Bringing Models to the Domain: Deploying Gaussian Processes in the Biological Sciences

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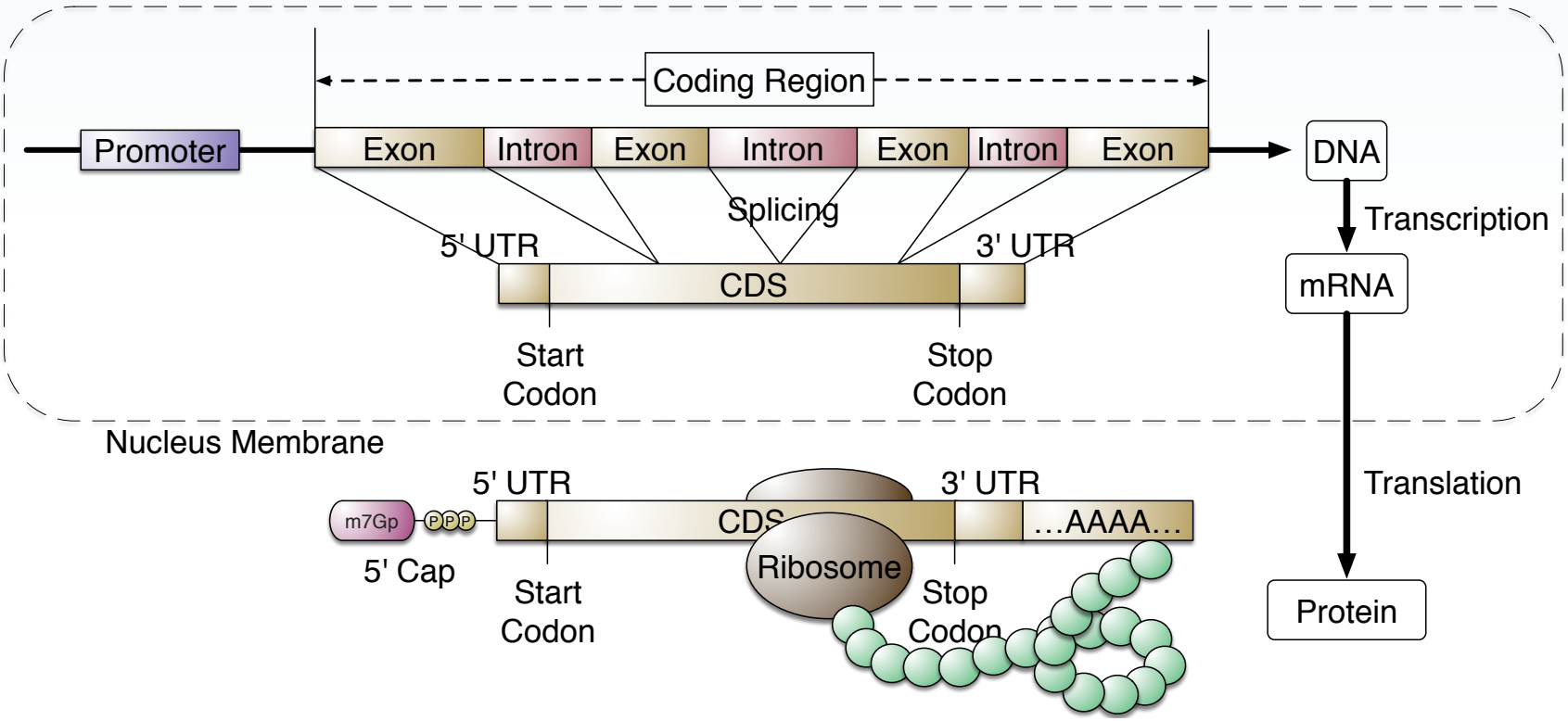
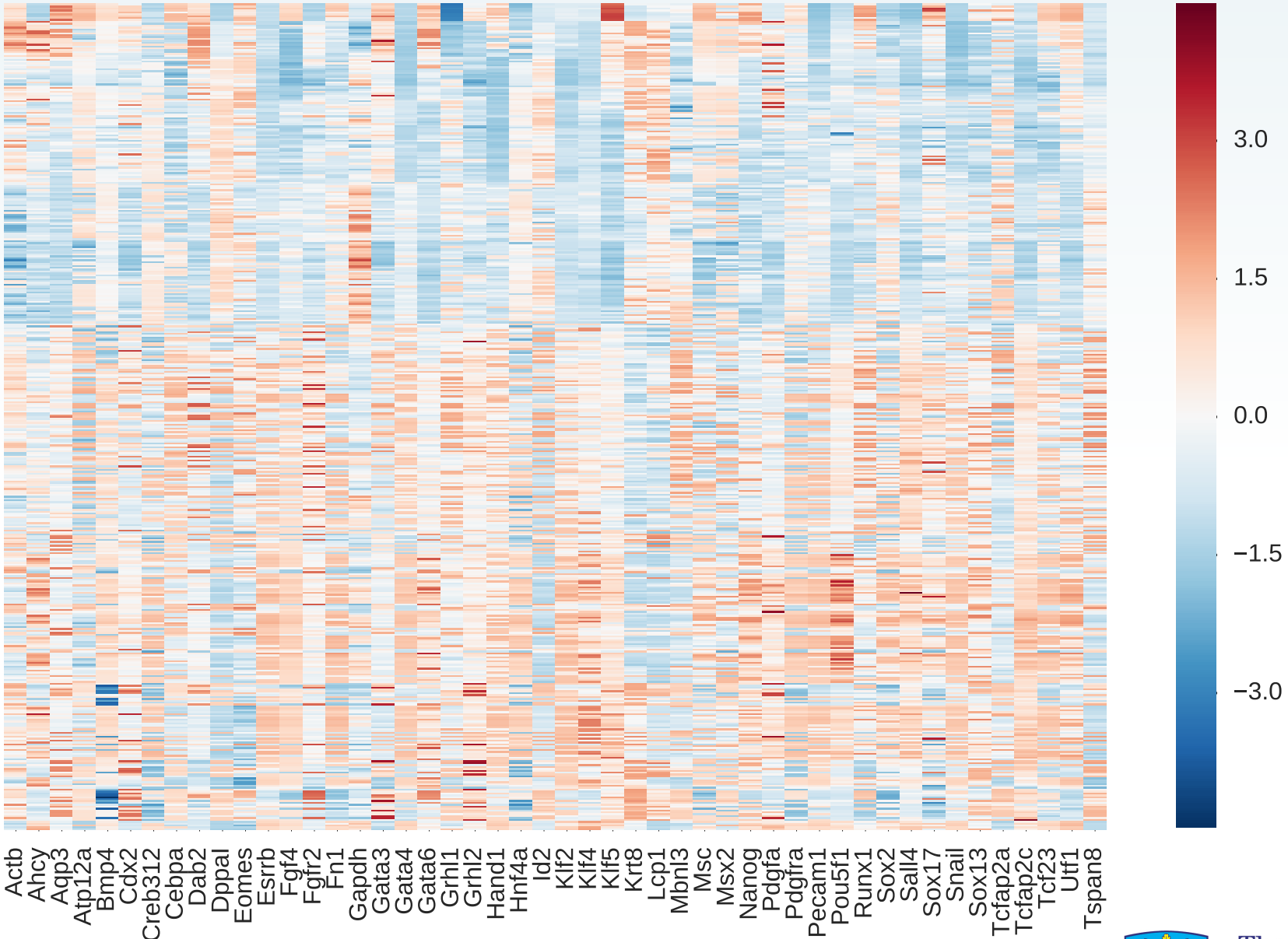
Gene Expression

From DNA to Proteins





[Guo et al., 2010]

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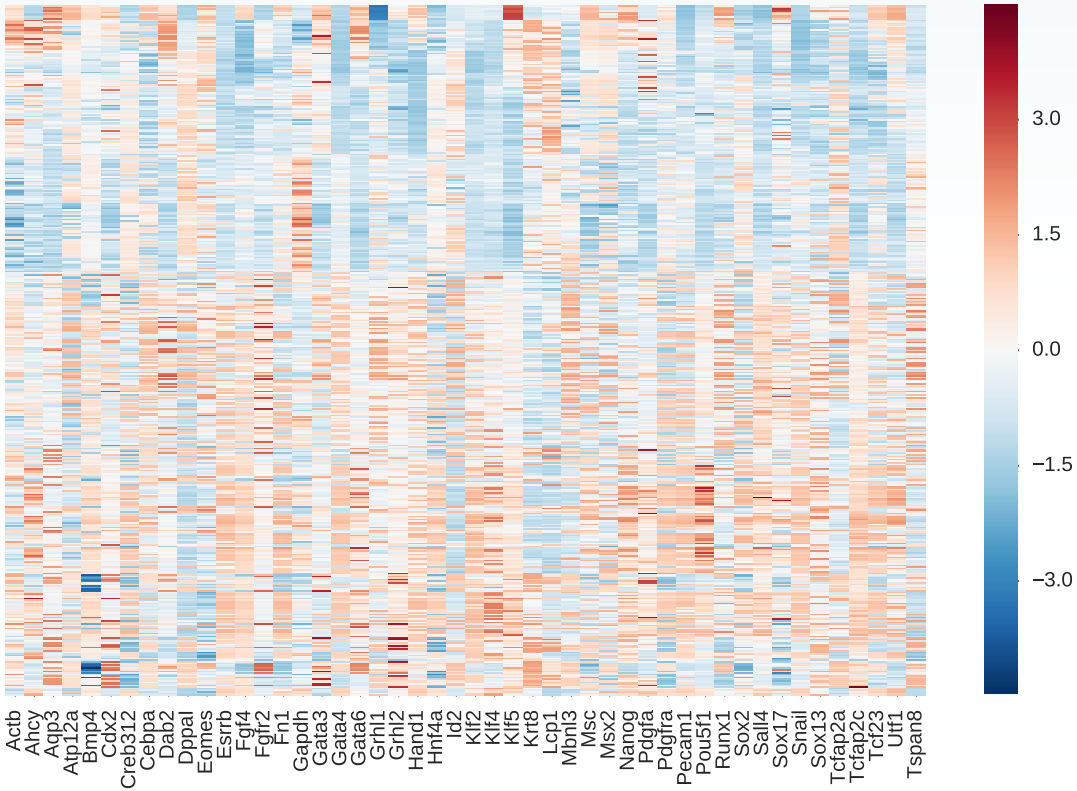
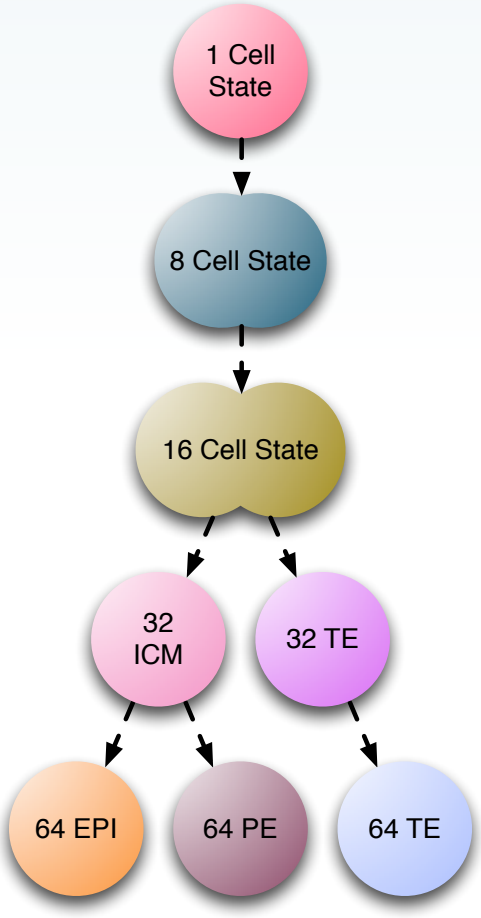
Intrinsic Signal Discovery: Pseudo Time





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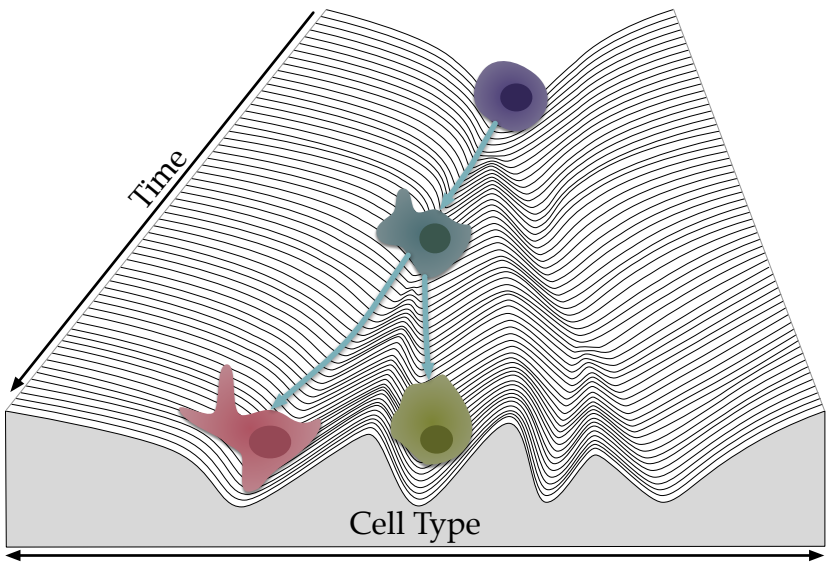
Pseudo Time Ordering: State of the Art

Two step approach:

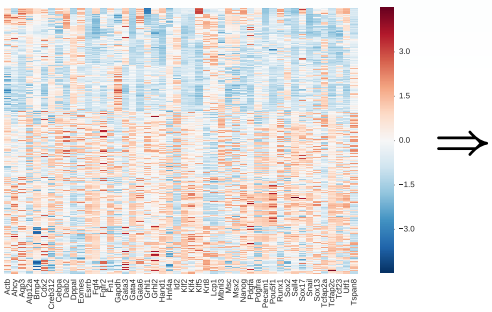
- Lower dimensional representation (usually 2D).
- Given Starting Cell.
- Find ordering in representation, following
  - Minimal spanning Tree (e.g. Monocle [Trapnell et al., 2014]).
  - K-Nearest-Neighbour graph (e.g. Wishbone [Setty et al., 2016]).
- (Post process ordering, smoothing, branching, shortcut detection etc.)

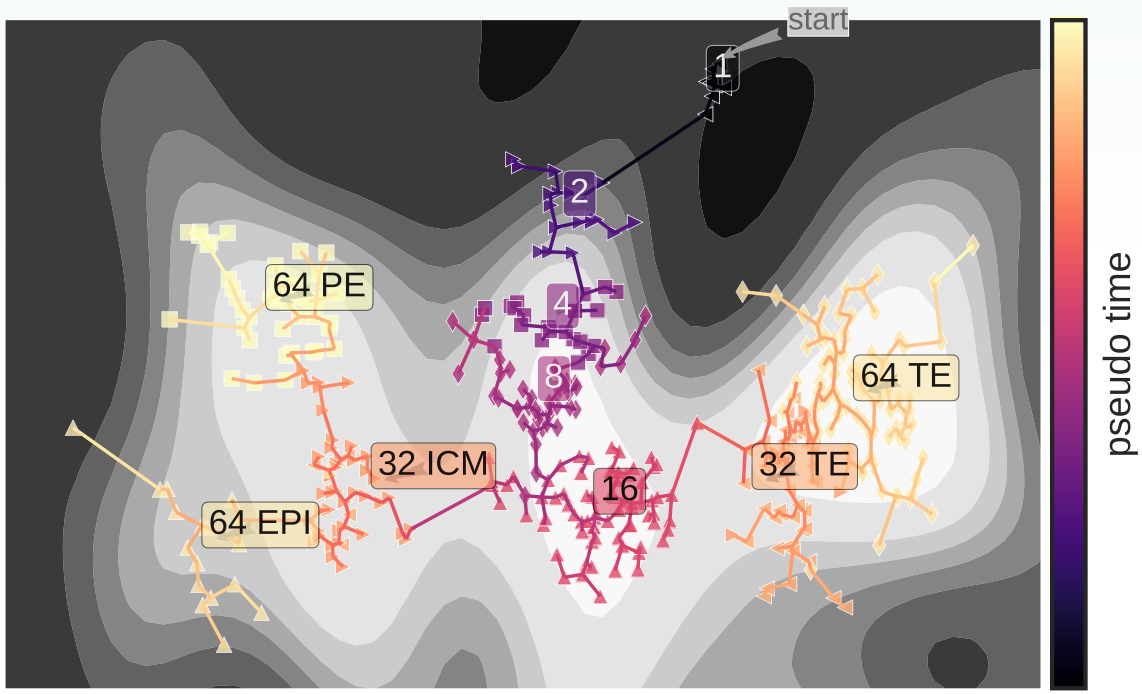
Landscape Learning

- Bayesian Gaussian Process Latent Variable Model (Probabilistic Landscape Modelling) [Titsias, 2009].
- Can be Interpreted as Probabilistic Waddington's Landscape [Waddington, 1966].
- Pairwise Distances in Landscape Distorted by Topography
- Correct Distances for Landscape Ridges and Hills.
- MST (or KNN) to Extract Pseudotime.



Topslam [Zwiessele and Lawrence, 2017]





Joint Modelling of Gene Subsets

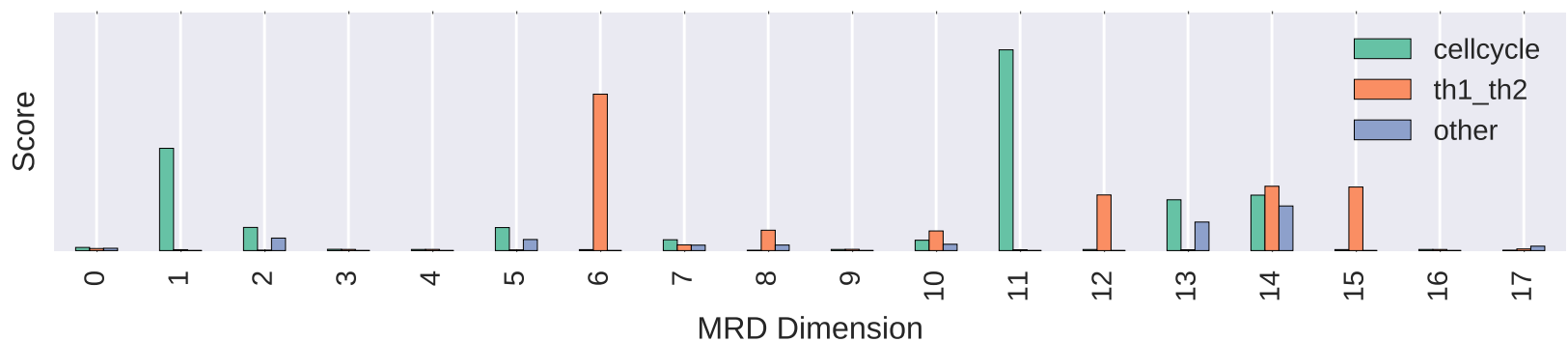
- In collaboration with Aleksandra Kolodziejczyk and Sarah Teichmann
- Singlecell RNASeq
- Naive Thelper to Th1 and Th2
- Samples mixed up during processing
- $\Rightarrow$ No reliable knowledge about time or differentiation state
- PCA (and others) don't reveal differentiation.

Data Cleanup through Prior Knowledge

MRD on gene subsets (similar [Buettner et al., 2015]).

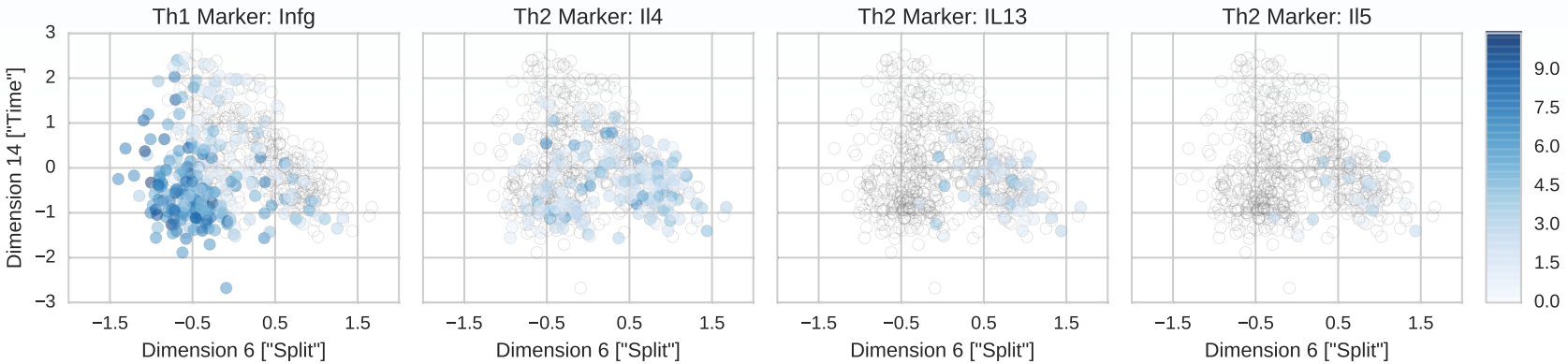
Define gene sets of interest:

Cell cycle related DE in bulk All other



Data Cleanup through Prior Knowledge

Time dimension vs. Split dimension:



Takehome

Pseudo Time Extraction

- Taking landscape into account improves pseudotime extraction.
- Prior knowledge for gene subset detection improves/allows for signal detection.

Takehome

Code

MRD and Bayesian GPLVM [GPy, 2012]:
`https://github.com/SheffieldML/GPy`

topslam (based on GPy): [Zwiessele and Lawrence, 2017]
`https://github.com/mzwiessele/topslam`

GPclust (based on GPy): [Lázaro-Gredilla et al., 2012]
`https://github.com/SheffieldML/GPclust`

GPfates (based on GPy) [Lönnberg et al., 2017]:
`https://github.com/Teichlab/GPfates`

Acknowledgements

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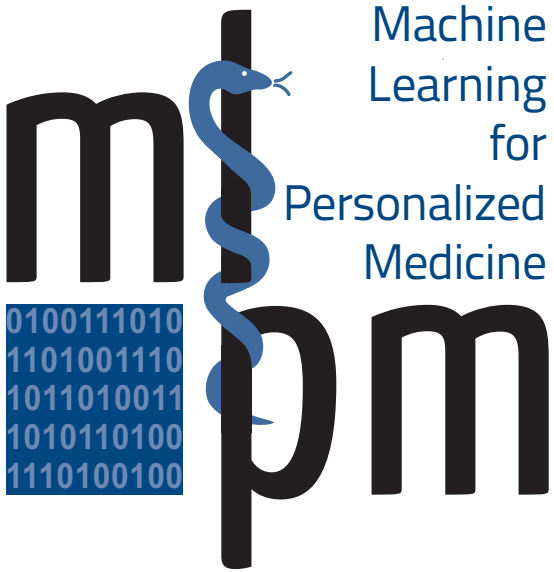

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Thanks!

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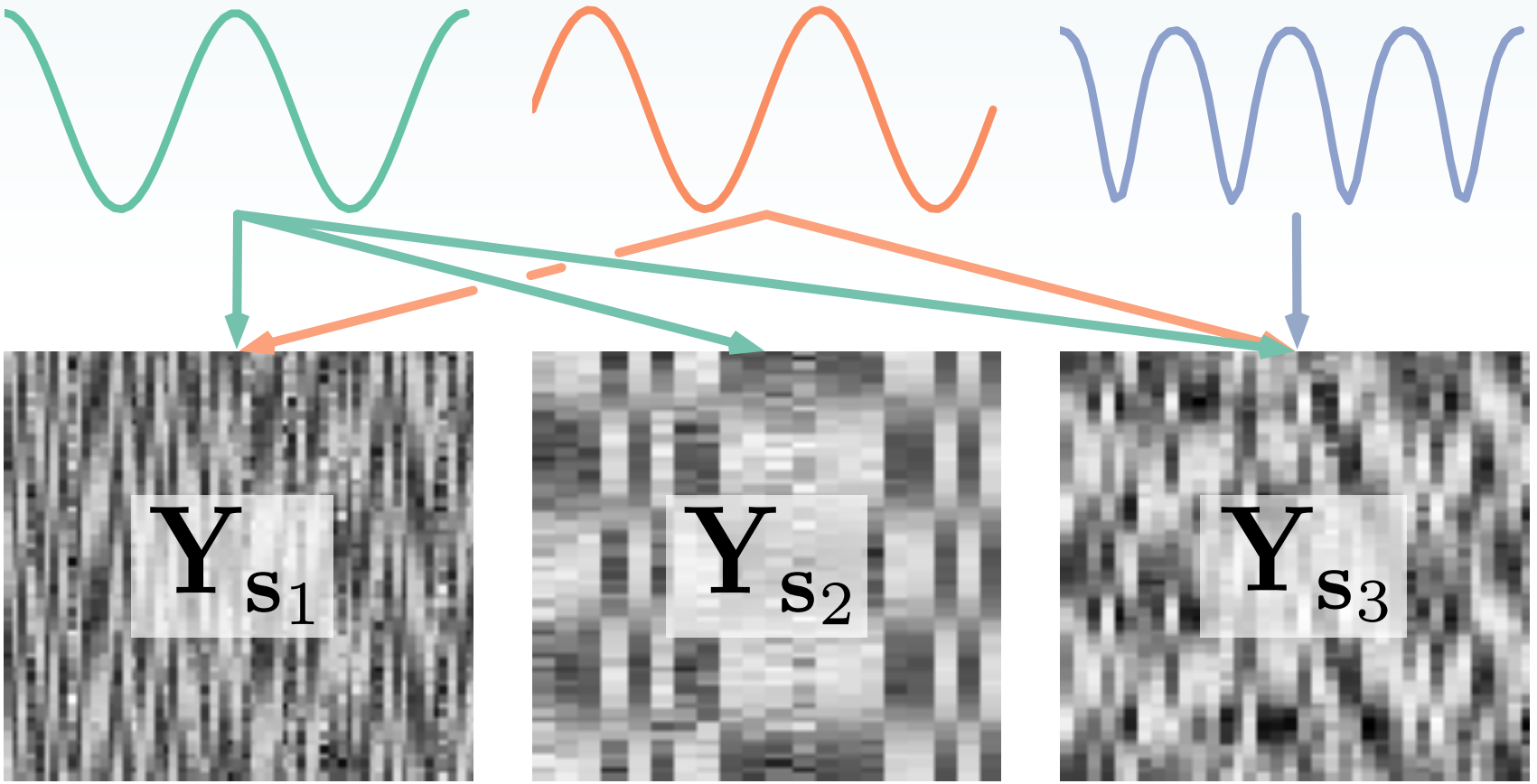
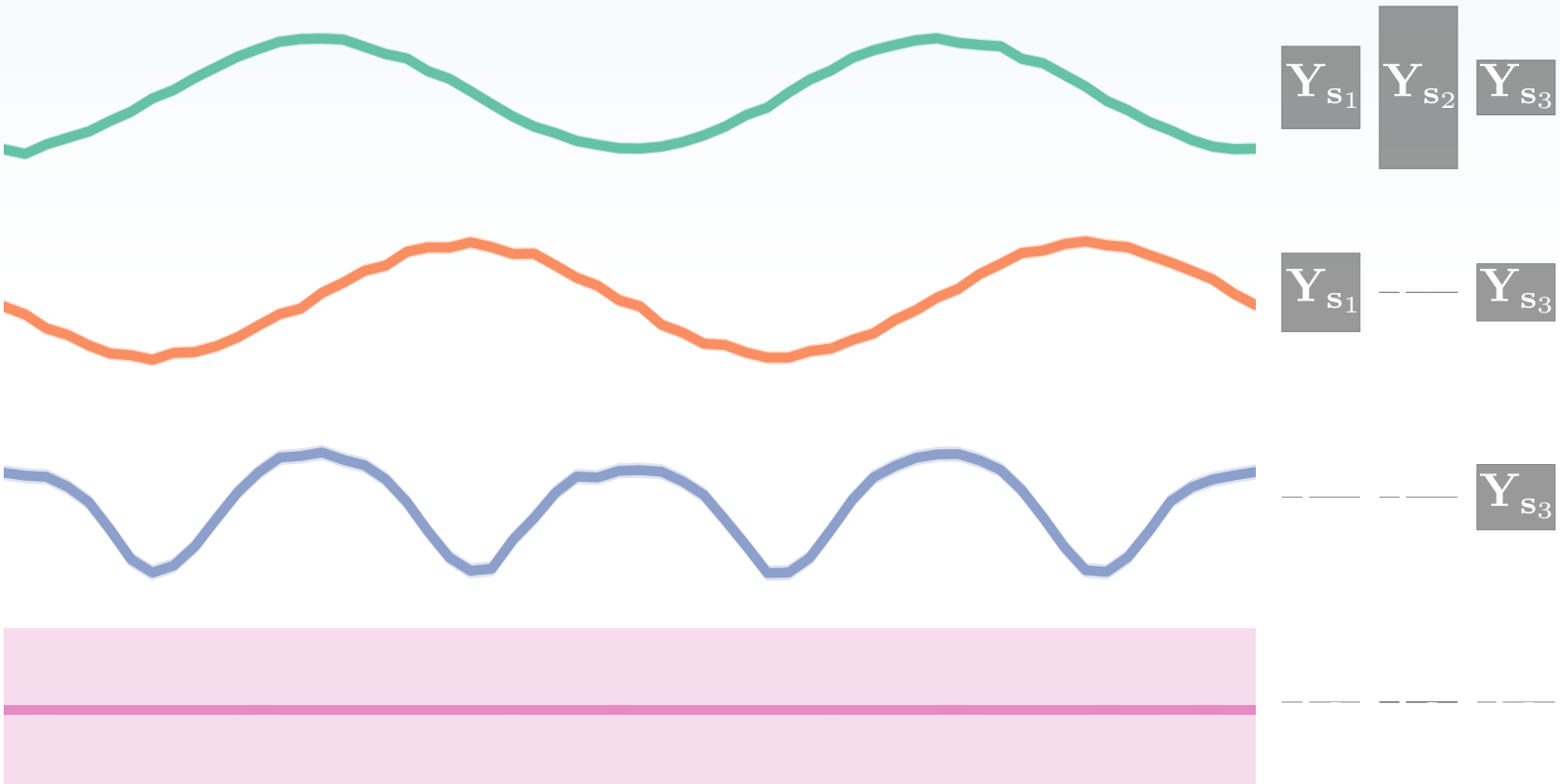
Appendix

MRD



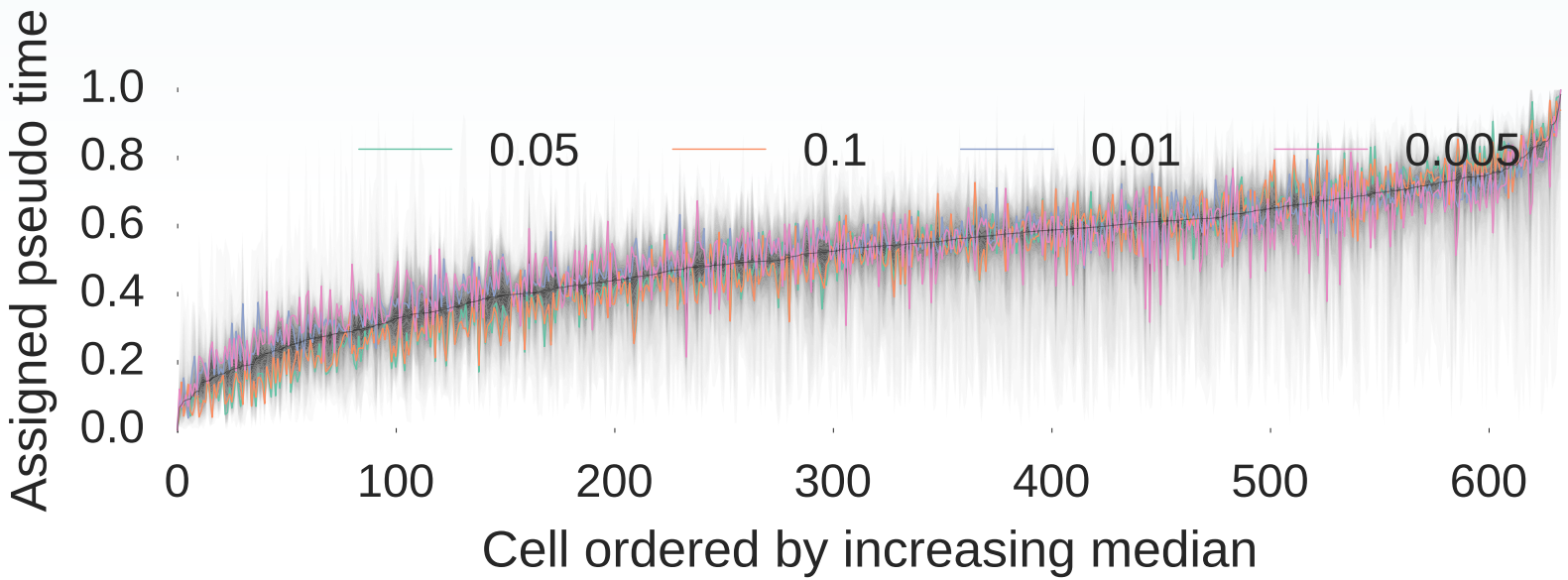
Appendix

MRD



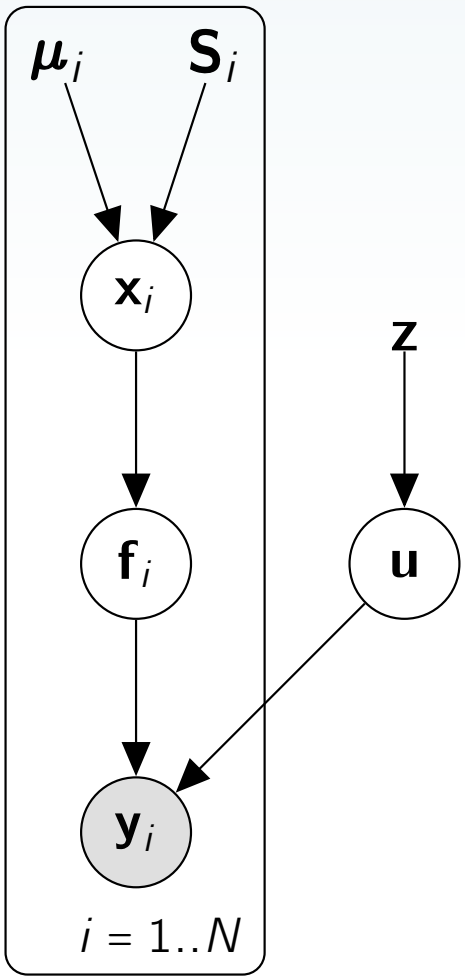
Appendix

Topslam Stability



Appendix

Bayesian GPLVM



$$\log p(\mathbf{y}) = \log \iint p(\mathbf{y}|\mathbf{x},\mathbf{u})p(\mathbf{u})p(\mathbf{x}) \; \mathrm{d}\mathbf{u}\,\mathbf{x}$$

$$= \log \iint p(\mathbf{y}|\mathbf{x},\mathbf{u})p(\mathbf{u}) \; \mathrm{d}\mathbf{u} p(\mathbf{x}) \frac{q(\mathbf{x})}{q(\mathbf{x})} \; \mathrm{d}\mathbf{x}$$

$$\geq \left\langle \langle \log p(\mathbf{y}|\mathbf{x},\mathbf{u}) \rangle_{p(\mathrm{u})} - \log \frac{q(\mathbf{x})}{p(\mathbf{x})} \right\rangle_{q(\mathrm{x})}$$

$$= \left\langle \langle \log p(\mathbf{y}|\mathbf{x},\mathbf{u}) \rangle_{p(\mathrm{u})} \right\rangle_{q(\mathrm{x})} - \mathrm{KL}\left(q(\mathbf{x})||p(\mathbf{x})\right)$$

$$=: \mathcal{L}_3$$

$$q(\mathbf{x}_i) = \mathcal{N}(\mathbf{x}_i|\boldsymbol{\mu}_i, \mathbf{S}_i)$$

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Appendix

Magnification Factor

[Tosi et al., 2014]'s Magnification Factor:

$$D_{ij}^{\text{euclidean}} = \sqrt{(\mathbf{X}_i - \mathbf{X}_j)^\top \mathbf{I} (\mathbf{X}_i - \mathbf{X}_j)}$$

$$\mathbf{J} = \frac{\partial p(\mathbf{y})}{\partial \mathbf{X}}$$

$$\mathbf{M} := \left\langle \mathbf{J}^\top \mathbf{J} \right\rangle = \left\langle \mathbf{J} \right\rangle^\top \left\langle \mathbf{J} \right\rangle + D \cdot \text{cov}(\mathbf{J}, \mathbf{J})$$

$$D_{ij}^{\text{corrected}} = \sqrt{(\mathbf{X}_i - \mathbf{X}_j)^\top \frac{\mathbf{M}_i + \mathbf{M}_j}{2} (\mathbf{X}_i - \mathbf{X}_j)}$$