# Triadas, lazos y funciones genéticas
# cuando las redes sociales y la filogenética se encuentran

George G Vega Yon, Ph.D.

University of Southern California, Department of Preventive Medicine

Seminario de Data Science UAI

19 de Mayo, 2021

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# Contents

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NIH NATIONAL CANCER INSTITUTE

National Cancer Institute Grant #1P01CA196596.

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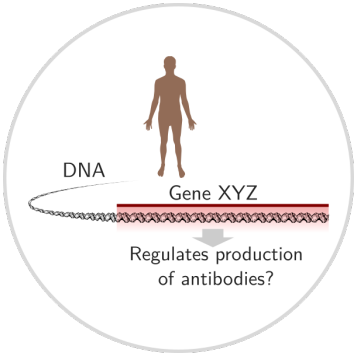
## Parsimonious modeling of gene functional evolution

*Joint with*: Paul D Thomas, Paul Marjoram, Huaiyu Mi, Duncan Thomas, and John Morrison

(Published at *PLOS Computational Biology*)

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




Complex to directly assess

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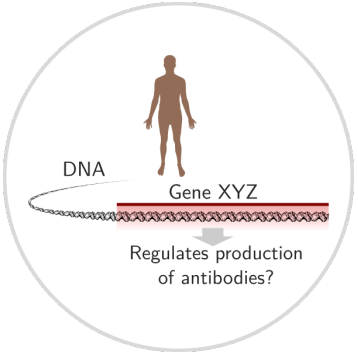


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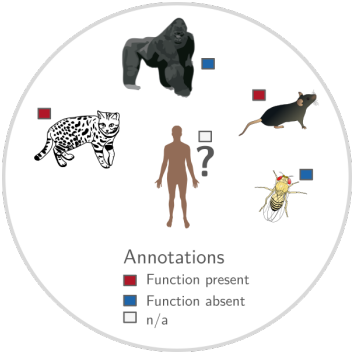


But we may know from other species

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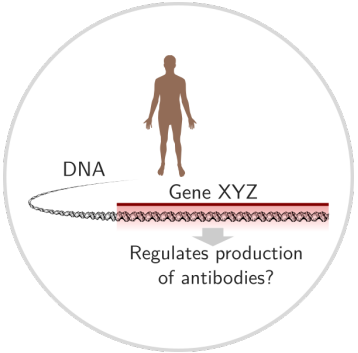


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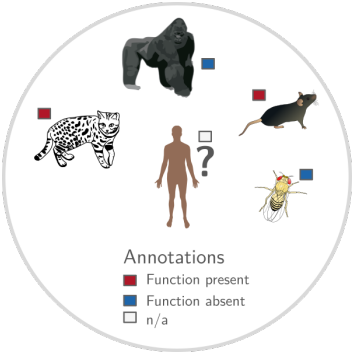


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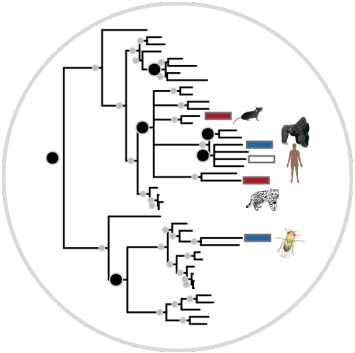

And we further know how these *genetically* connected

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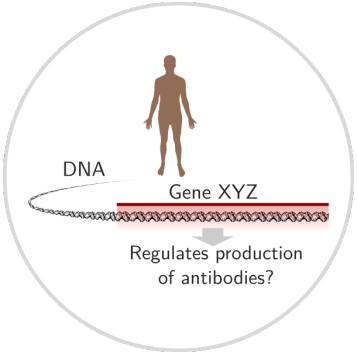


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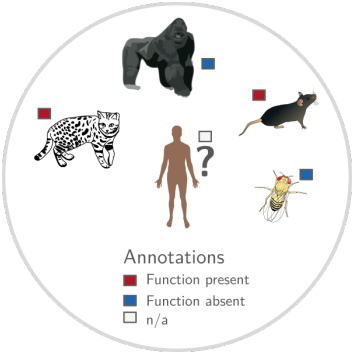


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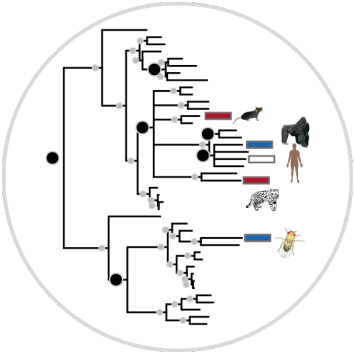
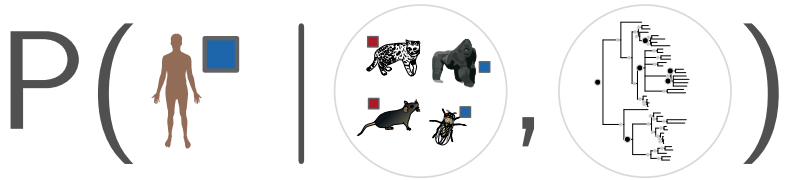


And we further know how these *genetically* connected

... let's rephrase the question.

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

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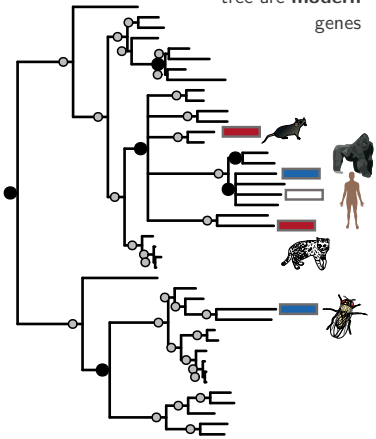
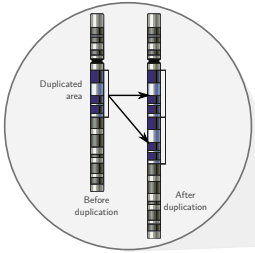
The tips of the tree are **modern** genes



● nodes are **Duplication** Events

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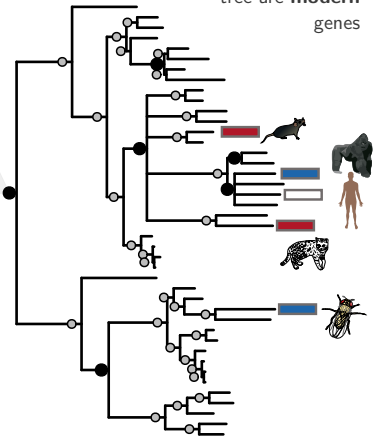

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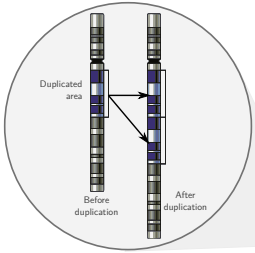


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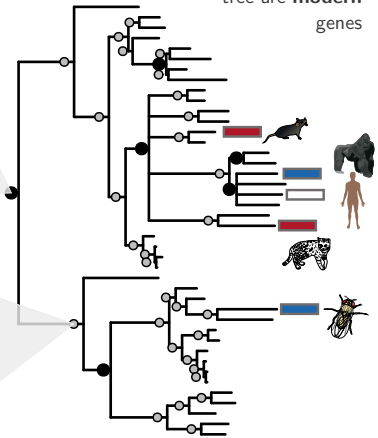

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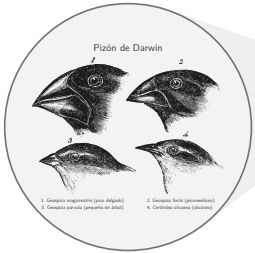

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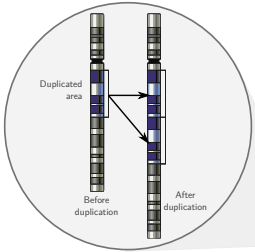


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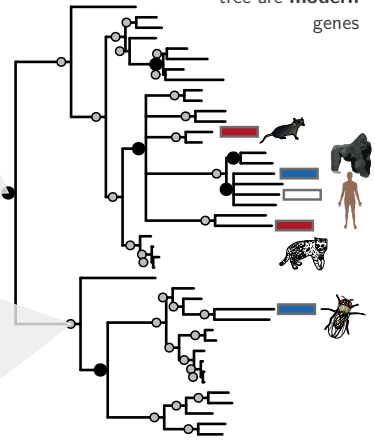

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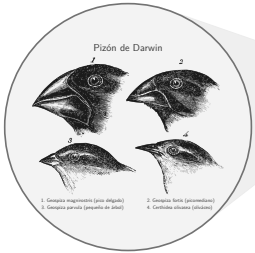


... Where is all this data?

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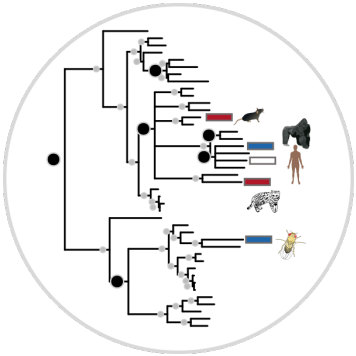

GENEONTOLOGY
Unifying Biology

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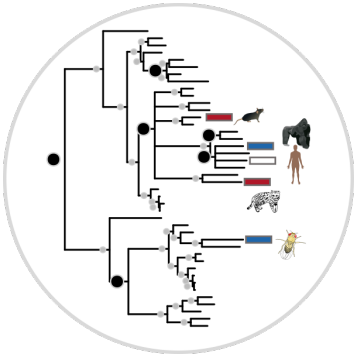

GENEONTOLOGY
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- $\sim$ 15,000 phylogenetic trees

more

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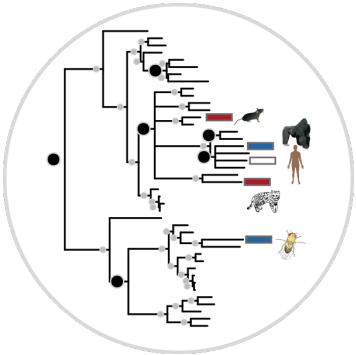

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- $\sim$ 8 million annotations

more

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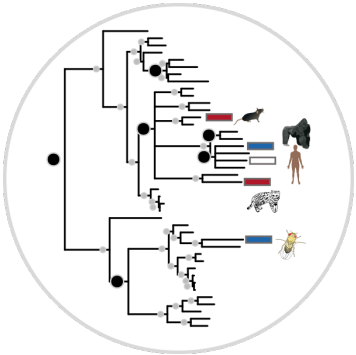

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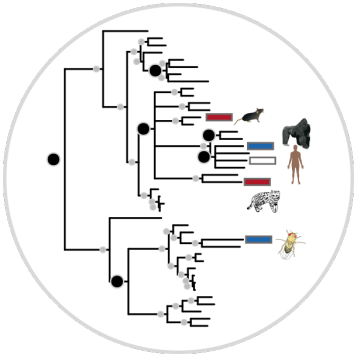

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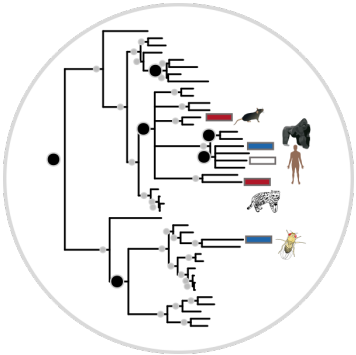

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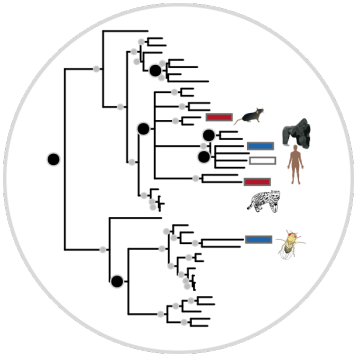

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Only on 2021, 2,500+ Cancer papers using the GO (Google Scholar)

more

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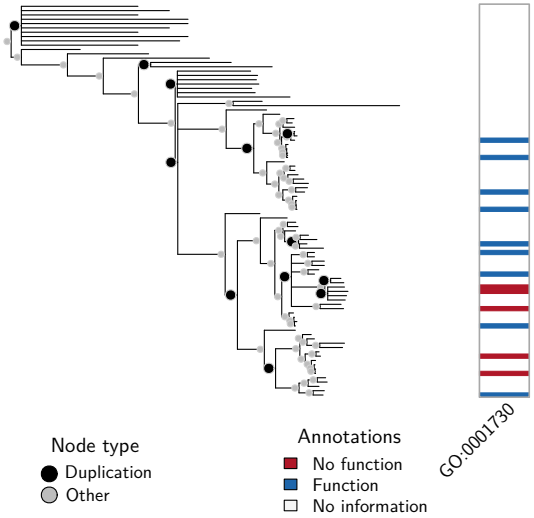
**Family: PTHR11258**
**Type:** Molecular Function
**Name:** 2'-5'-oligoadenylate synthetase activity
**Desc:** GO:0001730 involved in the process of cellular antiviral activity (wiki on interferon).

see details



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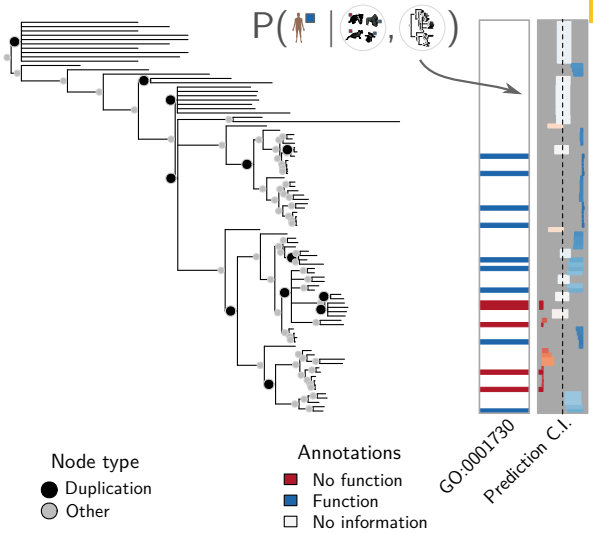

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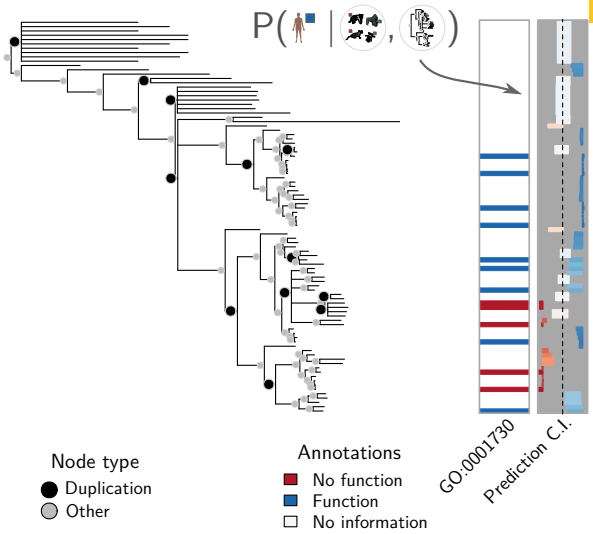
I implemented this model in the **aphylo** R package

see details



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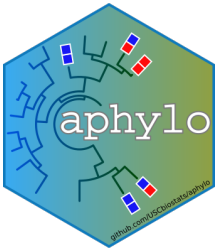


**Large scale**

Estimate **pooled-data models** involving **hundreds of families**
(1,300 genes at a time)

▸ comp. feats ▸ details

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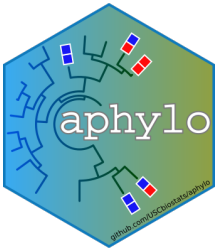


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Pooled-data model provides inference **aligned with theoretical results** (gene duplication is key)

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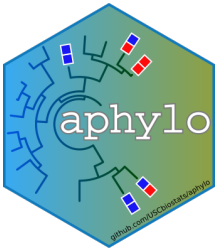


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**Fast**

Computational efficiency allows making **inference and prediction fast** (1 second vs 2 hours)

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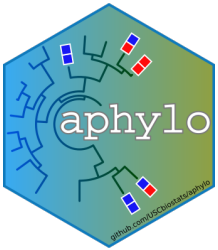


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**Accuracy**

Outperforms state-of-the-art phylo-models (0.72 vs 0.60 AUC)

▸ comp. feats ▸ details

## A general framework for modeling functional evolution

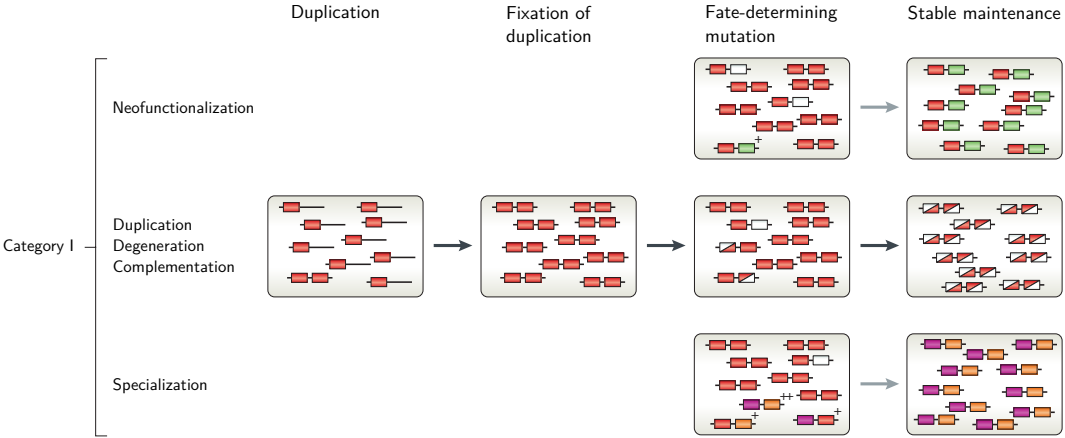
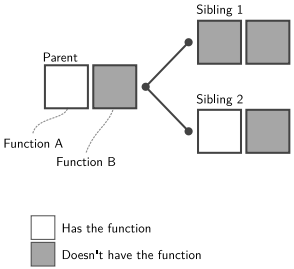
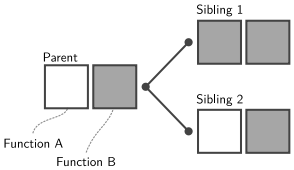
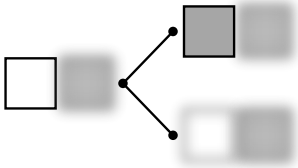



**Figure 1** *Category I (neutral fixation).* After the duplicated genes fixed, the new copy either: generate a new function, complements the original, or, if multiple functions originally present, specializes (including the original copy). Source: Adapted from Innan and Kodrashov (2010, nature rev. gen.)

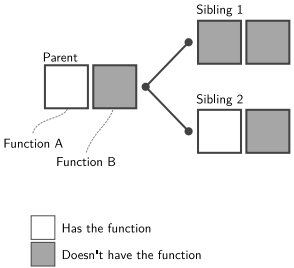
More

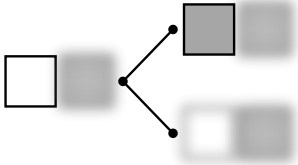

Sibling 1
Parent
Sibling 2
Function A
Function B
Has the function
Doesn't have the function



(a) Sibling and Function Conditional Independence



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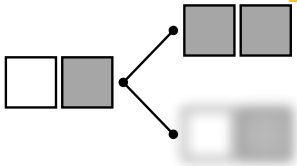

(b) Sibling Conditional Independence

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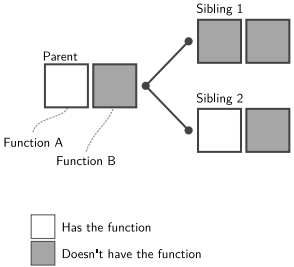


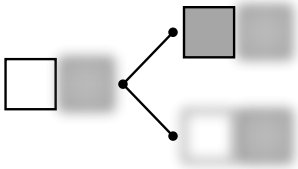

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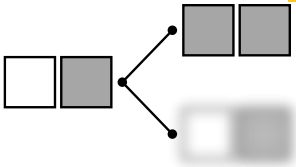
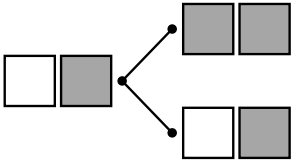


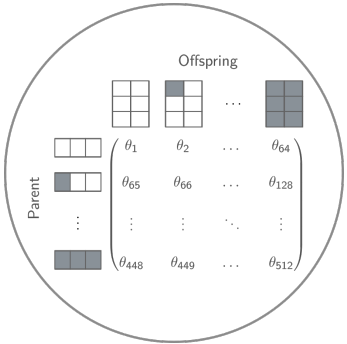
(b) Sibling Conditional Independence



(c) No conditional independence

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

**Full Markov Transition Matrix**



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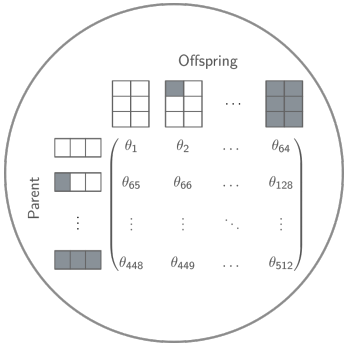


- 512 parameters

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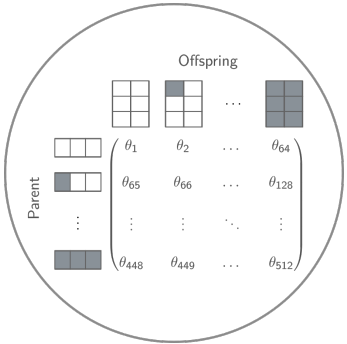


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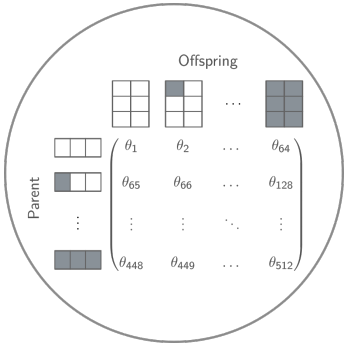


- 512 parameters
- Finding this many parameters not easy.
- Even if you can, interpretation is awkward.

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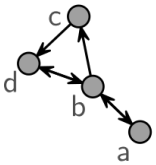
## Social Network




| | a | b | c | d |
|---|---|---|---|---|
| a | | ■ | | |
| b | ■ | | ■ | ■ |
| c | | | | ■ |
| d | | ■ | | |

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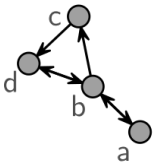
## Social Network




| | a | b | c | d |
|---|---|---|---|---|
| a | | ■ | | |
| b | ■ | | ■ | ■ |
| c | | | | ■ |
| d | | ■ | | |

- Not about individual ties.

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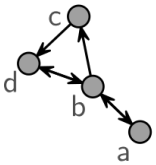
Social Network




| | a | b | c | d |
|---|---|---|---|---|
| a | | ■ | | |
| b | ■ | | ■ | ■ |
| c | | | | ■ |
| d | | ■ | | |

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

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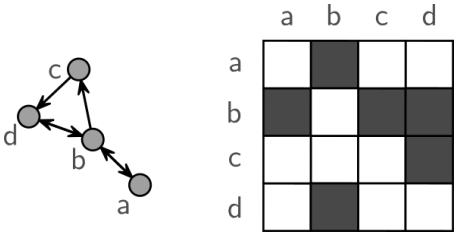
Social Network

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Ultimately...

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

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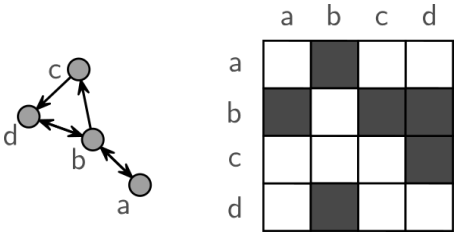
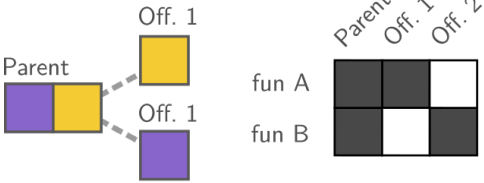
Social Network



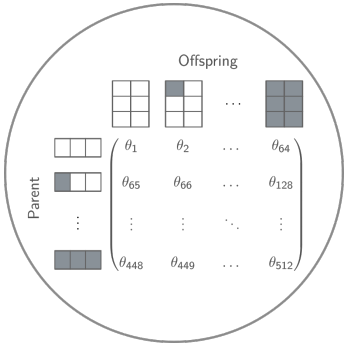

Evolutionary Event




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

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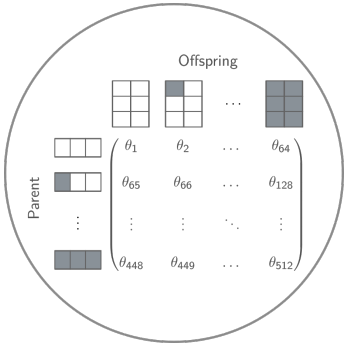
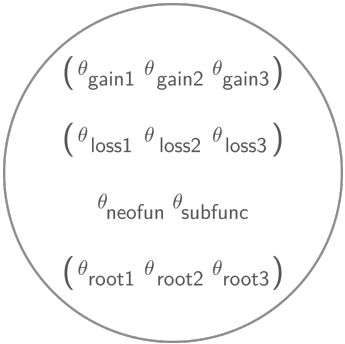



512 parameters

**Sufficient statistics**




11 parameters (for example)

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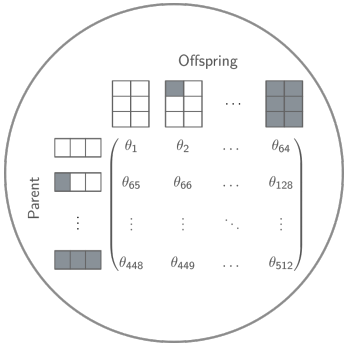


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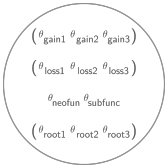



Easier to fit

Easier to interpret

## Sufficient statistics

$(\theta_{gain1}\ \theta_{gain2}\ \theta_{gain3})$

$(\theta_{loss1}\ \theta_{loss2}\ \theta_{loss3})$

$\theta_{neofun}\ \theta_{subfunc}$

$(\theta_{root1}\ \theta_{root2}\ \theta_{root3})$

11 parameters (for example)

numeric example

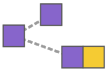
| Representation | Description | Definition |
|---|---|---|
|  | Gain of function | $(1 - x_p) \sum_{n:n \in Off} x_n$ |
|  | Loss of function | $x_p \sum_{n:n \in Off} (1 - x_n)$ |
|  | Subfunctionalization | $x_p^k x_p^j \sum_{n \neq m} x_n^k (1 - x_n^j)(1 - x_m^k) x_m^j$ |
|  | Neofunctionalization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

**Table 1** Example of sufficient statistics for evolutionary transitions.

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

Transition Probability (ERGM)

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

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Model Parameters

Vector of Sufficient Statistics

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

Normalizing Constant

the ***lingua franca*** of SNA

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It's parent state given the data

$$\mathbb{P}\left(x_n^p \,\middle|\, \tilde{D}\right) = \sum_{x_p} \mathbb{P}\left(x_p \,\middle|\, \tilde{D}\right) \left\{ \sum_{\{\mathbf{x}^p : x_n^p = x\}} \mathbb{P}\left(\mathbf{x}^p \mid x_p\right) \right\}$$

Gene state given the data

ways to get there

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

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Gene state given the data

ways to get there

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


**GE**ne functional **E**volution using **S**ufficiency

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

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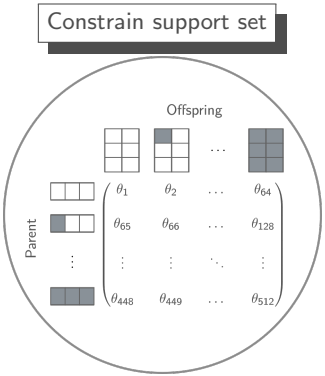

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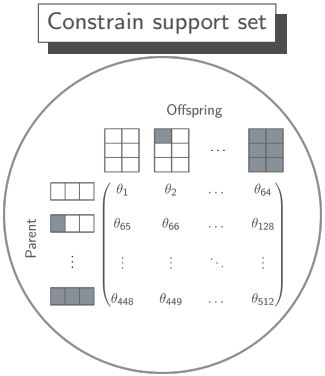


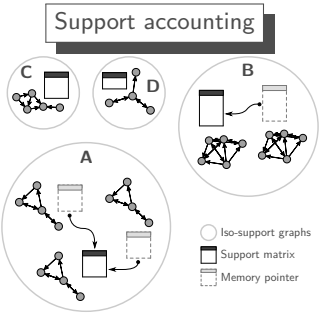

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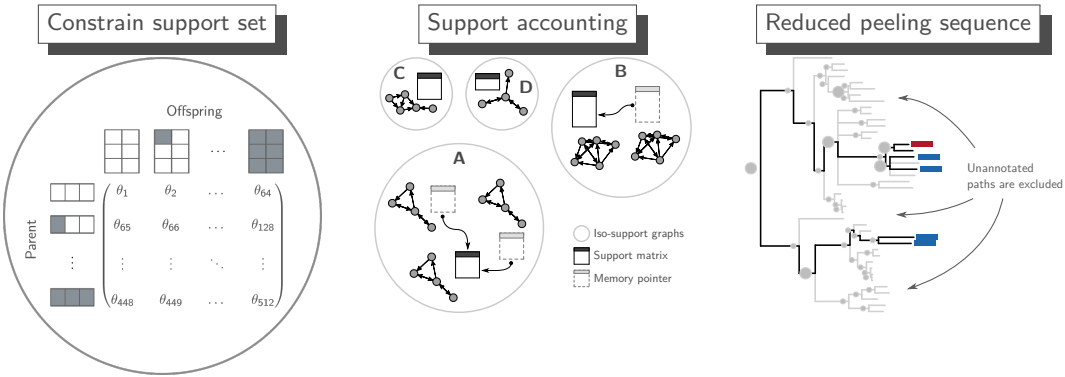

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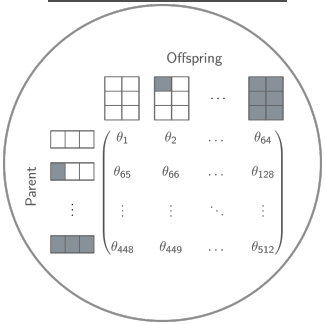
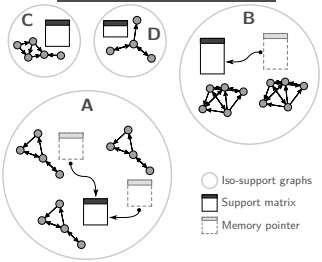
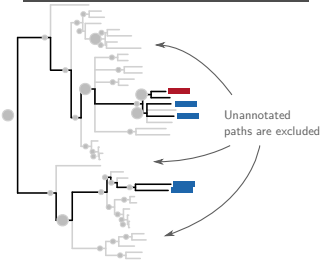
## Constrain support set




## Support accounting




## Reduced peeling sequence




… how big can we go?

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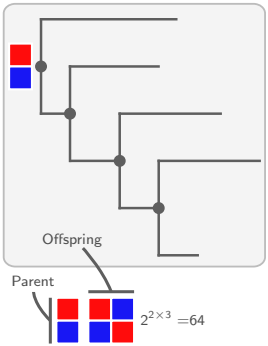
Whether the likelihood is tracktable or not depends on how large is the **"largest event"**

(a) Reconciled tree 2 functions



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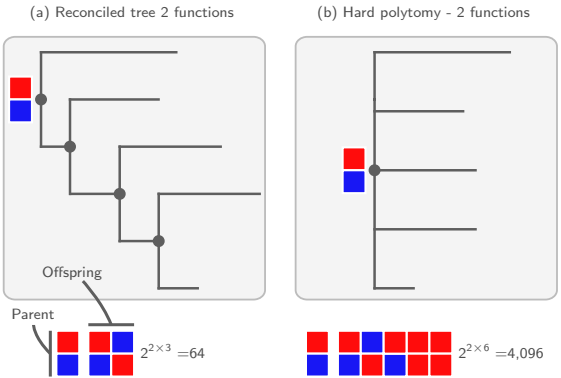

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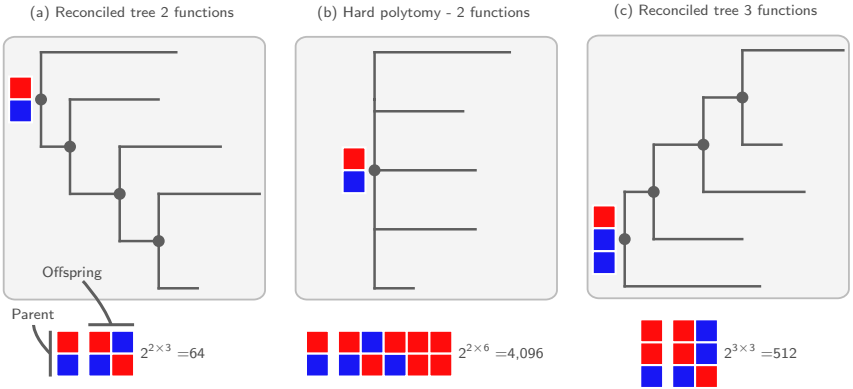

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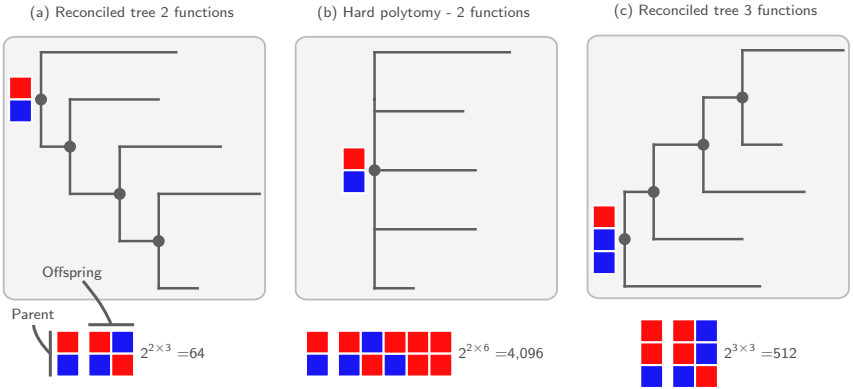


(in practice, arrays up to 32 cells, i.e., 4.3 billion comb., are feasible.)

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

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

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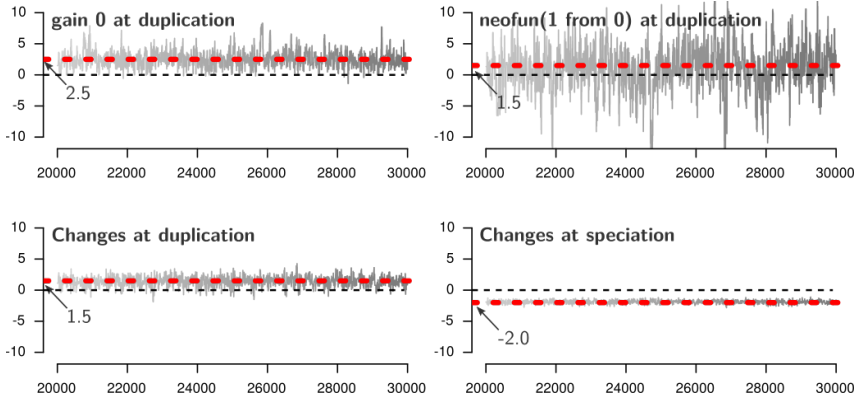


**Figure 2** MCMC Trace of the functional gain of 0, neofunctionalization (1 from 0), and change rate (by event type).

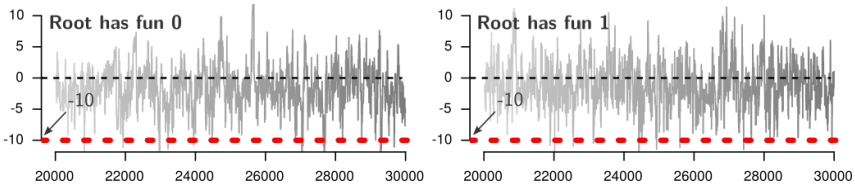


**Figure 3** MCMC Trace of root parameters. The true population parameters are $(\theta_{root0}, \theta_{root1}) = (-10.0, -10.0)$. Root node probabilities are always hard to get.

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Repeated this experiment 5,000 times:

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

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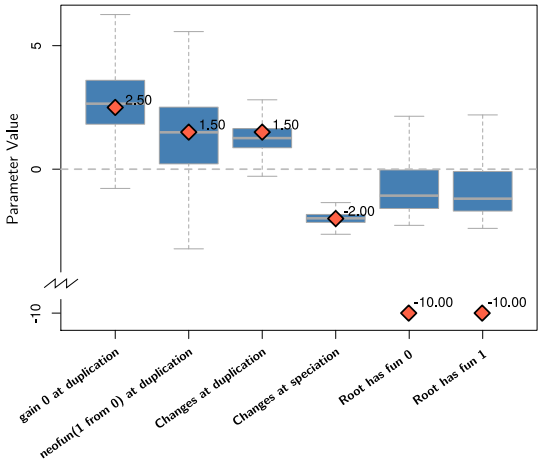
**Figure 4** Distribution of parameter estimates from 5,000 phylo trees w/ 100 leafs.



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- Potentially improve prediction accuracy.
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  "Function A or function B, which came first?"

  "When was subfunctionalization more likely to happen?"

  "Where functions A and B gained at the same time?"

# What questions?

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- Potentially improve prediction accuracy.
- Make inferences of the sort of:

  "Function A or function B, which came first?"

  "When was subfunctionalization more likely to happen?"

  "Where functions A and B gained at the same time?"
- and much more...

## Data Application

### Using experimentally annotated phylogenies

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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:

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- 77 experimentally annotated trees

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

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

Keck School of Medicine of USC

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Keck School of Medicine of USC

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

  i.e., half billion
- Both models used "informative" priors.
- Both were fitted using Adaptive Metropolis (**fmcmc** R package).

# Example of code (R)

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After initializing a geese object named `model2fit`:

# Example of code (R)

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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 and loss at duplication
term_gains(model2fit, funs = 0:1, duplication = TRUE)
term_loss(model2fit, funs = 0:1, duplication = TRUE)

# Gain and loss at speciation
term_gains(model2fit, funs = 0:1, duplication = FALSE)
term_loss(model2fit, funs = 0:1, 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)
```

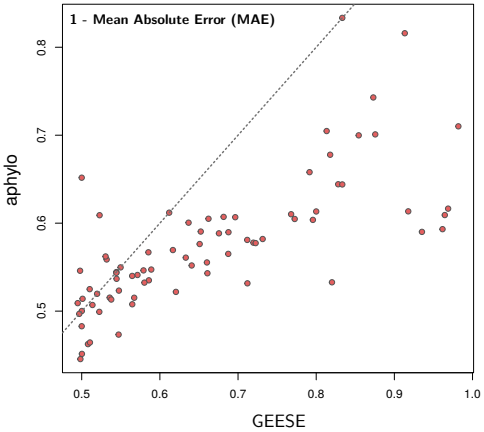


**Figure 5** *Performance as Mean Absolute Error (MAE)*. Each set of coordinates shows the value of 1 minus the MAE of **GEESE**, x-axis, and **aphylo** (y-axis). The statistics were computed using leave-one-out based on individual parameter estimates. Overall, GEESE performs better than aphylo in most cases.

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Results from the **aphylo** model:

| | *Pooled-data* | One-at-a-time | |
|---|---|---|---|
| | Beta prior | Unif. prior | Beta Prior |
| *Pooled-data* | | | |
| Unif. prior | [-0.02,-0.01] | [-0.14,-0.10] | [-0.06,-0.03] |
| Beta prior | - | [-0.12,-0.09] | [-0.04,-0.01] |
| *One-at-a-time* | | | |
| Unif. prior | - | - | [ 0.06, 0.09] |

**Table 2** Differences in Mean Absolute Error [MAE]. Each cell shows the 95% confidence interval for the difference in MAE resulting from two methods (row method minus column method). Cells are color coded blue when the method on that row has a significantly smaller MAE than the method on that column; Conversely, cells are colored red when the method in that column outperforms the method in that row. Overall, predictions calculated using the parameter estimates from *pooled-data* predictions outperform *one-at-a-time*.

# Tapping into computational scalability

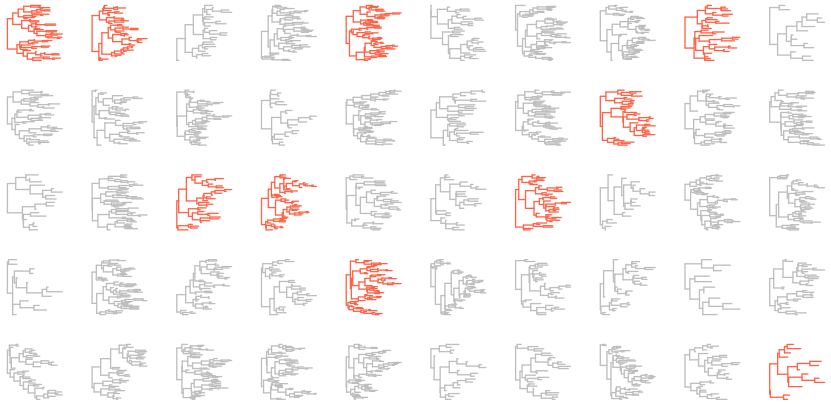

**Figure 6** A dramatization of how a group of GEESE, i.e., a flock, looks like.

# Take home

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**Goal**


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

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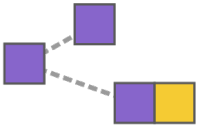
**Today**



- Many alternatives... many unrealistic **assumptions**.
- **geese** (Sufficient Stats.): a general framework for gene function evolution.

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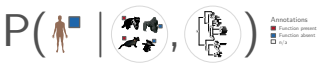
## Goal

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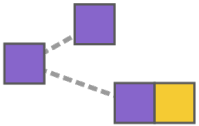

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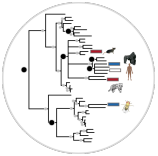
## Next steps



- Further study its properties (bias, power, accuracy).

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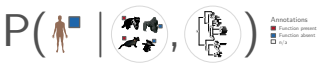
## Goal

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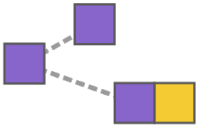

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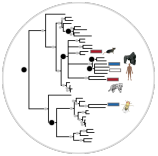

- Further study its properties (bias, power, accuracy).
- Fit pooled data models (flocks).

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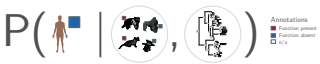
## Goal

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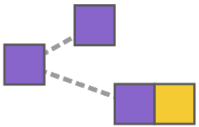

- Many alternatives... many unrealistic **assumptions**.
- **geese** (Sufficient Stats.): a general framework for gene function evolution.

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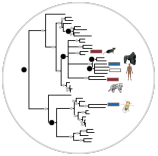

- Further study its properties (bias, power, accuracy).
- Fit pooled data models (flocks).
- Find applications for this ~~model~~ **modeling framework**.

"GEne functional Evolution using SufficiEncy"

or

# GEESE

George G Vega Yon

https://ggvy.cl

vegayon@usc.edu

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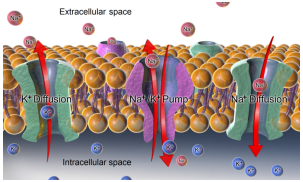
Gene functions can be classified in three types:

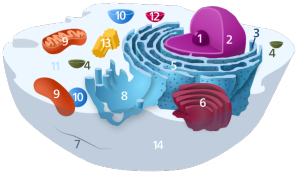
**Molecular function**

Active transport GO:0005215



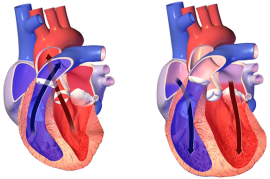

**Cellular component**

Mitochondria GO:0004016



**Biological process**

Heart contraction GO:0060047




go back

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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 3** Heart Contraction Function. source: amigo.geneontology.org

You know what is interesting about this function?

go back

These four species have a gene with that function... and two of these are part of the same evolutionary tree!

Felis catus pthr10037

Oryzias latipes **pthr11521**

Anolis carolinensis **pthr11521**

Equus caballus pthr24356

go back

# Example of Data + Predictions

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**Family: PTHR11258**

**Type:** Molecular Function

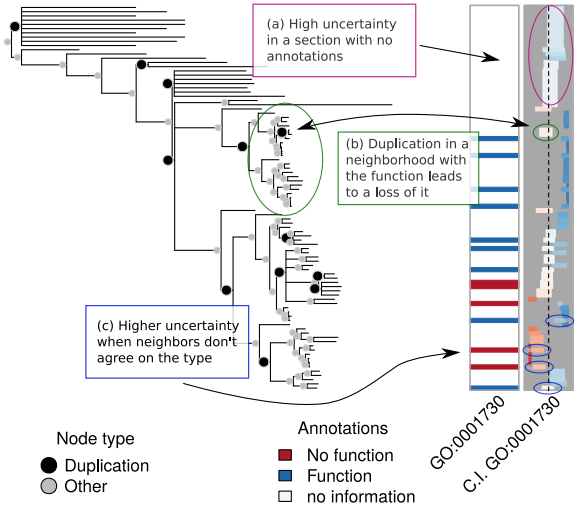
**Name:** 2'-5'-oligoadenylate synthetase activity

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

**MAE:** 0.34

**AUC:** 0.91

see a bad one | go back



# Example 2: Bad quality prediction

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**MAE:** 0.52

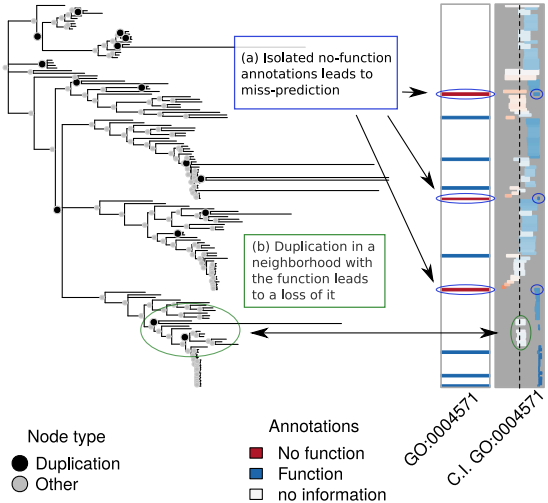
**AUC:** 0.33

**Type:** Molecular Function

**Name:** mannosyl-oligosaccharide 1,2-alpha-mannosidase activity

**Desc:** GO:0004571 involved in synthesis of glycoproteins (wiki and examples).

go back



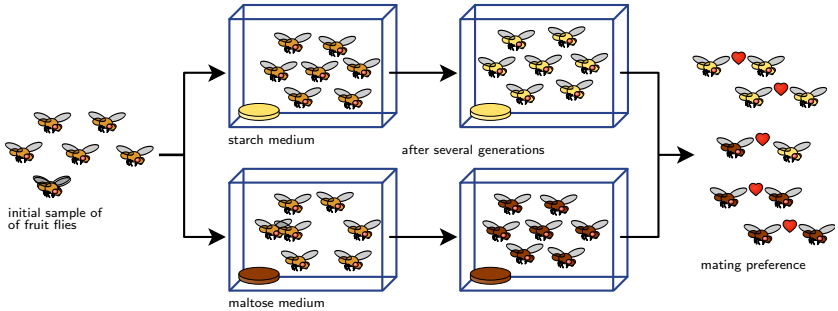



**Figure 7** Dodd (1989): After one year of isolation, flies showed a significant level of assortativity in mating (wikimedia)

go back

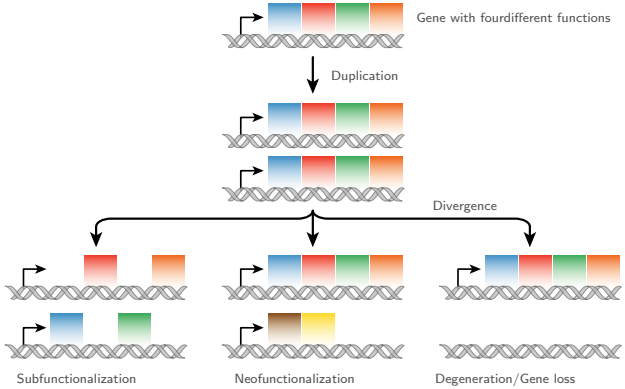



**Figure 8** A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

go back

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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 |

go back

# Data: Node type (events)

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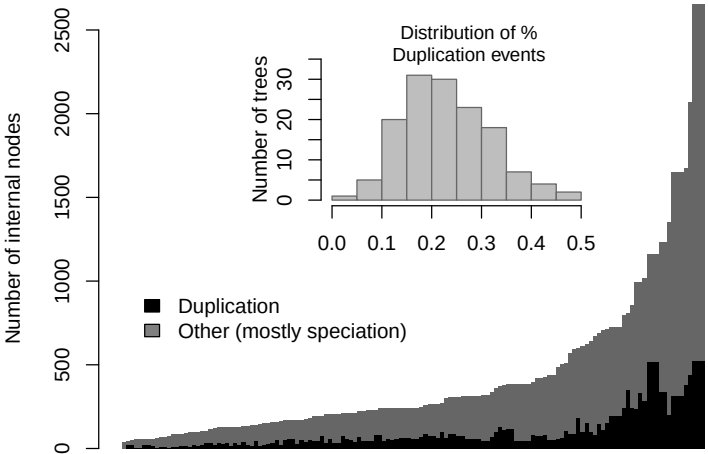


go back

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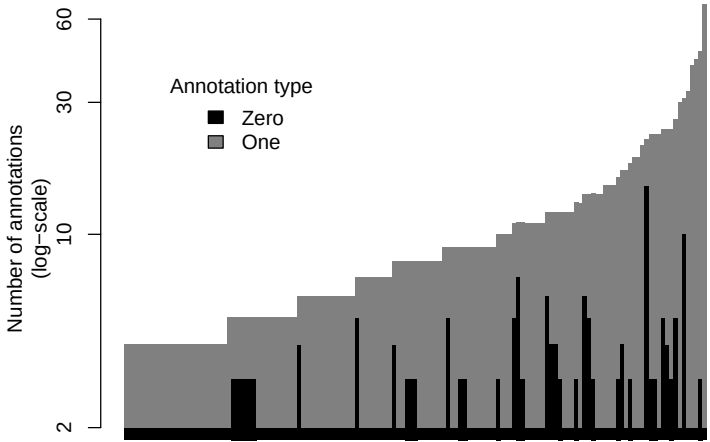
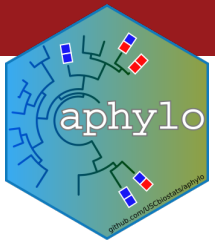
This is the first 10 of $\sim$ 400,000 experimental annotations used:

| | 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 | |

go back


Number of annotations
(log−scale)
2
10
30
60
Annotation type
Zero
One

go back

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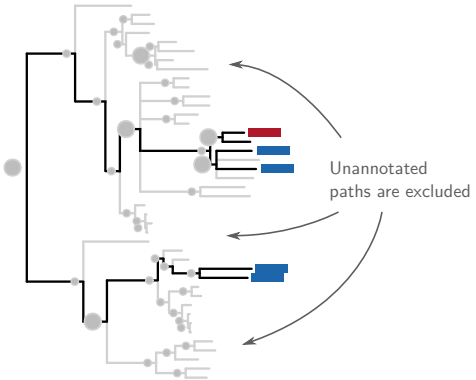
**Baseline features**

- Parsimony: Conditional independence across functions/siblings.
- Post-order Tree traversal: Linear complexity $O(|\text{tree}|)$.

**Additional features**

- Reduced pruning sequence: Induced sub-tree of nodes connected to annotated leafs
  $\implies$ Complexity $O(|\text{Induced sub-tree}|) \leq O(|\text{tree}|)$
- Implemented in C++ (**pruner** library)




return

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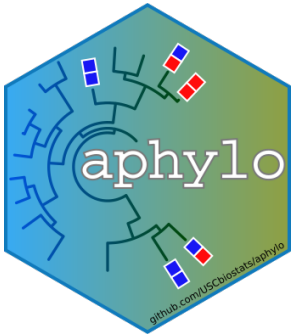
- Simulation, estimation, and prediction: **aphylo** R package.
- Large simulation study (all known trees, about 15,000) on USC's HPC cluster.
- Prediction quality assessment on $\sim$ 1,300 genes involving $\sim$ 130 families... estimation of parameters using a pooled-data model ($<$ 5 min). ◂ modeling ◂ estimates
- In a subset of $\sim$ 200 predictions we found 46 novel annotations ▸ more




◂ go back

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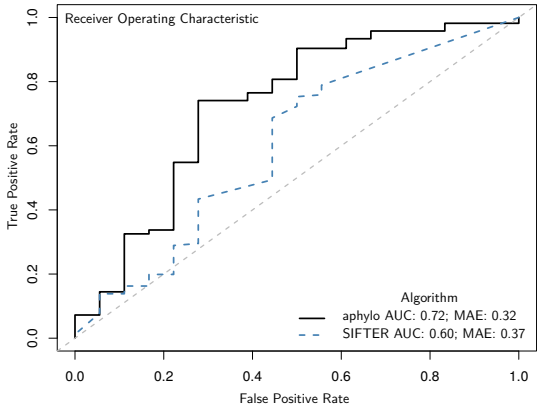
aphylo vs SIFTER (state-of-the-art phylo-based model) on 147 genes.




**Fast** 110 minutes (SIFTER) to calculate the posterior probabilities, aphylo took 1 second.

**Accurate** aphylo reported higher accuracy levels in LOO cross-validation (0.72 vs 0.60 AUC).

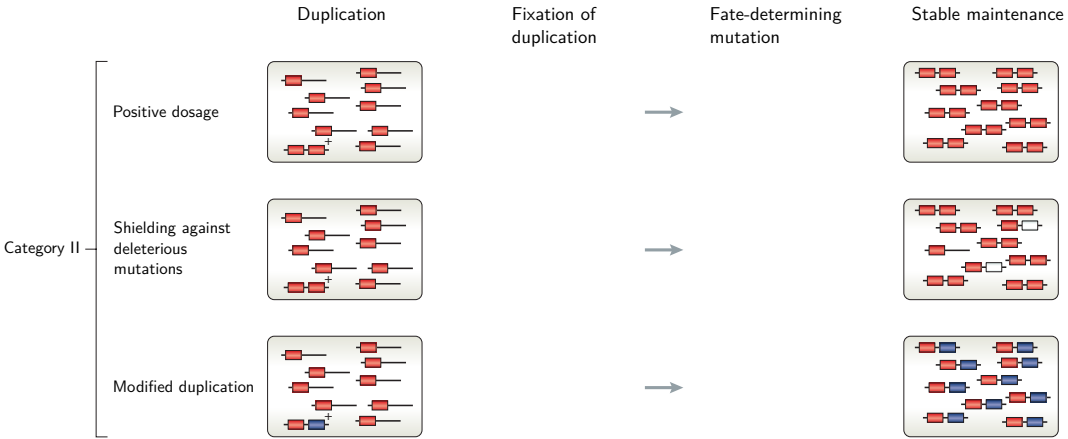



**Figure 9** *Category II (advantageous duplication).* Source: Adapted from Innan and Kodrashov (2010, nature rev. gen.)

return

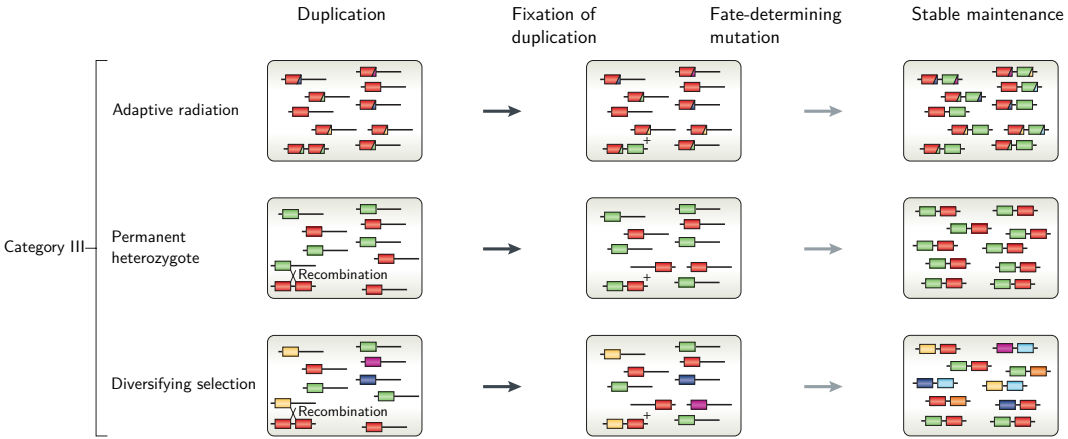



**Figure 10** *Category III (advantageous duplication).* Source: Adapted from Innan and Kodrashov (2010, nature rev. gen.)

return

# Overview of Prediction Results

| | Pooled | Type of Annotation: Molecular Function | Type of Annotation: Biological Process | Type of Annotation: 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

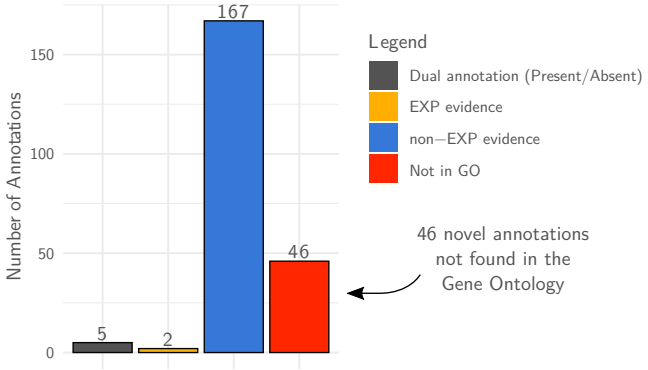



**Figure 11** Distribution of predictions

go back

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

return

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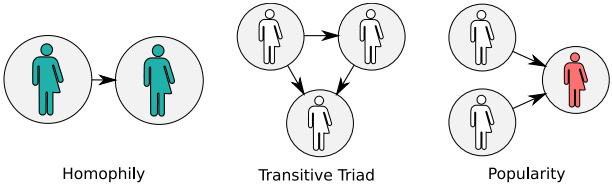
Exponential Family Random Graph Models, aka ERGMs are:

- Statistical models of (social) networks.
- Social Network Analysis: What drives social connections?
- Not about individual ties, but about local structures (sufficient statistics).




- Social Networks $\equiv$ Adjacency Matrix $\equiv$ Binary arrays

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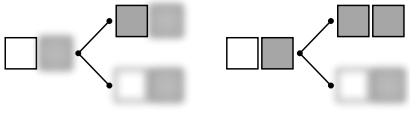
In the model with 3 functions and 2 offspring per node:

- Full Markov transition matrix: $2^3 \times 2^6 = 512$
- Using sufficient statistics:

  Pairwise co-evolution: 3 terms,
  Pairwise Neofunctionalization: 3 terms,
  Pairwise Subfunctionalization: 3 terms,
  Function specific gain: 3 terms,
  Function specific loss: 3 terms,
  Total: 15 parameters.

- Easier to fit and interpret.



(a) Sibling and Function Conditional Independence

(b) Sibling Conditional Independence

(c) No conditional independence

return