A partial history of latent variable models in genomics

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LPSM, Sorbonne université

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Introduction

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Y = observed variables (data), θ = model parameters, Z = latent variables

Parameters $\neq$ latent variables.

- θ can be fixed or random (e.g. frequentist vs Bayesian)
- Z is random, $\simeq$ same dimension as Y

Inference

Intractable likelihood.

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and apply the iterative expectation-maximization (EM) algorithm:

$$\theta^{(h+1)} = \underbrace{\arg\max_\theta}_{\text{M step}} \underbrace{\mathbb{E}_{\theta^{(h)}}}_{\text{E step}} [\log p_\theta(Y, Z) \mid Y]$$

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Critical step = E step. Given the current $\theta^{(h)}$, compute some moments of the conditional distribution $p_{\theta^{(h)}}(Z \mid Y)$:

$$\mathbb{E}_{\theta^{(h)}}[f(Z) \mid Y].$$

Outline

Differentially expressed genes

Multiple testing. $n \simeq 10^3, 10^4$ genes,

$$H_i = \{\text{gene } i \text{ has the same expression level under conditions } A \text{ and } B\},$$

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Mixture model [MBBTJ06]. 2 component mixture

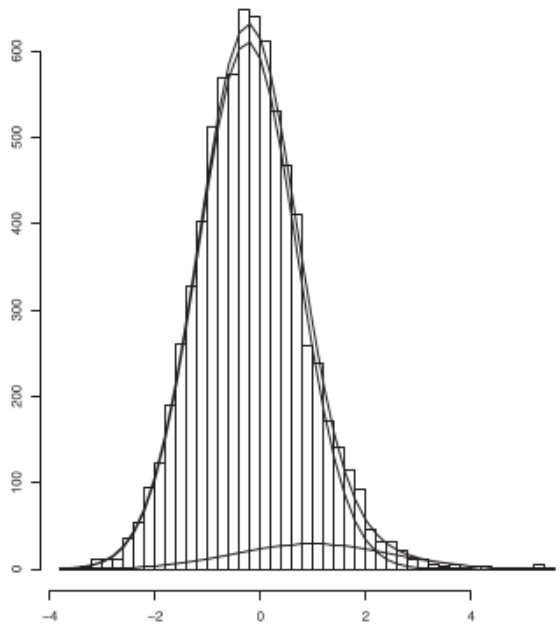
- $Z_i = 0$ if H_i holds, 0 otherwise

$$\pi = \Pr\{Z_i = 1\}$$

- $Y_i = -\Phi^{-1}(P_i)$ (Φ^{-1} = probit):

$$Y_i \mid Z_i = 0 \sim \mathcal{N}(0,1), \quad Y_i \mid Z_i = 0 \sim \mathcal{N}(\mu, \sigma^2)$$

- $\theta = (\pi, \mu, \sigma^2)$



Mixture model

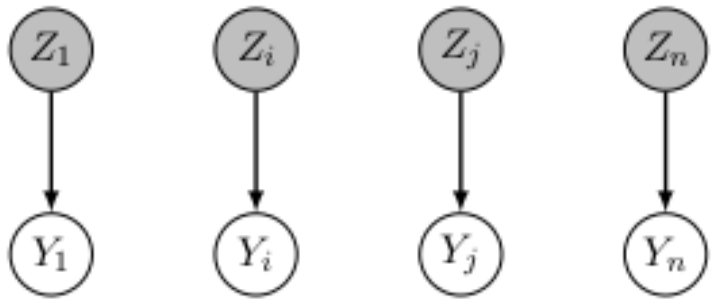
Easy EM. Independent couples (Z_i, Y_i)

$$p_\theta(Z_i \mid Y) = p_\theta(Z_i \mid Y_i)$$

→ Bayes formula:

$$\widehat{\tau}_i = \mathbb{P}_{\widehat{\theta}}\{Z_i = 1 \mid Y_i\}.$$

Graphical model:



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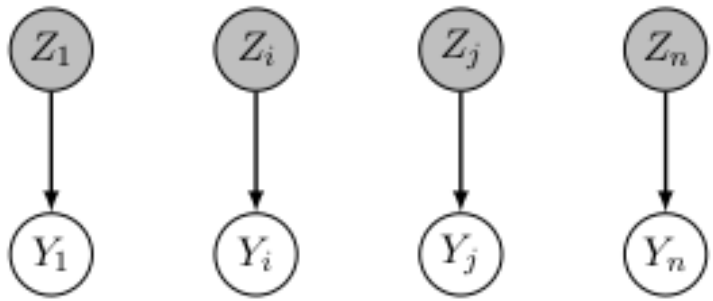


False discovery rate = fraction of false positives among positives:

$$\widehat{FDR}(t) = \sum_{i:\widehat{\tau}_i > t} (1 - \widehat{\tau}_i) \Big/ \#\{i : \widehat{\tau}_i > t\}.$$

- Choose the detection threshold t so that $\widehat{FDR}(t) \leqslant 5\%$ (say).

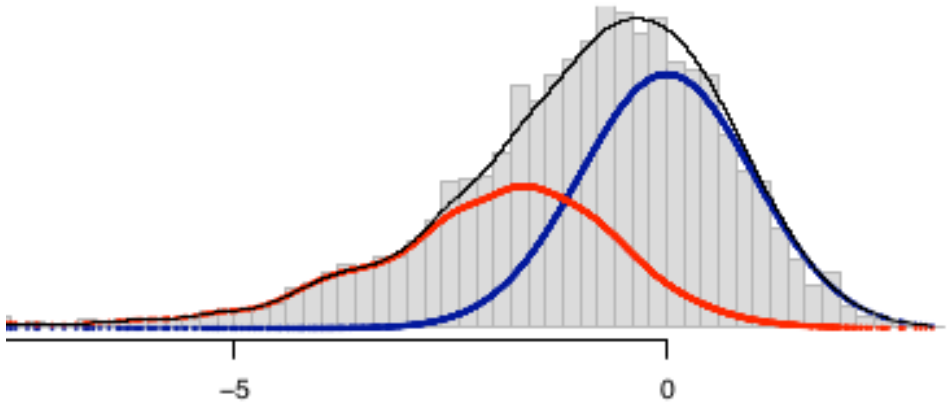
Semi-parametric mixture model

Non-parametric emission distribution.

- Available prior estimate $\widehat{\pi}$ [Sto02]
- Known null distribution

$$p_\theta(Y_i \mid Z_i = 0) = \mathcal{N}(Y_i; 0, 1)$$

- Free alternative distribution



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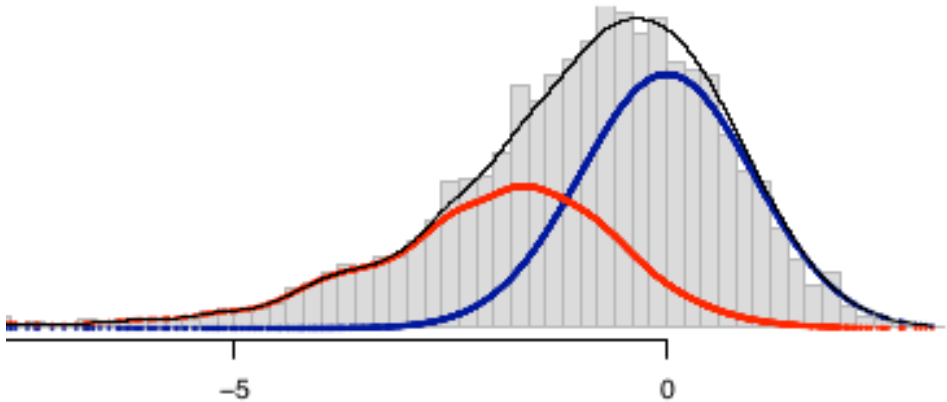

Kernel density estimate of $f_1 = p_\theta(Y_i \mid Z_i = 1)$:

$$\widehat{f}_1(y) = \sum_i \widehat{\tau}_i k(y - y_i) \Big/ \sum_i \widehat{\tau}_i.$$

Composed hypotheses

More complex latent distribution. n genes, Q comparison tests:

$$H_i^q = \{\text{gene } i \text{ is not differentially expressed in comparison } q\}$$

$\rightarrow$ Latent variable: $Z_i = (Z_i^1, \dots Z_i^Q) \in \{0,1\}^Q$, $\Rightarrow 2^Q$ possible configurations.

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- Y_i = probit p-values

$$p_\theta(Y_i \mid Z_i) = \prod_q p_\theta(Y_i^q \mid Z_i^q)$$

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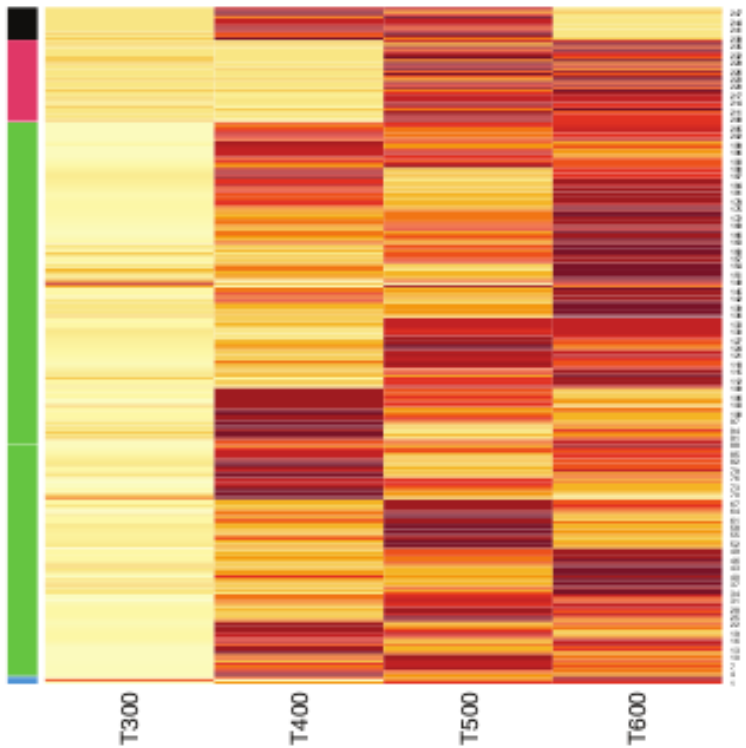
- Right: 5 time points.

$$H^q = \{\mathbb{E}Y(t_{q-1}) = \mathbb{E}Y(t_q)\}.$$

Genes with at least 2 successive differences.



$Z = (0110), (0011), (0111), (1111)$

And also

Avatars of the Poisson distribution.

- Zero inflated Poisson = Mixture Dirac(0) + Poisson
  $\rightarrow$ Regular mixture

- Over-dispersed Poisson = Negative binomial = Poisson-Gamma
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Gaussian mixed models.

- Z = Gaussian random effect
  $\rightarrow$ Close form conditional distribution

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Copy number variation

Data. n locus along the genome,

$$Y_t = \text{noisy measurement of the number of copies at locus } t$$

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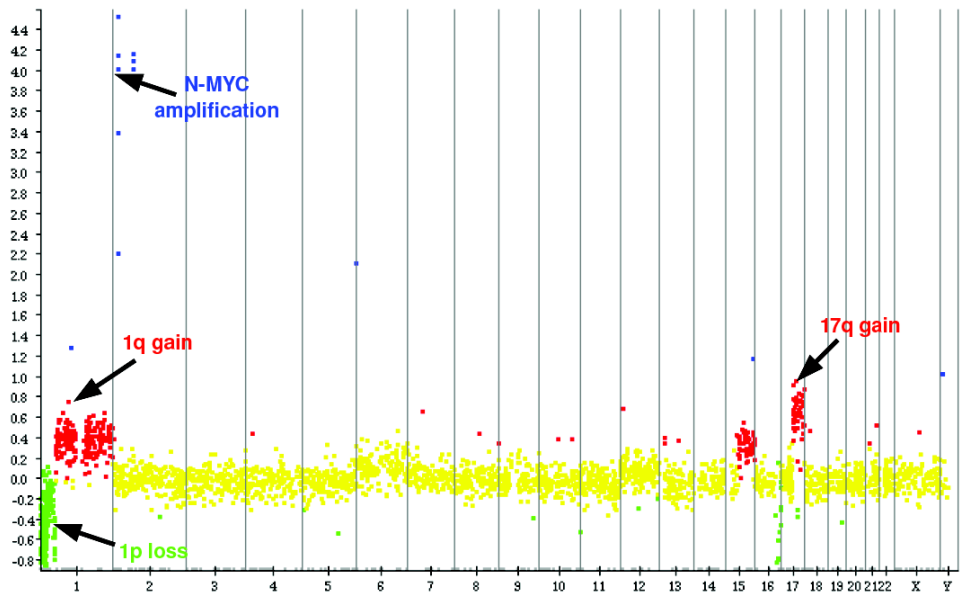
Example. [Hup08]



Hidden Markov model

Latent variable model.

- Z_t = status at locus t:

$$Z = (Z_t)_{1 \leqslant t \leqslant n} \sim MC(\nu, \pi), \qquad (\nu = \text{initial dist}, \pi = \text{transition matrix})$$

- $(Y_t)_{1 \leqslant t \leqslant n}$ independent $\mid Z$:

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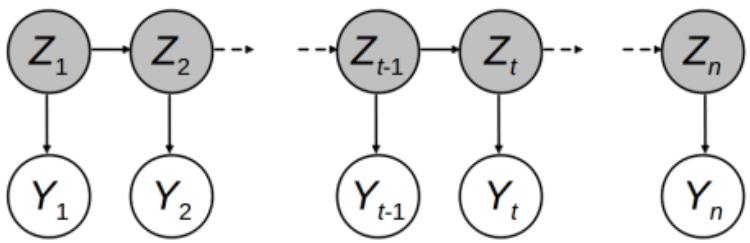
- Graphical model:



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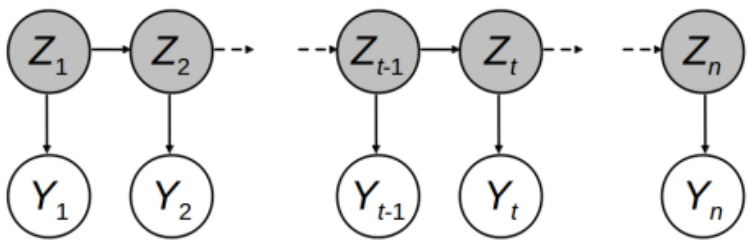

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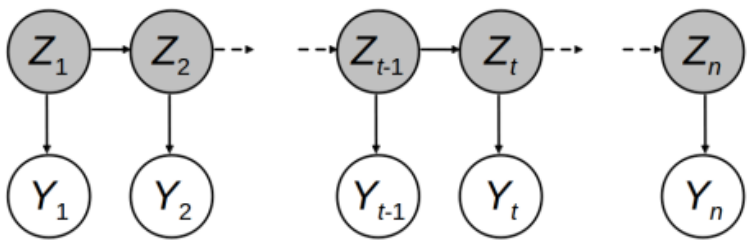

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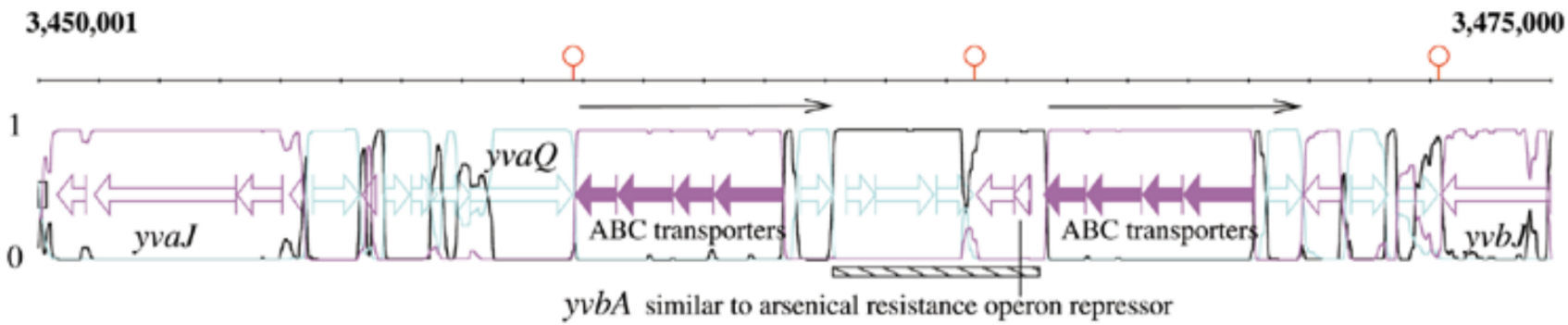
Classification. Most probable hidden path $\hat{Z}$ = Viterbi (dynamic programming) algorithm.

Gene detection

Aim starting from $Y =$

```
ATCTTTTTCGGCTTTTTTTAGTATCCACAGAGGTTATCGACAACATTTTCACATTACCAACCCCTGTGGACAAGGTTTTT
TCAACAGGTTGTCCGCTTTGTGGATAAGATTGTGACAACCATTGCAAGCTCTCGTTTATTTTGGTATTATATTTGTGTTT
TAACTCTTGATTACTAATCCTACCTTTCCTCTTTATCCACAAAGTGTGGATAAGTTGTGGATTGATTTCACACAGCTTGT
GTAGAAGGTTGTCCACAAGTTGTGAAATTTGTCGAAAAGCTATTTATCTACTATATTATATGTTTTCAACATTTAATGTG
TACGAATGGTAAGCGCCATTTGCTCTTTTTTTGTGTTCTATAACAGAGAAAGACGCCATTTTCTAAGAAAAGGAGGGACG
...
```

get



Modelling the Markov structure

Gene detection. [NBM+02]

- $Y = (Y_t)_{1 \leqslant t \leqslant n}$ = (bacterial) genome ($n \sim 10^6$)
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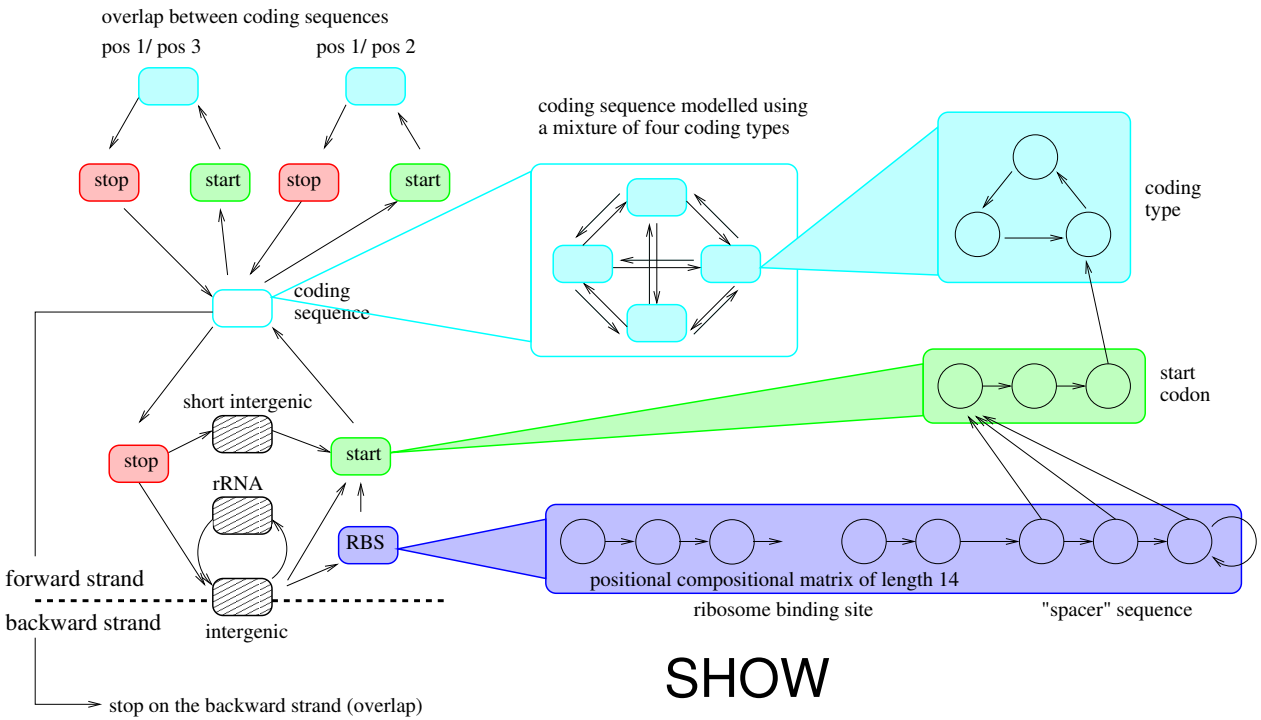
Transition graph of (Z_t).



Not modelling the emission distribution

Non-parametric HMM. Application of [AMR09] to HMM

- HMM with non-parametric emission distributions are generically identifiable.
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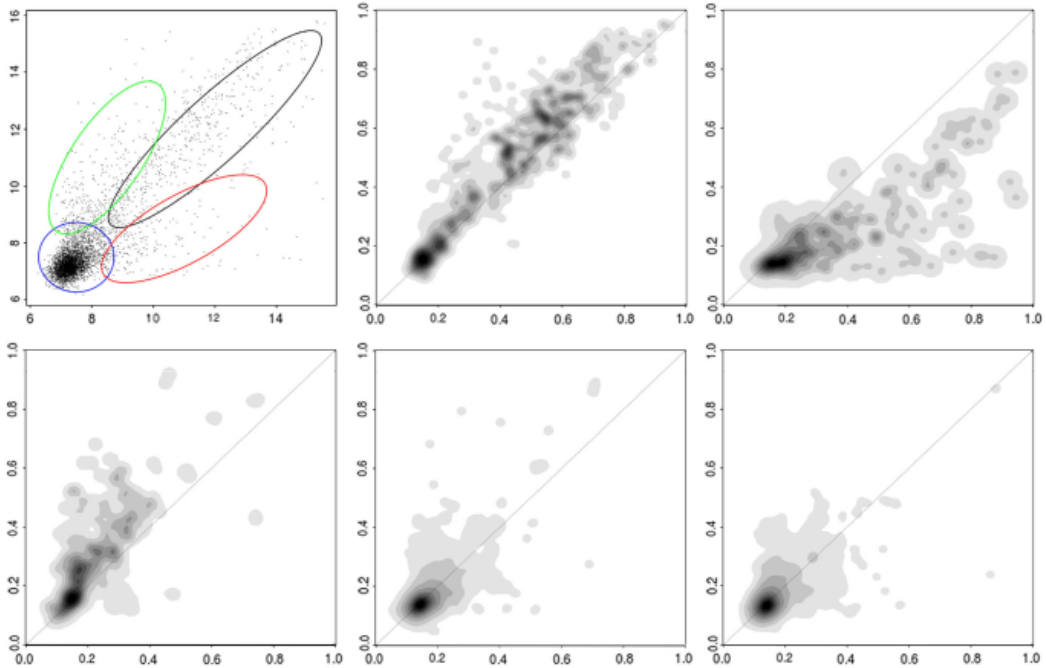
Differentially expressed regions along the genome. Kernel-density estimates in each of the $K = 5$ states



Tree-shaped Markov models

Remark. The graphical model of an HMM is tree-shaped, likewise this of many evolutionary models.

[1] Main problem in phylogeny = find the tree

[2] Breaks down for a network (e.g. horizontal transfert)

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Phylogeny.

- Y = genomes of extant species
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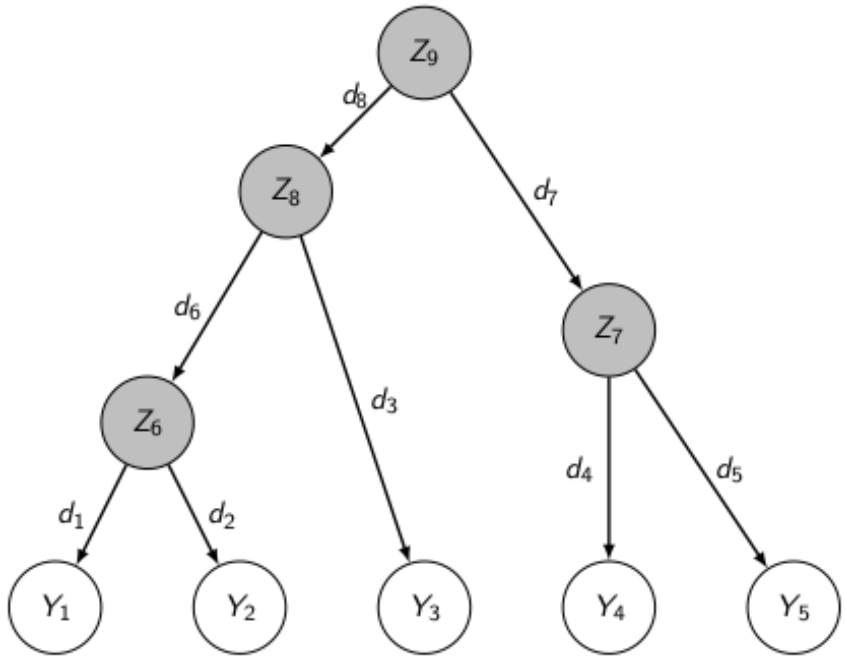
Likelihood for a given[1] tree[2].
Felsentein's algorithm [Fel81]
= 'upward-downward' recursion



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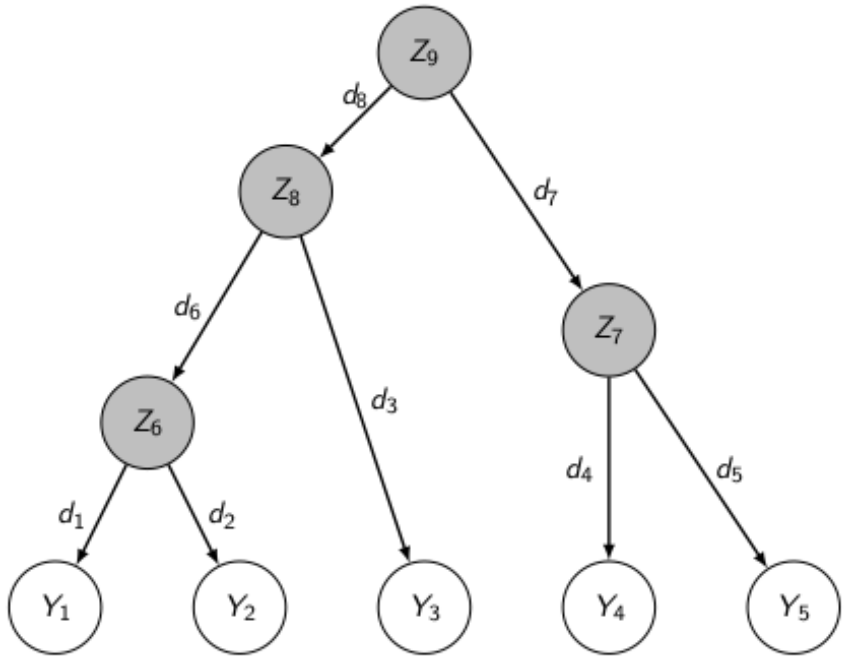

Ancestral trait reconstruction. Same problem and same solution for continuous (e.g. Brownian) latent Z [Lar14].

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Other complex latent structures

More complex latent structures may remain manageable using relevant algebraic properties.

- Sequence partitioning (segmentation): dynamic programming [AL89] and/or simple matrix products
  → quadratic complexity

- Spanning tree[3]-shaped graphical models: maximum spanning tree [Kru56] and/or simple determinant calculation [Cha82]
  → cubic complexity

. . . no generic rule to identify manageable E-steps.

[3] Phylogenetic trees are not spanning trees

Outline

Interaction networks

Data. $Y = n \times n$ interaction matrix:

$$Y_{ij} = 1 \text{ if entities } i \text{ and } j \text{ interact}, \quad = 0 \text{ otherwise}$$

Entities = protein, genes, operons, ...

Aim. Cluster entities according to their interaction profile.

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Stochastic block-model.

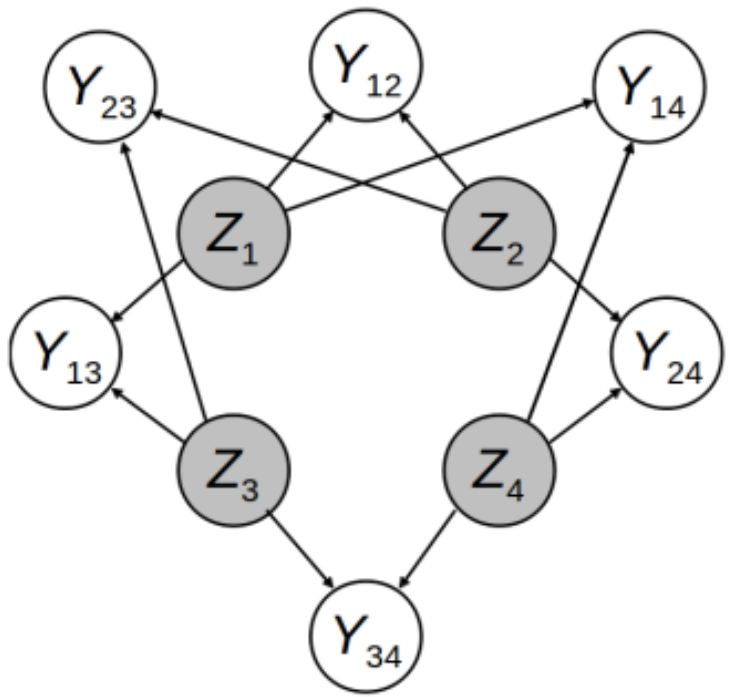
- Z_i cluster membership of entity i

$$\pi_i = \mathbb{P}\{Z_i = k\}$$

- Y_{ij} interaction (i, j)

$$\gamma_{k\ell} = \mathbb{P}\{Y_{ij} = 1 \mid Z_i = k, Z_j = \ell\}$$

(can include covariates, strength, ...).



Stochastic block-models

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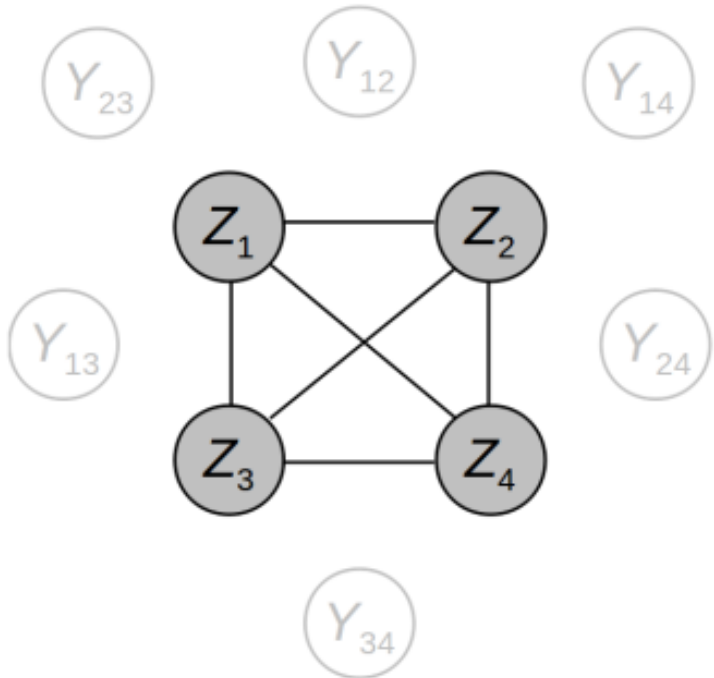
Nasty conditional distribution.

- 'Moralization' makes parents married
- The graphical model of $p_\theta(Z \mid Y)$ is a clique
- No nice factorization can be hoped to integrate it
- The E-step is intractable for, say, $n \geqslant 20$



→ Regular EM does not apply

Metabarcoding & PLN model

Data. n samples, p species,

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Poisson log-normal model.

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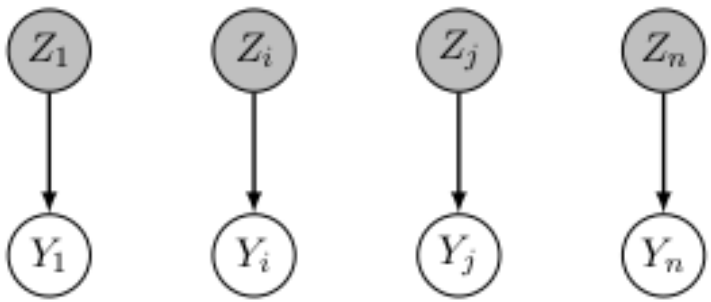

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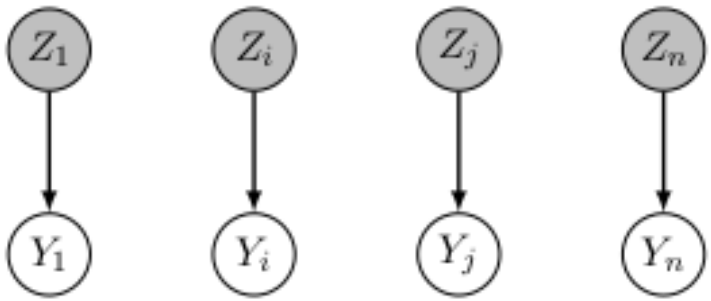

$Y_i, Z_i \in \mathbb{R}^p$

Nasty conditional distribution. $p_\theta(Z_i \mid Y_i) = p_\theta(Y_i, Z_i)/p_\theta(Y_i)$ but

$$\text{no close form for} \quad p_\theta(Y_i) = \int p_\theta(Y_i, z_i)\, \mathrm{d}z_i$$

- Intractable E step
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Variational EM

Principle. Replace $p_\theta(Z \mid Y)$ with some approximation $q_\psi(Z)$

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Evidence lower bound (ELBO).

$$\begin{aligned} ELBO(\theta, \psi) &= \log p_\theta(Y) - KL(q_\psi(Z) || p_\theta(Z \mid Y)) \\ &= \mathbb{E}_\psi[\log p_\theta(Y, Z)] - \mathcal{H}(q_\psi) \end{aligned}$$

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Variational EM.

$$\psi^{h+1} = \arg\max_\psi ELBO(\theta^{(h)}, \psi) = \arg\min_\psi KL(q_\psi(Z) || p_{\theta^{(h)}}(Z \mid Y)),$$

$$\theta^{(h+1)} = \arg\max_\theta ELBO(\theta, \psi^{(h+1)}) = \arg\max_\theta \mathbb{E}_{\psi^{(h+1)}}[\log p_\theta(Y, Z)]$$

Variational EM

Application. Critical choice = choice of $\mathcal{Q}$

SBM: $\mathcal{Q}$ = factorable distributions

$$q_\psi(Z) = \prod_i q_{\psi_i}(Z_i)$$

PLN: $\mathcal{Q}$ = Gaussian distributions

$$q_{\psi_i}(Z_i) = \mathcal{N}(Z_i; m_i, S_i)$$

Variational EM

Application. Critical choice = choice of $\mathcal{Q}$

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What do we know about VEM?

- Computationally efficient
- Works well in practice (estimation, classification, ...)
- Almost no theoretical guaranty
- Provides no measure of uncertainty

→ Need to consider alternatives or post-processing

Sequential Monte-Carlo for SBM

Weighted SBM with covariates.

$$Y_{ij} \sim \mathcal{P}(e^{\alpha_{k\ell} + x_i^\top \beta})$$

VEM provides : an estimate $\widehat{\theta}_{VEM}$ and an approximate $q_\psi(Z)$.
$\rightarrow$ Build an approximate posterior $p_{VEM}(Z, \theta \mid Y)$.

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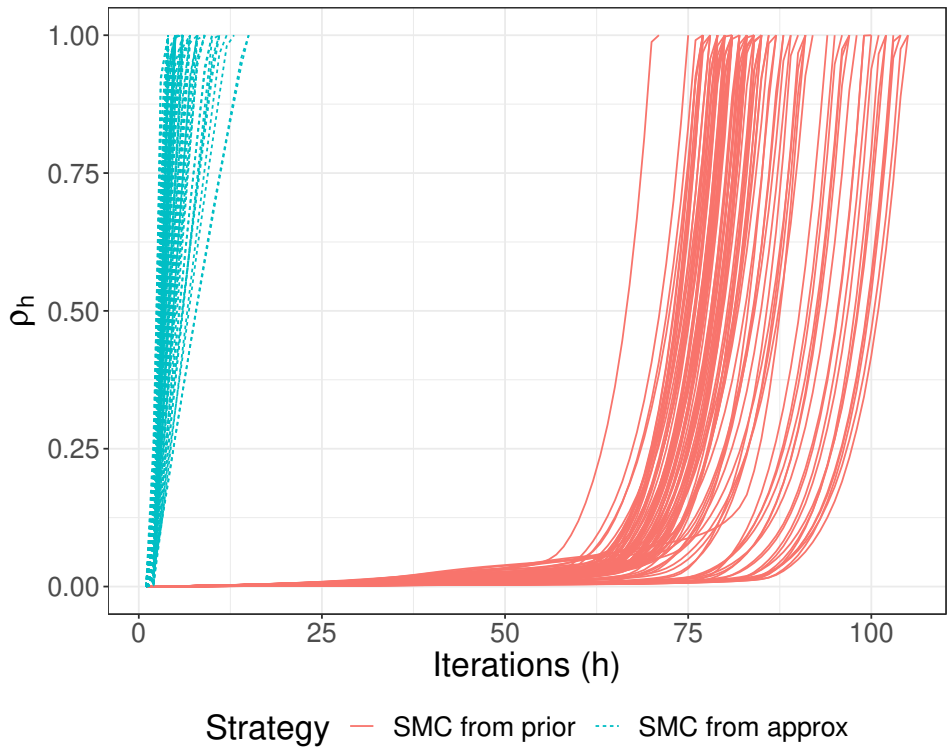
SMC algorithm. Sample from a sequence of distributions

$$p_h(Z, \theta \mid Y) \propto p(Z, \theta \mid Y)^{\rho_h} \; p_0(Z, \theta \mid Y)^{1-\rho_h}$$

- p_0 = starting distribution (p_{VEM}, prior, ...).
- p_H = posterior, when $\rho_H = 1$, .
- $\rho_1, \ldots, \rho_H$ tuned so to keep a sufficient effective sample size (ESS) at each step.

Sequential Monte-Carlo for SBM

Choice of p_0. Number of steps to reach the posterior from p_{VEM} or from the prior

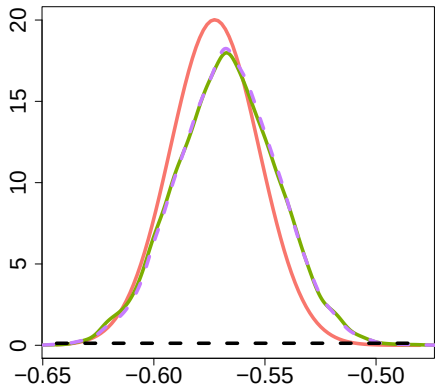


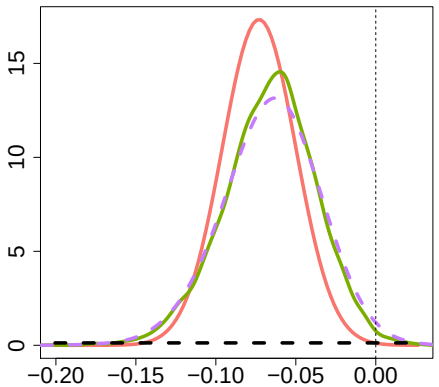
(Synthetic data)

An ecological example ($p = 51$ species)

Posterior distribution for β:

- p_{VEM}
- posterior with $\widehat{K}$
- (posterior with model averaging)





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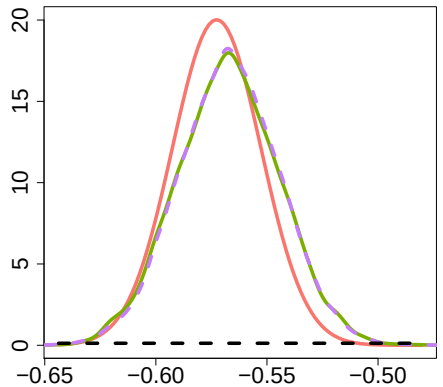
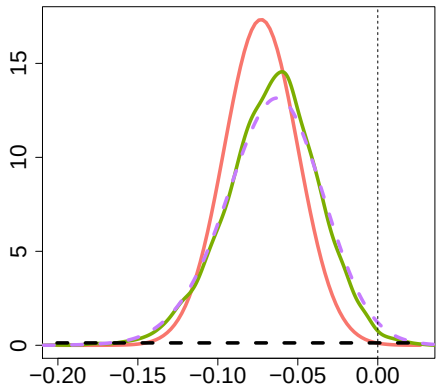
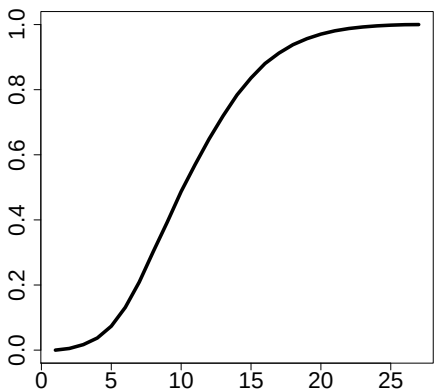




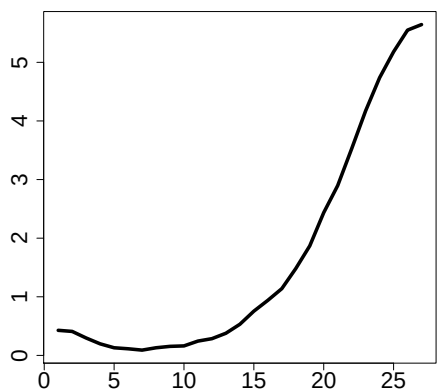
Path to the posterior:

- 25 steps to reach the posterior
- Mostly to recover the dependency structure between the Z_i

ρ_h



$MI(Z)$



Monte-Carlo EM for PLN

Monte-Carlo EM (MCEM). Replace the E step with a sampling step

$$(Z^m)_{1 \leqslant m \leqslant M} \overset{\text{iid}}{\sim} p_\theta(\cdot \mid Y) \qquad \rightarrow \quad \widehat{\mathbb{E}}[f(Z)] = M^{-1} \sum_{m=1}^{M} f(Z^m).$$

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Importance sampling. When $p_\theta(Z \mid Y)$ not available, sample from a surrogate proposal:

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Monte-Carlo EM.

- Regular M step to update $\theta^{(h)}$,
- Monte-Carlo E step, using a Gaussian q fitted to estimated the moments of $p_{\theta^{(h)}}(Z \mid Y)$,
- Starting with q_ψ from VEM.

Composite likelihood

Importance sampling has poor efficiency (low ESS) in 'large' dimension ($p \geqslant 5, 10$).

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Composite likelihood = linear combination of marginal likelihoods:

- Spread the p species into B overlapping blocks $\mathcal{C}_1, \ldots \mathcal{C}_B$ of size k;
- Define

$$c\ell_\theta(Y) = \sum_{b=1}^{B} \log p_\theta(Y^{\mathcal{C}_b});$$

- Get $\widehat{\theta}_{c\ell} = \arg\max_\theta c\ell_\theta(Y)$ using EM (which still applies);
- $\widehat{\theta}_{c\ell}$ is asymptotically normal, with known asymptotic variance (Godambe information replaces Fisher information).

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MCEM for composite likelihood. Same as before

- replacing the E step with e Monte Carlo step
- where importance sampling is made in dimension $k \ll p$.

Outline

Mixture models

More complex latent structure

Too complex latent structure

Summary

Latent variable model = generic and flexible modelling tool.

Inference mostly depends on the complexity of the conditional distribution $p_\theta(Z \mid Y)$.

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Latent variable model = generic and flexible modelling tool.

Inference mostly depends on the complexity of the conditional distribution $p_\theta(Z \mid Y)$.

Variational approximations provide efficient algorithms to manage too complex hidden structure, but with few statistical guaranties.

Monte Carlo-based methods can take advantage of variational approximations, but at a computational cost.

Some alternatives

Classical MCMC-based techniques often come at a prohibitive computational cost in genomics.

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Learning some basic useful transforms.
'Learn' a smooth 1D transform

$$\psi = \psi_{\mu,\sigma^2,y},$$

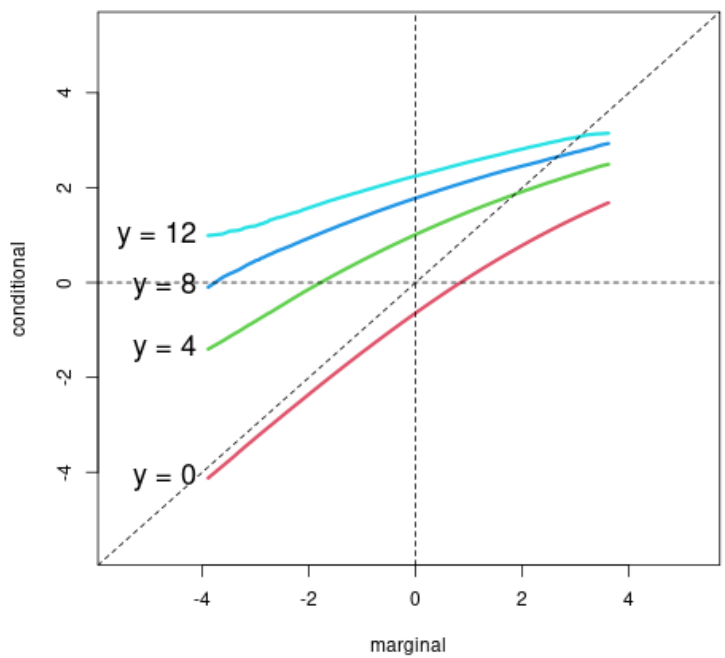
such that, if

$$Z \sim \mathcal{N}(\mu, \sigma^2)$$

then

$$\psi(Z) \sim p_{PLN(\mu,\sigma^2)}(Z \mid Y = y)$$

$\mu = 0, \quad \sigma^2 = 1$



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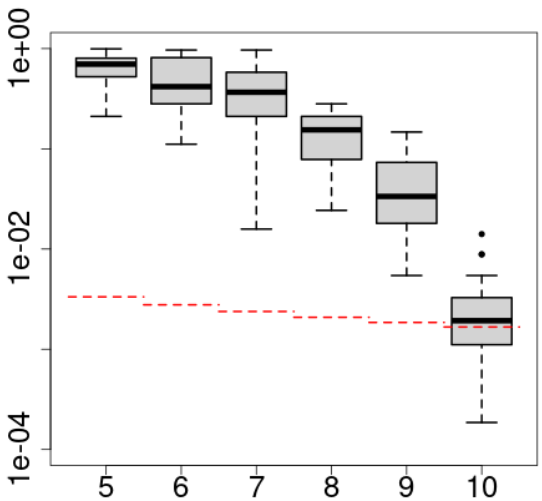
Monte-Carlo EM for PLN

p species, blocks of size k

Log-likelihood $\log p_\theta(Y)$

Synthetic data

Normality

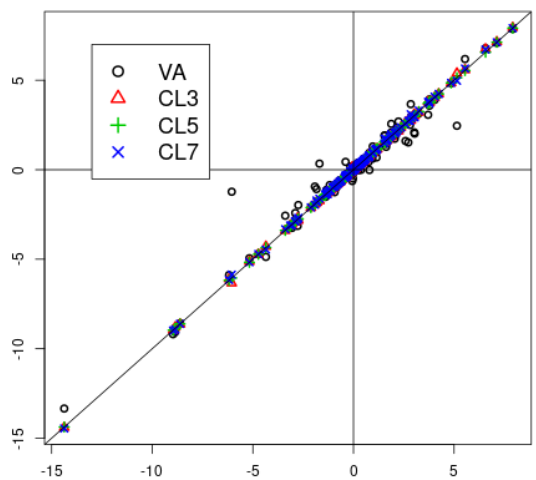


KS p-val = f(p)

Composite log-likelihood $c\ell_\theta(Y)$

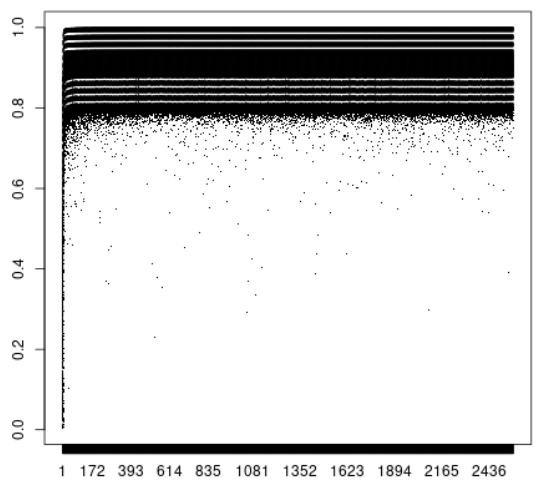
Barents fish ($n = 89$, $p = 30$)

Estimates $\widehat{B}$



Color = k

ESS ($k = 5$)



ESS = f(iteration)