# Triads, Dyads, and Gene Functions

## When Social Network Analysis meets Phylogenetics

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(virtual)

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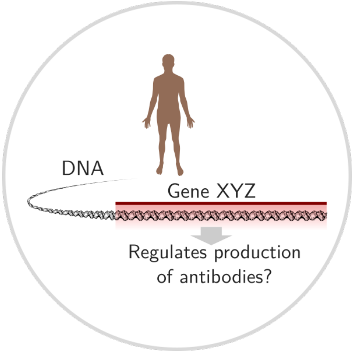
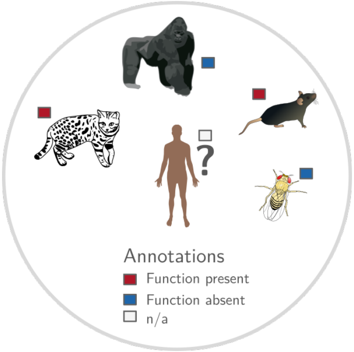
Keck School of Medicine of USC

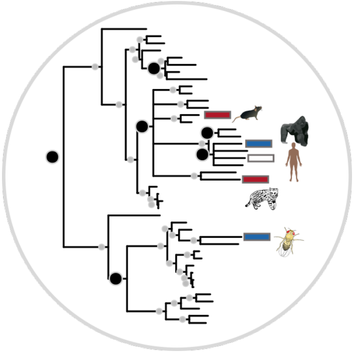
You can download the slides from ggv.cl/slides/networks2021

## The problem of genes' functions

Is gene *XYZ* involved in process *ABC*?



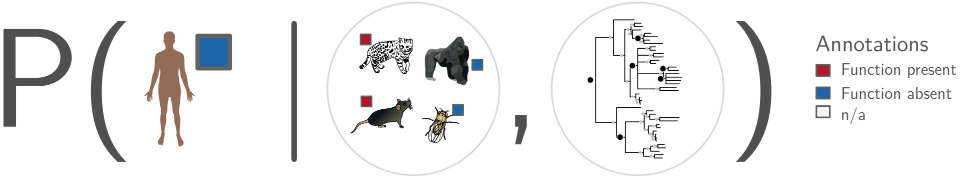
Complex to directly assess

But we may know from other species

And we further know how these *genetically* connected

... let's rephrase the question.

Is the human gene **XYZ** involved in process **ABC**, given what we know about that for other *related* species?



# The Gene Ontology Project

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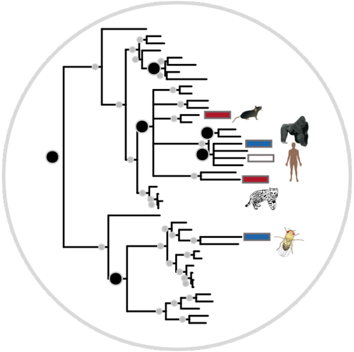


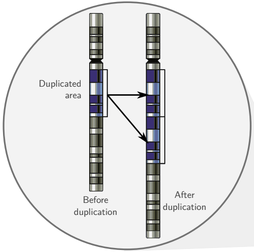
GENEONTOLOGY
Unifying Biology

- $\sim$ 15,000 phylogenetic trees
- $\sim$ 8 million annotations
- $\sim$ 600 thousand on human genes
- $\sim < 10\%$ are based on experimental evidence... Improving our knowledge on genetics is fundamental for advancing Biomedical Research

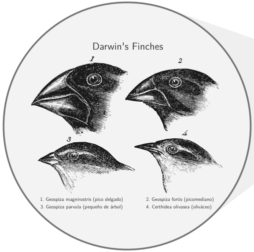
Only on 2020, 2,000+ COVID-19 papers using the GO (Google Scholar)

more

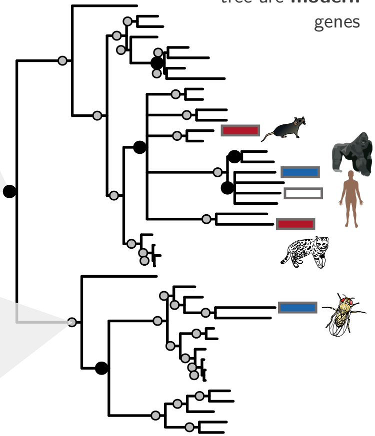
● nodes are **Duplication** Events



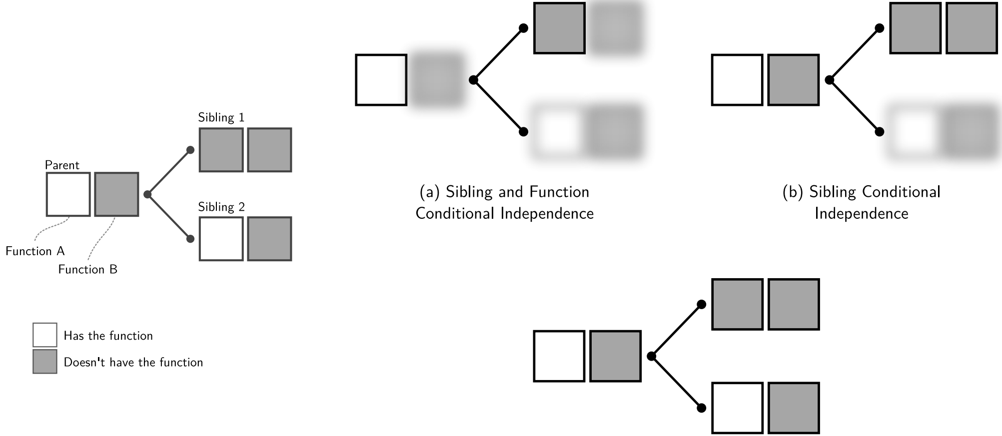

○ nodes are **Speciation** Events




The tips of the tree are **modern** genes



▸ example




(a) Sibling and Function Conditional Independence

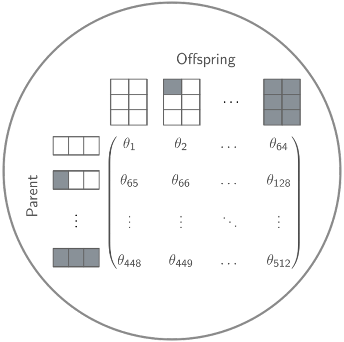
(b) Sibling Conditional Independence

(c) No conditional independence

## Avoiding the Curse of dimensionality

If we wanted to build a model with 3 functions, we would need to estimate...

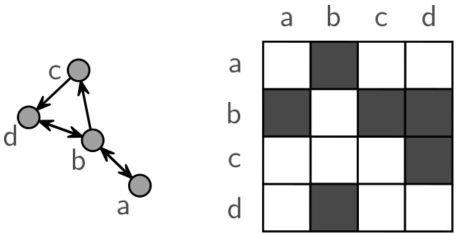
## Full Markov Transition Matrix




- 512 parameters
- Finding this many parameters not easy.
- Even if you can, interpretation is awkward.

# Exponential Random Graph Models (ERGMs)

Social Network



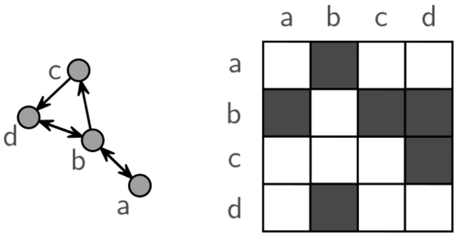

- Not about individual ties.
- Statistical inference on *motifs* (triangles, dyads, homophily, etc.)

Ultimately...

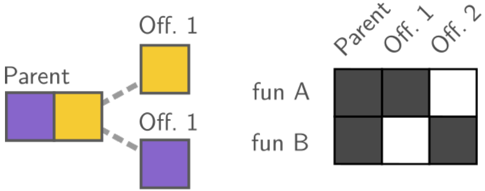
**ERGM $\equiv$ Modeling binary arrays**

# Exponential Random Graph Models (ERGMs)

## Social Network



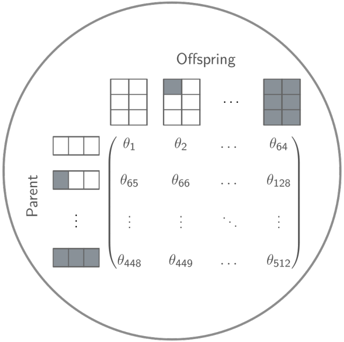

## Evolutionary Event




Social Networks are usually represented as **adjacency matrices**, and so can evolutionary events!

If we wanted to build a model with 3 functions, we would need to estimate...

## Full Markov Transition Matrix




512 parameters

$$\left(\theta_{\text{gain1}}\ \theta_{\text{gain2}}\ \theta_{\text{gain3}}\right)$$
$$\left(\theta_{\text{loss1}}\ \theta_{\text{loss2}}\ \theta_{\text{loss3}}\right)$$
$$\theta_{\text{neofun}}\ \theta_{\text{subfunc}}$$
$$\left(\theta_{\text{root1}}\ \theta_{\text{root2}}\ \theta_{\text{root3}}\right)$$

Easier to fit

Easier to interpret

## Sufficient statistics

$$\left(\theta_{\text{gain1}}\ \theta_{\text{gain2}}\ \theta_{\text{gain3}}\right)$$
$$\left(\theta_{\text{loss1}}\ \theta_{\text{loss2}}\ \theta_{\text{loss3}}\right)$$
$$\theta_{\text{neofun}}\ \theta_{\text{subfunc}}$$
$$\left(\theta_{\text{root1}}\ \theta_{\text{root2}}\ \theta_{\text{root3}}\right)$$

11 parameters (for example)

term examples

# Tree likelihoods: Felsenstein's Pruning algorithm

Also known as *dynamic programming* or *postorder tree traversal*

All possible transitions from $\mathbf{x}_n$

Transition Probability (ERGM)

$$\mathbb{P}\left(\tilde{D}_n \,\middle|\, \mathbf{x}_n, \Theta\right) = \sum_{\mathbf{x}} \mathbb{P}\left(\mathbf{x} \mid \mathbf{x}_n\right) \prod_{m \in \mathbf{O}(n)} \mathbb{P}\left(\tilde{D}_m \,\middle|\, \mathbf{x}_m\right)$$

Model Parameters

Vector of Sufficient Statistics

$$\mathbb{P}\left(\mathbf{x} \mid \mathbf{x}_n\right) = \frac{\exp\left\{\Theta^{\mathbf{t}} s(\mathbf{x}, x_n)\right\}}{\sum_{\mathbf{x}'} \exp\left\{\Theta^{\mathbf{t}} s(\mathbf{x}', x_n)\right\}}$$

Normalizing Constant

the ***lingua franca*** of SNA

# Predicting

Gene state
given the data


It's parent state
given the data


$$\mathbb{P}\left(\mathbf{x}^p = \mathbf{x} \,\middle|\, \tilde{D}\right) = \underbrace{\left\{\prod_{m\in \mathbf{O}(p)} \mathbb{P}\left(\tilde{D}_m \,\middle|\, x_m\right)\right\}}_{\text{Everything below } \mathbf{x}^p} \underbrace{\sum_{x_p} \mathbb{P}\left(x_p \,\middle|\, \tilde{D}\right)\frac{\mathbb{P}\left(\mathbf{x}^p = \mathbf{x} \mid x_p\right)}{\mathbb{P}\left(\tilde{D}_p \,\middle|\, x_p\right)}}_{\text{Everything above } \mathbf{x}^p}$$

... I implemented this (and more) on **geese**

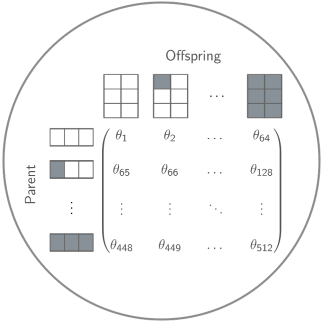
**GE**ne functional **E**volution using **S**uffici**E**ncy

... as part of **barry**, your to-go motif accountant

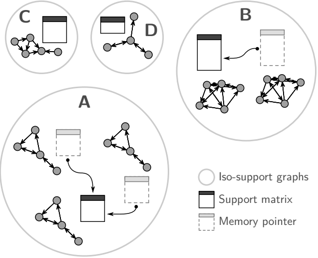
# Computational Features of **geese**



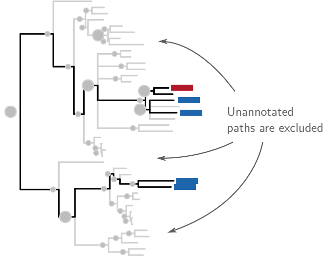
Constrain support set




Support accounting




Reduced peeling sequence




... how big can we go?

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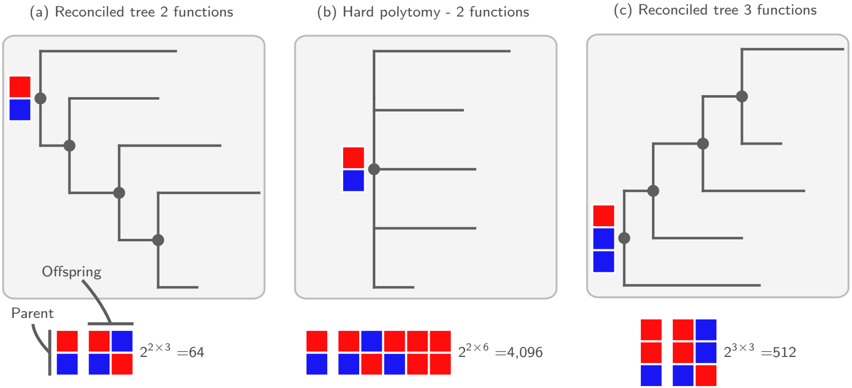
Whether the likelihood is tracktable or not depends on how large is the **"largest event"**




(in practice, arrays up to 32 cells, i.e., 4.3 billion comb., are feasible.)

## Analyzing 77 experimentally annotated trees

(Vega Yon, *et al.*, WIP)

# Analyzing 77 experimentally annotated trees

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Using data from Vega Yon et al. (2021), we re-estimated the models using **GEESE** and compared the results to those in the **aphylo** paper:

- 77 experimentally annotated trees
- We only used trees in which

$$2^{(\max \text{Polytomy}+1)\times \text{nfuns}} < 0.5 \times 10^9$$

  i.e., half billion

- Both sets of models used "informative" priors.
- Both sets of were fitted using Robust Adaptive Metropolis (**fmcmc** R package).

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After initializing a geese object named `model2fit`:

```r
# For later use (see last two lines)
term_overall_changes(model2fit, duplication = TRUE)
term_overall_changes(model2fit, duplication = FALSE)

# Couting how many genes change
term_genes_changing(model2fit, duplication = TRUE)

# Gain at duplication
term_gains(model2fit, funs = 0:nfuns, duplication = TRUE)

# Gain and loss at speciation
term_gains(model2fit, funs = 0:nfuns, duplication = FALSE)
term_loss(model2fit, funs = 0:nfuns, duplication = FALSE)

# Constraining the support set
rule_limit_changes(model2fit, id = 0, lb = 0, ub = 4, duplication = TRUE)
rule_limit_changes(model2fit, id = 1, lb = 0, ub = 4, duplication = FALSE)
```

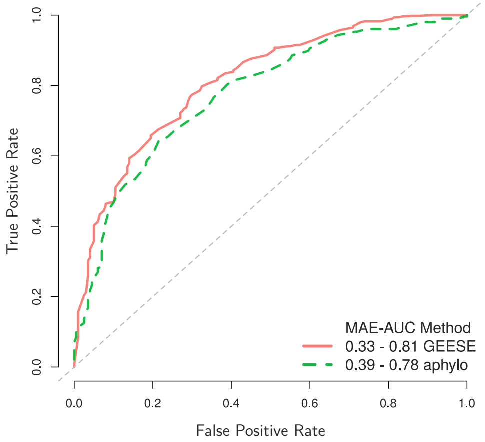


**Figure 1** *Receiver Operating Characteristic Curve.* Comparing each set of genes from the 77 trees totaling 709 present/absent annotations in 77 phylogenetic trees. **GEESE** outperforms **aphylo** in both MAE and AUC.

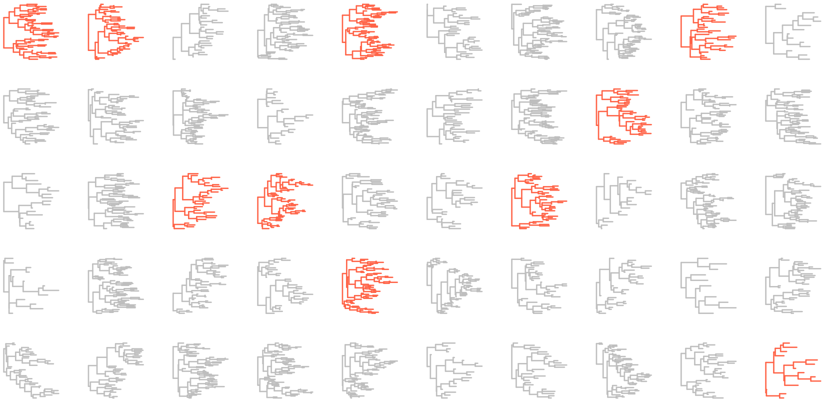

**Figure 2** A dramatization of how a group of GEESE, i.e., a flock, looks like.

# Analyzing 70 experimentally annotated trees (Flock)

Same as before, with the exception of:

- 70 experimentally annotated trees
- Reduced the set to trees with a single function
- A single pooled-model with ≈**34,000 arrays**.
- Largest polytomy 27, meaning about **250,000,000 combinations**.
- Fitted within 15 minutes

| | MCMC est. | |
|---|---|---|
| # of genes changing at dupl | -1.85 | (0.05) |
| Gains at dupl. | -1.14 | (4.30) |
| Gains at spec. | -2.50 | (0.09) |
| Loss at spec. | -3.70 | (0.07) |
| Root has the fun. | 5.83 | (3.78) |

# Preliminary analysis

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## Transition Probabilities

Model Parameters

Vector of Sufficient Statistics

$$\mathbb{P}\left(\mathbf{x} \mid x_n\right) = \frac{\exp\left\{\Theta^{\mathbf{t}} s(\mathbf{x}, x_n)\right\}}{\sum_{\mathbf{x}'} \exp\left\{\Theta^{\mathbf{t}} s(\mathbf{x}', x_n)\right\}}$$

Normalizing Constant

the *lingua franca* of SNA

| Event type | Duplication | Speciation |
|---|---|---|
| **Both gain** | 0.02 | 0.01 |
| **Both lose** | 0.02 | $<$0.01 |

## Conditional Probabilities ("Gibbs")

Probability gene ***n*** gains function ***k***

Model Parameters

$$\mathbb{P}\left(x_{nk}^{p} = 1 \mid x_{pk} = 0, x_{-n}\right) = \text{logistic}\left(\Theta^{\mathbf{t}} \Delta\delta\left(x_{nk} : 0 \to 1\right)\right)$$

Given the state of its parent ***p*** and its siblings ***-n***

Change Statistics

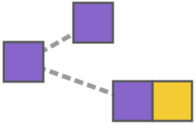
| Event type | Duplication | Speciation |
|---|---|---|
| **Preserve 0** | 0.85 | 0.90 |
| **Preserve 1** | 0.86 | 0.97 |

# Take home

## Goal

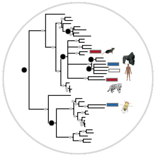

- We are in a race for uncovering **what genes do**.
- **Automatic algorithms** provide a way.

## Today



- Many alternatives... many unrealistic **assumptions**.
- **geese** (ERGMs): **GE**ne function **E**volution using **S**uffici**E**ncy.

## Next steps



- Further study its properties (bias, power, accuracy).
- Find applications for this ~~model~~ **modeling framework**.

# Triads, Dyads, and Gene Functions
# When Social Network Analysis meets Phylogenetics

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https://ggvy.cl

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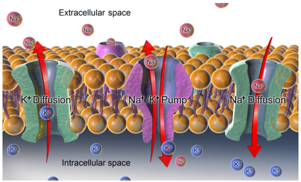
# Thank you!

Gene functions can be classified in three types:

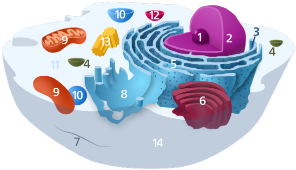
**Molecular function**

Active transport GO:0005215



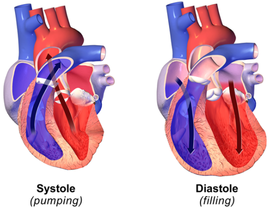

**Cellular component**

Mitochondria GO:0004016



**Biological process**

Heart contraction GO:0060047




go back

Example of GO term

| | |
|---|---|
| **Accession** | GO:0060047 |
| **Name** | heart contraction |
| **Ontology** | biological_process |
| **Synonyms** | heart beating, cardiac contraction, hemolymph circulation |
| **Alternate** | IDs None |
| **Definition** | The multicellular organismal process in which the heart decreases in volume in a characteristic way to propel blood through the body. Source: GOC:dph |

**Table 1** Heart Contraction Function. source: amigo.geneontology.org

go back

# Example: Molecular function in family PTHR1128

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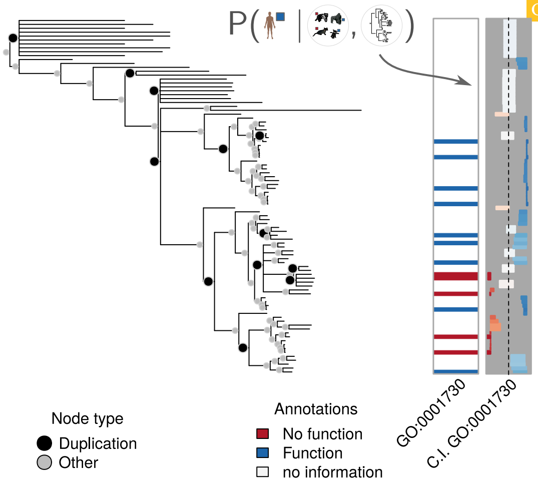
**Name:** 2'-5'-oligoadenylate synthetase activity

**Desc:** GO:0001730 involved in the process of cellular antiviral activity (wiki on interferon).

**MAE:** 0.34

**AUC:** 0.91




**Note**: Prediction made using **aphylo** (Vega Yon and *et al*, PLOS Comp. Bio 2021)

go back

## Data: Phylogenetic trees

Sample of annotations (first 10 in a single tree, Phosphoserine Phosphatase [PTHR10000])

| Internal id | Branch Length | type | ancestor |
|---:|---:|---|---|
| AN0 | | S | LUCA |
| AN1 | 0.06 | S | Archaea-Eukaryota |
| AN2 | 0.24 | S | Eukaryota |
| AN3 | 0.44 | S | Unikonts |
| AN4 | 0.42 | S | Opisthokonts |
| AN6 | 0.68 | D | |
| AN9 | 0.79 | S | Amoebozoa |
| AN10 | 0.18 | D | |
| AN15 | 0.57 | S | Dictyostelium |
| AN18 | 0.52 | S | Alveolata-Stramenopiles |

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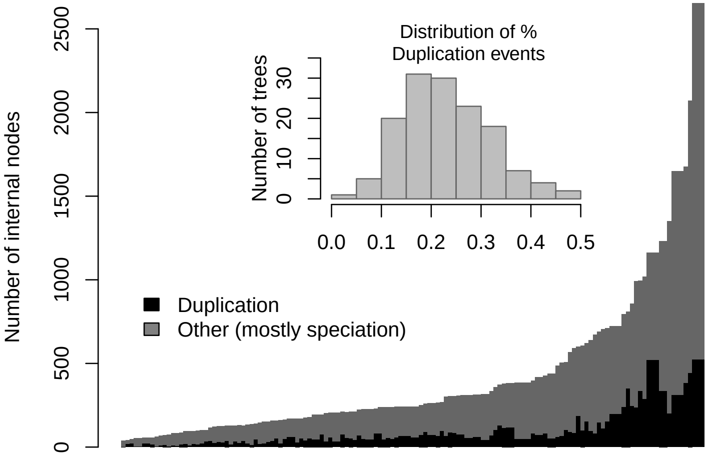


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# Data: Annotations (example)

This is the first 10 of $\sim$ 400,000 experimental annotations used:

| | Family | Id | GO term | Qualifier |
|---|---|---|---|---|
| 1 | PTHR12345 | HUMAN\|HGNC=15756\|UniProtKB=Q9H190 | GO:0005546 | |
| 2 | PTHR11361 | HUMAN\|HGNC=7325\|UniProtKB=P43246 | GO:0016887 | CONTRIBUTES_TO |
| 3 | PTHR10782 | MOUSE\|MGI=MGI=3040693\|UniProtKB=Q6P1E1 | GO:0045582 | |
| 4 | PTHR23086 | ARATH\|TAIR=AT3G09920\|UniProtKB=Q8L850 | GO:0006520 | |
| 5 | PTHR32061 | RAT\|RGD=619819\|UniProtKB=Q9EPI6 | GO:0043197 | |
| 6 | PTHR46870 | ARATH\|TAIR=AT3G46870\|UniProtKB=Q9STF9 | GO:1990825 | |
| 7 | PTHR15204 | MOUSE\|MGI=MGI=1919439\|UniProtKB=Q9Z1R2 | GO:0045861 | |
| 8 | PTHR22928 | DROME\|FlyBase=FBgn0050085\|UniProtKB=Q9XZ34 | GO:0030174 | |
| 9 | PTHR35972 | HUMAN\|HGNC=34401\|UniProtKB=A2RU48 | GO:0005515 | |
| 10 | PTHR10133 | DROME\|FlyBase=FBgn0002905\|UniProtKB=O18475 | GO:0097681 | |

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# Data: Experimental Annotations

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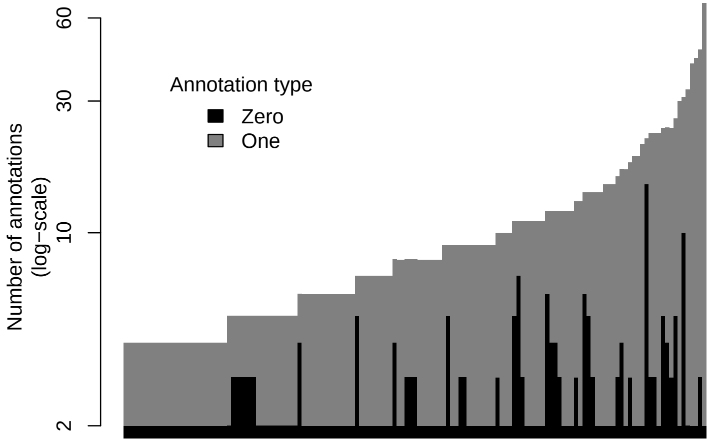


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# Overview of Prediction Results: aphylo

| | Pooled | Type of Annotation: Molecular Function | Biological Process | Cellular Comp. |
|---|---|---|---|---|
| Mislabeling | | | | |
| $\psi_{01}$ | 0.23 | 0.18 | 0.09 | |
| $\psi_{10}$ | 0.01 | 0.01 | 0.01 | |
| Duplication Events | | | | |
| $\mu_{d01}$ | 0.97 | 0.97 | 0.10 | |
| $\mu_{d10}$ | 0.52 | 0.51 | 0.03 | |
| Speciation Events | | | | ? |
| $\mu_{s01}$ | 0.05 | 0.05 | 0.05 | |
| $\mu_{s10}$ | 0.01 | 0.01 | 0.02 | |
| Root node | | | | |
| $\pi$ | 0.79 | 0.71 | 0.88 | |
| Trees | 141 | 74 | 45 | 22 |
| Accuracy under the by-aspect model | | | | |
| AUC | - | 0.77 | 0.83 | |
| MAE | - | 0.34 | 0.26 | |
| Accuracy under the pooled-data model | | | | |
| AUC | - | 0.77 | 0.75 | |
| MAE | - | 0.35 | 0.34 | |

Previously, joint estimates out-performed one-at-a-time

- **Molecular Function** No change.
- **Biological Process** Significantly better.
- **Cellular Component** Does not converge.

Molecular Function $\neq$ Biological Process ? Cellular Component

data

go back

# Barry: your go-to *motif* accountant



- Sparse matrix represented using double hashmaps (fast row/column access).
- Template implementation for flexible weights and metadata.
- Fast counting using change statistics (Ch. 4).
- Calculation of support for sufficient stats.

`https://USCbiostats.github.io/binaryarrays`

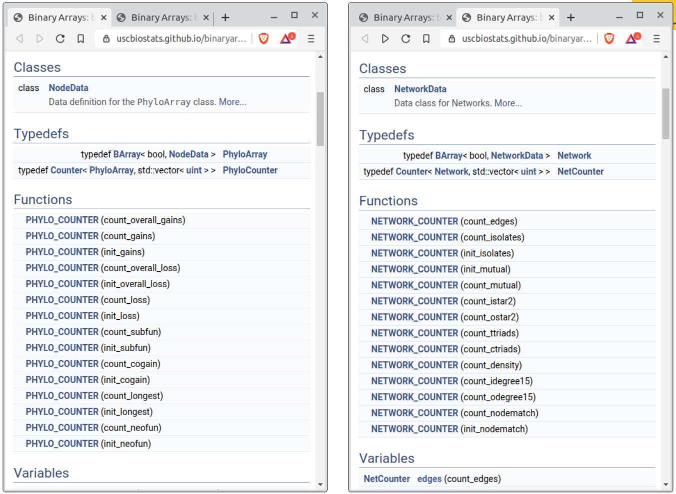


**Figure 3** Screenshots from the project's website on GitHub.

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Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

| | | | Transitions to | |
|---|---|---|---|---|
| | | | Case 1 | Case 2 |
| **Parent** | $\begin{array}{c} A \\ B \\ C \end{array}$ | $\begin{bmatrix} 0 \\ 1 \\ 1 \end{bmatrix}$ | $\begin{bmatrix} 0 & 1 \\ 1 & 0 \\ 1 & 1 \end{bmatrix}$ | $\begin{bmatrix} 0 & 1 \\ 1 & 0 \\ 0 & 1 \end{bmatrix}$ |
| **Sufficient statistics** | | | | |
| # Gains | | | 1 | 1 |
| Only one offspring changes (yes/no) | | | 1 | 0 |
| # Changes (gain+loss) | | | 2 | 3 |
| Subfunctionalizations (yes/no) | | | 0 | 1 |

return

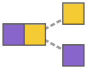
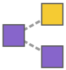
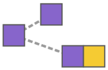
| Representation | Description | Definition |
|---|---|---|
|  | Gain of function | $(1 - x_p) \sum_{n:n \in Off} x_n$ |
|  | Loss of function | $x_p \sum_{n:n \in Off} (1 - x_n)$ |
|  | Subfunctionalization | $x_p^k x_p^j \sum_{n \neq m} x_n^k (1 - x_n^j)(1 - x_m^k) x_m^j$ |
|  | Neofunctionalization | $x_p^k (1 - x_p^j) \sum_{n \neq m} x_n^k (1 - x_n^j)(1 - x_m^k) x_m^j$ |
|  | Longest branch gains | $(1 - x_p^k)\mathbf{1}\left(x_m^k : m = \text{argmax}_n \text{blength}_n\right)$ |

**Table 2** Example of sufficient statistics for evolutionary transitions.

go back

# Example: Simple model with two functions

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To illustrate, we will **simulate** and then **estimate** the parameters for the following process:

1. 100 genes on a simulated phylogenetic tree.
2. Two functions, **0** and **1**,
3. **Function 0** is likely to be gain **gained at a dupl. event**,
4. **Function 1** is gained as **neofunctionalization** (**from 0**) **at a dupl. event**,
5. There is a higher chance of **changes at duplication** (explicit).
6. Root node starts off without either function (i.e. prob $\rightarrow 0$).

We will fit the model using Robust Adaptive Metropolis with a logistic prior centered at 0 with scale 2.

go back

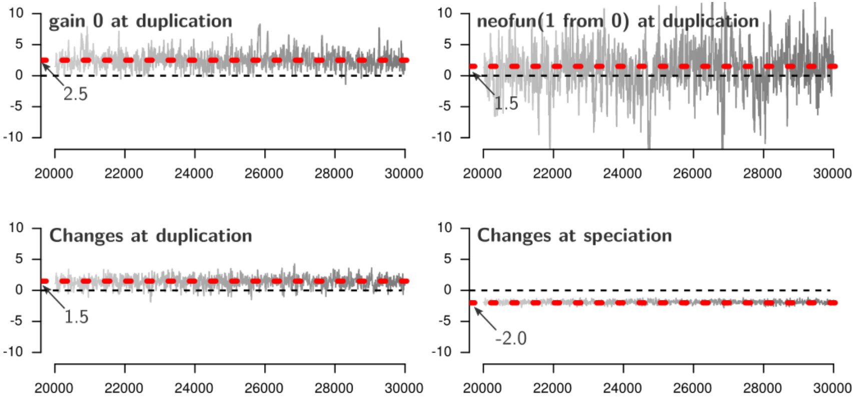


**Figure 4** MCMC Trace of the functional gain of 0, neofunctionalization (1 from 0), and change rate (by event type).

# Example: Simple model with two functions

## posterior distributions (contd')

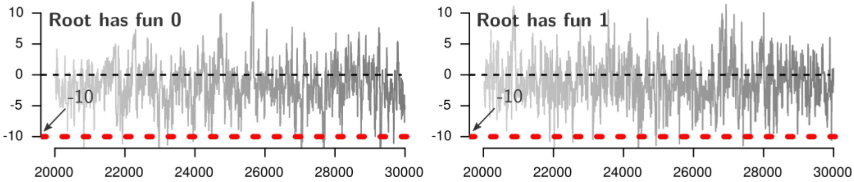


**Figure 5** MCMC Trace of root parameters. The true population parameters are $(\theta_{root0}, \theta_{root1}) = (-10.0, -10.0)$.

Root node probabilities are always hard to get.

Repeated this experiment 5,000 times:

- MCMC for fitting.
- RAM kernel.
- Logistic prior at zero with scale two.
- Each tree took $<$ 1min estimation.

**Figure 6** Distribution of parameter estimates from 5,000 phylo trees w/ 100 leafs.