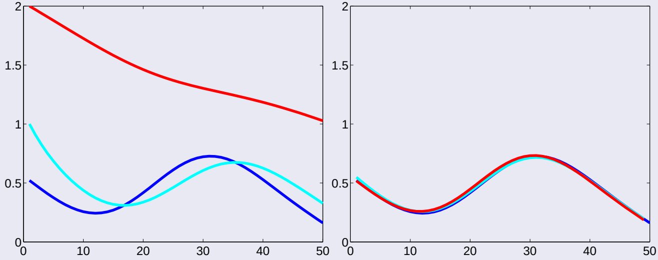

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Results — Transcription Rates

Estimation of Equation Parameters demBarenco1

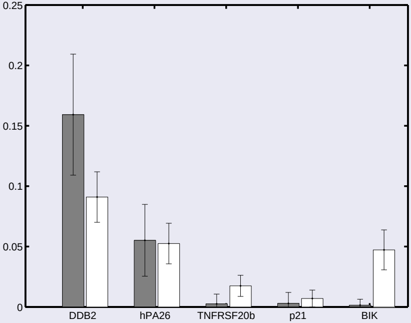


Figure: Basal transcription rates. Our results (black) compared with Barenco et al. [2006] (white).

Results — Transcription Rates

Estimation of Equation Parameters `demBarenco1`

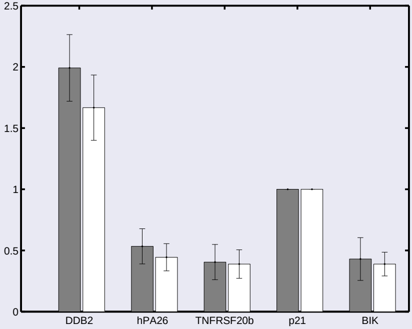


Figure: Sensitivities. Our results (black) compared with Barenco et al. [2006] (white).

Results — Transcription Rates

Estimation of Equation Parameters demBarenco1

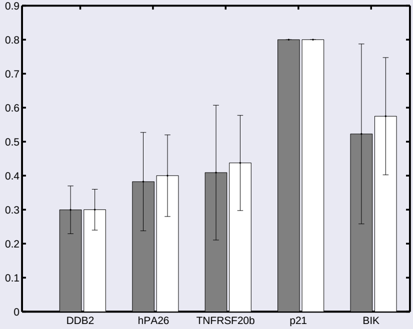
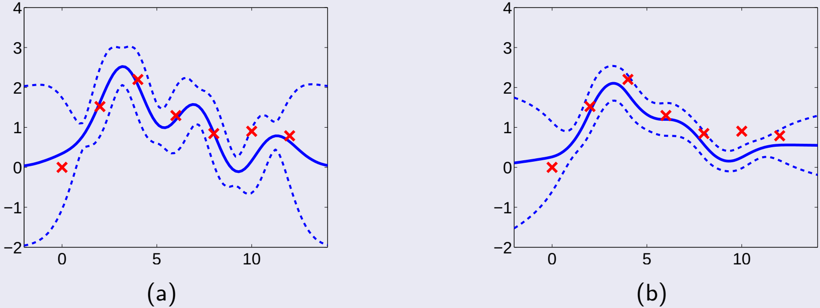


Figure: Decays. Our results (black) compared with Barenco et al. [2006] (white).

Results — Protein Concentration

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



(a)

(b)

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

Results — Positive Constrained

GP predictions in log space.

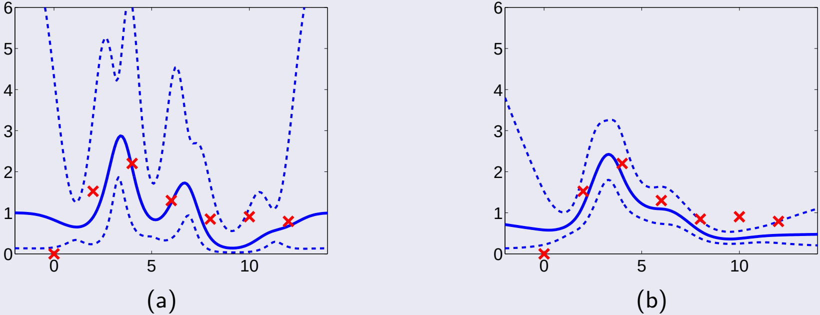


Figure: (a) RBF covariance function (b) MLP covariance function. Also included are results from Barenco et al. [2006] as crosses.

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*.
- Gives results in 13 minutes vs 10^7 Monte-Carlo iterations.

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).
  - Clean up gene expression profiles (NPPCA).
- 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 interations.
- And finally ...

Acknowledgements

Team:

- Prinicipal 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

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First Frame