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

George G. Vega Yon
vegayon@usc.edu

Department of Preventive Medicine

University of Southern California

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Agenda

Gene Functions

Model

Peeling algorithm

The `aphylo` R package

The `amcmc` R package

Bayesian Estimation of the parameters

Concluding Remarks

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Introduction

- Manual Curation (GO): Good but infeasible
- Sparse gene functional annotation
- Take advantage of the phylogenetic information to make inference of
- This predicted functional information will serve as prior covariates (and prior gene-gene connections) in the second level of the hierarchical models in Projects 1 and 3. In particular, this project is the first to make predictions at large scale in a probabilistic manner.

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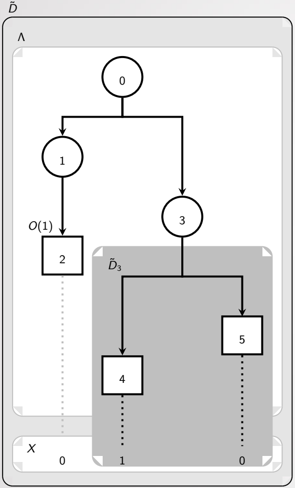
Some definitions



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	Experimental annotation

Where

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

Formal definitions

A probabilistic model of function propagation

1. For any given node, we can write down the probability of observing a *functional state* as a function of some model parameters and its offspring.
2. This version of our model has five parameters (probabilities):

   2.1 Root node had a function: π,
   2.2 Gain of function: μ_0,
   2.3 Loss of function: μ_1.
   2.4 Misclassification of:

   - A missing function as present, ψ_0, and
   - A present function as missing, ψ_1

   All five parameters are assumed to be equal across functions, this is, $\pi, \mu_0, \mu_1, \psi_0$, and ψ_1 are assumed to be independent of the functions that are analyzed.
3. In this presentation, we will focus on the case that $P = 1$.

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Peeling phylogenies

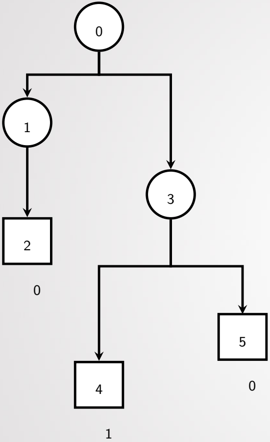
Given an Experimentally Annotated (PO) Phylogenetic Tree, the likelihood computation on a single function is as follows.

```
1. Create an matrix Pr of size $2 \times |N|$,
2. For node $n \in \{|N|, |N|-1, \dots, 1, 0\}$ do:
    2.1 For $z_n \in \{0,1\}$ do:
        2.1.1 Set $\mathrm{Pr}_{n,z_n} = \begin{cases} \Pr\left(Z_n = z_n \mid X_n = X_n\right) & \text{If n is a leaf} \\ \Pr\left(Z_n = z_n \,\middle|\, \tilde{D}_n\right) & \text{otherwise} \end{cases}$
        2.1.2 Next $z_n$
    2.2 Next $n$
3. At this point the matrix Pr should be completely filled, so following (3), we
   can compute
```

$$L\left(\psi, \mu, \pi \middle| \tilde{D}\right) = \sum_{z_0 \in \{0,1\}} \Pr\left(Z_0 = z_0 \mid \pi\right) \mathrm{Pr}_{0,z_0}$$

Let's see an example! details

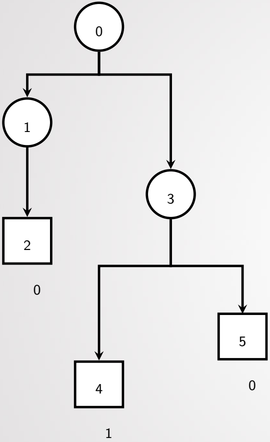
Peeling algorithm



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

$$
\begin{aligned}
\psi_0 &= 0.1 \\
\psi_1 &= 0.05 \\
\mu_0 &= 0.04 \\
\mu_1 &= 0.01 \\
\pi &= 0.5
\end{aligned}
$$

Peeling algorithm (cont. 1)



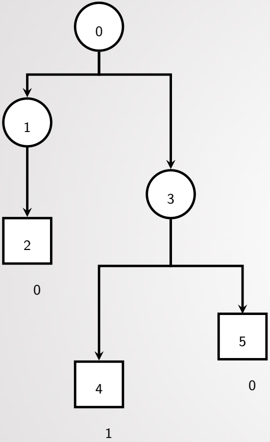
	State 0	State 1
0		
1		
2	0.9000	0.0500
3		
4	0.1000	0.9500
5	0.9000	0.0500

$$\Pr(Z_2 = 0 \mid X_2 = 0) = 1 - \psi_0 = 0.9$$
$$\Pr(Z_2 = 1 \mid X_2 = 0) = \psi_1 = 0.05$$

$$\Pr(Z_4 = 0 \mid X_4 = 1) = \psi_0 = 0.1$$
$$\Pr(Z_4 = 1 \mid X_4 = 1) = 1 - \psi_1 = 0.95$$

$$\Pr(Z_5 = 0 \mid X_5 = 0) = 1 - \psi_0 = 0.9$$
$$\Pr(Z_5 = 1 \mid X_5 = 0) = \psi_1 = 0.05$$

Peeling algorithm (cont. 2)

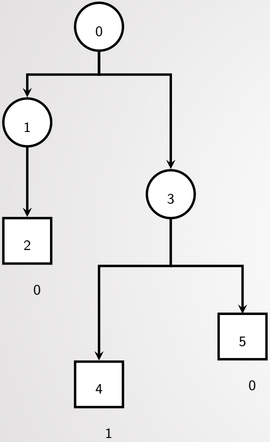


	State 0	State 1
0		
1	0.8660	0.0585
2	0.9000	0.0500
3		
4	0.1000	0.9500
5	0.9000	0.0500

$$\begin{aligned}\Pr\left(Z_1 = 0 \,\middle|\, \tilde{D}_1\right) &= \Pr(Z_2 = 0 \mid X_2 = 0)\Pr(Z_2 = 0 \mid Z_1 = 0) + \\ &\quad \Pr(Z_2 = 1 \mid X_2 = 0)\Pr(Z_2 = 1 \mid Z_1 = 0) \\ &= 0.9000 \times 0.96 + 0.0500 \times 0.04 = 0.866\end{aligned}$$

$$\begin{aligned}\Pr\left(Z_1 = 1 \,\middle|\, \tilde{D}_1\right) &= \Pr(Z_2 = 0 \mid X_2 = 0)\Pr(Z_2 = 0 \mid Z_1 = 1) + \\ &\quad \Pr(Z_2 = 1 \mid X_2 = 0)\Pr(Z_2 = 1 \mid Z_1 = 1) \\ &= 0.9000 \times 0.01 + 0.0500 \times 0.99 = 0.0585\end{aligned}$$

Peeling algorithm (cont. 3)



	State 0	State 1
0	0.0947	0.0037
1	0.8660	0.0585
2	0.9000	0.0500
3	0.1160	0.0551
4	0.1000	0.9500
5	0.9000	0.0500

$$
\begin{aligned}
\Pr\left(Z_3 = 0 \mid \tilde{D}_3\right) &= \prod_{m \in \{4,5\}} \sum_{z_m \in \{0,1\}} \Pr\left(Z_m = z_m \mid \tilde{D}_m\right) \Pr\left(Z_m = z_m \mid Z_3 = 0\right) \\
&= \left(0.1(1 - \mu_0) + 0.95 \times \mu_0\right) \times \left(0.9(1 - \mu_0) + 0.05 \times \mu_0\right) \\
&= (0.1(1 - 0.04) + 0.95 \times 0.04) \times (0.9(1 - 0.04) + 0.05 \times 0.04) \\
&= 0.116
\end{aligned}
$$

Finally, the likelihood of this tree is:

$$
\begin{aligned}
\mathrm{L}\left(\psi, \mu, \Pi \mid \tilde{D}\right) &= (1 - \pi)\Pr\left(Z_0 = 0 \mid \tilde{D}_0\right) + \pi \Pr\left(Z_0 = 1 \mid \tilde{D}_0\right) \\
&= (1 - 0.5) \times 0.0947 + 0.5 \times 0.0037 = 0.0492
\end{aligned}
$$

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`aphylo` in a nutshell

With `C++` (`RcppArmadillo`) under-the-hood, `aphylo`:

1. Defines an S3 class for representing partially ordered trees, including validation of it.
2. Includes from the basic methods: `print`, `plot`, and `summary`; to more advanced such as `prune`.
3. Defines an S3 class for representing *annotated* partially ordered trees.
4. Includes functions for converting from and to `phylo` class objects from the ape package (most used/cited package in Phylogenetics in R with ~25K downloads/month)
5. Implements the loglikelihood calculation of our model.

We'll talk about estimation later. . .

Examples: 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
```

Examples: Visualizing annotated data

```
plot(atree)
```

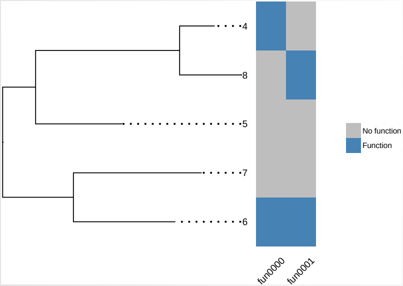
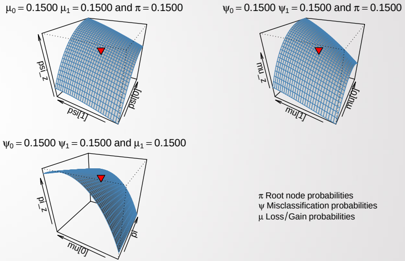


Figure 1: Visualization of annotations and tree structure.

```
plot_LogLike(atree)
```



$\mu_0 = 0.1500$ $\mu_1 = 0.1500$ and $\pi = 0.1500$

$\psi_0 = 0.1500$ $\psi_1 = 0.1500$ and $\pi = 0.1500$

$\psi_0 = 0.1500$ $\psi_1 = 0.1500$ and $\mu_1 = 0.1500$

Figure 2: LogLikelihood surface of the simulated data

Example: Interaction with ape

```r
as.apephylo(atree)
```

```
##
## Phylogenetic tree with 5 tips and 4 internal nodes.
##
## Tip labels:
## [1] "6" "7" "8" "4" "5"
## Node labels:
## [1] "0" "3" "2" "1"
##
## Rooted; includes branch lengths.
```

```r
# we can go back using:
# as.po_tree(as.apephylo(atree))
```

Example: Tree pruning

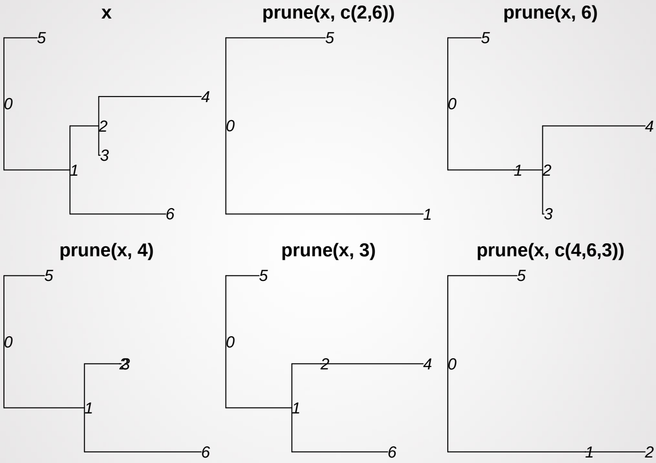
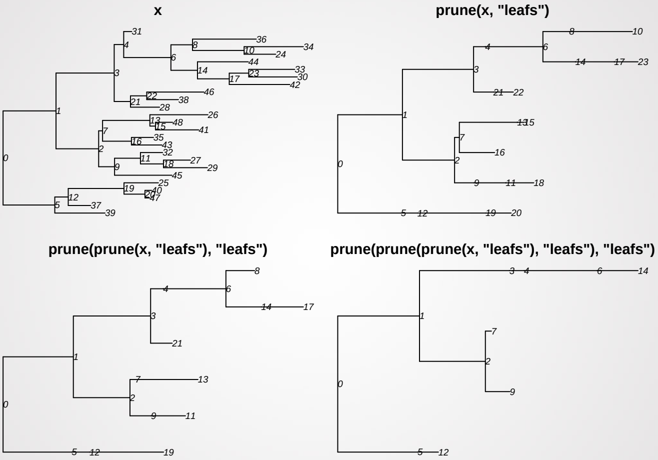


Figure 3: Pruning trees

Example: Tree pruning (cont.)



x

prune(x, "leafs")

prune(prune(x, "leafs"), "leafs")

prune(prune(prune(x, "leafs"), "leafs"), "leafs")

Figure 4: Pruning trees recursively

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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)

# 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 = 1e5, thin=10, burnin = 1e4,
  # 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)

ans is of class `mcmc` from the coda package

```
summary(ans)
```

```
##
## Iterations = 10010:1e+05
## Thinning interval = 10
## Number of chains = 4
## Sample size per chain = 9000
##
## 1. Empirical mean and standard deviation for each variable,
##    plus standard error of the mean:
##
##        Mean     SD Naive SE Time-series SE
## mu    2.51 0.0935 0.000493       0.000579
## sigma 2.96 0.0668 0.000352       0.000373
##
## 2. Quantiles for each variable:
##
##        2.5%  25%  50%  75% 97.5%
## mu    2.33 2.45 2.51 2.58  2.70
## sigma 2.83 2.91 2.96 3.00  3.09
```

Example: MCMC (cont. 2)

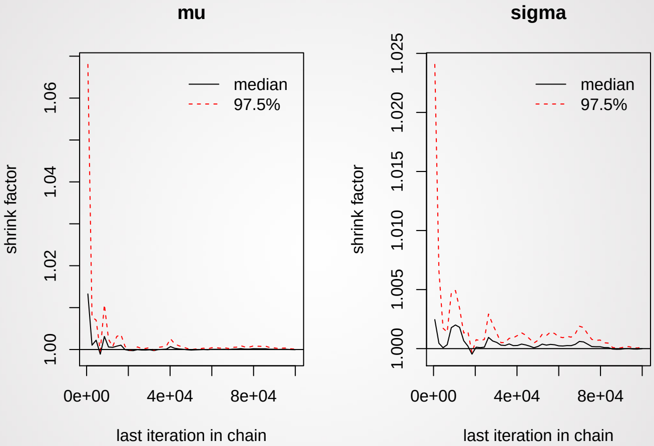

Figure 5: Gelman diagnostic for convergence

Example: MCMC (cont. 3)

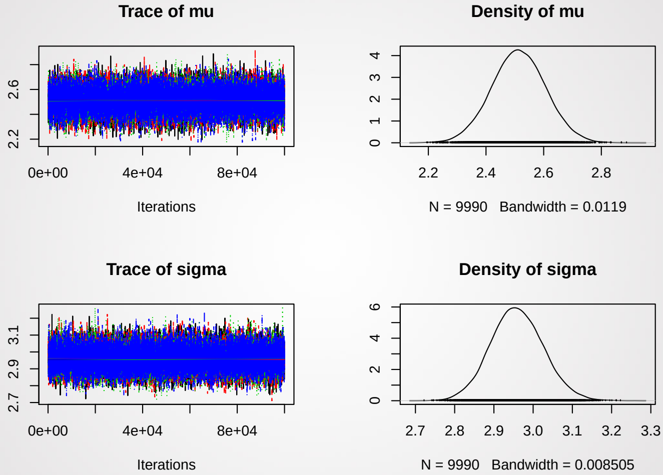

Figure 6: Posterior distribution

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Putting all together

Let's start by reading some 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.
```

Putting all together (cont.)

```r
# 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
```

Putting all together: MCMC of the model

In this example, using data from PANTHERDB, we will simulate a single function and use the `aphylo_mcmc` function for obtaining parameter estimates

```r
tree <- dat$tree

# Simulating a function
set.seed(123)
atree <- sim_annotated_tree(
  tree= as_po_tree(tree),
  Pi = .05, mu = c(.1, .05), psi = c(.01, .02)
)

# Estimation
ans <- aphylo_mcmc(
  params  = rep(.05, 5),
  dat     = atree,
  # Passing a Beta prior
  priors  = function(p) dbeta(p, 2, 20),
  # Parameters for the MCMC
  control = list(nchain=4, nbatch=1e4, thin=20, burnin=1e3)
  )
```

Putting all together: MCMC of the model (cont. 1)

```
ans
```

```
##
## ESTIMATION OF ANNOTATED PHYLOGENETIC TREE
## ll:  -57.0072,
## Method used: mcmc (10000 iterations)
## Leafs
##  # of Functions 1
##  # of 0:    99 (68%)
##  # of 1:    46 (32%)
##
##          Estimate  Std. Error
##  psi[0]    0.0527      0.0289
##  psi[1]    0.0502      0.0312
##  mu[0]     0.0777      0.0226
##  mu[1]     0.0397      0.0266
##  Pi        0.0907      0.0620
```

How good is our prediction

```r
# Looking at the posterior probabilities
head(predict(ans, what="leafs"))
```

```
##                                                             fun0000
## AN87:STAA8|EnsemblGenome=SAOUHSC_01375|UniProtKB=Q2FYR0     0.06121
## AN88:DEIRA|EnsemblGenome=DR_2147|UniProtKB=Q9RSH7           0.06033
## AN219:LEPIN|EnsemblGenome=LB_007|UniProtKB=Q8EY50           0.06032
## AN223:CHLTR|EnsemblGenome=CT_103|UniProtKB=O84105           0.06032
## AN29:CHLRE|EnsemblGenome=CHLREDRAFT_196269|UniProtKB=A8HYJ4 0.10564
## AN65:PYRAE|EnsemblGenome=PAE3495|UniProtKB=Q8ZT04           0.10611
```

```r
# And to the prediction score
prediction_score(ans)
```

```
## PREDICTION SCORE: ANNOTATED PHYLOGENETIC TREE
## Observed : 0.06 (146.89)
## Random   : 0.25 (591.44)
## Best     : 0.00 (0.00)
## Worse    : 1.00 (2365.77)
## ---------------------------------------------------------------------------
## Values between 0 and 1, 0 being best. Absolute scores in parenthesis.
```

How good is our prediction (cont.)

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

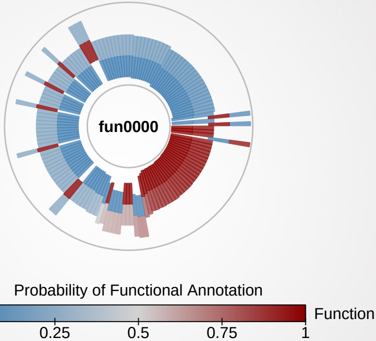

Figure 7: Predicted versus Observed values. Each slice of the pie represents a gene, the outer half of a slice is the predicted value, while the inner half is the observed value. Good predictions will coincide in color and show the slice closer to the center of the plot.

Concluding Remarks

- A parsimonious model of gene functions: easy to apply on a large scale (we already ran some simulations using all 14,000 trees from the Panther DB).
- Already implemented, we are currently in the stage of writing the paper and setting up the simulation study.
- Unfortunately, since annotation data is so sparse, we lack of a significant number of useful datasets on which we can test our method.
- For the next steps, we are evaluating ways of solving the sparseness issue: either by imposing correlation structures accross functions, or jumping into another model.

Thank you!

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George G. Vega Yon
vegayon@usc.edu

Department of Preventive Medicine

University of Southern California

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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, $Z \equiv \{z_n \in \{0, 1\}^P : n \in L(\Lambda)\}$
6. Annotated Phylogenetic Tree $D \equiv (\Lambda, Z)$
7. Observed Annotated Annotations $X = \{x_l\}_{l \in L(\Lambda)}$,
8. Experimentally Annotated Phylogenetic Tree $\tilde{D} \equiv (\Lambda, X)$

Leaf node probabilities

go back

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

$$\Pr\left(Z_l = z_l \mid X_l = x_l\right) = \begin{cases} \psi & \text{if } x_l \neq z_l \\ 1-\psi & \text{otherwise} \end{cases} \tag{1}$$

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

$$\Pr\left(Z_n = z_{lp} \;\middle|\; Z_{r(n)} = z_{r(n)}\right) = \begin{cases} \mu & \text{if } z_n \neq z_{r(n)} \\ 1-\mu & \text{otherwise} \end{cases}$$

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

- Assuming independence accross offspring, we can write

$$\Pr\left(Z_n = z_n \;\middle|\; \tilde{D}\right) = \prod_{m \in O(n)} \sum_{z_m \in \{0,1\}} \Pr\left(Z_m = z_m \;\middle|\; \tilde{D}\right) \Pr\left(Z_m = z_m \mid Z_n = z_n\right) \quad (2)$$

  Notice that if m is a leaf node, then $\Pr\left(Z_m = z_m \;\middle|\; \tilde{D}\right) = \Pr\left(X_m = x_m \mid Z_m = z_m\right)$.

Likelihood of the tree

go back

- Once the computation reaches the root node, $n = 0$, equations (1) and (2):

$$\Pr\left(Z_l = z_l \mid \tilde{D}\right) = \Pr\left(Z_l = z_{lp} \,\middle|\, X_l = x_l\right) \tag{1}$$

$$\Pr\left(Z_n = z_n \mid \tilde{D}\right) = \prod_{m \in O(n)} \sum_{z_m \in \{0,1\}} \Pr\left(Z_m = z_m \mid \tilde{D}\right) \Pr\left(Z_m = z_{mp} \mid Z_n = z_n\right) \tag{2}$$

Allow us writing the likelihood of the entire tree

$$\mathrm{L}\left(\psi, \mu, \pi \middle| \tilde{D}\right) = \sum_{z_0 \in \{0,1\}} \Pr\left(Z_0 = z_0 \mid \pi\right) \Pr\left(Z_0 = z_0 \,\middle|\, \tilde{D}\right) \tag{3}$$

Where $\Pr\left(Z_0 = z_0 \mid \pi\right) = \pi^{z_0}\left(1 - \pi\right)^{1 - z_0}$