Hierarchical Bayesian Modelling Identifies Shared Gene Function

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Methodological Discussions: David J. C. MacKay & Inference Group

Problem Statement

- Assumption: Several microarray experiments are obtained such that slides can be mapped to a biological state of interest.
- Shared genetic function: Interesting genes are across experiments informative about these biological states.
- Task: find those genes! Actually two problems:
  - Cross annotation of genes (potentially different species)
  - Calculate a measure across experiments

This talk shows how we may obtain such a measure using a probabilistic approach.

Biological States of Experiments

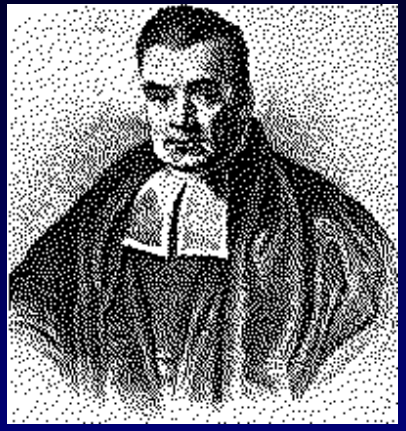
Mammary Gland tc. (lact. day & hours of involution)

biol. state	L_0	L_5	L_{10}	I_{12}	I_{24}	I_{48}	I_{72}	I_{96}
Type 1 Apoptosis	-	-	-	+	+	?	-	-
Type 2 Apoptosis	-	-	-	-	-	?	+	+
Apoptosis	-	-	-	+	+	+	+	+
Differentiation	+	+	+	?	-	-	-	-
Inflammation	?	-	-	+	+	?	-	-
Remodelling	-(?)	-	-	-	-	?	+	+
Acute Phase	+	-	-	-	+	+	+	+

Serum Deprived Apoptosis (duration in hours)

biol. state	t_0	t_{28}	t_{48}
Type 2 Apoptosis	-	+	+
Apoptosis	-	+	+
Differentiation	+	-	-

Probabilistic Approach



Thomas Bayes (1701 - 1763)
Learning from data based on a decision theoretic framework

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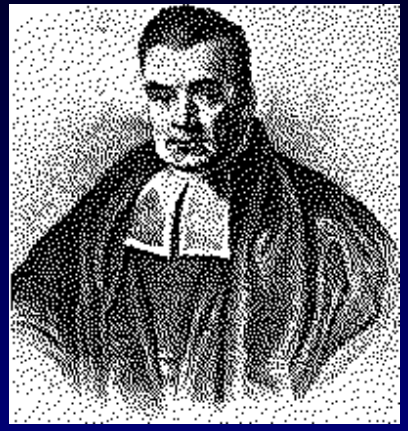
$$p(I|\mathcal{D}) = \frac{p(\mathcal{D}|I)p(I)}{p(\mathcal{D})}$$

First consequence: we must revise beliefs according to Bayes theorem

Probabilistic Approach



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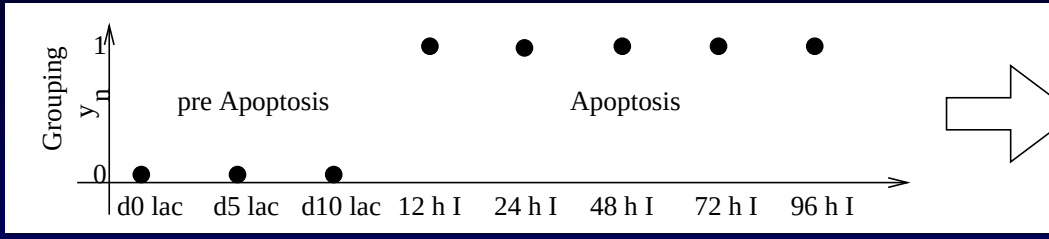
$$\alpha_{opt} = \text{argmax}_{\alpha} < u(\alpha) >$$, where

$$< u(\alpha) >= \int_G u(\alpha, I)p(I|\mathcal{D})dI.$$

Second consequence: Decisions by maximising expected utilities

Probabilistic Gene Ranking

Apoptosis (lac. vs. inv.!) in the Mouse Mammary Gland



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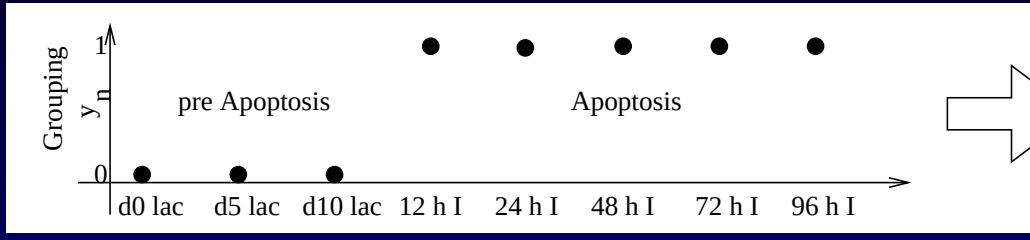

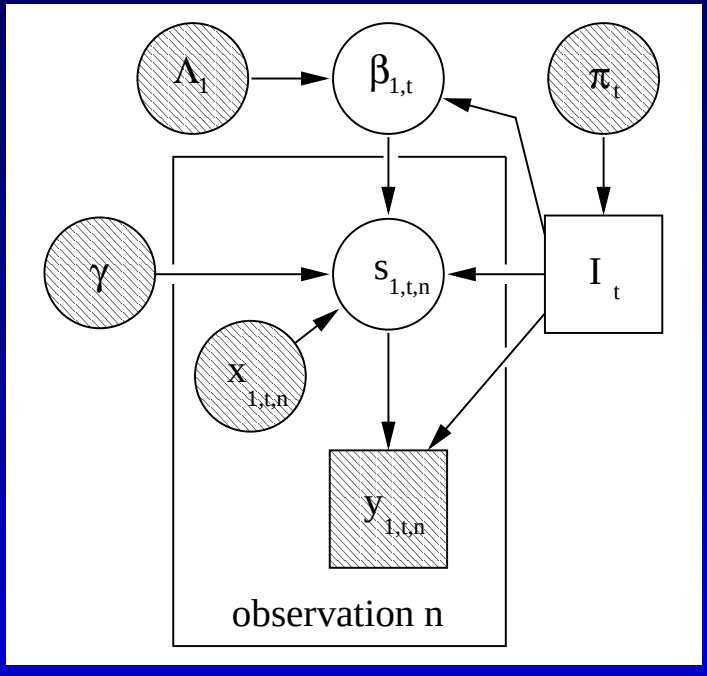

Latent variable probit GLM.

$$\text{if } I_t = \begin{cases} 1 : s_{1,t,n} \sim 1 + x_{t,n} \\ 0 : s_{1,t,n} \sim 1 \end{cases}$$

$s_{1,t,n}$ is a one dimensional Gaussian random variable with mean $\boldsymbol{\beta}_{t,1}^T \boldsymbol{x}_{t,n}$ and precision γ.

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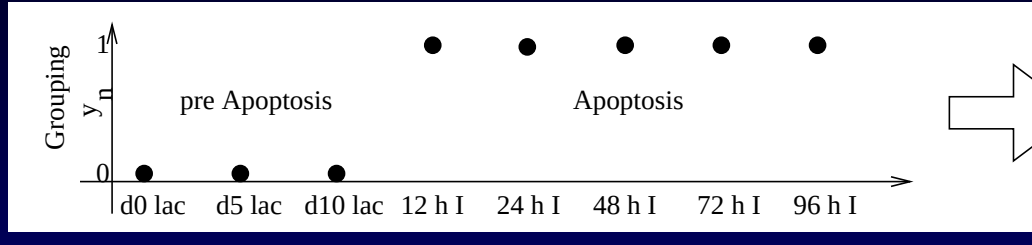

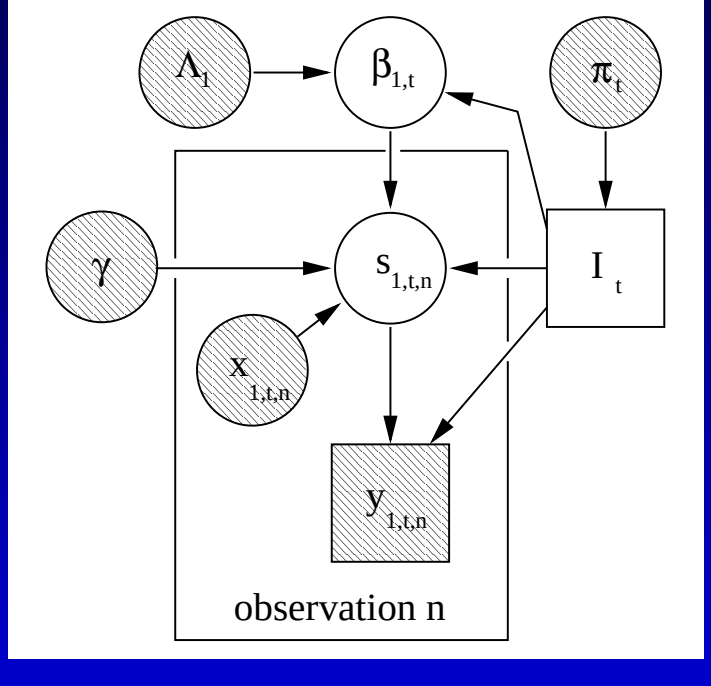

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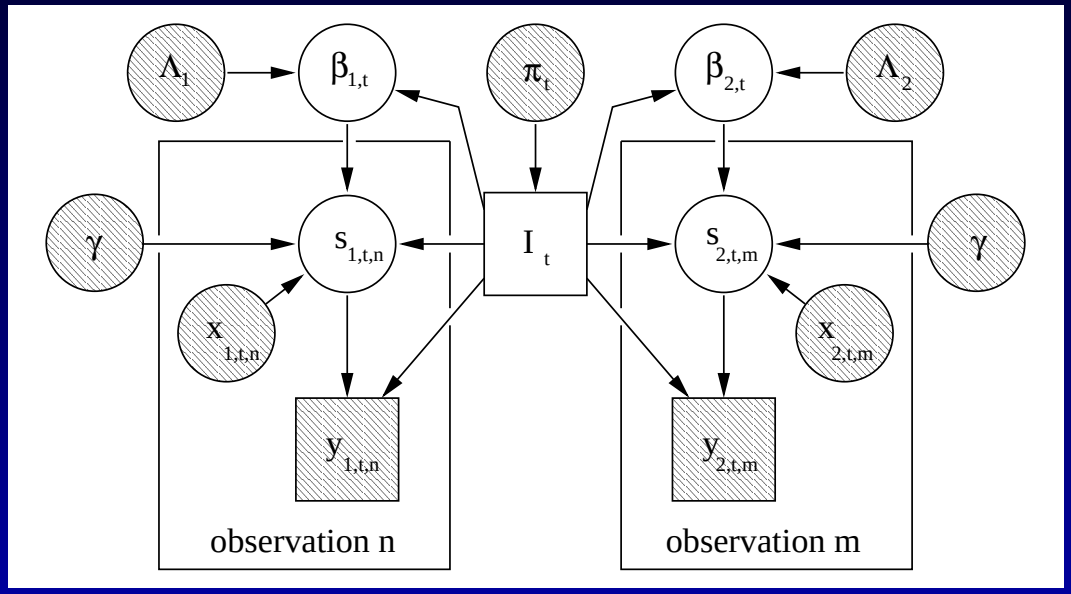
As an alternative to p-values, the posterior $P(I_t|\mathcal{D}_1)$, serves as a probabilistic rank measure. (VB-eqns.)

Shared Gene Function

Include Information about Endothelial Cell Death

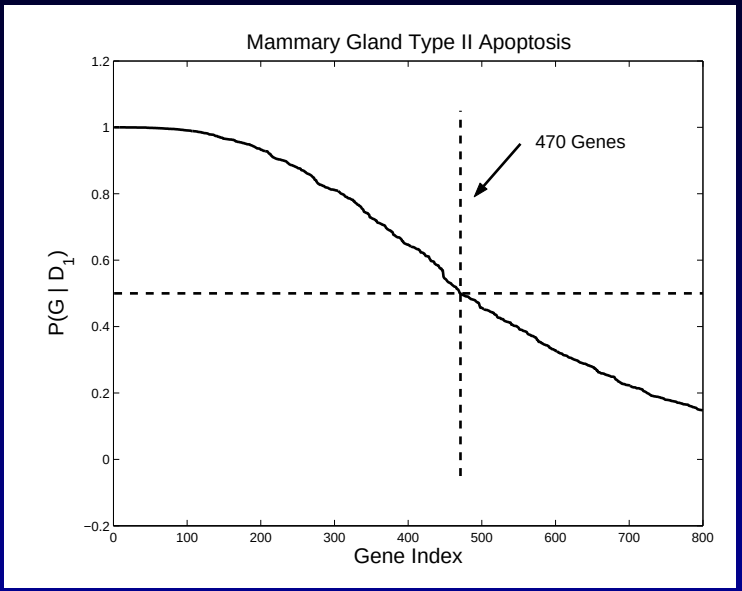


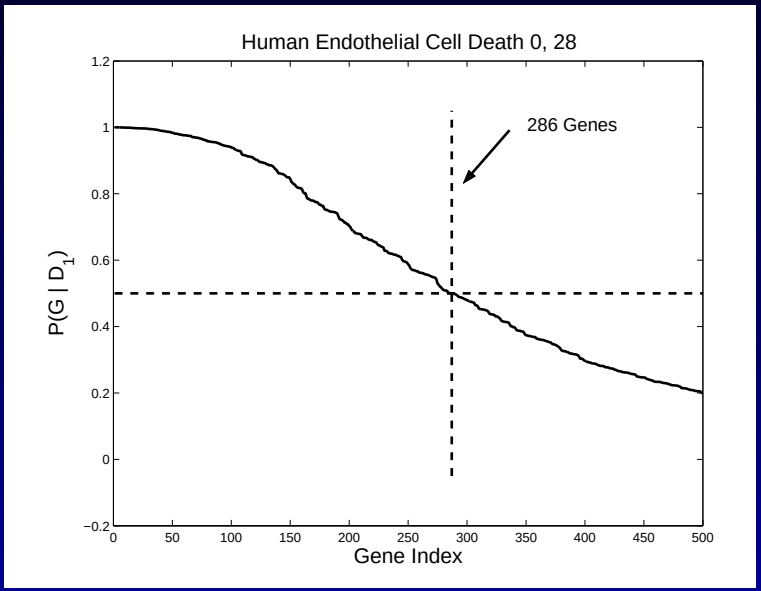
Model 0 hrs. vs. 28 hrs. as latent variable probit GLM. Calculate $P(\mathcal{D}_2|I_t)$, the marginal likelihood.

Bayes theorem gives a *principled* measure for ranking

$$P(I_t|\mathcal{D}_1,\mathcal{D}_2) = \frac{P(I_t|\mathcal{D}_1)p(\mathcal{D}_2|I_t)}{p(\mathcal{D}_2|\mathcal{D}_1)}$$

Don’t Do That at Home!





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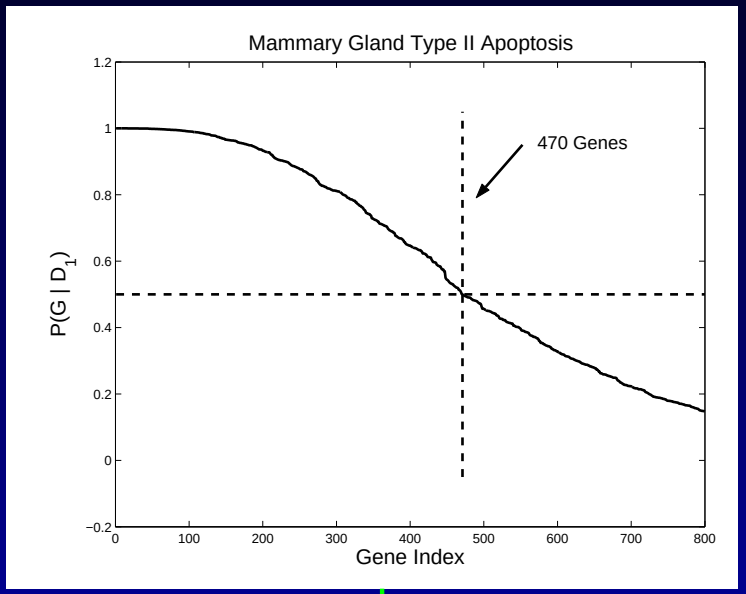

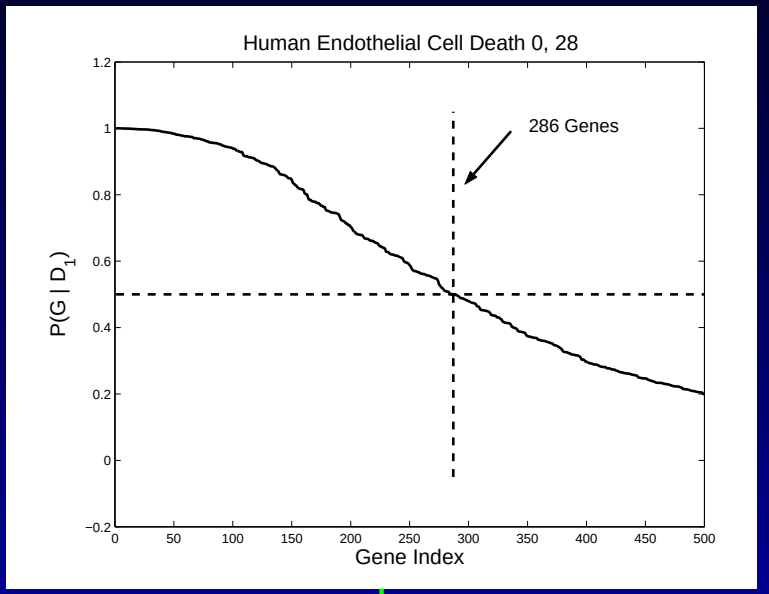

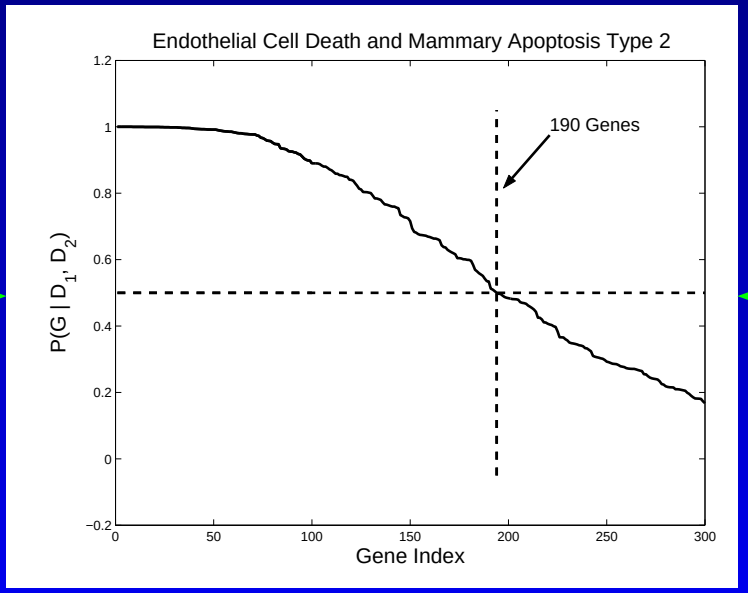

Improving on Previous Model

- Hyper parameters (π_t, $\mathbf{\Lambda}_1$ and $\mathbf{\Lambda}_2$) influence probability measure $P(I_t|\mathcal{D}_1, \mathcal{D}_2)$.
- Less critical for $P(I_t = 1|\pi_t)$ (e.g. 0.5 for ignorance). However even a pragmatic approach for adjusting $\mathbf{\Lambda}$ like $\min_t p(\hat{\boldsymbol{\beta}}_t|\mathbf{\Lambda}) = 0.95\ p(\mathbf{0}|\mathbf{\Lambda})$ is not convincing. (Why 0.95 ?)

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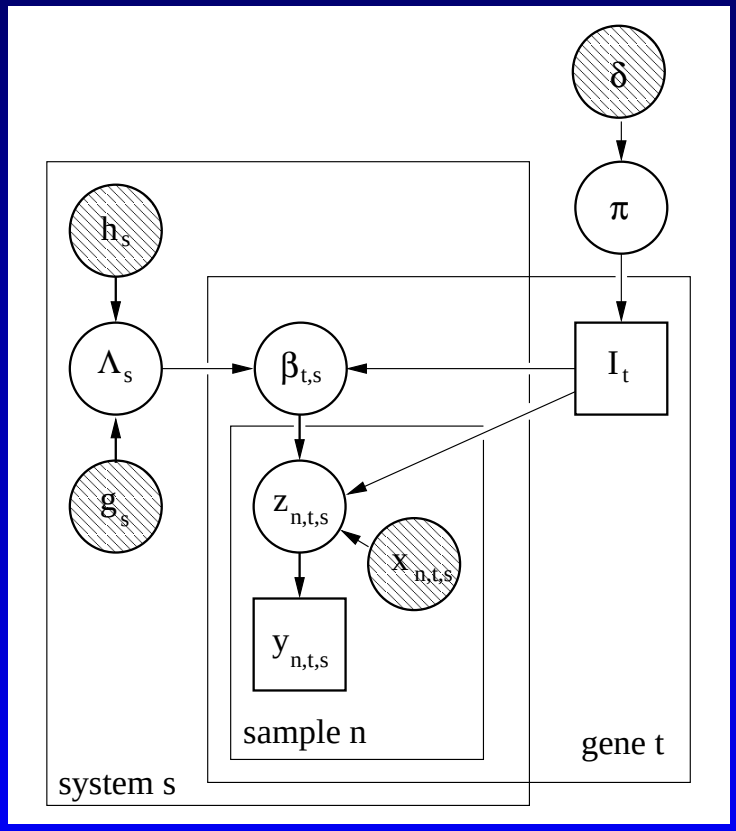
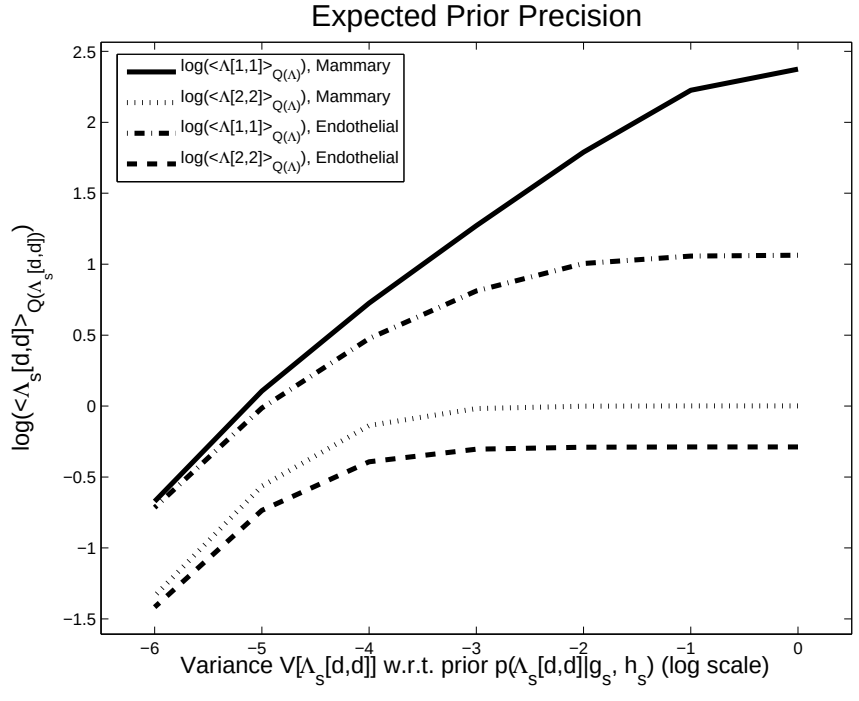
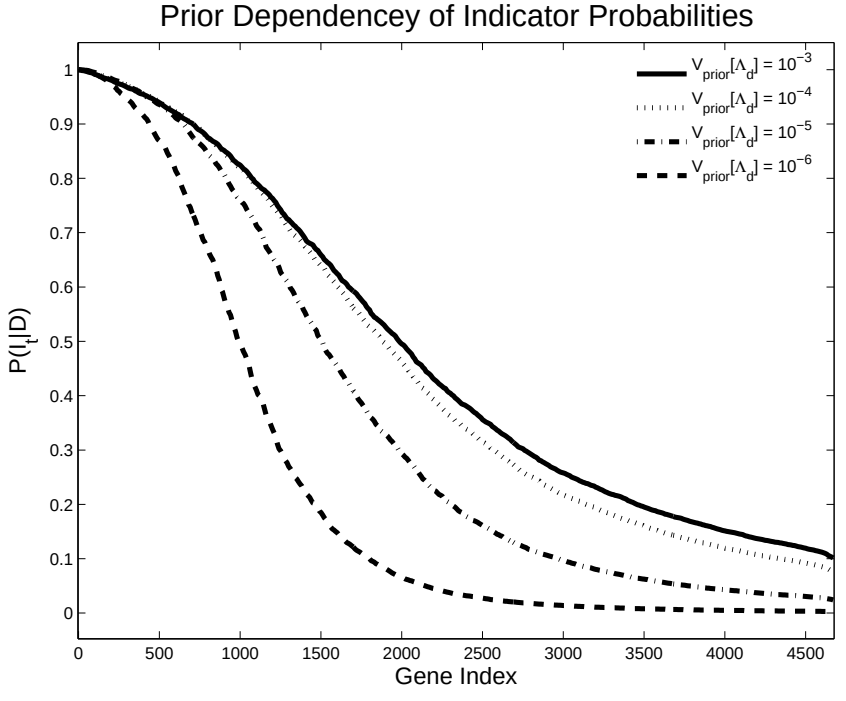
Better solution uses hierarchical priors



- all genes contribute to inference of $\mathbf{\Lambda}_s$
- hierarchical priors for sensitivity analysis
- $Q(I_t)$ approximates gene measure
- using *one* model gets all marginals right

Sensitivity Check

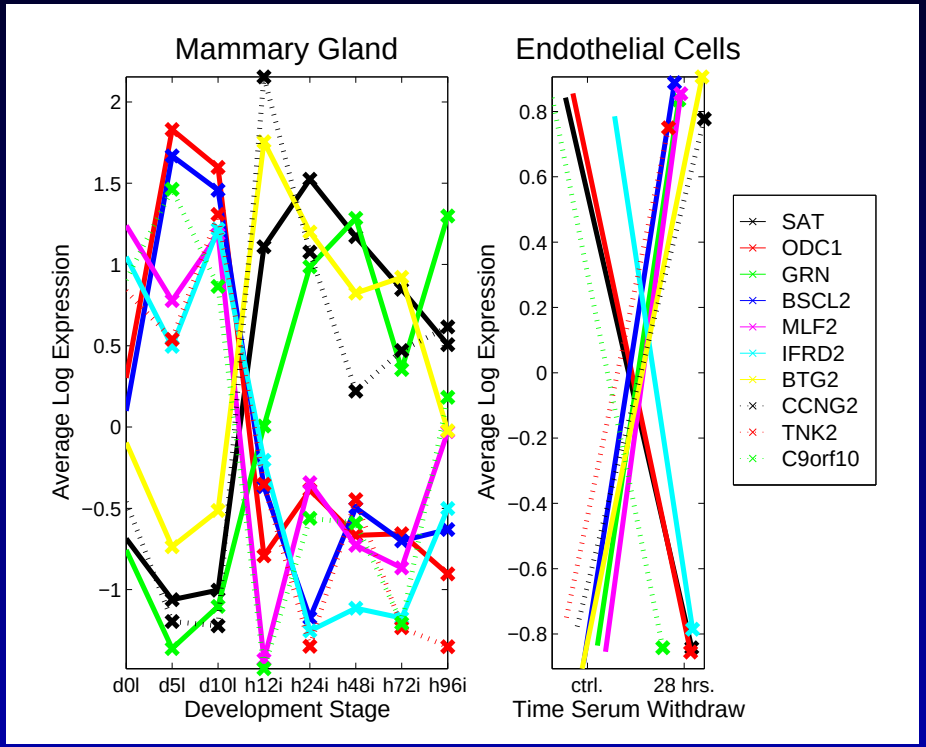




For the hyper parameters this suggests $g \leq 0.01$ and $h \leq 1$.

We also conclude that equal cost results in many potential candiate genes.

Top Ten



Top 10 $P(I_t = 1|\mathcal{D}_1, \mathcal{D}_2)$ for Mammary lactation vs. involution *and* Endothelial cell death (result updated 01 2007).

Gene Symbol	$P(I_t\|\mathcal{D})$
SAT	0.99951
ODC1	0.99921
GRN	0.99921
BSCL2	0.99919
MLF2	0.99884
IFRD2	0.99867
BTG2	0.99843
CCNG2	0.99826
TNK2	0.99789
C9orf10	0.99783

Summary

- A realtively straight forward approach allows inference of shared gene function.
- Beware of non hierarchical models - arbitrary gene measures can be adjusted for using the “right” prior.
- Variational methods provide a rather efficient tool to explore models before deciding for a final possibly MCMC based implementation.

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Variational Bayes

Mean field ansatz plus Jensens inequality. For all pdfs $Q(\theta)$:

$$\log\left(\int_\theta p(D|\theta)p(\theta)d\theta\right) \geq$$
$$\int_\theta \big(\log(p(D|\theta)) + \log(p(\theta)) - \log(Q(\theta))\big)Q(\theta)d\theta$$
$$= \log(p(D)) + \int_\theta \big(\log(p(\theta|D)) - \log(Q(\theta))\big)Q(\theta)d\theta$$

the last integral is a negative Kullback Leibler divergence and thus smaller or equal zero.

\+ easy to compute; - systematic error as only an approximation.

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Variational Bayes II

Joint Distribution implied by the previous DAG

$$p(I_t, \boldsymbol{\beta}_{1,t}, S_{1,t}, D_{1,t} | \boldsymbol{\Lambda}_1, \pi_t, \gamma, X_{1,t}) = P(I_t|\pi_t) p(\boldsymbol{\beta}_{1,t}|\boldsymbol{\Lambda}_1, I_t) \times \prod_n \Big(p(s_{1,t,n}|\boldsymbol{\beta}_{1,t}, \boldsymbol{x}_{1,t,n}, I_t, \gamma) P(y_{1,t,n}|s_{1,t,n}, I_t) \Big)$$

where $S_{1,t} = \{s_{1,t,1}, ..., s_{1,t,N}\}$ and $D_{1,t} = \{y_{1,t,1}, ..., y_{1,t,N}\}$.

- Approximate posterior by a mean field expansion $Q(\boldsymbol{\beta}_{1,t}|I_t) \prod_n Q(s_{1,t,n}|I_t)$.
- Write down negative free energy and maximize the functional iteratively w.r.t. all Q-distributions.
- The negative free energy $F_{\max}(Q)$ approximates the log marginal likelihood and thus $P(I_t|D_{1,t}, \boldsymbol{\Lambda}_1, \pi_t, \gamma, X_{1,t})$.

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