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

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November 14th, 2018

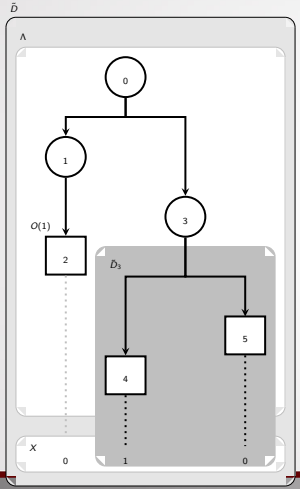
Recap: Model

1. A probabilistic model of gene function evolution,
2. The probability that the root node has the function is π,
3. Conditional on its parent state, the probabilties that any given node has to either gain or lose a function are (μ_{01}, μ_{10}),
4. Finally, at the leaf node, the probability that a node with no function is mislabeled as having the function is ψ_{01}. Conversely, the probability that a node with a function is mislabeled as not having the function is ψ_{10}.

Parameter	Probability
π	The root node has the function
μ_{01}	Gaining a function
μ_{10}	Loosing a function
ψ_{01}	Mislabeling a 0
ψ_{10}	Mislabeling a 1

Table 1: Model parameters

Recap: Notation



Symbol	Description
$\Lambda \equiv (\mathcal{N}, \mathcal{E})$	Phylogenetic Tree.
$\mathbf{p}(n)$	Parent of node n.
$\mathbf{O}(n)$	Offspring of node n.
$\mathbf{X} \equiv \{x_n\}_{n \in \mathcal{N}}$	True annotations.
$\mathbf{Z} \equiv \{z_n\}_{n \in \mathcal{N}}$	Experimental annotations.
$D \equiv (\Lambda, \mathbf{X})$	Annotated Phylogenetic Tree.
$\tilde{D} \equiv (\Lambda, \mathbf{Z})$	Experimentally Annotated Phylogenetic Tree.
$\tilde{D}_n$	Induced Experimentally Annotated Subtree of node n.
$\tilde{D}_n^c$	Complement of $\tilde{D}_n$.

Table 2: Mathematical Notation

Changes from last year

From the formal (statistical) stand

- Prediction function: Right mathematical definition of the model prediction.
- New set of parameters: Propensity to report a finding.
- Flexible model specification: Definition of the likelihood function for different sets of parameters

By products generated during the implementation

- The `sluRm` R package: A light-weight interface to slurm.
- Improvements on the `amcmc` R package, notably: automatic convergence.

Recap: The aphylo R package

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Some new features

- Model specification via formula.
- Added he propensity to report discovery parameters.
- Two implementations of the prediction function (using a post-order algorithm as suggested by Prof. Suchard), and a brute force method... we use this for unit tests.
- (in the `amcmc` R package) Convergence monitoring and automatic stop of the MCMC algorithm

Nice visualizations

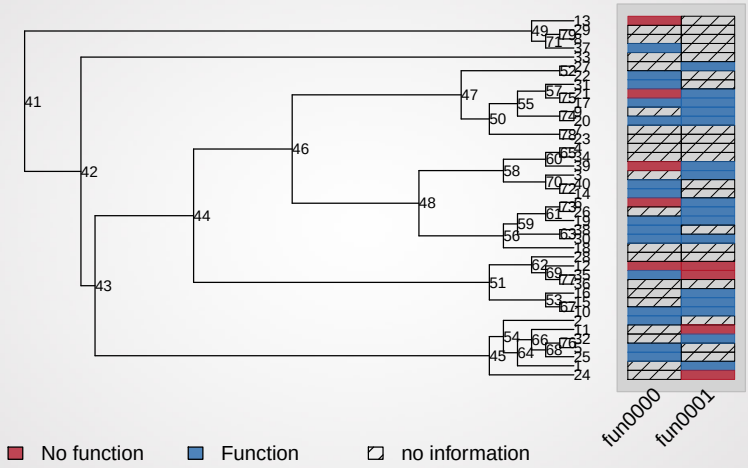


Figure 1: Annotated Phylogenetic Tree

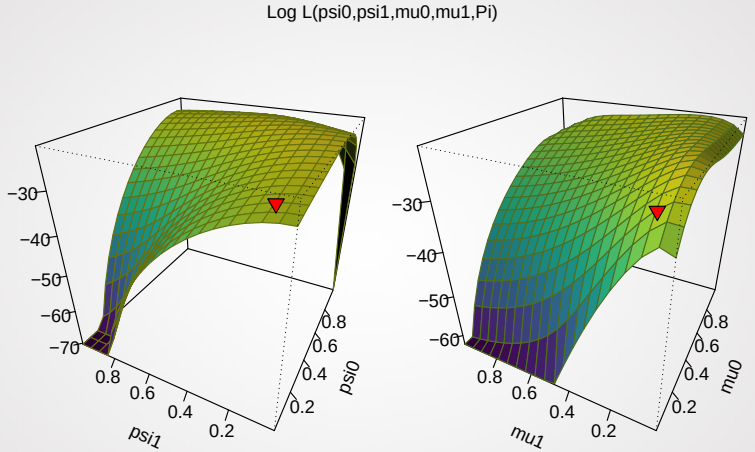


Figure 2: Surface of the likelihood of a given annotated tree.

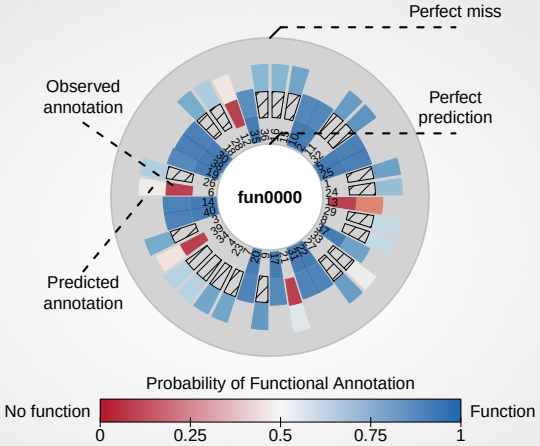


Figure 3: Prediction Accuracy: Observed versus predicted values

Flexible model specification

Automatic specification of the likelihood function, e.g.

- `x ~ mu` baseline model
- `x ~ mu + psi + Pi` model including mislabeling and root node probabilities
- `x ~ mu + Pi` same as before, but excluding mislabeling
- `x ~ mu + psi(1) + Pi` mislabeling of 1 is fixed
- `x ~ mu + psi(0, 1) + Pi` mislabeling of 0s and 1s is fixed

Flexible model specification

```
##
## ESTIMATION OF ANNOTATED PHYLOGENETIC TREE
##
##  Call: aphylo_mcmc(model = x ~ mu + psi + Pi, priors = bprior())
##  ll: -15.1028 ,
##  Method used: mcmc (748 iterations)
##  Leafs:
##  # of Functions 2
##          Estimate  Std. Err.
##  psi0    0.0998    0.0782
##  psi1    0.0955    0.0679
##  mu0     0.2379    0.0902
##  mu1     0.0499    0.0379
##  Pi      0.0888    0.0781
```

Results on the new specification (adventure)

The data generating process was `x ~ mu + psi + eta + Pi` (`eta` are the propensity to publication parameters).

Figure 4: Correct specification (includes 'eta')

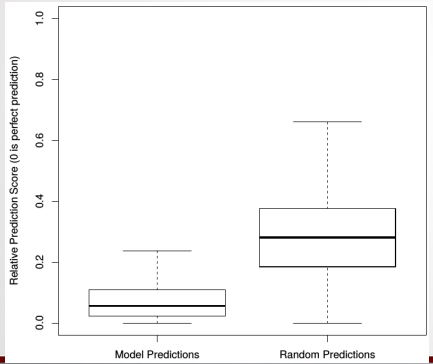
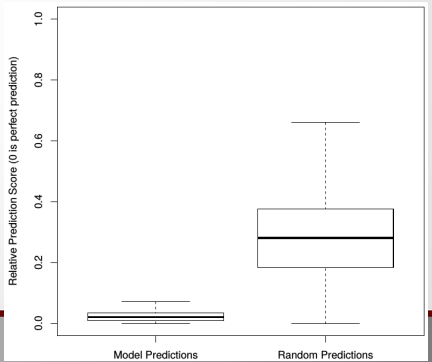


Figure 5: Miss specified model (does not include 'eta'). Missingness is confounded with propensity to fail to report



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~~ hour with ~~10~~ 240 processors ~~only~~).

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- Already implemented, we are currently in the stage of ~~writing the paper and setting up the simulation study~~ finishing and submiting the paper.
- 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.
- We are still unsure about how to procede with the software: R journal? Journal of Open Source Software? Journal of Statistical Software? Bioinformatics? etc.

Thank you!

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