Detecting and modeling time shifts in microarray time series data applying Gaussian processes

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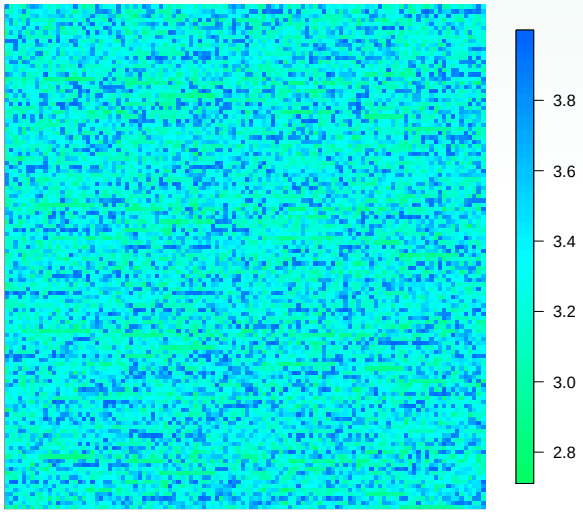
Why Time Shifts in Microarray Time Series?

Why Microarrays?

Microarray Advantages:

- Huge capacity (thousands of gene expression levels at a time).
- Multiple experiments over time (and replicates):
  - → Time Series of experiment.
  - → Time Series with several replicates.
- Different conditions:
  - → Detect differentially expressed genes.



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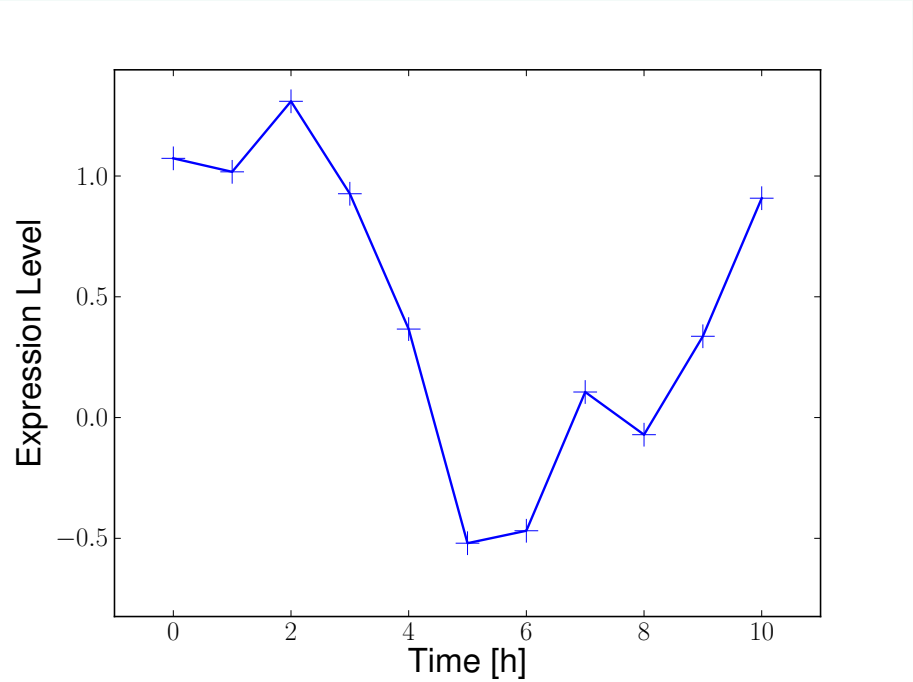

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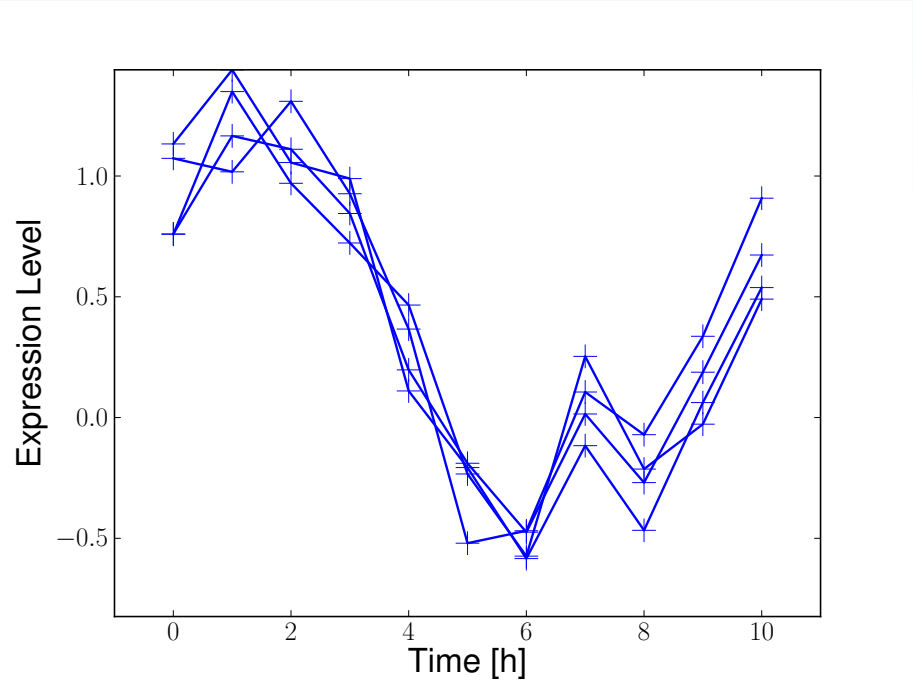

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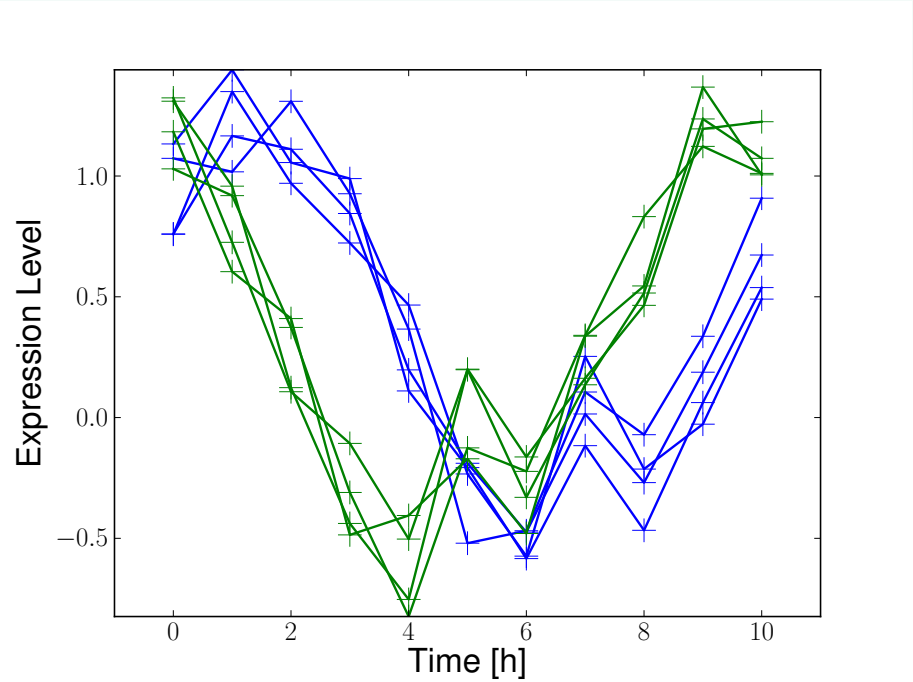

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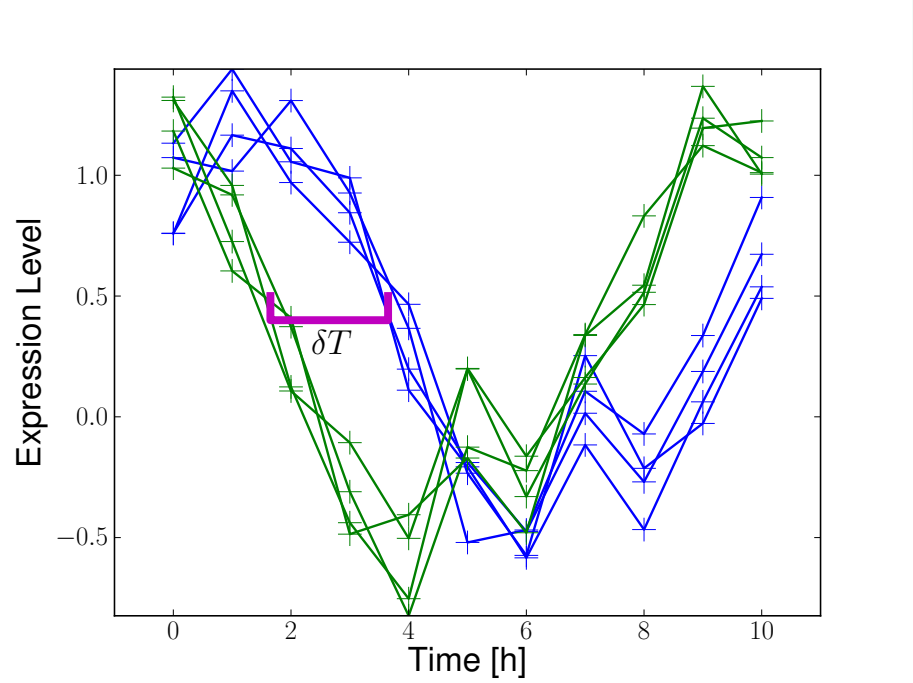
Why Time Shifts in Microarray Time Series?

Why Time Shifts?

1. *Technical Problems:* [3]
   - Varying efficiencies of intermediary steps:
   - → Imaging scanner (Laser).
   - → Amount of oligos per cell.
2. *Biological Problems:*
   - Dependency to environmental conditions.
   - Synchronization of replicates is hard. (Cell-Cycle)

Assumption:

Time shifts in data



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Outline

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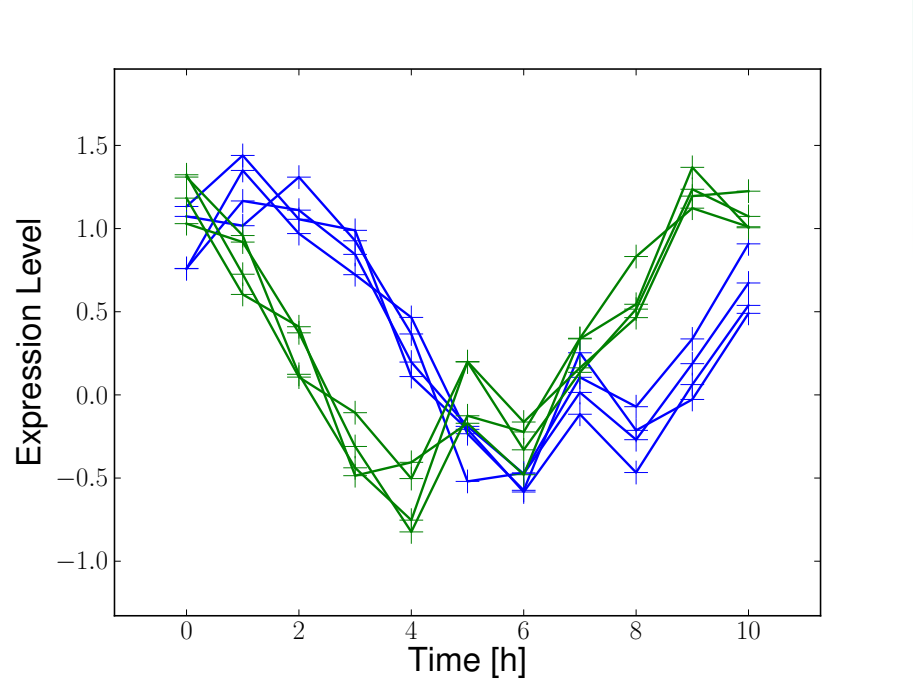
Dealing with Time Shifts in Data

Stegle *et al*'s Approach

- Used Gaussian Processes (GPs) to search functions

$$f : \mathbf{x} \mapsto f(\mathbf{x}) = \mathbf{y} \quad . \qquad (1)$$

- For differential expression detection, they compared:
  - individual model against
  - shared model.



- Providing the Bayes factor:

$$BF = \log \frac{p(A|\mathcal{H}_{GP}, \hat{\theta}_{\mathcal{I}})p(B|\mathcal{H}_{GP}, \hat{\theta}_{\mathcal{I}})p(\hat{\theta}_{\mathcal{I}})}{p(A, B|\mathcal{H}, \hat{\theta}_{\mathcal{S}})p(\hat{\theta}_{\mathcal{S}})} \qquad (2)$$

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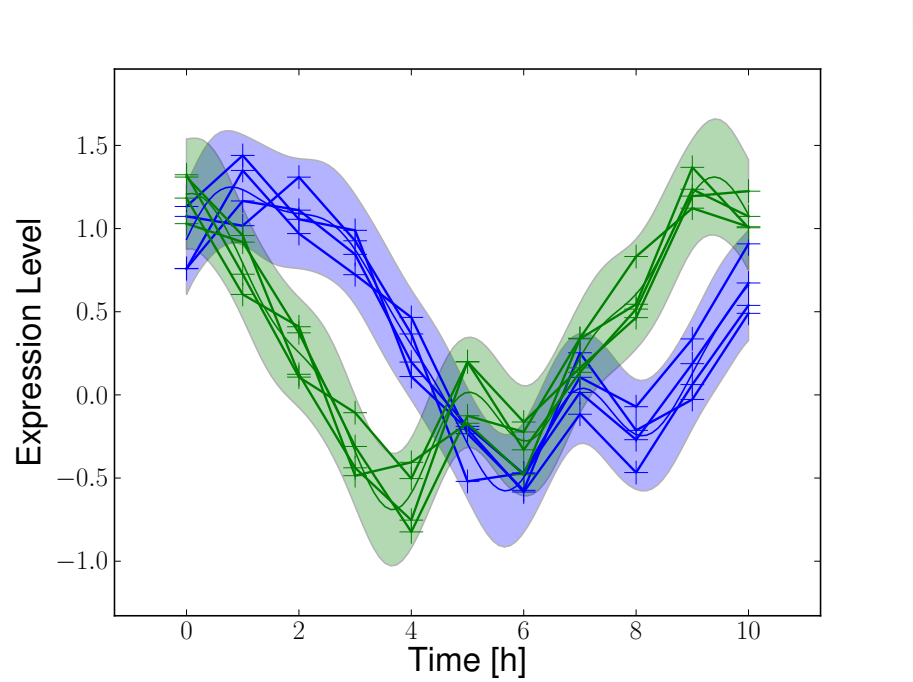

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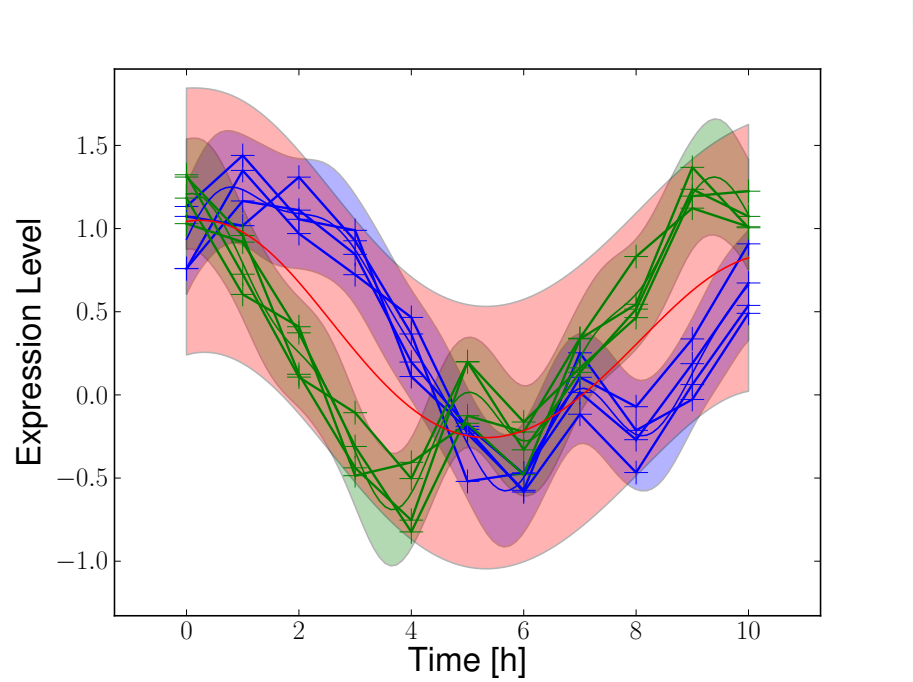

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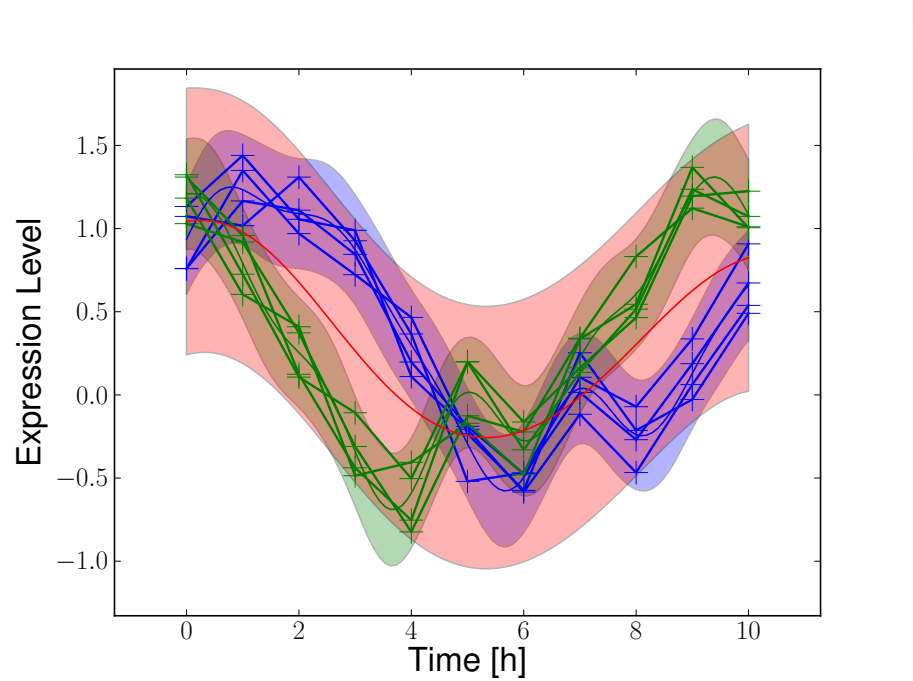

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Dealing with Time Shifts in Data

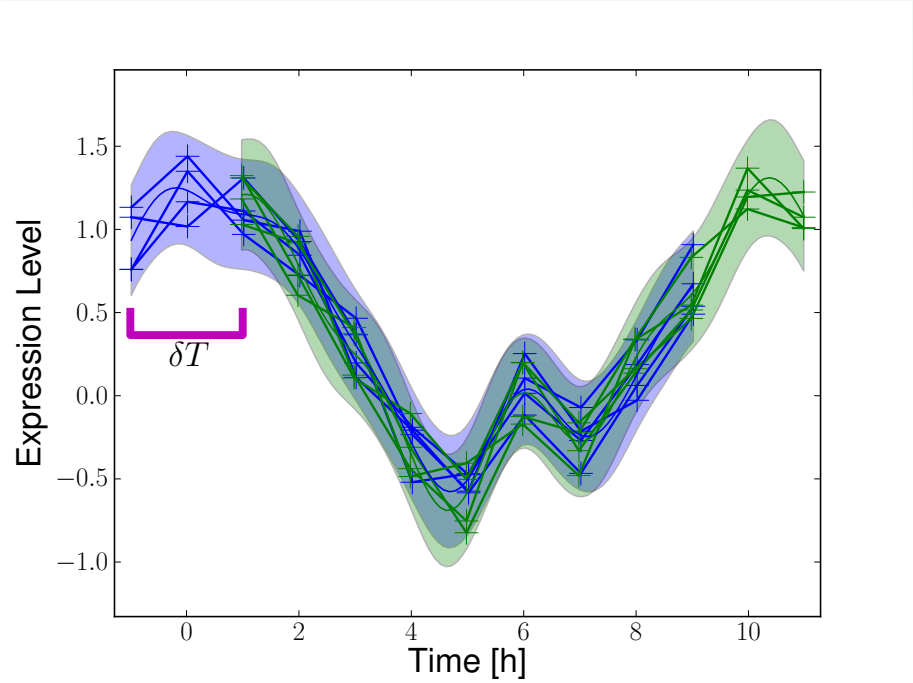
Regression w.r.t. Time Shifts

- We allow functions f to shift time line

$$f : \mathbf{x} \mapsto f(\mathbf{x} - \delta T) = \mathbf{y} \quad , \quad (3)$$

$\rightarrow$ Matching time series .

- Now compare
  - individual model against
  - shared model.



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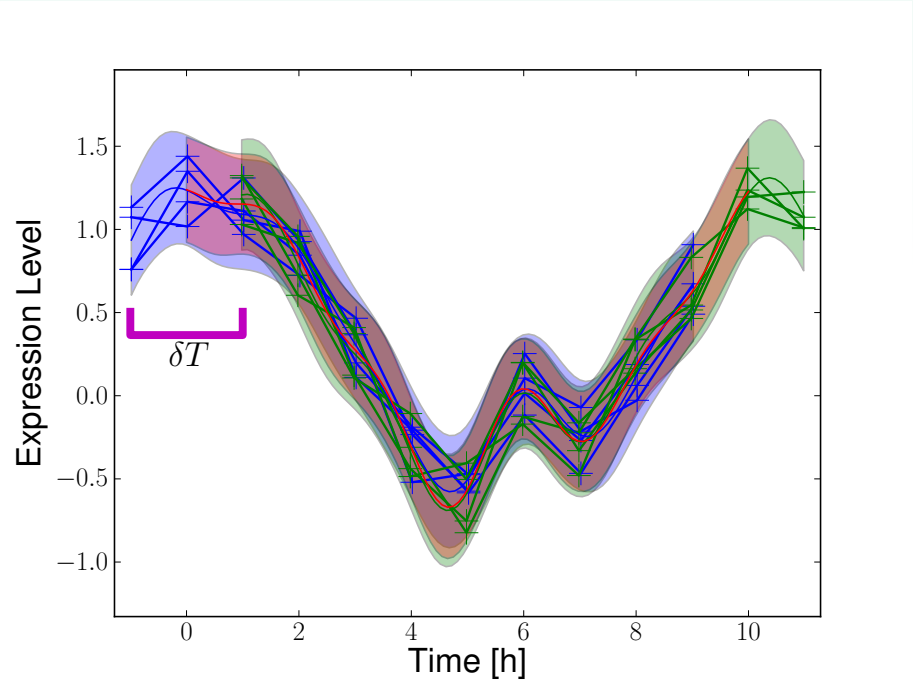

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Gaussian Process Regression w.r.t. Time Shifts

Probability for unseen data

Two main results of GP regression [1] of interest:

1. Probability for previous unseen outputs $\mathbf{y}^*$:

$$p(\mathbf{y}^*|\mathbf{x}^*, \mathbf{D}, \theta) = \mathcal{N}\big(\mathbf{y}^*|\underline{\mathbf{y}}^*, \mathrm{cov}(\mathbf{y}^*)\big), \quad \text{where} \tag{4}$$

$$\underline{\mathbf{y}}^* = K_{\mathrm{x}^*,\mathrm{x}}[K_{\mathrm{x}} + \sigma^2\mathbf{E}]^{-1}\mathbf{y} \ , \tag{5}$$

$$\mathrm{cov}(\mathbf{y}^*) = K_{\mathrm{x}^*} - K_{\mathrm{x}^*,\mathrm{x}}[K_{\mathrm{x}} + \sigma^2\mathbf{E}]^{-1}K_{\mathrm{x},\mathrm{x}^*} \ , \tag{6}$$

and $\mathbf{E}$ denotes the identity matrix.

2. Probability for hyperparameters to describe the training data:

$$\log p(\mathbf{y}|\mathbf{x}, \theta) = -\frac{1}{2}\mathbf{y}^\top\mathbf{K}^{-1}\mathbf{y} - \frac{1}{2}\log|\mathbf{K}| - \frac{n}{2}\log 2\pi \ , \tag{7}$$

$$\mathbf{K} = K_{\mathrm{x}} + \sigma^2\mathbf{E} \ . \tag{8}$$

Gaussian Process Regression w.r.t. Time Shifts

Novel Covariance Function with Time Shift Parameter

Requirements:

- Covariance matrix $K_{\mathrm{x},\mathrm{x}^*} = [k(x_r, x'_{r'}) : \forall x_r, x'_{r'} \in \mathbf{x}, \mathbf{x}^*]$.
- Time shift $T_r \in \mathbf{T}$ per replicate $(\mathbf{x}, \mathbf{y})_r$.

New covariance function with time shift per replicate:

$$k(x_r, x'_{r'}) := A^2 \cdot \exp\left(-\frac{d^2}{2L^2}\right) + \sigma \quad , \tag{9}$$

$$d = \left\|(x_r - T_r) - (x'_{r'} - T_{r'})\right\| \quad . \tag{10}$$

Important: The most probable set of hyperparameters $\hat{\theta} = (A, L, \mathbf{T}, \sigma)$ are learned from data! (Appendix 1)

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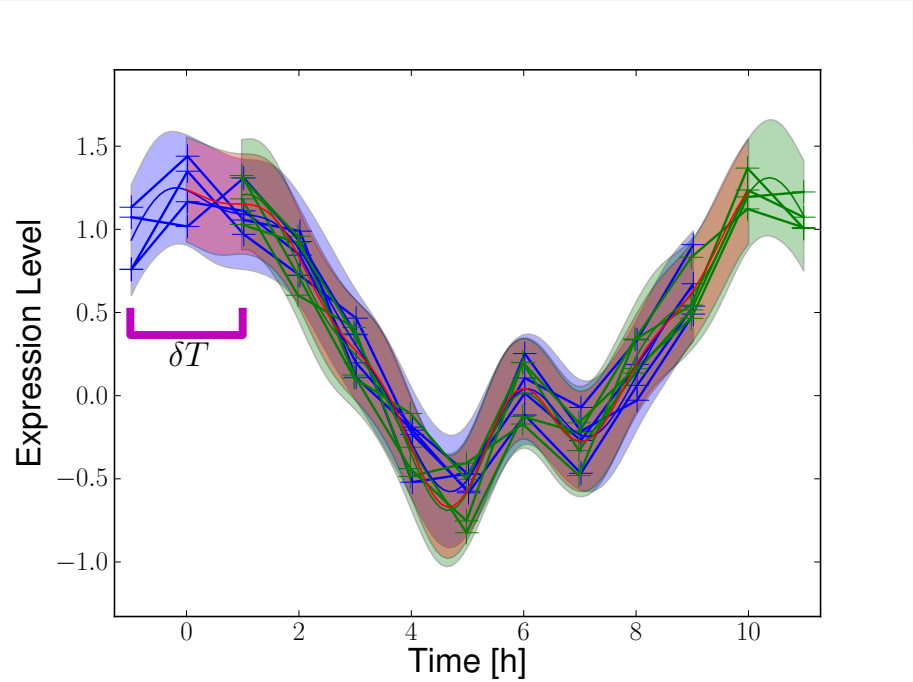
Gaussian Processes Regression w.r.t. Time Shifts

Bayes Factors [2]

Three Bayes factors for hypothesis testing:

1. Individual vs. shared regression, included $\mathbf{T}$:
2. Individual vs. shared regression, where for shared $\mathbf{T} = (0, \ldots, 0)$:
3. Shared with, vs. shared without time shift:



$$\mathcal{S}^{\mathcal{I}}_{\delta T} := \log \frac{p(\mathbf{C}_k|\mathcal{H}_{GP}, \hat{\theta}^{\mathbf{T}}_{\mathcal{I}}) \cdot p(\mathbf{C}_{k'}|\mathcal{H}_{GP}, \hat{\theta}^{\mathbf{T}}_{\mathcal{I}}) \cdot p(\hat{\theta}^{\mathbf{T}}_{\mathcal{I}})}{p(\mathbf{C}_k \cup \mathbf{C}_{k'}|\mathcal{H}_{GP}, \hat{\theta}^{\mathbf{T}}_{\mathcal{S}}) \cdot p(\hat{\theta}^{\mathbf{T}}_{\mathcal{S}})} = 2.225 \quad (11)$$

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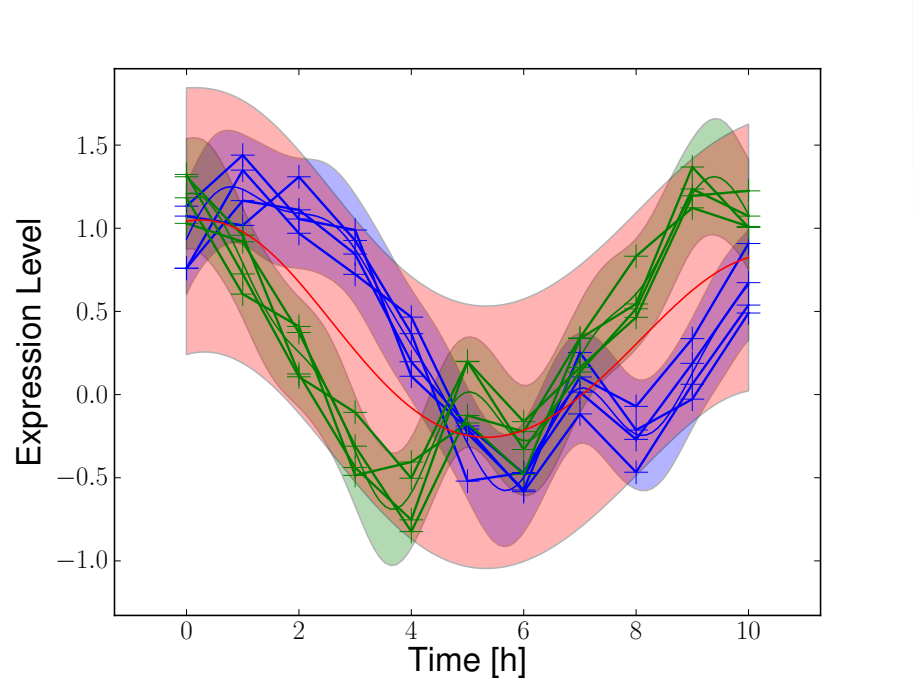

$$\mathcal{S}_0^{\mathcal{I}} := \log \frac{p(\mathbf{C}_k | \mathcal{H}_{GP}, \hat{\theta}_{\mathcal{I}}^{\mathsf{T}}) \cdot p(\mathbf{C}_{k'} | \mathcal{H}_{GP}, \hat{\theta}_{\mathcal{I}}^{\mathsf{T}}) \cdot p(\hat{\theta}_{\mathcal{I}}^{\mathsf{T}})}{p(\mathbf{C}_k \cup \mathbf{C}_{k'} | \mathcal{H}_{GP}, \hat{\theta}_{\mathcal{S}}^{(0,\ldots,0)}) \cdot p(\hat{\theta}_{\mathcal{S}}^{(0,\ldots,0)})} = 82.780 \quad (12)$$

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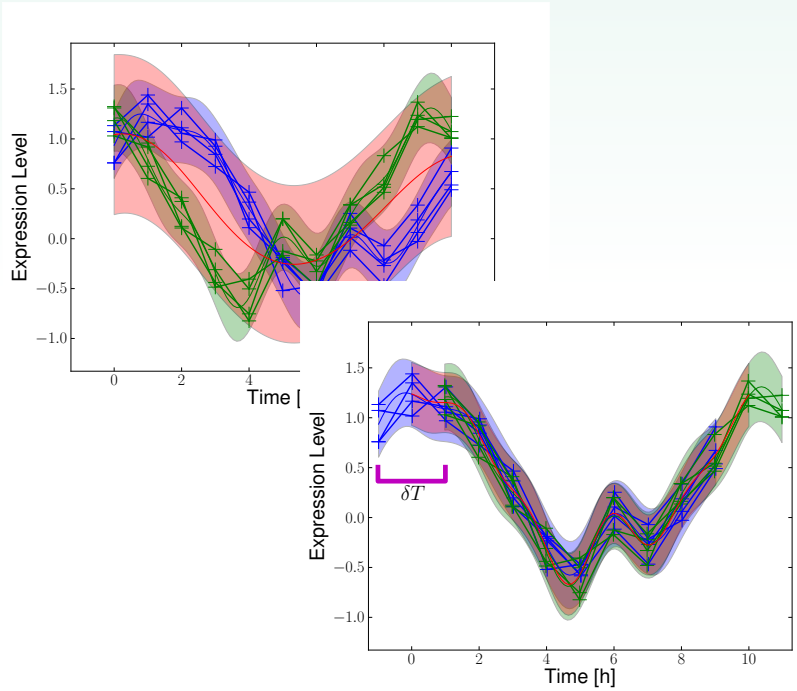

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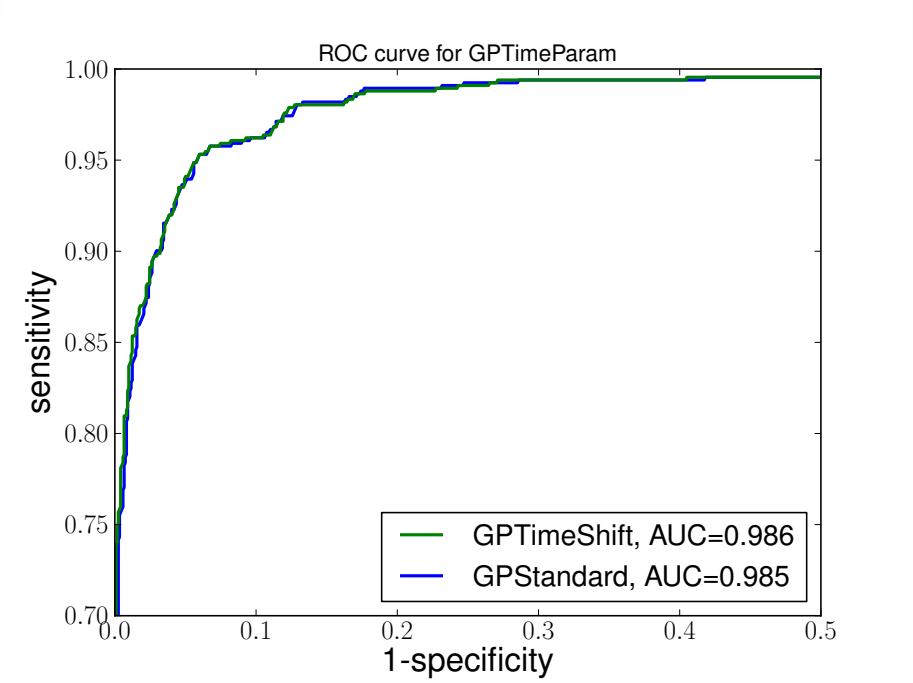
Detecting Differentially Expressed Genes

Experiment

- GPTimeShift applied on *Arabidopsis thaliana* data set
  - Plant leafs inoculated by fungal pathogen *Botrytis cinerea*.
  - Harvested every 2h up to 48h post-inoculation.
  - Contains four replicates for each condition of $n = 30,336$ genes.
- Goal: Detect differentially expressed genes.

Detecting Differentially Expressed Genes

Result



Test set of $n = 1,890$ genes, manually classified into either 'differentially expressed' or '**not** differentially expressed'.

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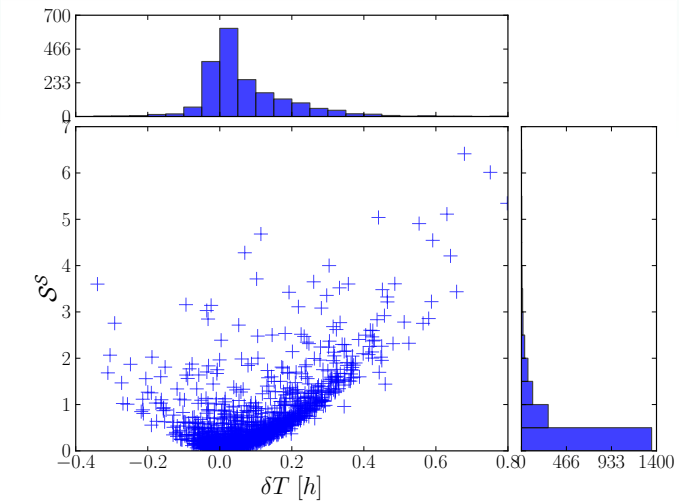
Detecting Differentially Expressed Genes

Conclusion

No significant improvement by including time shifts:

- Microarray problems solved by preprocessing and normalization.
- No significant time shifts in data.



Correlation of Transcription Factors and Time Shifts

Experiment

- GPTimeShift applied on *yeast* data set:
  - Knocked out *mei4* (coding for a TF).
  - Harvested every 1h up to 8h post-perturbation.
  - Only one replicate per condition of $n = 4,410$ genes.
- Goal: Detect TFs and corresponding targets by time shift correlations.

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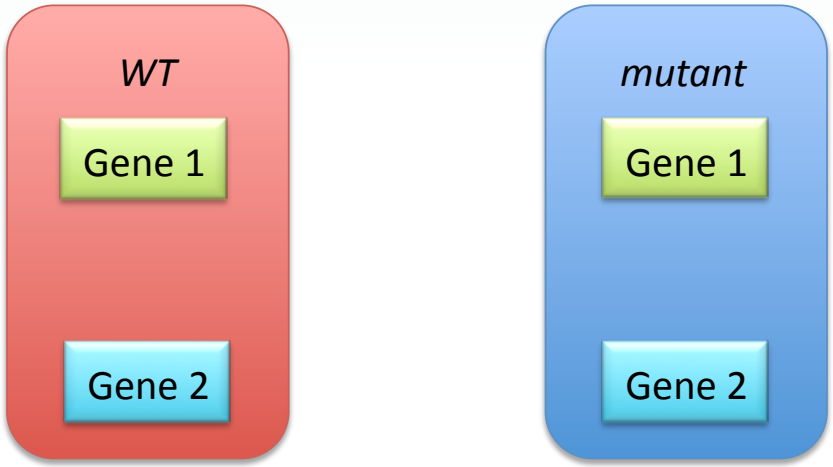
Correlation of Transcription Factors and Time Shifts

Results

- Compare time shifts within conditions (*WT* and *mutant*) of gene pairs against each other.
- Get correlated gene pairs ($-\mathcal{S}^{\mathcal{I}}_{\delta T} > -2.5$), due to comparing time series of different genes.
- Select only tails of time shift difference distribution.



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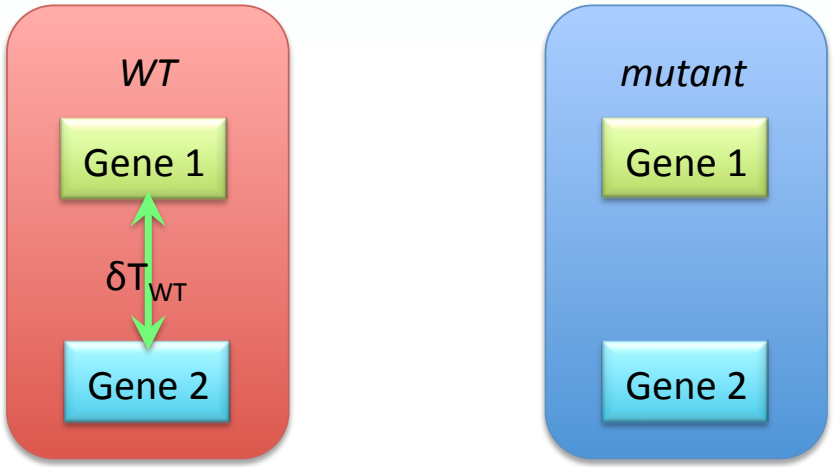

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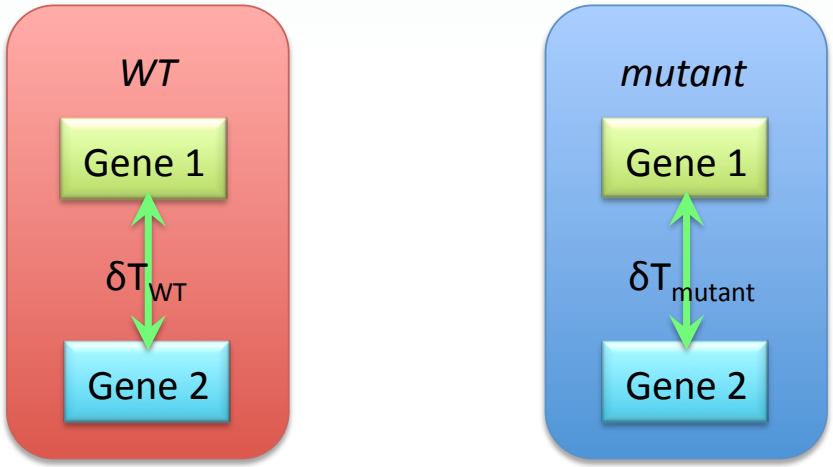

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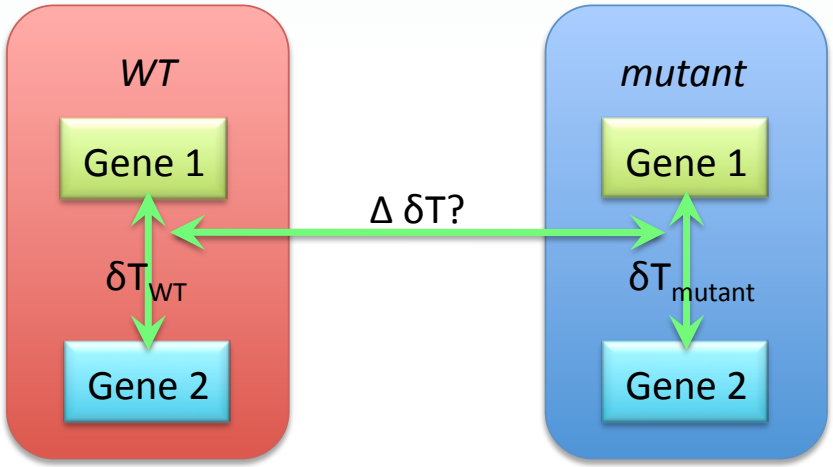

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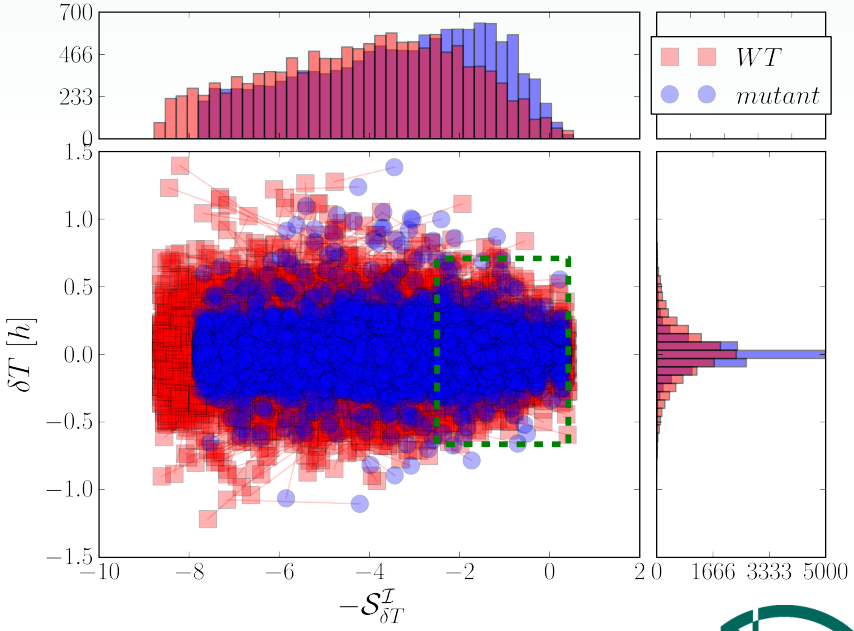

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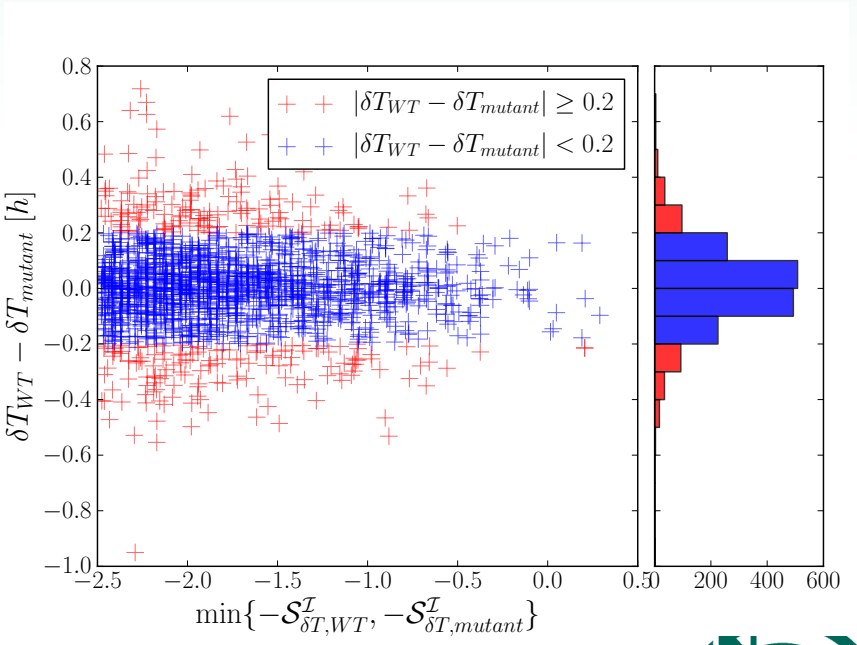

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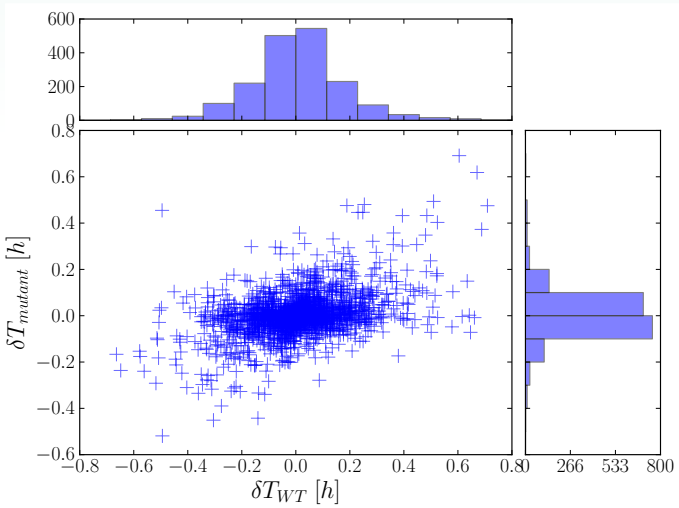
Correlation of Transcription Factors and Time Shifts

Conclusion

- Unfortunately only a subset of predicted pairs are TFs:
  - Algorithm for searching TFs and targets has to be adapted.
- Proof of principle:
  - TFs lead to time shifts in data.
  - Knocking out a TF leads to less time shifts.



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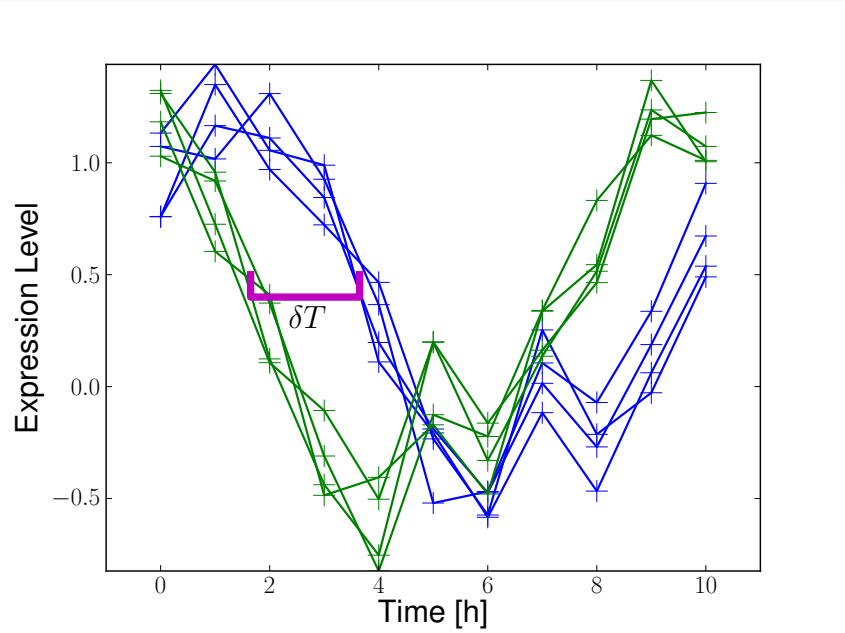
  - analyze TF(-target) and time shift correlations.



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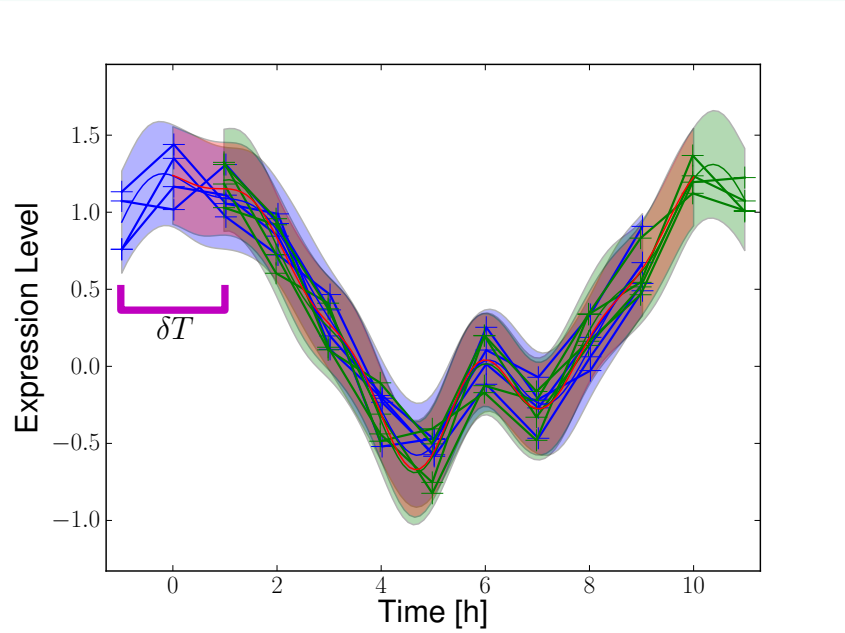

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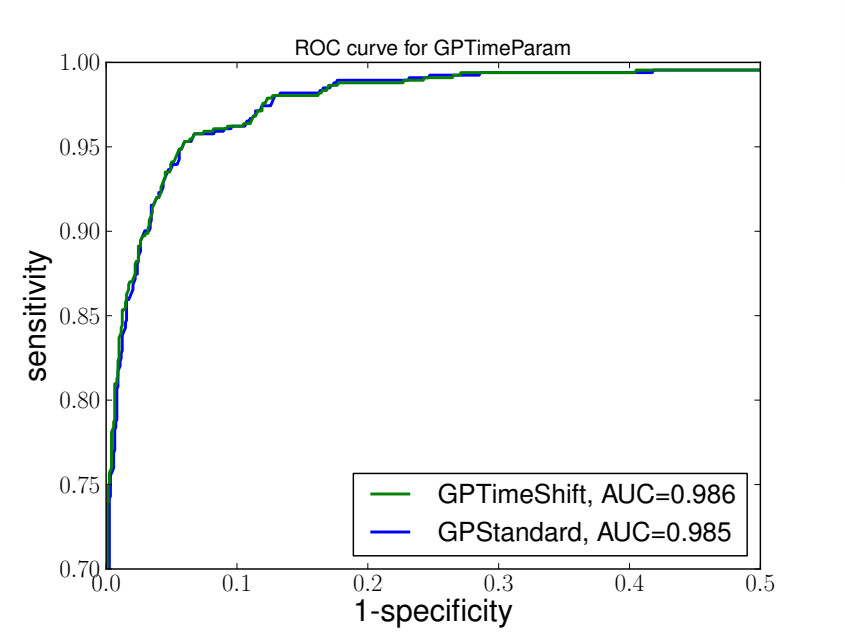

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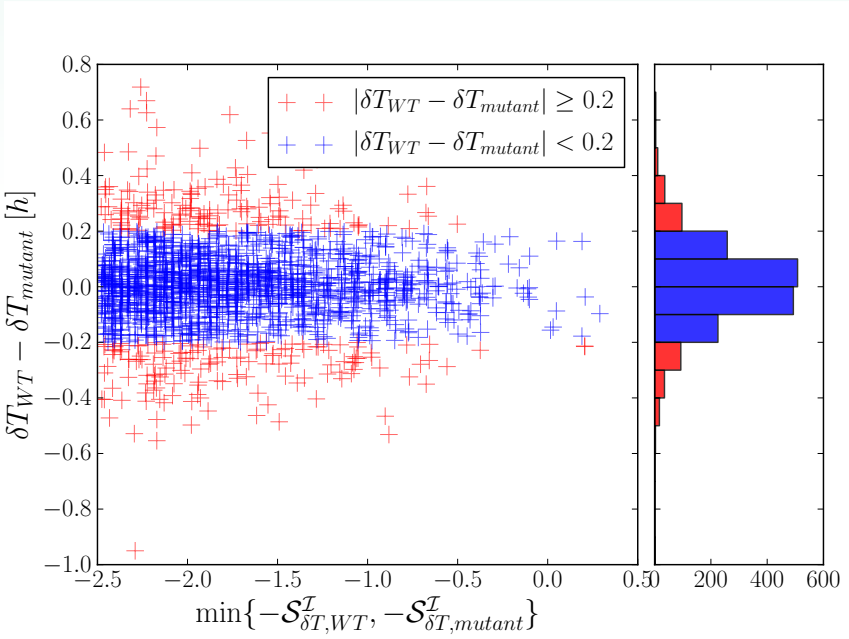

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Discussion

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Learning Hyperparameters [1]

With the probability for the outputs being described by the hyperparameters

$$\log p(\mathbf{y}|\mathbf{x},\theta) = -\frac{1}{2}\mathbf{y}^{\top}\mathbf{K}^{-1}\mathbf{y} - \frac{1}{2}\log|\mathbf{K}| - \frac{n}{2}\log 2\pi \quad ,(7) \tag{15}$$

we can denote the most probable set of hyperparameters $\hat{\theta}$ with:

$$\hat{\theta} = \arg\max_{\theta}\{p(\theta|\mathbf{D})\} \tag{16}$$

$$= \arg\max_{\theta}\{p(\mathbf{y}|\mathbf{x},\theta)\cdot p(\theta)\} \tag{17}$$

$$= \arg\max_{\theta}\{\log\ p(\mathbf{y}|\mathbf{x},\theta) + \log\ p(\theta)\} \quad , \tag{18}$$

where $p(\theta)$ is the hyperprior probability for the hyperparameters θ.