Project 2: Augmenting functional information about human genes using probabilistic phylogenetic modeling

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Agenda

On Genes and Trees

Model

Peeling algorithm

The `amcmc` R package

The `aphylo` R package

Preliminary Results

Concluding Remarks

Agenda

Overview

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- Functional knowledge (e.g. Gene Ontology (GO) terms annotations) for human genes is very incomplete.
- Increase in association detection power using prior biological knowledge depends strongly on annotation completeness.
- Phylogenetic inference of annotations (i.e. using evolutionary trees) allows vast experimental knowledge in model systems (e.g. mouse, fruit fly, yeast) to augment human gene annotations.

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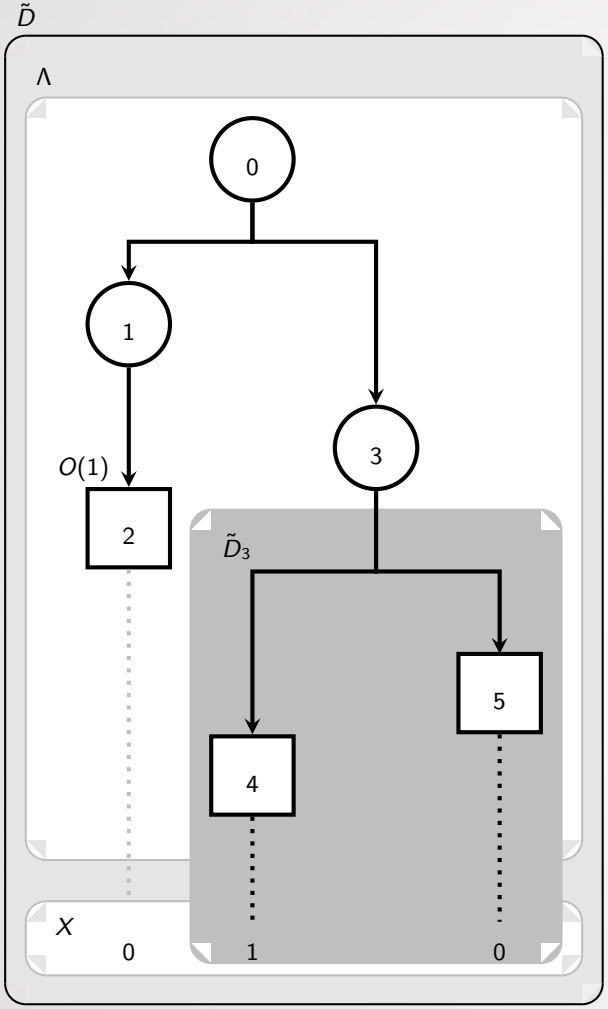
  to infer annotations on un-annotated genes in a *probabilistic way* (so it is not a 0/1 prediction).
- This predicted functional information will serve as prior covariates in Projects 1 and 3.

Agenda

Some definitions



Symbol	Description
$\tilde{D}$	Observed Annotated Tree
Λ	Partially ordered phylogenetic tree (PO tree)
$O(n)$	Offspring of node n
$\tilde{D}_n$	n-induced Annotated Sub-tree
X	True Annotation
X_{obs}	Experimental annotation

Where

$$x_{obs\,lp} = \begin{cases} 1 & \text{if the function is believed to be present} \\ 0 & \text{if the function is believed to be absent} \\ 9 & \text{if we don't have information for this node} \end{cases}$$

more details

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3. In this presentation, we will focus on the case that we are dealing with a single function.

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2. For node $n \in \{\text{peeling sequence}\}$ (from leafs to root) do:
   - 2.1 For $x_n \in \{0, 1\}$ do:

     Set $P_{n,x_n} = \begin{cases} \Pr(X_n = x_n \mid X_{obs\,n} = X_{obs\,n}) & \text{If n is a leaf} \\ L\left(X_n = x_n \,\middle|\, \tilde{D}_n\right) & \text{otherwise} \end{cases}$
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   - 2.2 Next n
3. At this point the matrix P should be completely filled, we can compute

$$L\left(\psi, \mu, \pi \middle| \tilde{D}\right) = \pi L\left(X_0 = 1 \,\middle|\, \tilde{D}_0\right) + (1 - \pi) L\left(X_0 = 0 \,\middle|\, \tilde{D}_0\right)$$

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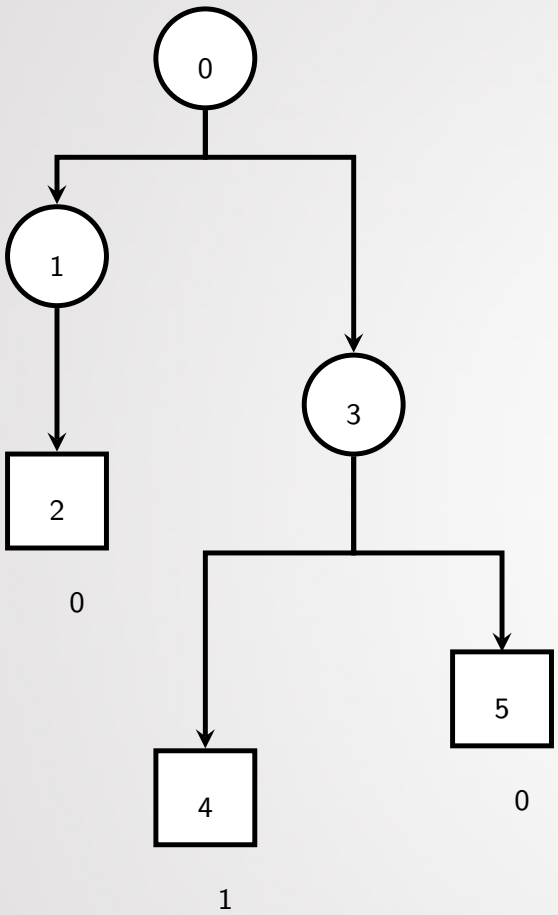
Let's see an example! more details

Peeling algorithm

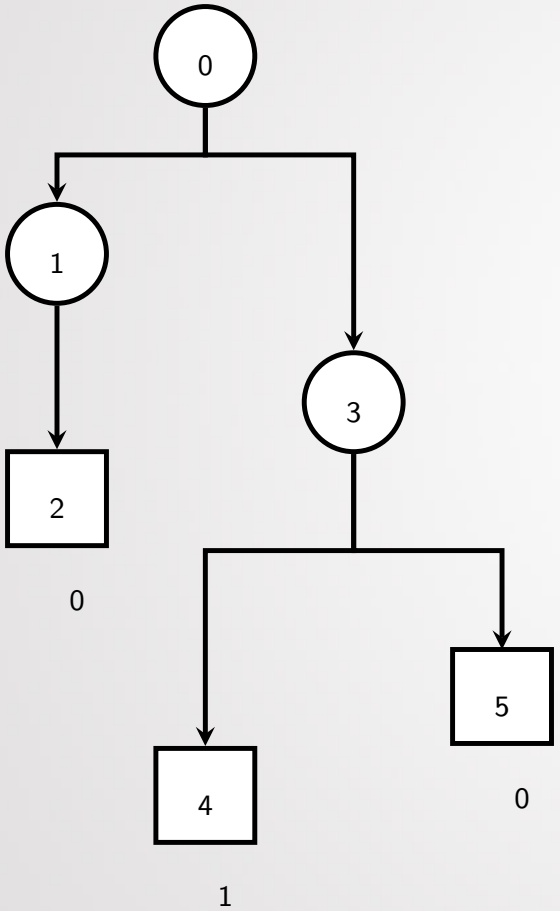


- Let's calculate the likelihood of observing this tree with the following parameters:

$$\begin{aligned} \text{Mislabeling a 0} : \psi_0 &= 0.05 \\ \text{Mislabeling a 1} : \psi_1 &= 0.01 \\ \text{Functional gain} : \mu_0 &= 0.04 \\ \text{Functional loss} : \mu_1 &= 0.01 \\ \text{Root node has the function} : \pi &= 0.05 \end{aligned}$$

Peeling algorithm (cont. 1)

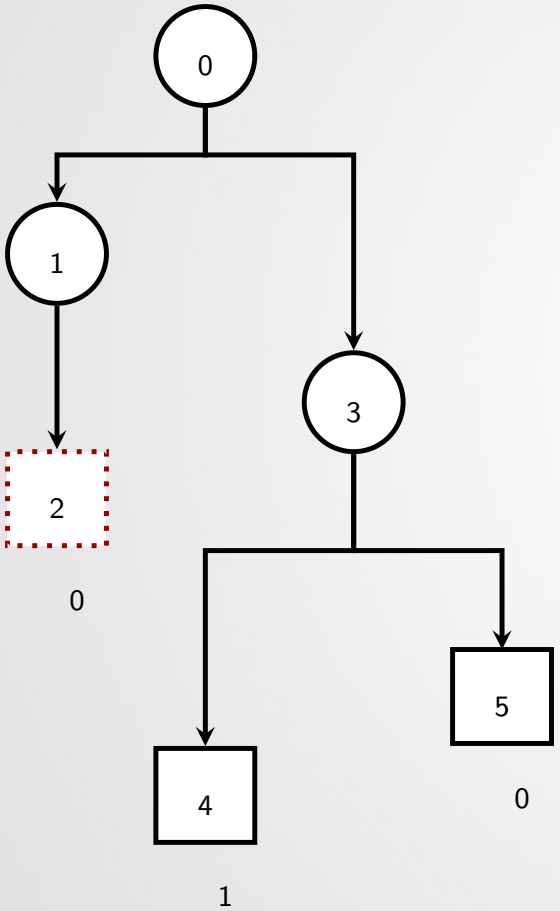
$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



	State 0	State 1
0		
1		
2		
3		
4		
5		

Peeling algorithm (cont. 1)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$

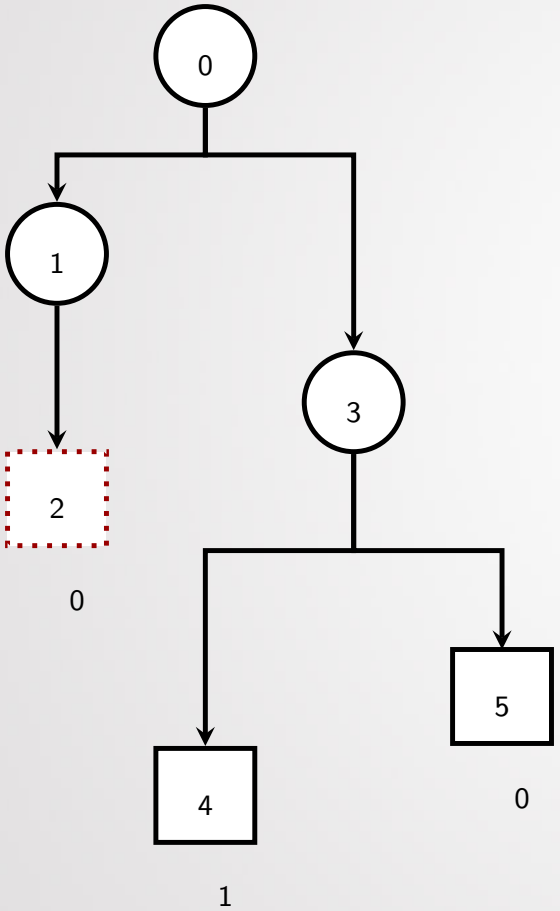


	State 0	State 1
0		
1		
2	0.9500	
3		
4		
5		

$\Pr(X_{obs2} = 0 \mid X_2 = 0) = 1 - \psi_0 = 0.95$

Peeling algorithm (cont. 1)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



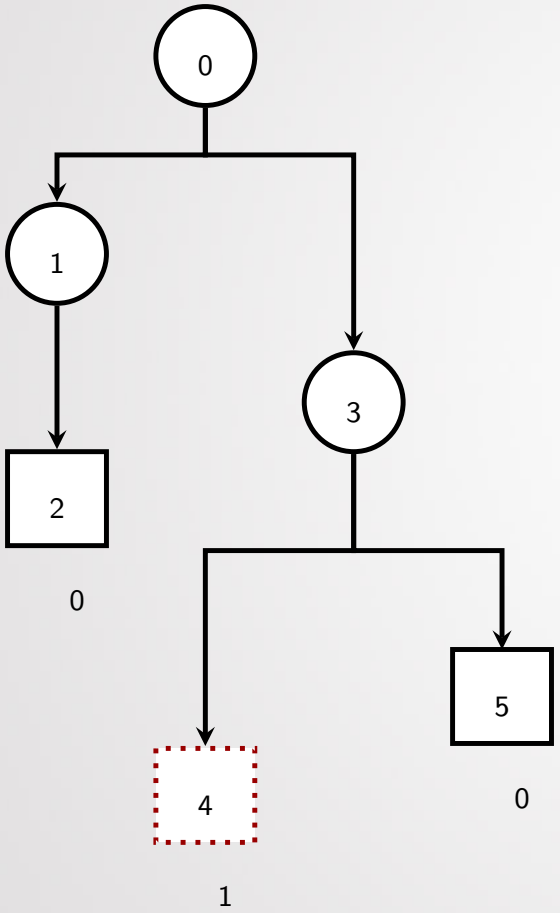
	State 0	State 1
0		
1		
2	0.9500	0.0100
3		
4		
5		

$\Pr(X_{obs2} = 0 \mid X_2 = 0) = 1 - \psi_0 = 0.95$

$\Pr(X_{obs2} = 0 \mid X_2 = 1) = \psi_1 = 0.01$

Peeling algorithm (cont. 1)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



	State 0	State 1
0		
1		
2	0.9500	0.0100
3		
4	0.0500	
5		

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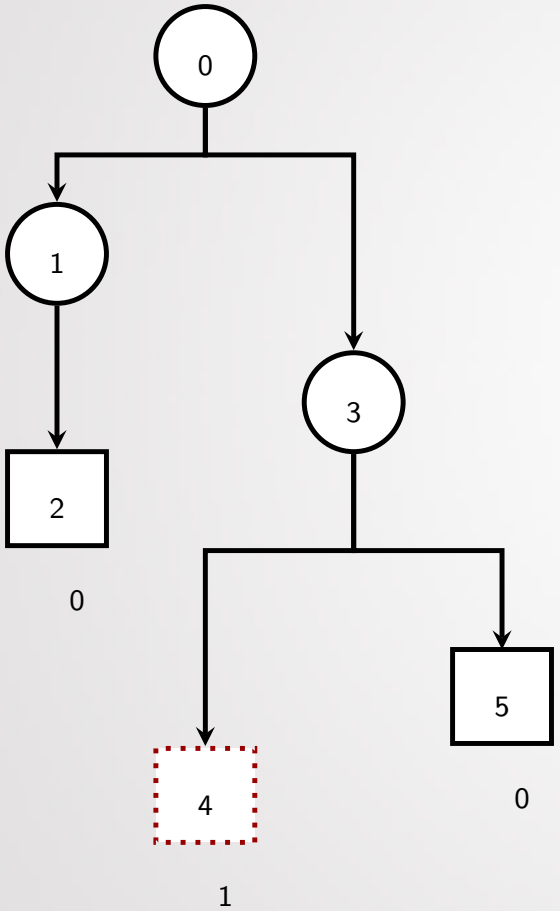
$\Pr(X_{obs2} = 0 \mid X_2 = 1) = \psi_1 = 0.01$

$\Pr(X_{obs4} = 1 \mid X_4 = 0) = \psi_0 = 0.05$

Peeling algorithm (cont. 1)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



	State 0	State 1
0		
1		
2	0.9500	0.0100
3		
4	0.0500	0.9900
5		

$$\Pr(X_{obs2} = 0 \mid X_2 = 0) = 1 - \psi_0 = 0.95$$
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$$\Pr(X_{obs4} = 1 \mid X_4 = 0) = \psi_0 = 0.05$$
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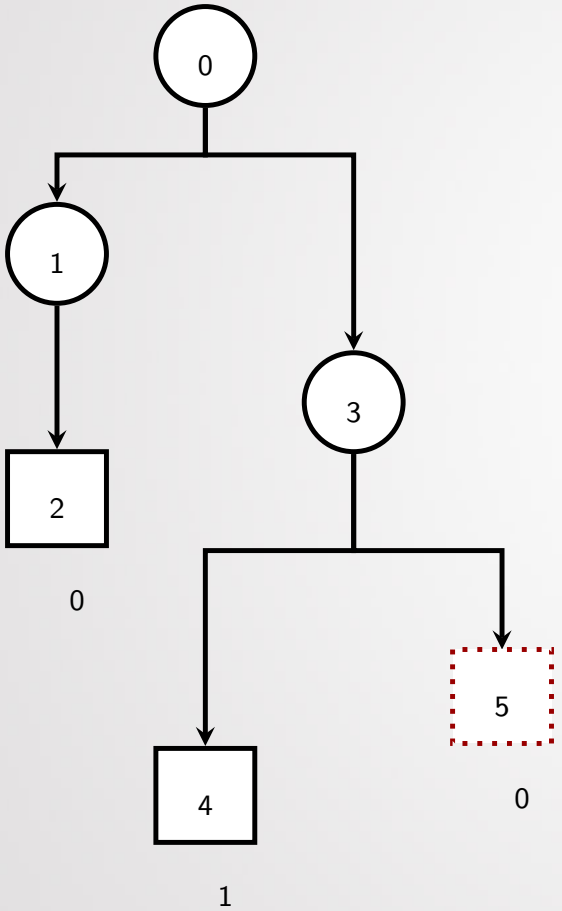
Peeling algorithm (cont. 1)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



	State 0	State 1
0		
1		
2	0.9500	0.0100
3		
4	0.0500	0.9900
5	0.9500	

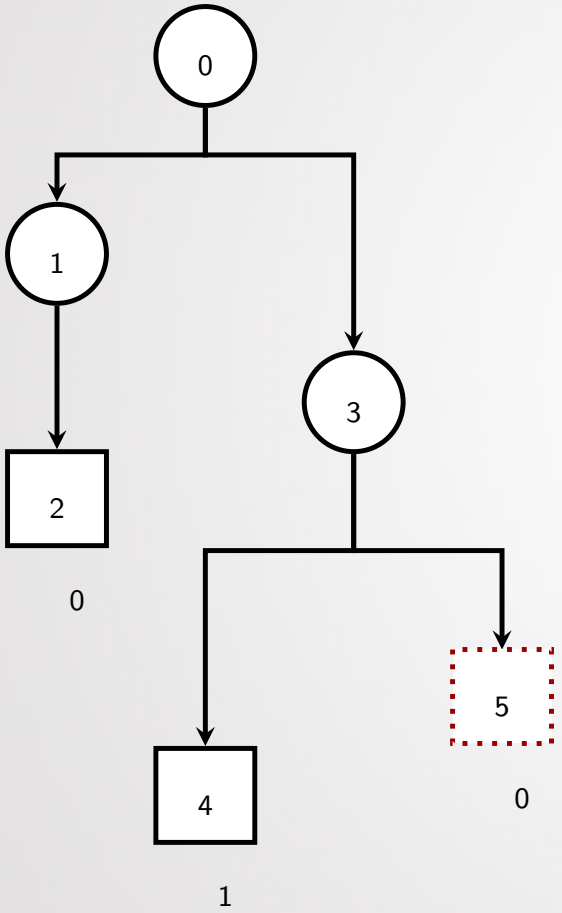
$$\Pr(X_{obs2} = 0 \mid X_2 = 0) = 1 - \psi_0 = 0.95$$
$$\Pr(X_{obs2} = 0 \mid X_2 = 1) = \psi_1 = 0.01$$

$$\Pr(X_{obs4} = 1 \mid X_4 = 0) = \psi_0 = 0.05$$
$$\Pr(X_{obs4} = 1 \mid X_4 = 1) = 1 - \psi_1 = 0.99$$

$$\Pr(X_{obs5} = 0 \mid X_5 = 0) = 1 - \psi_0 = 0.95$$

Peeling algorithm (cont. 1)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



	State 0	State 1
0		
1		
2	0.9500	0.0100
3		
4	0.0500	0.9900
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$$\Pr(X_{obs5} = 0 \mid X_5 = 0) = 1 - \psi_0 = 0.95$$
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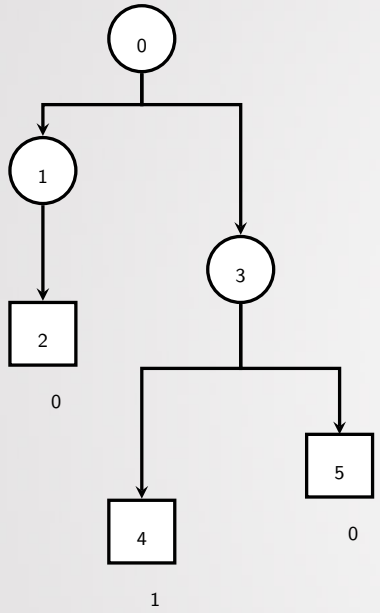
Peeling algorithm (cont. 2)

$\psi_0 = 0.05$ $\psi_1 = 0.01$ $\mu_0 = 0.04$ $\mu_1 = 0.01$ $\pi = 0.05$



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1		
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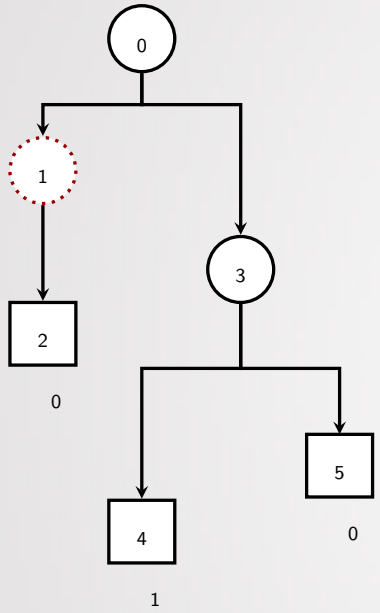
$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



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$$\mathsf{L}\left(X_1 = 0 \mid \tilde{D}_1\right) = \Pr\left(X_{obs2} = 0 \mid X_2 = 0\right)(1 - \mu_0) + \Pr\left(X_{obs2} = 0 \mid X_2 = 1\right)\mu_0$$

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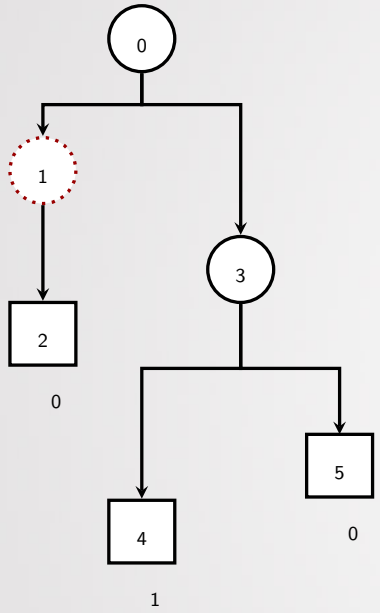

	State 0	State 1
0		
1	0.9124	
2	0.9500	0.0100
3		
4	0.0500	0.9900
5	0.9500	0.0100

$$\mathsf{L}\left(X_1 = 0 \mid \tilde{D}_1\right) = \Pr\left(X_{obs2} = 0 \mid X_2 = 0\right)(1 - \mu_0) + \Pr\left(X_{obs2} = 0 \mid X_2 = 1\right)\mu_0$$
$$= 0.9500 \times 0.96 + 0.0100 \times 0.04 = 0.9124$$

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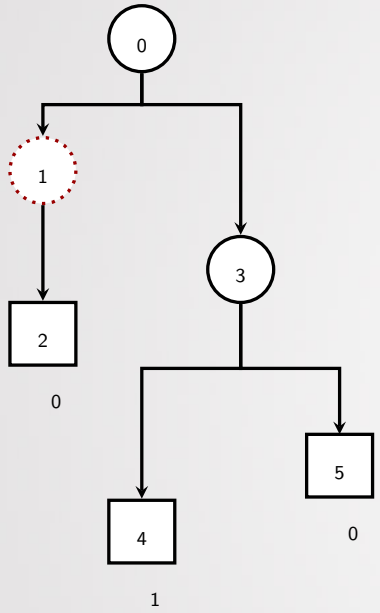

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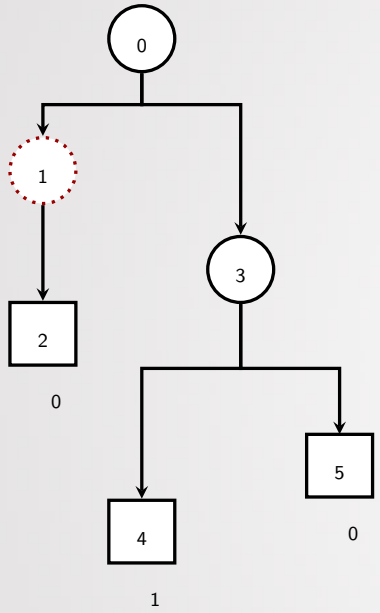

	State 0	State 1
0		
1	0.9124	0.0194
2	0.9500	0.0100
3		
4	0.0500	0.9900
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Peeling algorithm (cont. 3)

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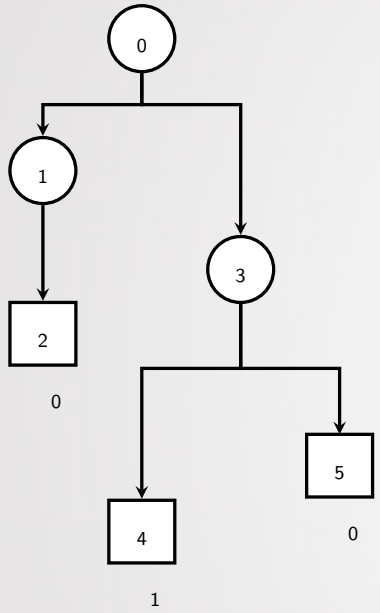

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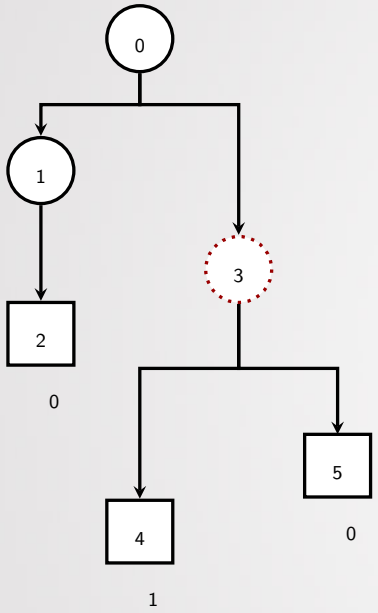

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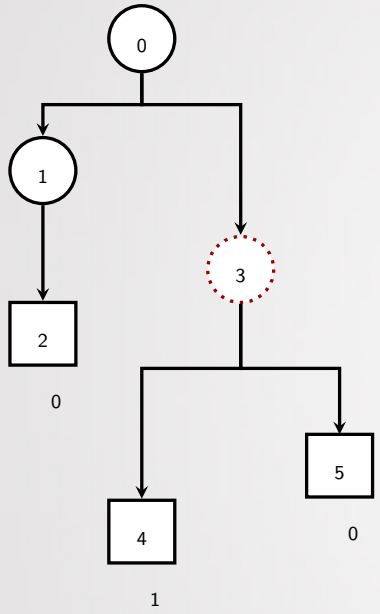
3		
4	0.0500	0.9900
5	0.9500	0.0100

$$\mathrm{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m \in \{4,5\}} \sum_{x_m \in \{0,1\}} \mathrm{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



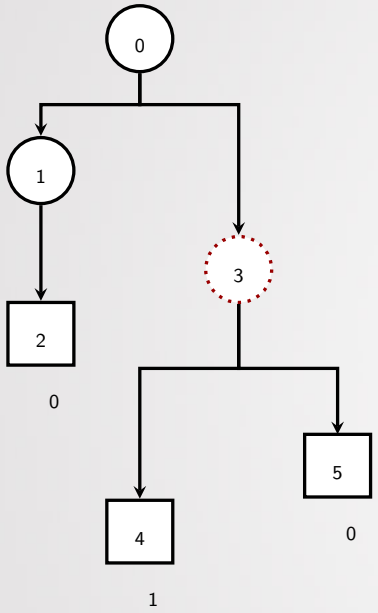
	State 0	State 1
0		
1	0.9124	0.0194
2	0.9500	0.0100
3		
4	0.0500	0.9900
5	0.9500	0.0100

$$\mathrm{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m \in \{4,5\}} \sum_{x_m \in \{0,1\}} \mathrm{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



	State 0	State 1
0		
1	0.9124	0.0194
2	0.9500	0.0100
3		
4	0.0500	0.9900
5	0.9500	0.0100

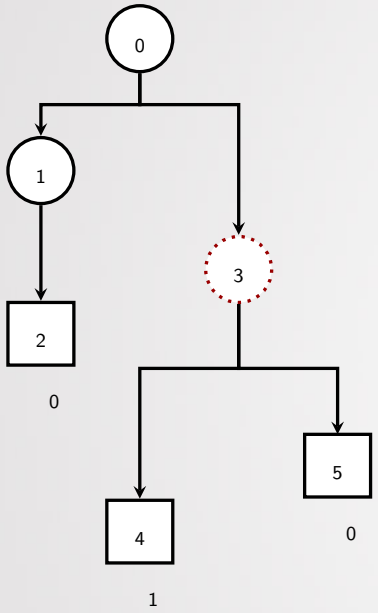
$$\mathrm{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m \in \{4,5\}} \sum_{x_m \in \{0,1\}} \mathrm{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

$$= (0.05(1-0.04) + 0.99 \times 0.04) \times (0.95(1-0.04) + 0.01 \times 0.04)$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



	State 0	State 1
0		
1	0.9124	0.0194
2	0.9500	0.0100
3	0.0799	
4	0.0500	0.9900
5	0.9500	0.0100

$$\mathrm{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m \in \{4,5\}} \sum_{x_m \in \{0,1\}} \mathrm{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

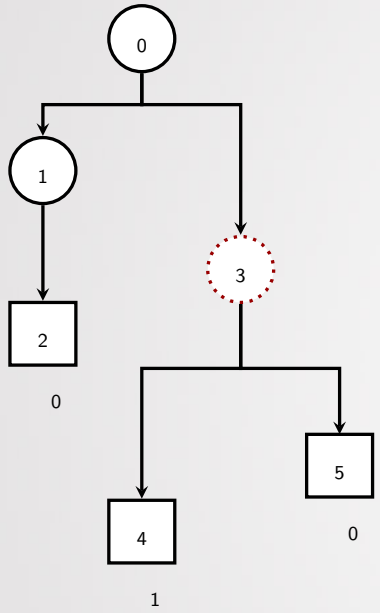
$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

$$= (0.05(1-0.04) + 0.99 \times 0.04) \times (0.95(1-0.04) + 0.01 \times 0.04)$$

$$= 0.0799$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



	State 0	State 1
0		
1	0.9124	0.0194
2	0.9500	0.0100
3	0.0799	0.0190
4	0.0500	0.9900
5	0.9500	0.0100

$$\mathrm{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m \in \{4,5\}} \sum_{x_m \in \{0,1\}} \mathrm{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

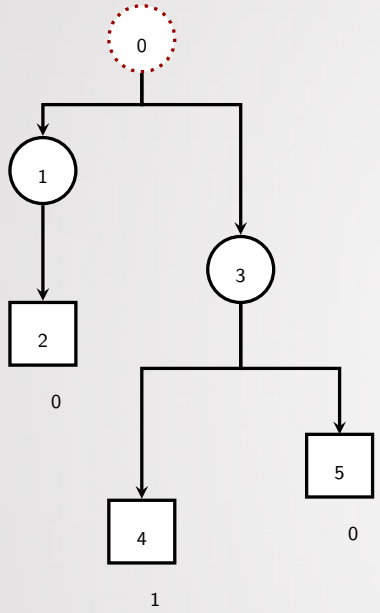
$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

$$= (0.05(1-0.04) + 0.99 \times 0.04) \times (0.95(1-0.04) + 0.01 \times 0.04)$$

$$= 0.0799$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



	State 0	State 1
0	0.0679	0.0006
1	0.9124	0.0194
2	0.9500	0.0100
3	0.0799	0.0190
4	0.0500	0.9900
5	0.9500	0.0100

$$\mathrm{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m\in\{4,5\}} \sum_{x_m\in\{0,1\}} \mathrm{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

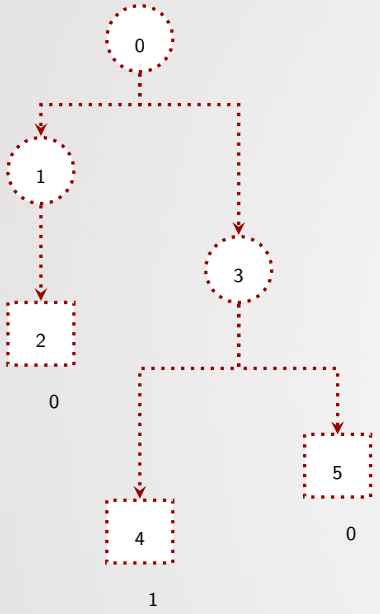
$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

$$= (0.05(1-0.04) + 0.99 \times 0.04) \times (0.95(1-0.04) + 0.01 \times 0.04)$$

$$= 0.0799$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



	State 0	State 1
0	0.0679	0.0006
1	0.9124	0.0194
2	0.9500	0.0100
3	0.0799	0.0190
4	0.0500	0.9900
5	0.9500	0.0100

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$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

$$= (0.05(1 - 0.04) + 0.99 \times 0.04) \times (0.95(1 - 0.04) + 0.01 \times 0.04)$$

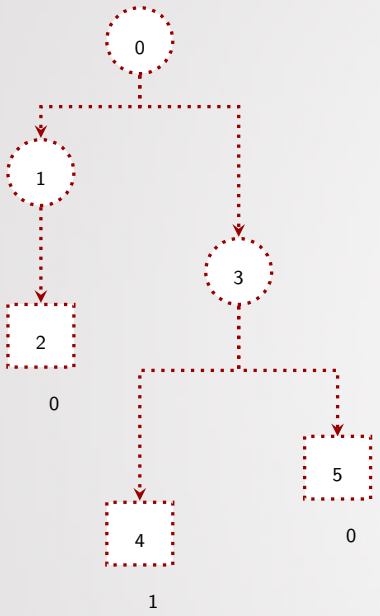
$$= 0.0799$$

Finally, the likelihood of this tree is:

$$\mathsf{L}\left(\psi, \mu, \Pi \mid \tilde{D}\right) = (1-\pi)\mathsf{L}\left(X_0 = 0 \mid \tilde{D}_0\right) + \pi \mathsf{L}\left(X_0 = 1 \mid \tilde{D}_0\right)$$

Peeling algorithm (cont. 3)

$$\psi_0 = 0.05 \qquad \psi_1 = 0.01 \qquad \mu_0 = 0.04 \qquad \mu_1 = 0.01 \qquad \pi = 0.05$$



	State 0	State 1
0	0.0679	0.0006
1	0.9124	0.0194
2	0.9500	0.0100
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$$\mathsf{L}\left(X_3 = 0 \mid \tilde{D}_3\right) = \prod_{m\in\{4,5\}} \sum_{x_m\in\{0,1\}} \mathsf{L}\left(X_m = x_m \mid \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_3 = 0\right)$$

$$= \left(0.05(1-\mu_0) + 0.99 \times \mu_0\right) \times \left(0.95(1-\mu_0) + 0.01 \times \mu_0\right)$$

$$= (0.05(1-0.04) + 0.99 \times 0.04) \times (0.95(1-0.04) + 0.01 \times 0.04)$$

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Finally, the likelihood of this tree is:

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$$= (1-0.05) \times 0.0679 + 0.05 \times 5.5619 \times 10^{-4} = 0.0646$$

Agenda

Yet another MCMC package

You may be wondering why, well:

1. Allows running multiple chains simultaneously (parallel)
2. Overall faster than other Metrop MCMC algorithms (from our experience)
3. Planning to include other types of kernels (the Handbook of MCMC)
4. Implements reflective boundaries random-walk kernel

Example: MCMC

```r
# Loading the packages
library(amcmc)
library(coda) # coda: Output Analysis and Diagnostics for MCMC

# Defining the ll function (data was already defined)
ll <- function(x, D) {
  x <- log(dnorm(D, x[1], x[2]))
  sum(x)
}

ans <- MCMC(
  # Ll function and the starting parameters
  ll, c(mu=1, sigma=1),
  # How many steps, thinning, and burn-in
  nbatch = 1e4, thin=10, burnin = 1e3,
  # Kernel parameters
  scale = .1, ub = 10, lb = c(-10, 0),
  # How many parallel chains
  nchains = 4,
  # Further arguments passed to ll
  D=D
  )
```

Example: MCMC (cont. 1)

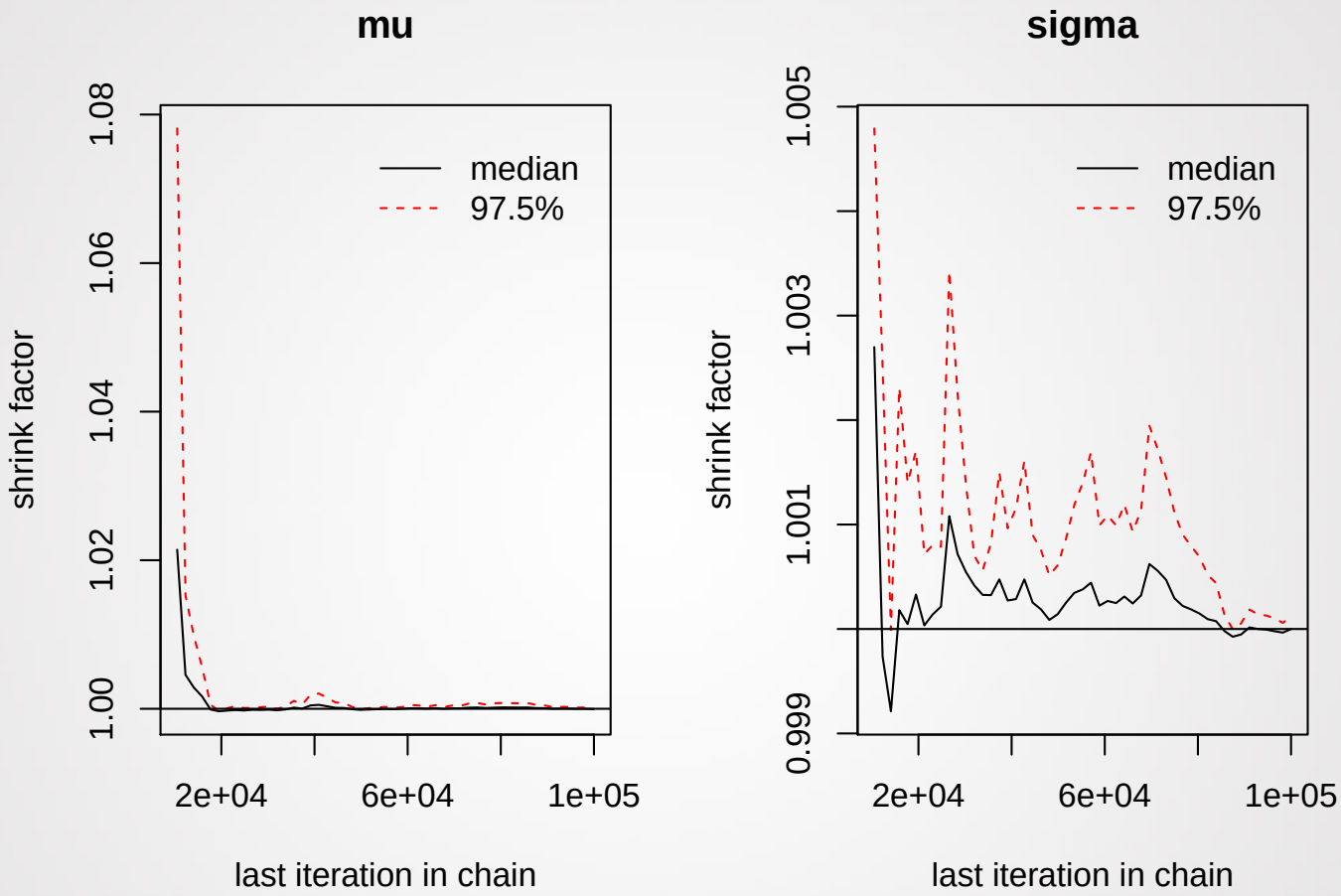

Figure 1: Gelman diagnostic for convergence. The closer to 1, the better the convergence. Rule of thumb: A chain has a reasonable convergence if it has a Potential Scale Reduction Factor (PSRF) below 1.15.

Example: MCMC (cont. 2)

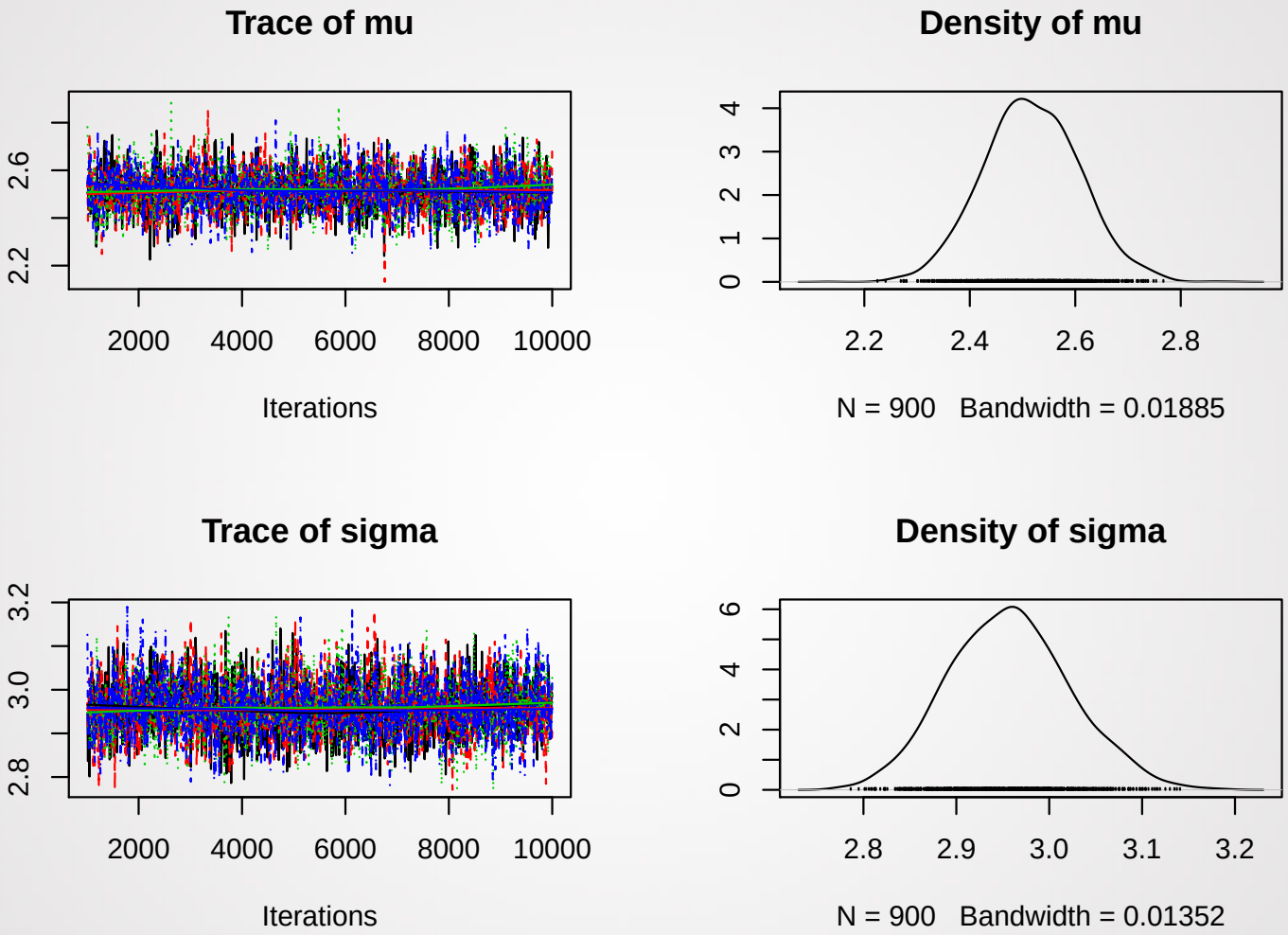

Figure 2: Posterior distribution

Agenda

aphylo in a nutshell

- Provides a representation of *annotated* partially ordered trees.

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- Interacts with the ape package (most used Phylogenetics R package with ~25K downloads/month)

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- Provides a representation of *annotated* partially ordered trees.
- Interacts with the ape package (most used Phylogenetics R package with ~25K downloads/month)
- Implements the loglikelihood calculation of our model (with C++ under-the-hood).

aphylo: Simulating Trees

```
set.seed(80)
tree <- sim_tree(5)
tree
```

```
##
## A PARTIALLY ORDERED PHYLOGENETIC TREE
##
##   # Internal nodes: 4
##   # Leaf nodes    : 5
##
##   Leaf nodes labels:
##     4, 5, 6, 7, 8.
##
##   Internal nodes labels:
##     0, 1, 2, 3.
```

```
atree <- sim_annotated_tree(
  tree = tree, P = 2,
  psi  = c(.05, .05),
  mu   = c(.2, .1),
  Pi   = .01
  )

atree
```

```
##
## A PARTIALLY ORDERED PHYLOGENETIC TREE
##
##   # Internal nodes: 4
##   # Leaf nodes    : 5
##
##   Leaf nodes labels:
##     4, 5, 6, 7, 8.
##
##   Internal nodes labels:
##     0, 1, 2, 3.
##
## ANNOTATIONS:
##      fun0000 fun0001
```

aphylo: Visualizing annotated data

```
plot(atree)
```

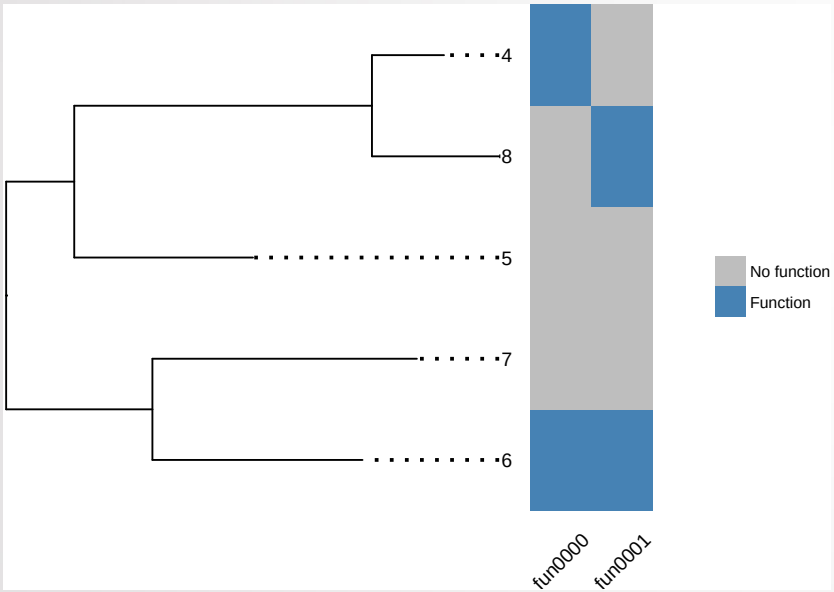

Figure 3: Visualization of annotations and tree structure.

```
plot_LogLike(atree)
```

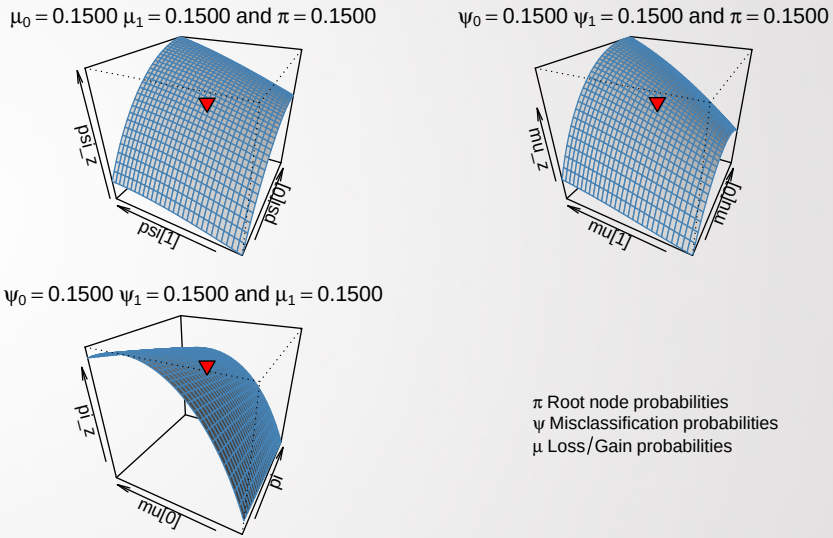

Figure 4: LogLikelihood surface of the simulated data

aphylo: Tree peeling

- The peeling algorithm requires visiting all nodes in a tree.

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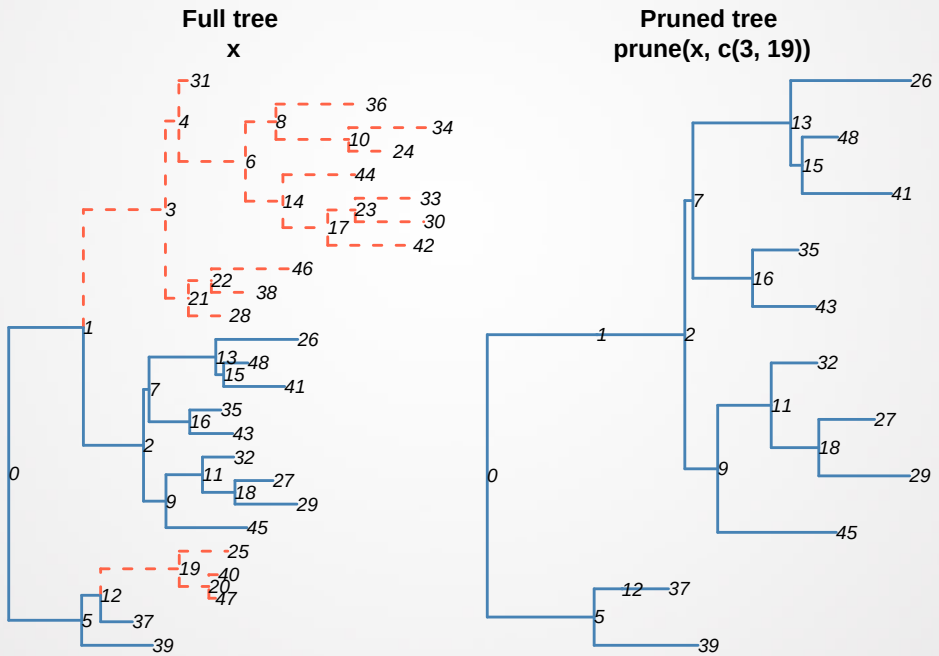

Figure 5: Peeling trees. In the original none of the leaf nodes under 3 and 9 have annotations. After peeling those branches, we go from having 49 nodes, to have 21

aphylo: Reading PantherDB data

```
# Reading the data
path <- system.file("tree.tree", package="aphylo")
dat <- read_panther(path)

# The tree
dat$tree
```

```
##
## Phylogenetic tree with 145 tips and 107 internal nodes.
##
## Tip labels:
##  AN5:MONBE|Gene=28576|UniProtKB=A9V8K6, AN7:SCHPO|PomBase=SPAC25B8.12c|UniProtKB=Q9UTA6
## Node labels:
##  AN0, AN1, AN2, AN3, AN4, AN6, ...
##
## Rooted; includes branch lengths.
```

aphylo: Reading PantherDB data (cont.)

```
# Extra annotations
head(dat$internal_nodes_annotations)
```

```
##     branch_length type          ancestor duplication
## AN0            NA    S              LUCA       FALSE
## AN1         0.057    S Archaea-Eukaryota       FALSE
## AN2         0.244    S         Eukaryota       FALSE
## AN3         0.436    S          Unikonts       FALSE
## AN4         0.417    S      Opisthokonts       FALSE
## AN6         0.684    D              <NA>        TRUE
```

aphylo: Predictions of the model

- Posterior probability:

$$\Pr\left(x_n = 1 \,\middle|\, \tilde{D}\right) = \frac{\Pr\left(\tilde{D} \,\middle|\, x_n = 1\right)}{\Pr\left(\tilde{D} \,\middle|\, x_n = 1\right) + \Pr\left(\tilde{D} \,\middle|\, x_n = 0\right) \frac{\left(1 - \Pr(x_n = 1)\right)}{\Pr(x_n = 1)}} \quad (1)$$

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Where

$$\Pr\left(x_n = 1\right) = \pi \Pr\left(x_n = 1 \mid x_0 = 1\right) + (1 - \pi) \Pr\left(x_n = 1 \mid x_0 = 0\right)$$

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- Posterior probability:

$$\Pr\left(x_n = 1 \,\middle|\, \tilde{D}\right) = \frac{\Pr\left(\tilde{D} \,\middle|\, x_n = 1\right)}{\Pr\left(\tilde{D} \,\middle|\, x_n = 1\right) + \Pr\left(\tilde{D} \,\middle|\, x_n = 0\right) \frac{\left(1 - \Pr(x_n = 1)\right)}{\Pr(x_n = 1)}} \quad (1)$$

Where

$$\Pr\left(x_n = 1\right) = \pi \Pr\left(x_n = 1 \mid x_0 = 1\right) + (1 - \pi) \Pr\left(x_n = 1 \mid x_0 = 0\right)$$

And

$$\begin{bmatrix} \Pr\left(x_n = 0 \mid x_0 = 0\right) & \Pr\left(x_n = 1 \mid x_0 = 0\right) \\ \Pr\left(x_n = 0 \mid x_0 = 1\right) & \Pr\left(x_n = 1 \mid x_0 = 1\right) \end{bmatrix} \approx \begin{bmatrix} 1 - \hat{\mu}_0 & \hat{\mu}_0 \\ \hat{\mu}_1 & 1 - \hat{\mu}_1 \end{bmatrix}^{dist_{0n}}$$

aphylo: Predictions of the model (cont.)

Gene	Posterior Prob
AN208:THEMA|EnsemblGenome=TM_0651|UniProtKB=Q9WZB9	0.10
AN22:PLAF7|EnsemblGenome=PFL1270w|UniProtKB=Q8I5F4	0.94
AN161:STRR6|EnsemblGenome=spr0263|UniProtKB=Q8DR95	0.22
AN168:BACSU|EnsemblGenome=BSU11140|UniProtKB=P70947	0.23
AN166:LISMO|Gene=CAD00341|UniProtKB=Q8Y515	0.60
AN192:BACSU|EnsemblGenome=BSU39550|UniProtKB=P54947	0.95

Table 2: Predicted probabilities for a subset of leafs of a phylogenetic tree using the `predict()` function after estimating the model parameters. The function analized was simulated on a phylogenetic tree from PantherDB.

aphylo: How good is our prediction

- Quality of the prediction

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$$\delta\left(X_{obs\,H}, \hat{X}_H\right) = \sum_{h,u \in H} \left[(x_{obs\,h} - \hat{x}_h)^2 (x_{obs\,u} - \hat{x}_u)^2\right]^{1/2} w_{hu}$$

aphylo: How good is our prediction

- Quality of the prediction

$$\delta\left(X_{obs\,H}, \hat{X}_H\right) = \sum_{h,u \in H} \left[(x_{obs\,h} - \hat{x}_h)^2 (x_{obs\,u} - \hat{x}_u)^2\right]^{1/2} w_{hu}$$

Which, assuming $\hat{x} \sim \text{Bernoulli}(\alpha)$, has expected value

$$\mathrm{E}(\delta) = \sum_{h,u \in H} w_{hu} \sum_{\hat{x}_h, \hat{x}_u \in \{0,1\}} \Pr(\hat{x}_h)\Pr(\hat{x}_u) \left[(x_{obs\,h} - \hat{x}_h)^2 (x_{obs\,u} - \hat{x}_u)^2\right]^{1/2}$$

```
prediction_score(ans)
```

```
## PREDICTION SCORE: ANNOTATED PHYLOGENETIC TREE
## Observed : 0.06
## Random   : 0.25
## ------------------------------------------------------------------------
## Values standarized to range between 0 and 1, 0 being best.
```

aphylo: How good is our prediction (cont. 1)

```
plot(prediction_score(ans), main="")
```

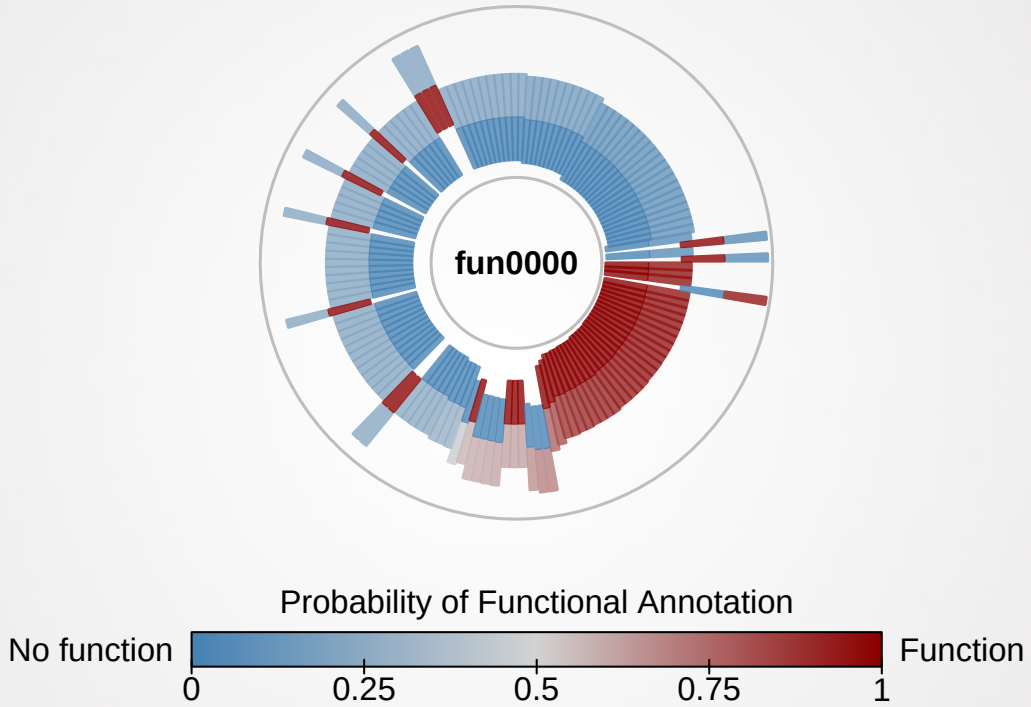


Figure 6: Predicted versus Observed values. Each slice of the pie represents a gene, the outer half of a slice is the predicted value, while the inner half is the observed value. Good predictions will coincide in color and show the slice closer to the center of the plot.

Agenda

A simulation study

Setup

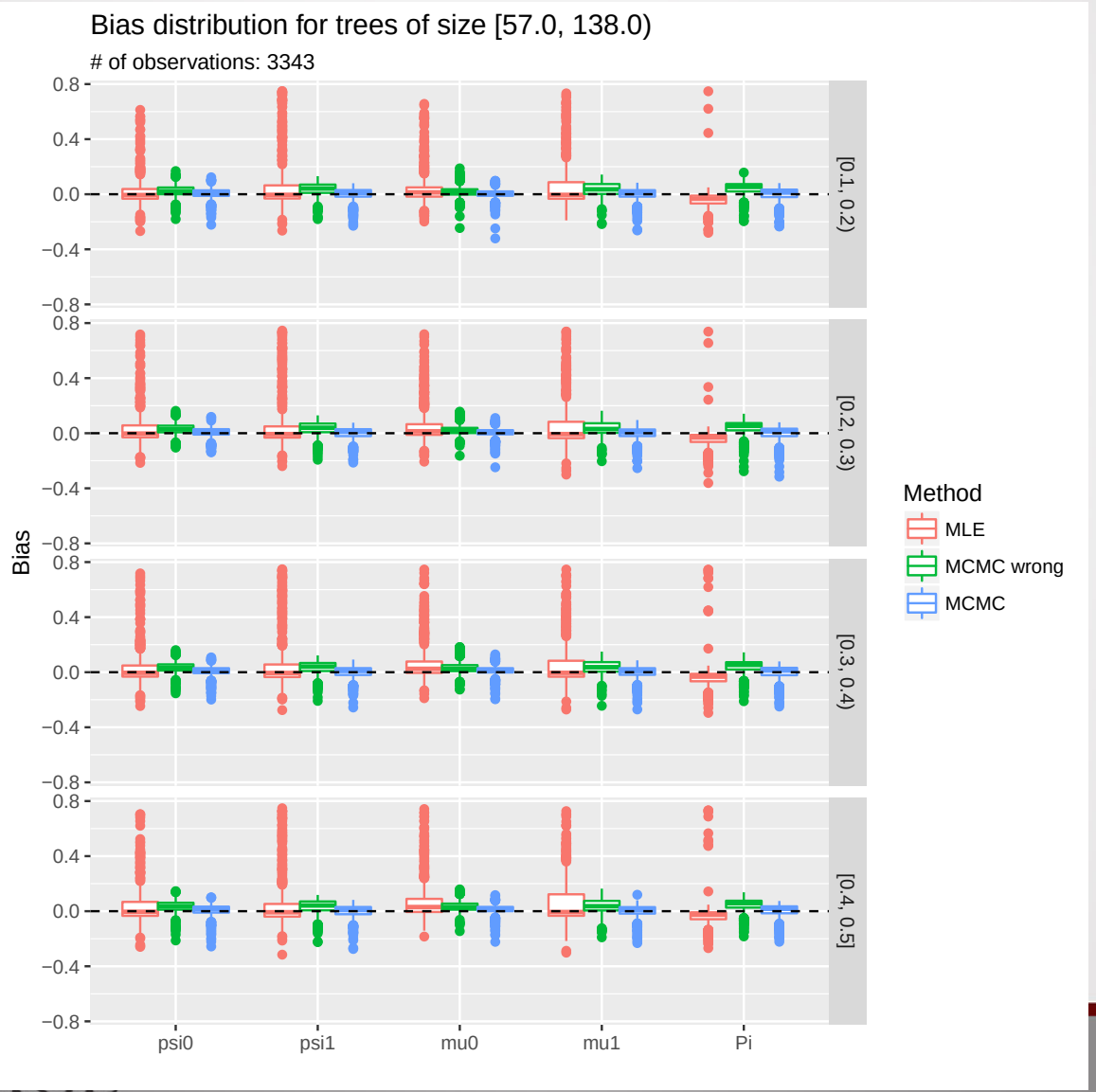
- Simulation study using ~13,000 families from PantherDB
- Using a Beta 1/20 prior, we simulated annotations:
  - Draw a set of the parameters $\{\psi_0, \psi_1, \mu_0, \mu_1, \pi\}$,
  - Simulated annotations using our model's Data Generating Process,
  - Randomly removed $p \in [.1, .5]$ proportion of annotations.
- With that data, we did parameter estimation and computed prediction scores using
  - MLE
  - MCMC with the right prior (Beta 1/20), and
  - MCMC with the wrong prior (Beta 1/10, twice the mean as the right prior).

  Both MCMC algorithms ran for 5×10^5 iterations, burn-in of 1×10^4, thinning of 100, and 5 chains.

more details

A simulation study

Bias



A simulation study

Prediction scores

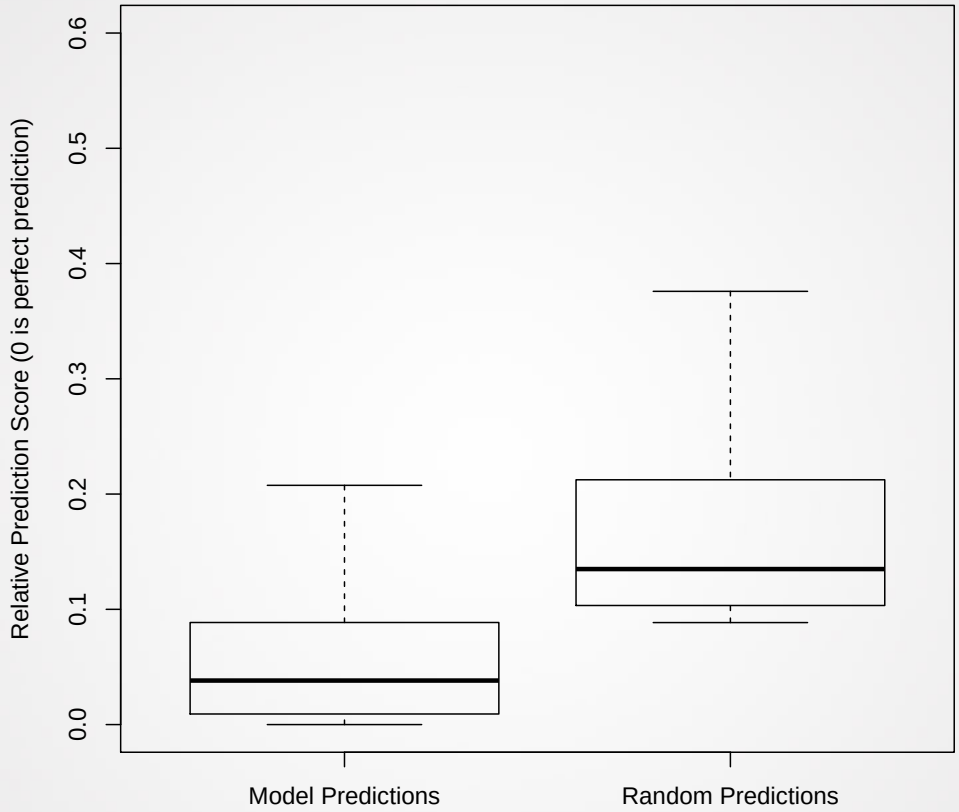


Figure 7: Distribution of prediction scores. The random prediction scores were computed analytically with parameter $p = 0.3$ (as resulting from the DGP).

Concluding Remarks

- A parsimonious model of gene functions: easy to apply on a large scale (we already ran some simulations using all 13,000 trees from PantherDB... and it took us less than 1 week with 10 processors only).

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- Already implemented, we are currently in the stage of writing the paper and setting up the simulation study.
- For the next steps, we are evaluating whether to include or how to include:
  - Type of node: speciation, duplication, horizontal transfer.
  - Branch lengths
  - Correlation structure between functions
  - Using Taxon Constraints to improve predictions
  - Hierarchical model: Use fully annotated trees by curators as prior information.

Thank you!

Project 2: Augmenting functional information about human genes using probabilistic phylogenetic modeling

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Formal definitions

go back

1. Phylogenetic tree: In our case, we talk about partially ordered phylogenetic tree, in particular, $\Lambda \equiv (N, E)$ is a tuple of nodes N, and edges

$$E \equiv \{(n, m) \in N \times N : n \mapsto m, n < m\}$$

2. Offspring of n: $O(n) \equiv \{m \in N : (n, m) \in E, n \in N\}$
3. Parent node of m: $r(m) \equiv \{n \in N : (n, m) \in E, m \in N\}$
4. Leaf nodes: $L(\Lambda) \equiv \{m \in N : O(m) = \{\emptyset\}\}$
5. Annotations: Given P functions, $X \equiv \{x_n \in \{0, 1\}^P : n \in L(\Lambda)\}$
6. Annotated Phylogenetic Tree $D \equiv (\Lambda, X)$
7. Observed Annotated Annotations $X_{obs} = \{x_{obs\,l}\}_{l \in L(\Lambda)}$,
8. Experimentally Annotated Phylogenetic Tree $\tilde{D} \equiv (\Lambda, X_{obs})$

Leaf node probabilities

go back

- The probability of the leaf nodes having annotations x_l conditional on the observed annotation is

$$\Pr(X_{obs\,l} = x_{obs\,l} \mid X_l = x_l) = \begin{cases} \psi & \text{if } x_{obs\,l} \neq x_l \\ 1 - \psi & \text{otherwise} \end{cases} \tag{2}$$

Where ψ can be either ψ_0 (mislabelling a zero), or ψ_1 (mislabelling a one).

Internal node probabilities

go back

- In the case of the internal nodes, the probability of a given state is defined in terms of the gain/loss probabilities

$$\Pr\left(X_n = x_l \,\middle|\, X_{r(n)} = x_{r(n)}\right) = \begin{cases} \mu & \text{if } x_n \neq x_{r(n)} \\ 1-\mu & \text{otherwise} \end{cases}$$

  Where μ can be either μ_0 (gain), or μ_1 (loss).

- Assuming independence accross offspring, we can write

$$\mathrm{L}\left(X_n = x_n \,\middle|\, \tilde{D}_n\right) = \prod_{m \in O(n)} \sum_{x_m \in \{0,1\}} \mathrm{L}\left(X_m = x_m \,\middle|\, \tilde{D}_m\right) \Pr\left(X_m = x_m \mid X_n = x_n\right) \quad (3)$$

  Notice that if m is a leaf node, then $\mathrm{L}\left(X_m = x_m \,\middle|\, \tilde{D}_m\right) = \Pr\left(X_m = x_m \mid X_{obs\,m} = x_{obs\,m}\right)$.

Likelihood of the tree

go back

- Once the computation reaches the root node, $n = 0$, equations (2) and (3): Allow us writing the likelihood of the entire tree

$$\mathrm{L}\left(\psi, \mu, \pi \middle| \tilde{D}\right) = \pi \mathrm{L}\left(X_0 = 1 \,\middle|\, \tilde{D}_0\right) + (1-\pi)\mathrm{L}\left(X_0 = 0 \,\middle|\, \tilde{D}_0\right) \quad (4)$$

A simulation study

Convergence

go back

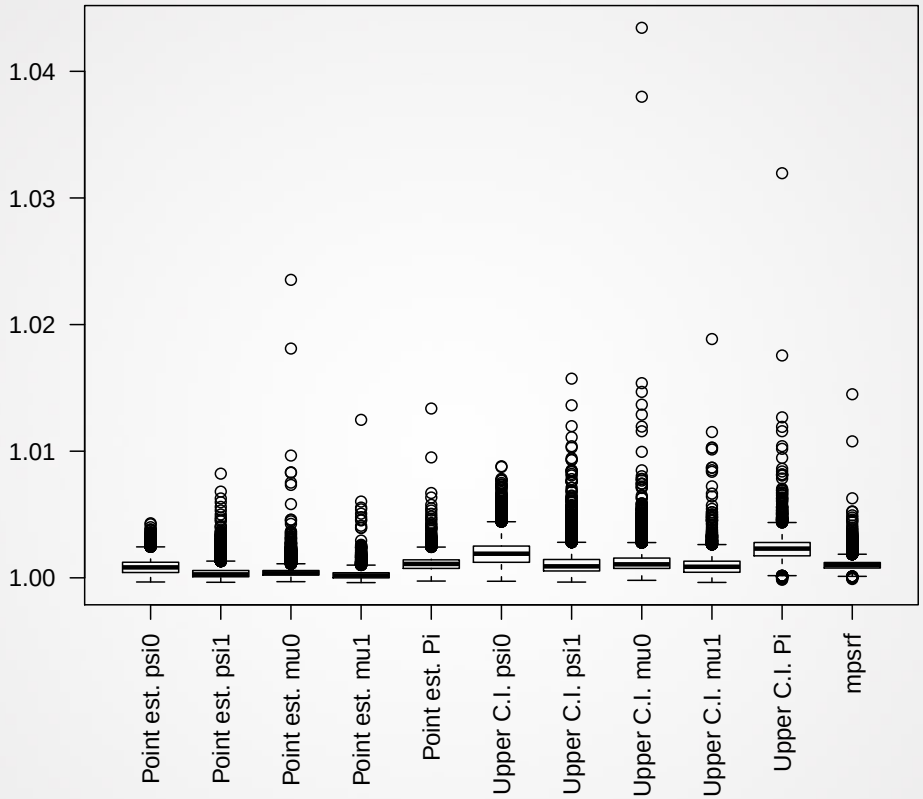

Figure 8: Gelman diagnostic for convergence. The closer to 1, the better the convergence. Rule of thumb: A chain has a reasonable convergence if it has a Potential Scale Reduction Factor (PSRF) below 1.15.