

Statistical and Computational Methods for Complex Systems

George G Vega Yon

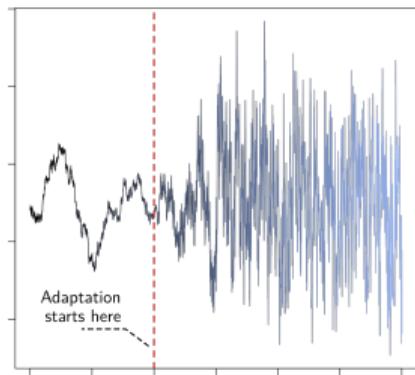
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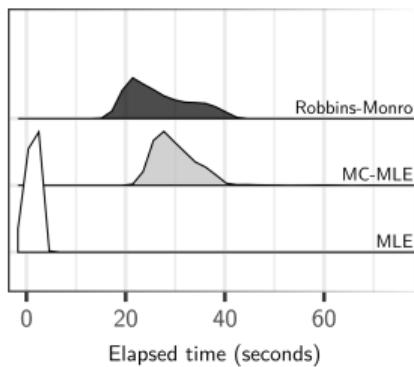
My work sits at the intersection between...

Statistics



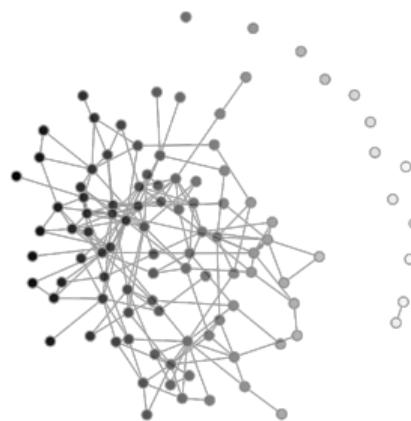
Bayesian, Non-parametric,
Spatial

Computer Science



parallel computing, HPC,
software

Complex Systems



social, biological, technical

Part 1: On the Prediction of Gene Functions Using Phylogenetic Trees

Part 2: Exponential Random Graph Models for Small Networks

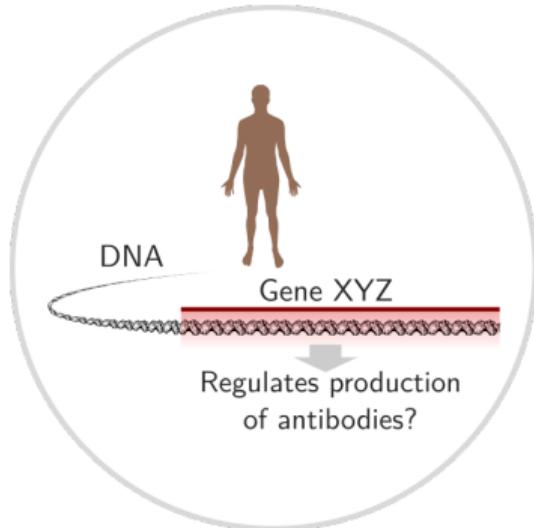
Part 3: Current and Future Research

You can download the slides from <https://github.com/gvegayon/faculty-talk>

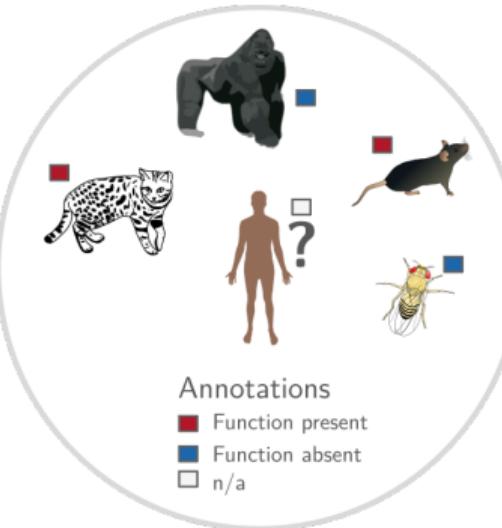
Part 1: On the Prediction of Gene Functions Using Phylogenetic Trees

Joint with: Paul D Thomas, Paul Marjoram, Huaiyu Mi, Duncan Thomas, and John Morrison
(Accepted at *PLOS Computational Biology*)

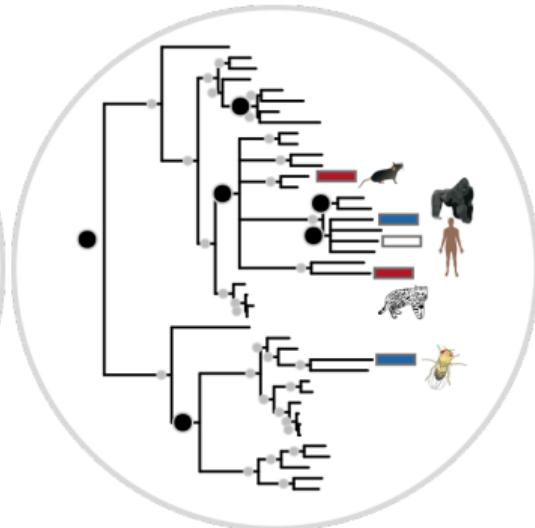
Is gene *XYZ* involved in process *ABC*?



Complex to directly assess



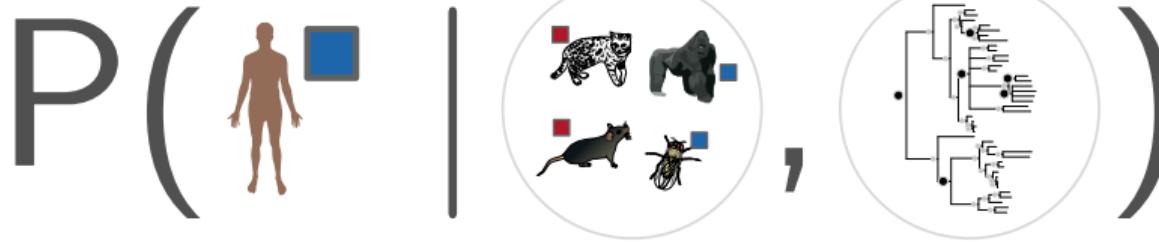
But we may know from other species



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*?



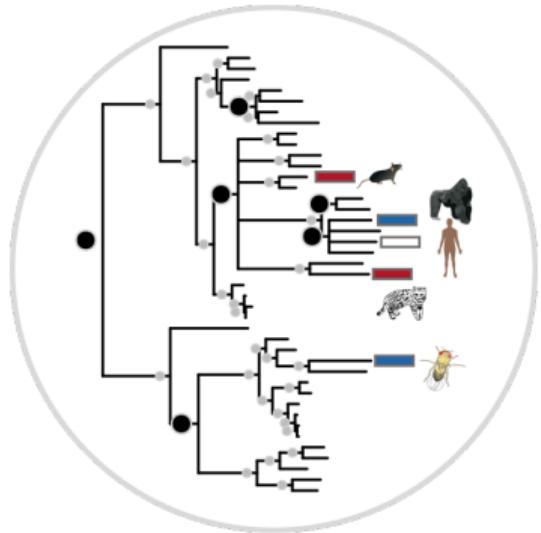
Annotations

- Function present
- Function absent
- n/a

... Where is all this data?

▶ more

The Gene Ontology Project



- ▶ ~ 15,000 phylogenetic trees
- ▶ ~ 8 million annotations
- ▶ ~ 600 thousand on human genes
- ▶ ~ < 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

An evolutionary model of gene functions

Family: PTHR11258

Type: Molecular Function

Name: 2'-5'-oligoadenylate synthetase activity

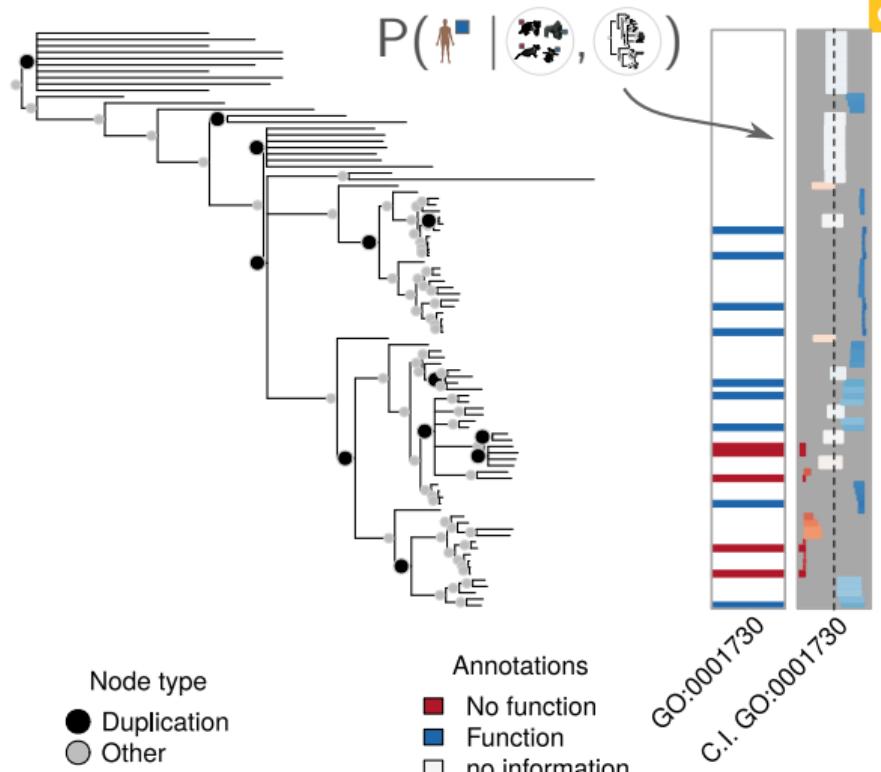
Desc: GO:0001730 involved in the process of cellular antiviral activity (wiki on [interferon](#)).

MAE: 0.34

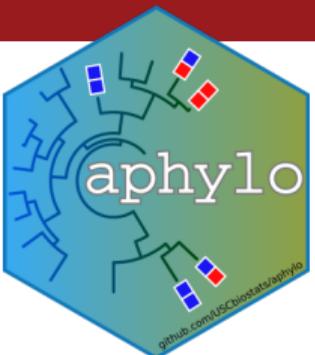
AUC: 0.91

This model is implemented in the **aphylo R** package

[see details](#)



Computational features of aphylo

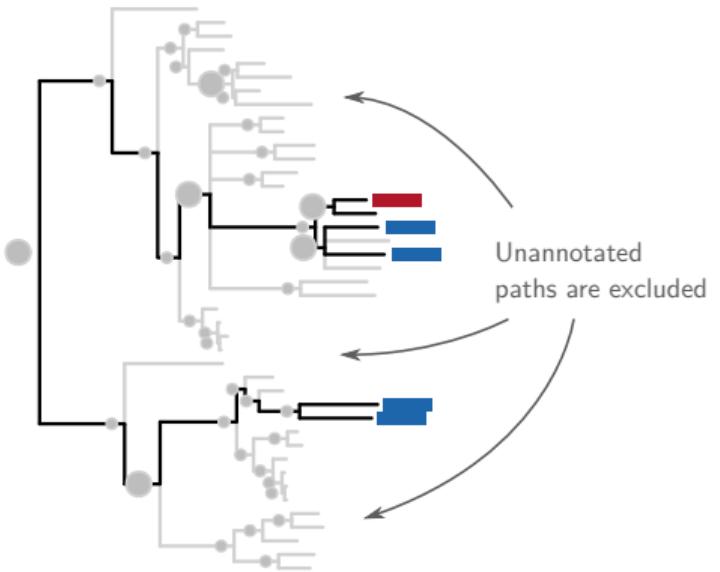


Baseline features

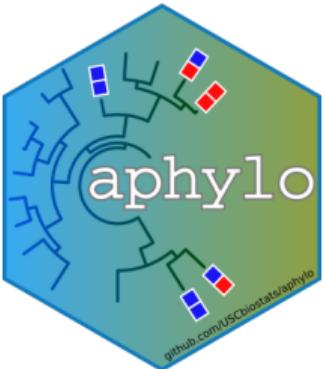
- ▶ Parsimony: Independence across functions/siblings.
- ▶ Post-order Tree traversal: Linear complexity $O(|\text{tree}|)$.

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)



Results: What does aphylo brings to the table?



Large scale

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

Interpretable

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

Fast

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

Accuracy

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

▶ details

Part 2: Exponential Random Graph Models for Small Networks

Joint with: Andrew Slaughter and Kayla de la Haye
(published in the journal *Social Networks*)

- ▶ If COVID-19 has taught us something it is that networks matter.
- ▶ And especially small networks: Families, teams, friends, etc. The cornerstone of larger social systems.
- ▶ We can study networks using ERGMs.

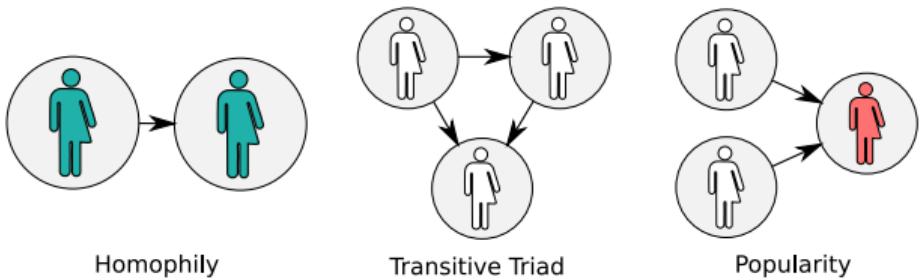
Data: Friendship network of a UK university faculty
from `igraphdata`. Viz: R package `netplot` (yours truly,
github.com/usccana/netplot)



What are Exponential Random Graph Models

Exponential Family Random Graph Models, aka **ERGMs** are:

- ▶ Statistical models of (social) networks.
- ▶ Not about individual ties, but about local structures (sufficient statistics).



Discrete Exponential-Family Models

$$\mathbb{P}(\mathbf{G} = \mathbf{g} \mid X = x) = \frac{\exp\{\theta^t s(\mathbf{g}, x)\}}{\sum_{\mathbf{g}' \in \mathcal{G}} \exp\{\theta^t s(\mathbf{g}', x)\}}, \quad \forall \mathbf{g} \in \mathcal{G}$$

A vector of
model parameters
A vector of
sufficient statistics


Observed data
The normalizing
constant
All possible
networks

- ▶ For any directed graph of size n , there are $2^{n(n-1)}$ possible realizations.
 - ▶ A directed graph of size 5 has 1,048,576 possible configurations!
 - ▶ Most (all) applications use **approximations**... yet, for sufficiently small graphs we “can be exact.”
... I implemented “exact calculations” in the **ergmito** package (ERGMito)

► more theory

► more terms

Computational Complexity: ergmito

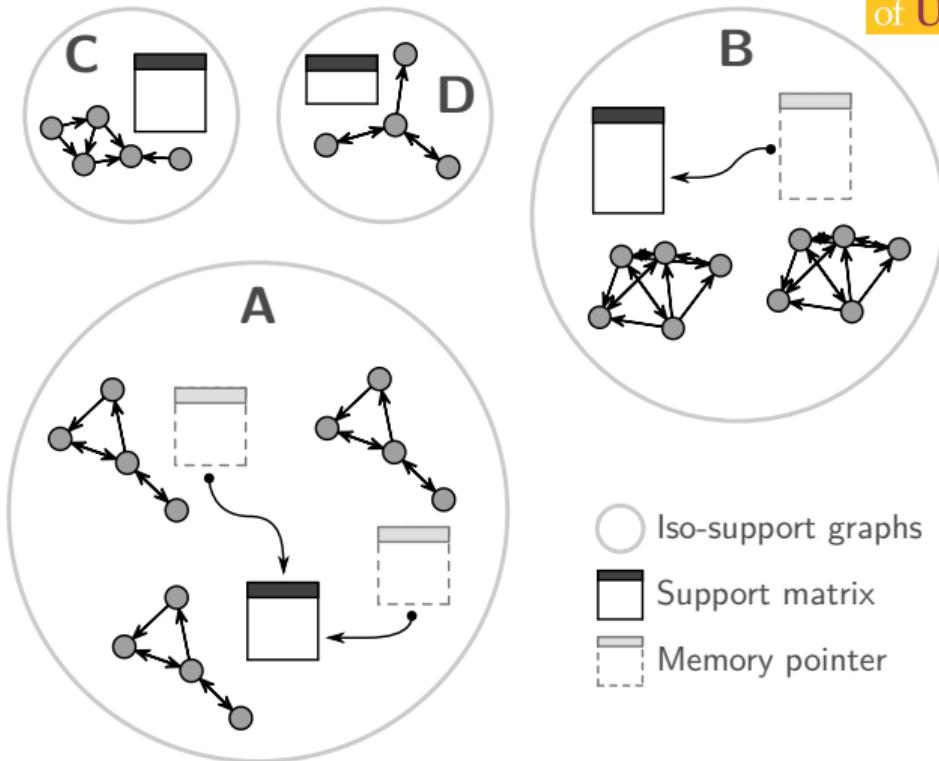
Premise

- ▶ Full enumeration \neq All networks with k ties

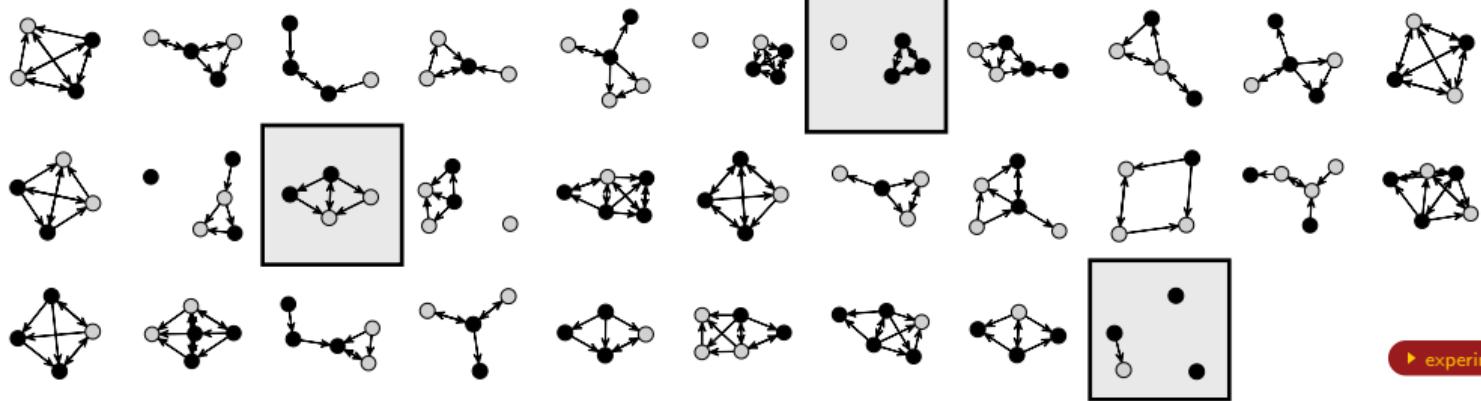
Extra features

- ▶ *Iso-support* structures (model) recycled
- ▶ Core algorithm written in C++
- ▶ Parallel computing using **OpenMP**

Simple ERGMito with 80,000 nodes $\sim 4s$



ergmito: Featured Example



▶ experiment

Key findings

- ▶ Low density.
- ▶ High balance (transitive triads).
- ▶ No evidence of gender homophily.
- ▶ Females are more likely to ask for advice.

What's different (from regular ERGMs)?

- ▶ Interaction effects: edges $\times \mathbf{1}$ ($n = 5$).
- ▶ Constrained support: edge > 4 .
- ▶ Transformed variables: $(\text{Homophily})^{1/2}$.
- ▶ Bootstrapping: 1,000 replicates in less than 1.5 minutes...
... if you are lucky, using “regular” ERGMs would take you about 5 hours.

▶ details

▶ gof

▶ data

Results: What does **ergmito** brings to the table?**Theoretical Goodies**

Higher convergence rate,
lower bias, lower type-I
error, higher power, ...

Fast

Orders of magnitude faster
than other methods
(x200 faster in some cases)

Flexible

Arbitrary transformations
and constraints
(interaction effects, for
example)

The right tool

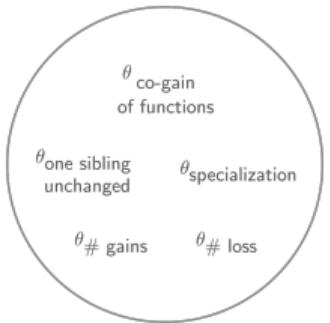
For ego networks, families,
small teams, etc.
( downloads 5649 others
think so)

 more

Part 3: Current and Future Research

Biology

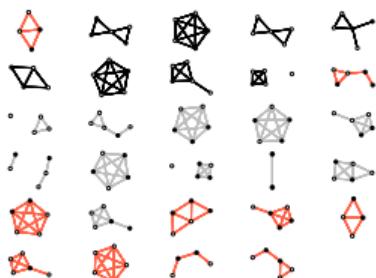
Extension of gene
functional-evolution model using
the ERGMs framework

**Criminology**

The role of social networks on
police use of force

**Sociology**

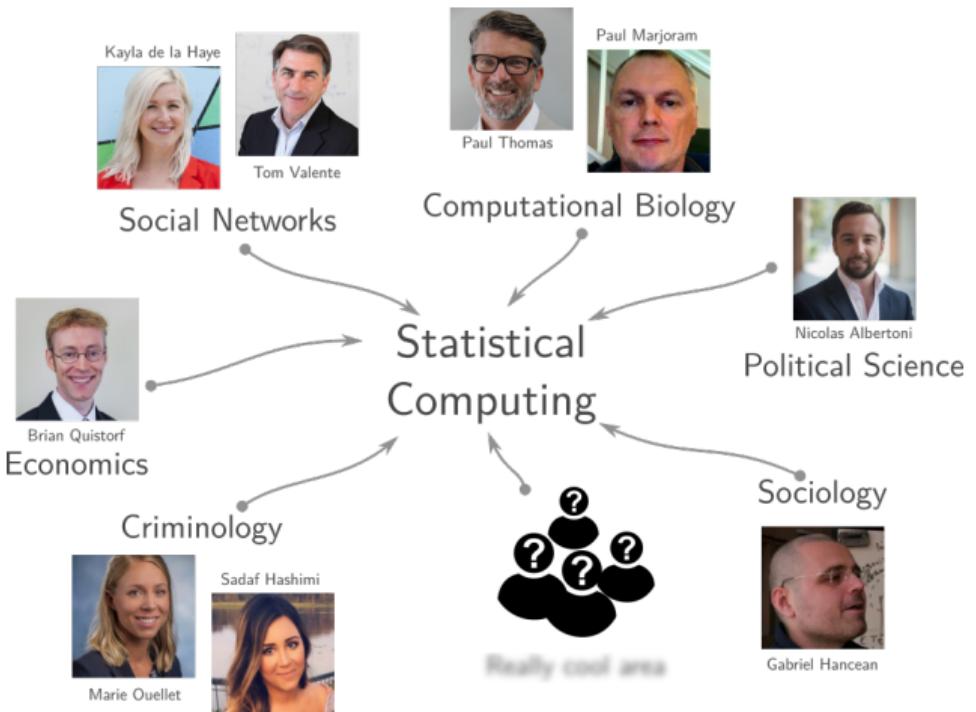
Using ERGMitos to model
political discussion networks in
Romania



Continue developing scientific software...



The future: Keep building bridges



...you could be next!

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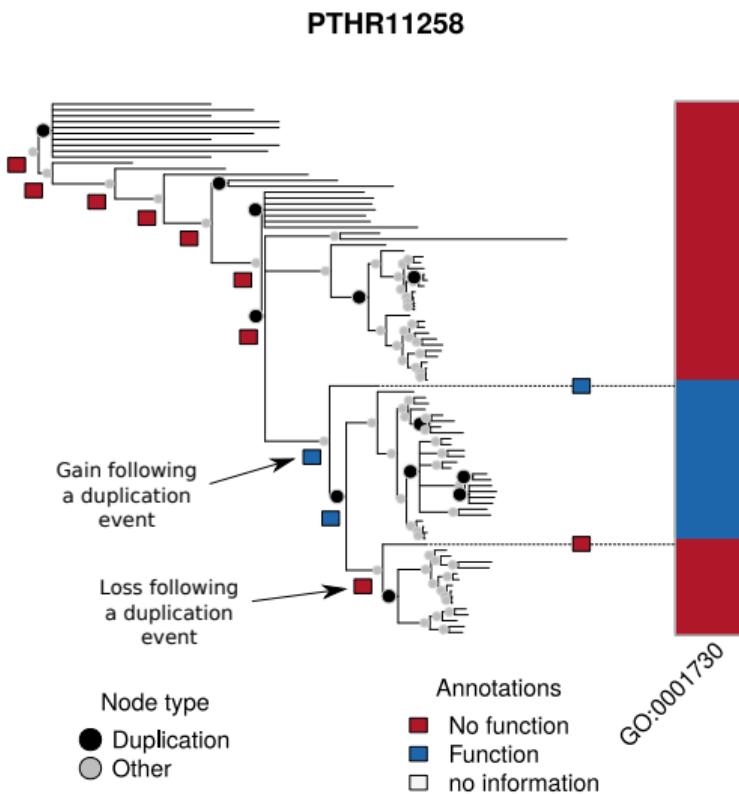
<https://ggyv.cl>

vegayon@usc.edu



Thank you!

An evolutionary model of gene functions



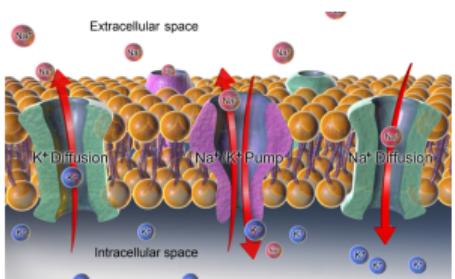
- ▶ Starting with the root node (no function in this case).
- ▶ Passes the baton to its offspring.
- ▶ Possibly without change (on this particular function).
- ▶ Or, with some probability, gaining... or loosing the function.
- ▶ Until it reaches the end of the tree (modern genes).

[▶ more on duplication](#)[▶ alt view](#)[◀ go back](#)

Gene functions can be classified in three types:

Molecular function

Active transport GO:0005215



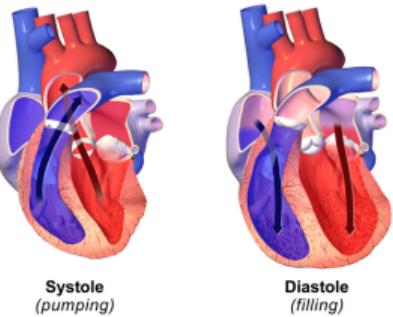
Cellular component

Mitochondria GO:0004016



Biological process

Heart contraction GO:0060047



◀ go back

The Gene Ontology Project

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

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



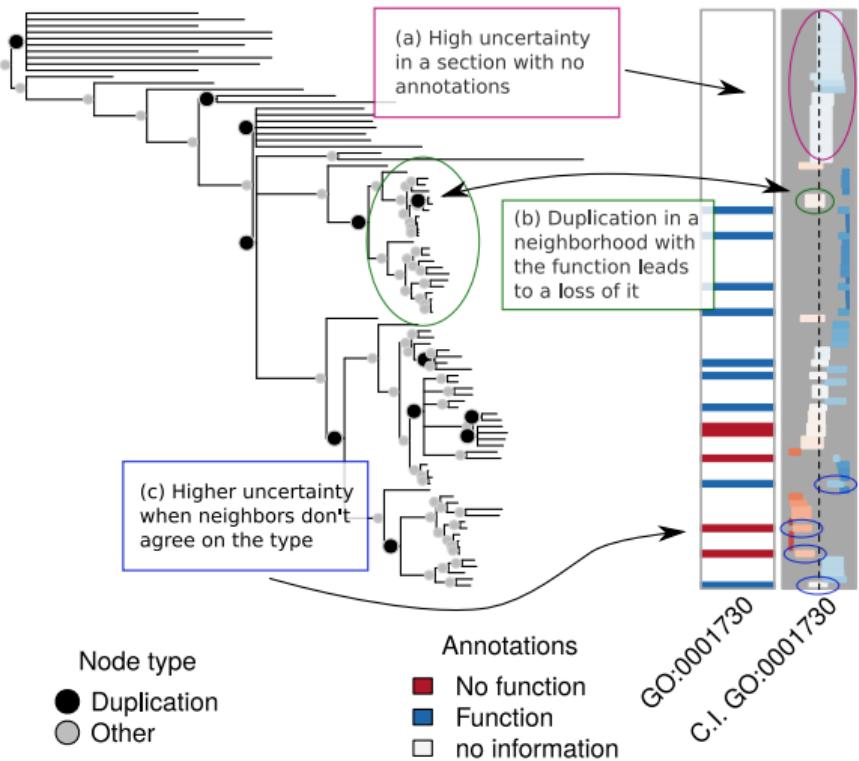
Anolis carolinensis pthr11521



Equus caballus pthr24356

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Example of Data + Predictions

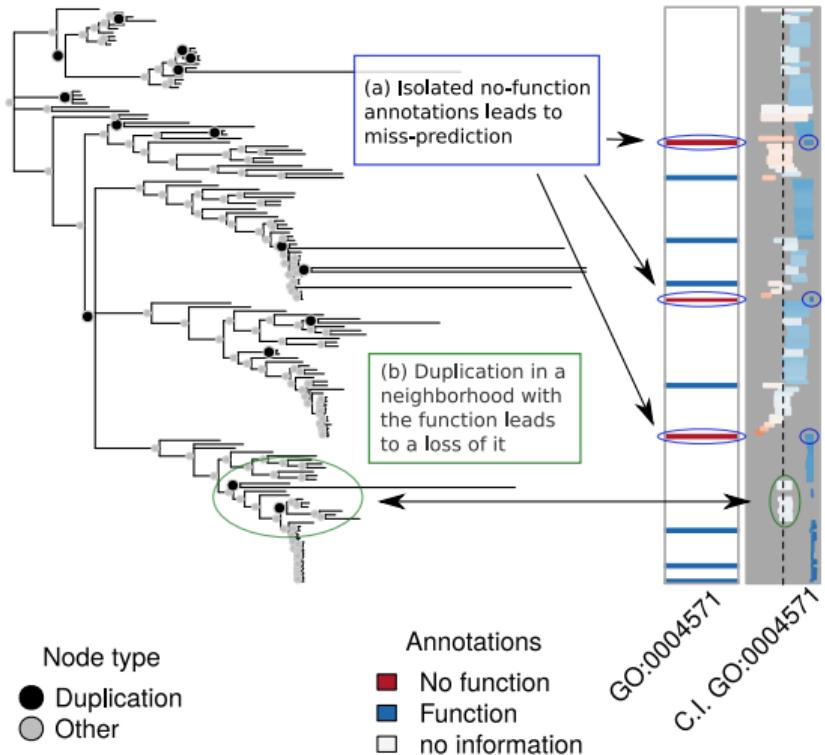
Family: PTHR11258**Type:** Molecular Function**Name:** 2'-5'-oligoadenylate synthetase activity**Desc:** GO:0001730 involved in the process of cellular antiviral activity (wiki on [interferon](#)).**MAE:** 0.34**AUC:** 0.91[see a bad one](#)[◀ go back](#)

Example 2: Bad quality prediction

MAE: 0.52

AUC: 0.33

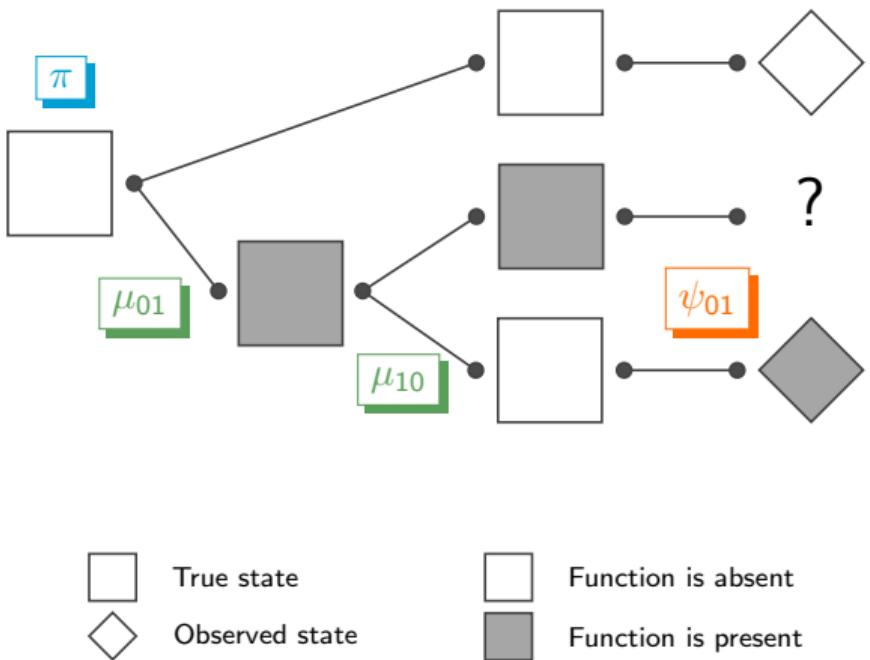
Type: Molecular Function

Name: mannosyl-oligosaccharide
1,2-alpha-mannosidase activityDesc: GO:0004571 involved in
synthesis of glycoproteins ([wiki](#)
and [examples](#)).[◀ go back](#)

		Pooled-data	One-at-a-time	
		Beta prior	Unif. prior	Beta Prior
Pooled-data				
Unif. prior	Beta 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	Beta 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*.

An evolutionary model of gene functions



- ▶ Root has the function.
- ▶ Gain and loss (also depends on the type of event [► more](#)).
- ▶ Observed annotations may be incorrect.
- ▶ Only a fraction of the known genes have some form of annotation.

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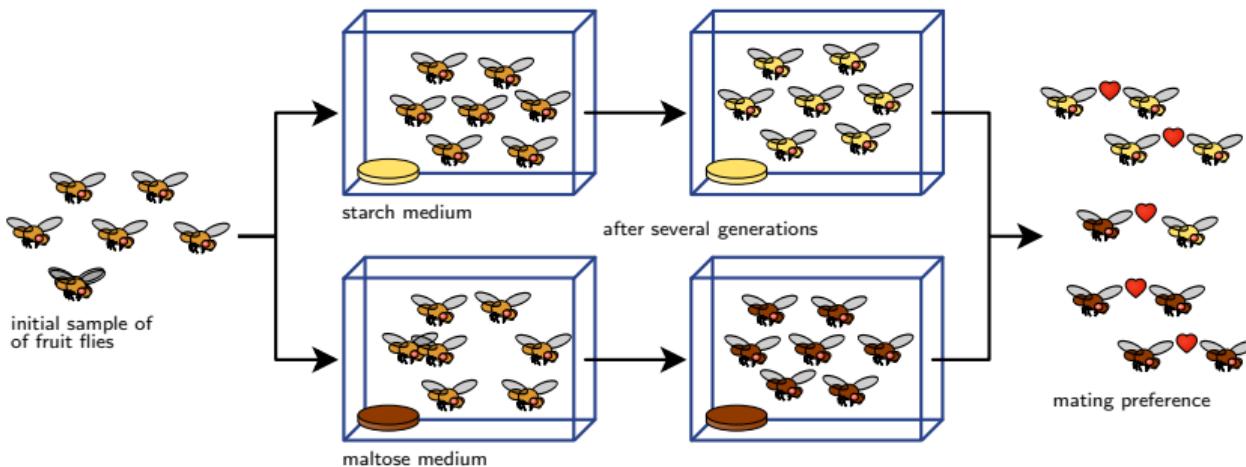


Figure 1 Dodd 1989: After one year of isolation, flies showed a significant level of assortativity in mating (wikimedia)

◀ go back

Duplication

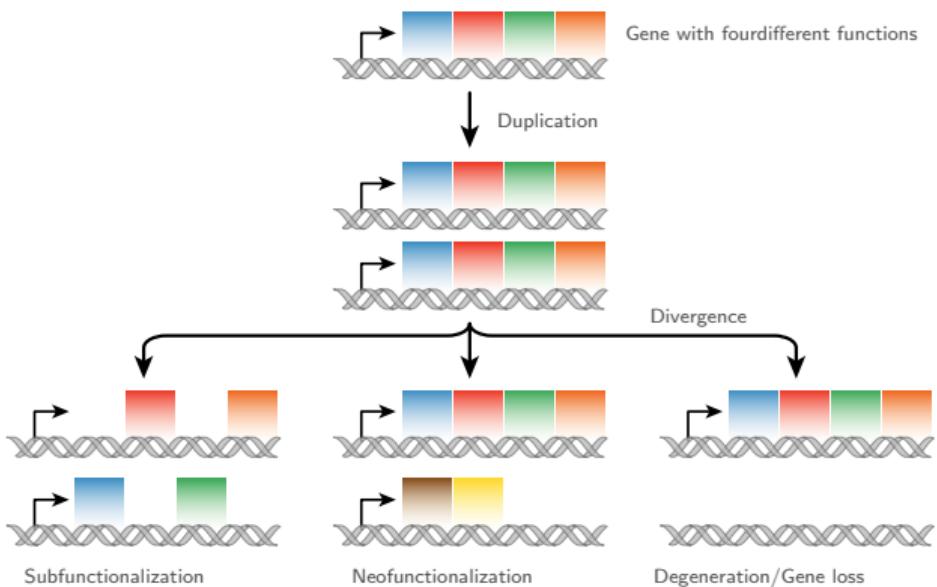


Figure 2 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge
(wikimedia)

◀ go back

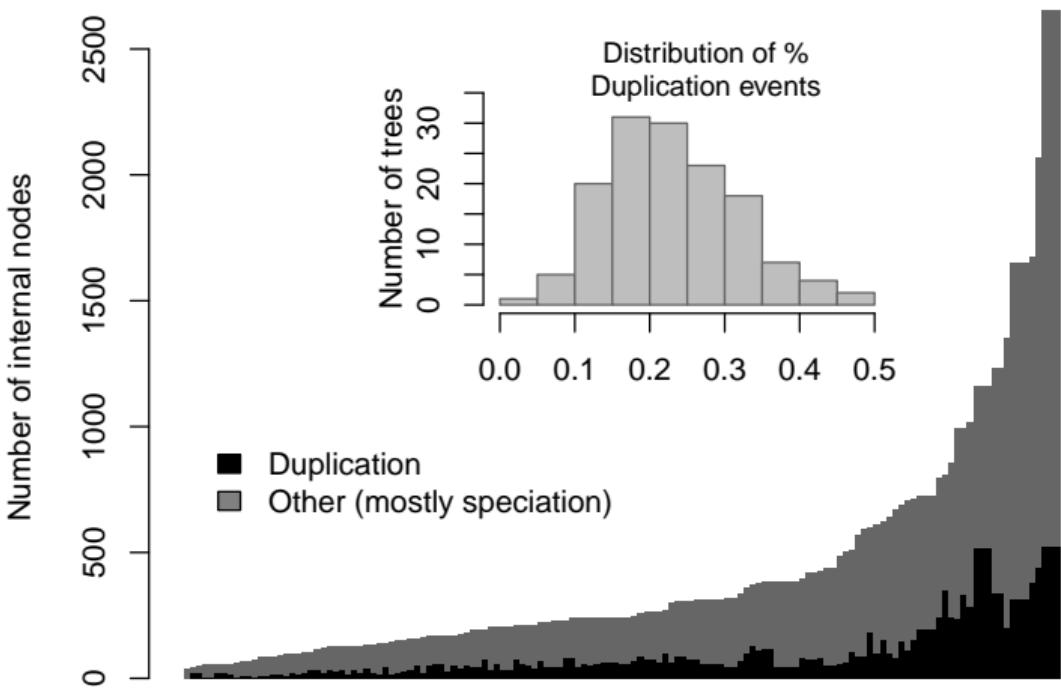
Data: Phylogenetic trees

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	Unikonta
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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Data: Node type (events)

[◀ go back](#)

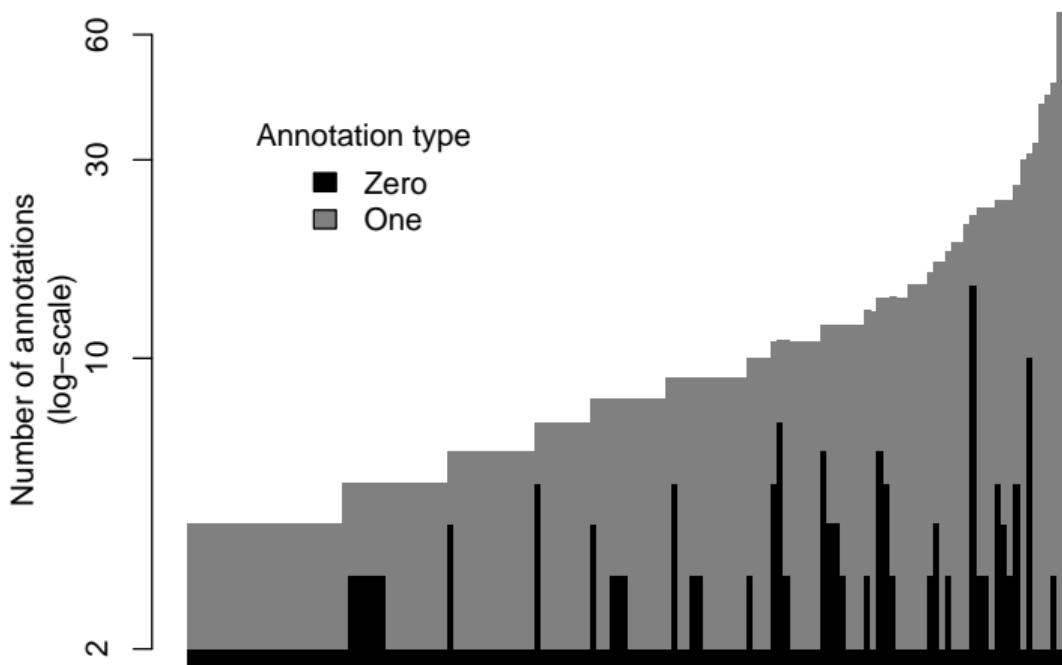
Data: Annotations (example)

This is the first 10 of ~ 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	

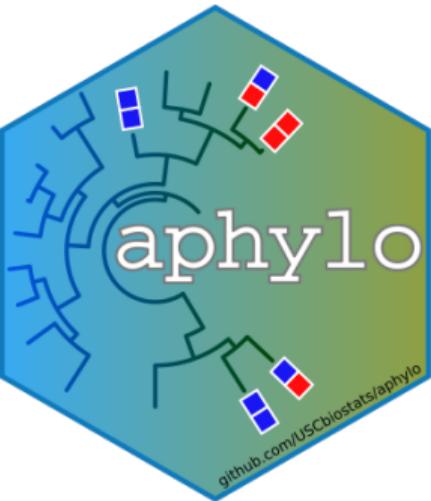
◀ go back

Data: Experimental Annotations

[◀ go back](#)

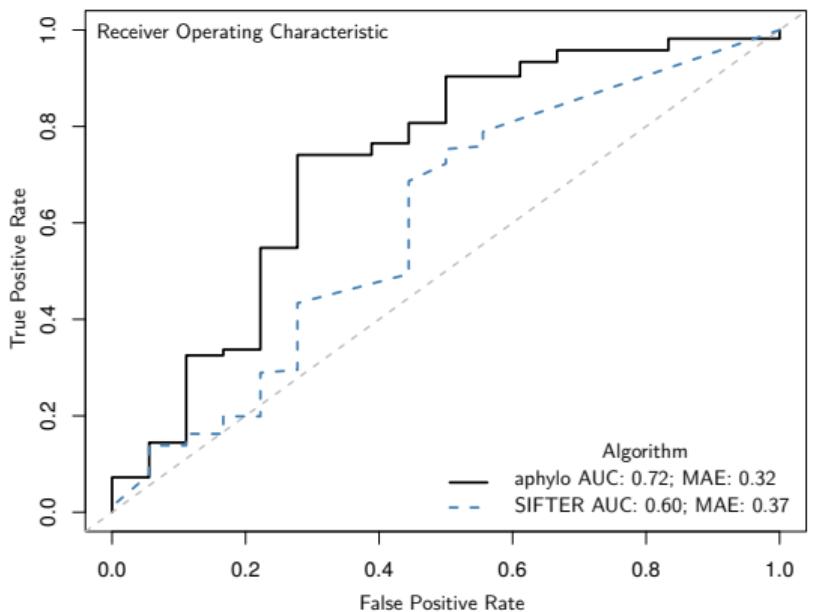
Results: Implementation and Large scale study

- ▶ 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 ~ 130 families... estimation of parameters using a pooled-data model (< 5 min). [◀ modeling](#) [◀ estimates](#)
- ▶ In a subset of ~ 200 predictions we found 46 novel annotations

[▶ more](#)[◀ go back](#)

Results: Performance and Scalability

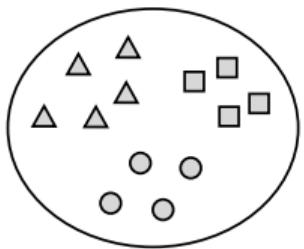
aphylo vs SIFTER (state-of-the-art phylo-based model) on 147 genes.



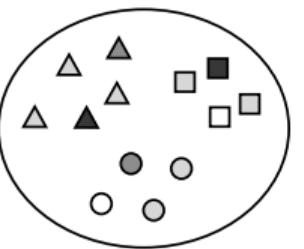
Fast 110 minutes (SIFTER) to calculate the posterior probabilities, aphylo took 1 second.

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

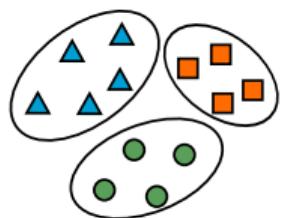
Phylogenetics Modeling: Pooling data



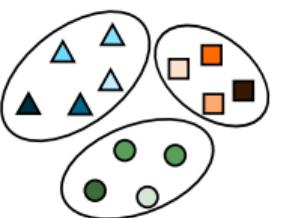
(a) Fixed rate accross functions



(b) Random rate accross functions



(c) Fixed rate within type



(d) Random rate within type

- (a) Featured in the first version of the model.
- (b) “Full glory” Hierarchical Bayes (1,001 parameters for the 141 functions).
- (c) Distilled version (a), improves accuracy.
- (d) Model estimated for Molecular Function (using Empirical Bayes) without significant improvements.

All methods are now available in the `aphylo` package: `aphylo_mle`, `aphylo_mcmc`, and `aphylo_hier`.

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Overview of Prediction Results

	Pooled	Type of Annotation		
		Molecular Function	Biological Process	Cellular Comp.
Mislabeling				
ψ_{01}	0.23	0.18	0.09	
ψ_{10}	0.01	0.01	0.01	
Duplication Events				
μ_{d01}	0.97	0.97	0.10	
μ_{d10}	0.52	0.51	0.03	
Speciation Events				
μ_{s01}	0.05	0.05	0.05	
μ_{s10}	0.01	0.01	0.02	
Root node				
π	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

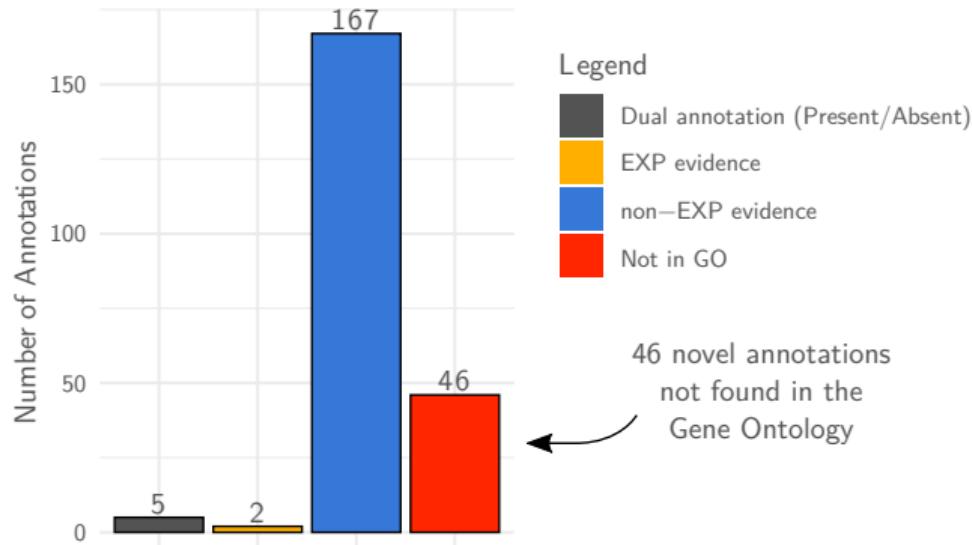


Figure 3 Distribution of predictions

◀ go back

Asymptotic Behavior of ERGMs

- ▶ In the case that $s_l = s(\mathbf{g}, x)$ is on the boundary: $s_l \rightarrow \pm\infty$
- ▶ Since the support space of $s(\mathbf{g}, x) \in \mathcal{S}$ is bounded, e.g. # edges $\in [0, n \times (n - 1)]$, we have:

$$\lim_{\theta_l \rightarrow \infty} l(\theta), \quad \lim_{\theta_l \rightarrow \infty} \nabla l(\theta), \quad \lim_{\theta_l \rightarrow \infty} \mathbf{H}(\theta)$$

log-likelihood, its gradient, and hessian are finite.

- ▶ The direct implication is that, while $s(\mathbf{g}, x)$ is on the boundary, the MLE for the other statistics exists.¹
- ▶ All equations ultimately involve realizations of $s(\mathbf{g}', x)$ that equal s_l , relevant in: Simulations, Bootstrapping, etc.

◀ go back

¹Handcock 2003 briefly mentions this

- ▶ Long history in (soc.) network science.
- ▶ Common usage: Hypothesis test prevalence of a feature.

Is the observed count of XYZ within the expected in a Bernoulli graph?

Are statistics A, B, and C different from graphs with 5 triangles?

- ▶ Different names, same thing, e.g. CUG tests and rewiring algorithms.
- ▶ $\{\text{CUG, Rewiring}\} \subset \text{ERGM}$
- ▶ We can talk about *Conditional* ERGMs.

$$\mathbb{P}(s(\mathbf{G})_k = s_k \mid s(\mathbf{G})_l = s_l, \theta) = \frac{\exp\{\theta_{-l}^t s(\mathbf{g})_{-l}\}}{\sum_{\mathbf{g}' : s(\mathbf{g}')_l = s_l} \exp\{\theta_{-l}^t s(\mathbf{g}')_{-l}\}}$$

In this equation θ_l becomes a nuisance parameter.

◀ go back

Sufficient statistics have various forms

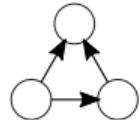
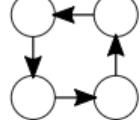
Representation	Description
	Mutual Ties (Reciprocity) $\sum_{i \neq j} y_{ij} y_{ji}$
	Transitive Triad (Balance) $\sum_{i \neq j \neq k} y_{ij} y_{jk} y_{ik}$
	Homophily $\sum_{i \neq j} y_{ij} \mathbf{1}(x_i = x_j)$
	Attribute-receiver effect $\sum_{i \neq j} y_{ij} x_j$
	Four Cycle $\sum_{i \neq j \neq k \neq l} y_{ij} y_{jk} y_{kl} y_{li}$

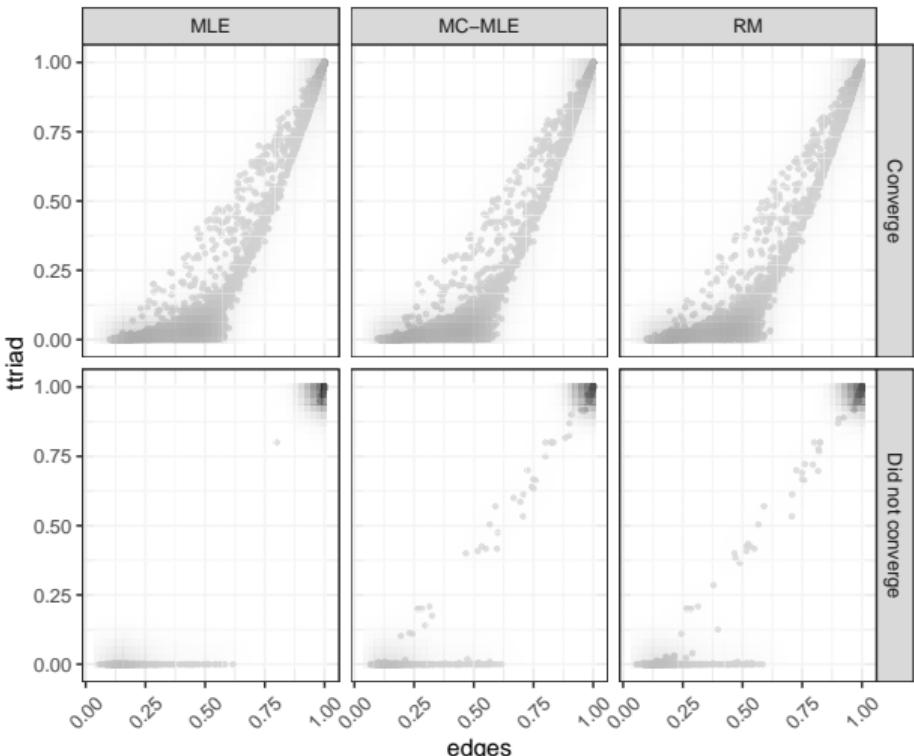
Figure 4 Besides the common edge count statistic (number of ties in a graph), ERGMs allow measuring other more complex structures that can be captured as sufficient statistics.

◀ go back

Simulation Study

1. Higher convergence rate

◀ return



Simulation Study

1. Higher convergence rate
2. **Smaller bias**

◀ return

	MLE	MC-MLE	RM
edges	[0.27, 0.36]	[1.23, 1.65]	[0.55, 1.54]
ttriads	[-0.05, -0.03]	[-0.22, -0.16]	[-0.15, 0.48]

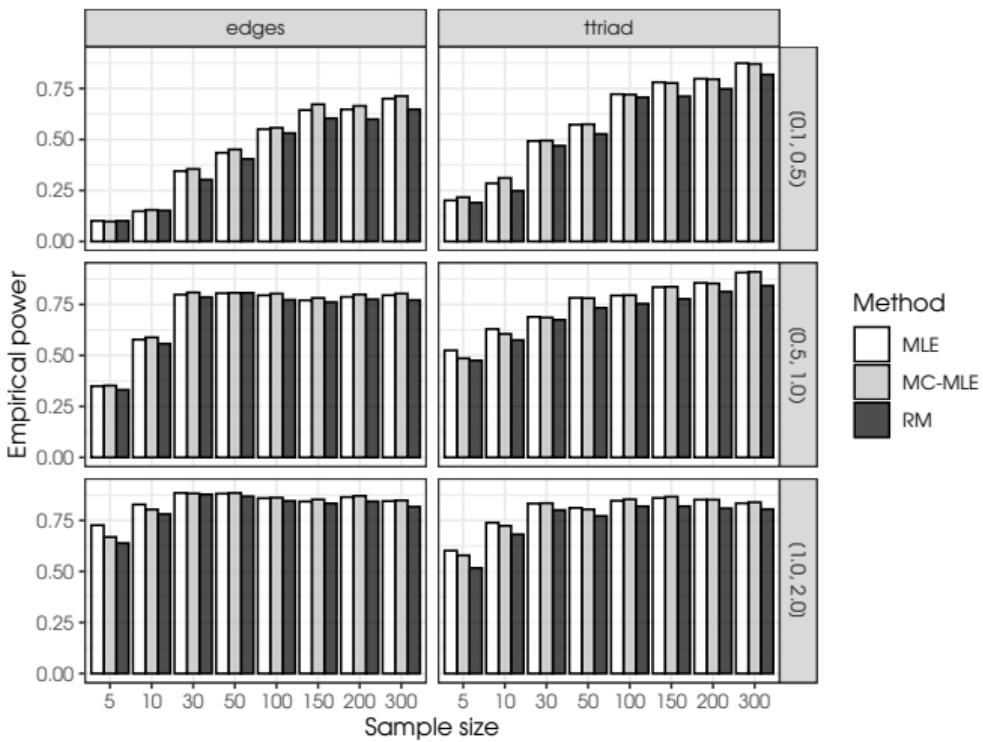
Table 3 Empirical bias. Each cell shows the 95% confidence interval of each methods' empirical bias.

▶ alt take

Simulation Study

1. Higher convergence rate
2. Smaller bias
3. **Higher power**

◀ return



Simulation Study

1. Higher convergence rate
2. Smaller bias
3. Higher power
4. **Smaller type I error**

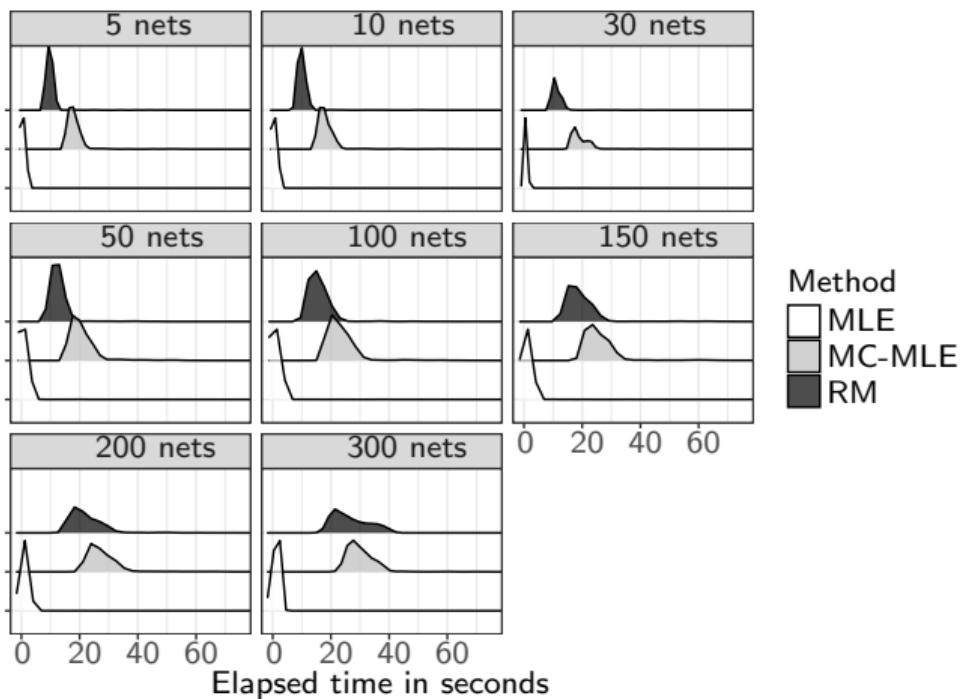
[◀ return](#)

	Sample size	N. Sims.	P(Type I error)		χ^2 (vs MLE)		RM
			MLE	MC-MLE	RM	MC-MLE	
	5	4,325	0.066	0.086	0.086	11.36 ***	11.36 ***
	10	4,677	0.063	0.078	0.073	8.44 ***	3.73 *
	15	4,818	0.060	0.072	0.063	5.50 **	0.41
	20	4,889	0.054	0.065	0.061	5.30 **	2.05
	30	4,946	0.053	0.059	0.055	1.60	0.07
	50	4,987	0.053	0.055	0.047	0.16	1.67
	100	4,999	0.054	0.054	0.050	0.00	0.81

Simulation Study

1. Higher convergence rate
2. Smaller bias
3. Higher power
4. Smaller type I error
5. **Elapsed time**

◀ return



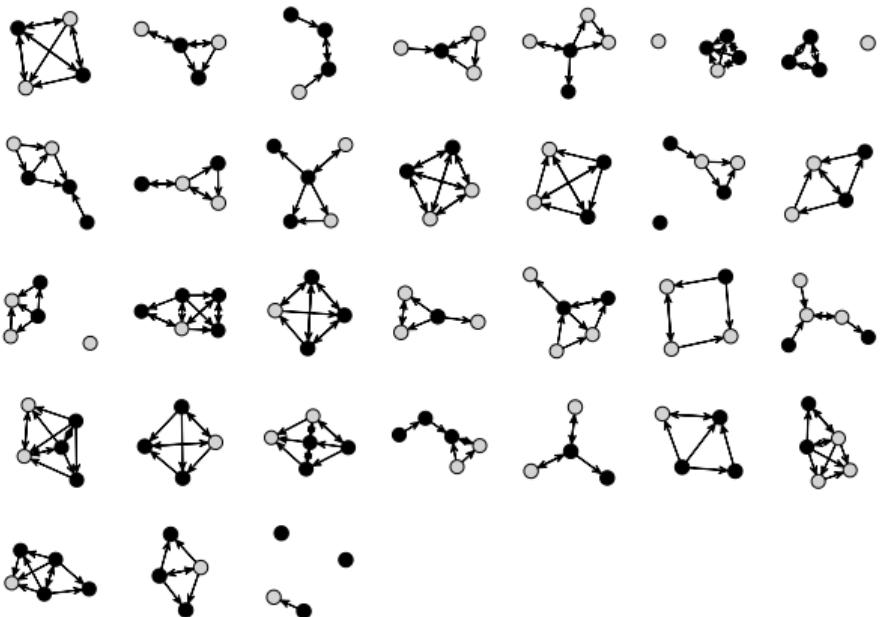
Featured Application: Small Teams

Sample

- ▶ 31 mixed-gender teams (4-5 members).
- ▶ University students.
- ▶ Don't know each other.
- ▶ At least one female/male per team.

Experiment

- ▶ Complete 1 hour of group tasks.
- ▶ Captured network data using name generator survey: *Who did you go to for advice, information or help to complete the group task?*



Is Gender Homophily a feature of these graphs?

[◀ go back](#)

	(1)	(2)	(3)	(4)	(5)	(4b)
edges	-0.52** (0.17)	-0.91*** (0.23)	-0.54** (0.18)	-0.72*** (0.19)	-0.48* (0.19)	-0.72*** (0.17)
ttriads	0.36*** (0.06)	0.46*** (0.06)	0.37*** (0.06)	0.36*** (0.06)	0.36*** (0.06)	0.36*** (0.05)
Homophily (gender)	-0.03 (0.20)	-0.01 (0.21)	-0.20 (0.46)	-0.12 (0.20)	-0.01 (0.20)	-0.12 (0.20)
edges × 1 ($n = 5$)	-0.53*** (0.12)	-0.47** (0.16)	-0.52*** (0.13)	-0.53*** (0.13)	-0.53*** (0.12)	-0.53*** (0.13)
(Homophily) $^{1/2}$			0.54 (1.32)			
Sender (female)				0.46* (0.18)		0.46* (0.18)
Receiver (female)					-0.08 (0.18)	
<i>Constraint (offset)</i>						
edge > 4		Yes				
AIC	639.26	569.93	641.08	634.68	641.07	634.68
BIC	655.99	586.66	661.99	655.59	661.98	655.59
Num. networks	31	28	31	31	31	31
Time (seconds)	2.26	2.32	2.28	5.10	5.19	83.97
N replicates					1000	

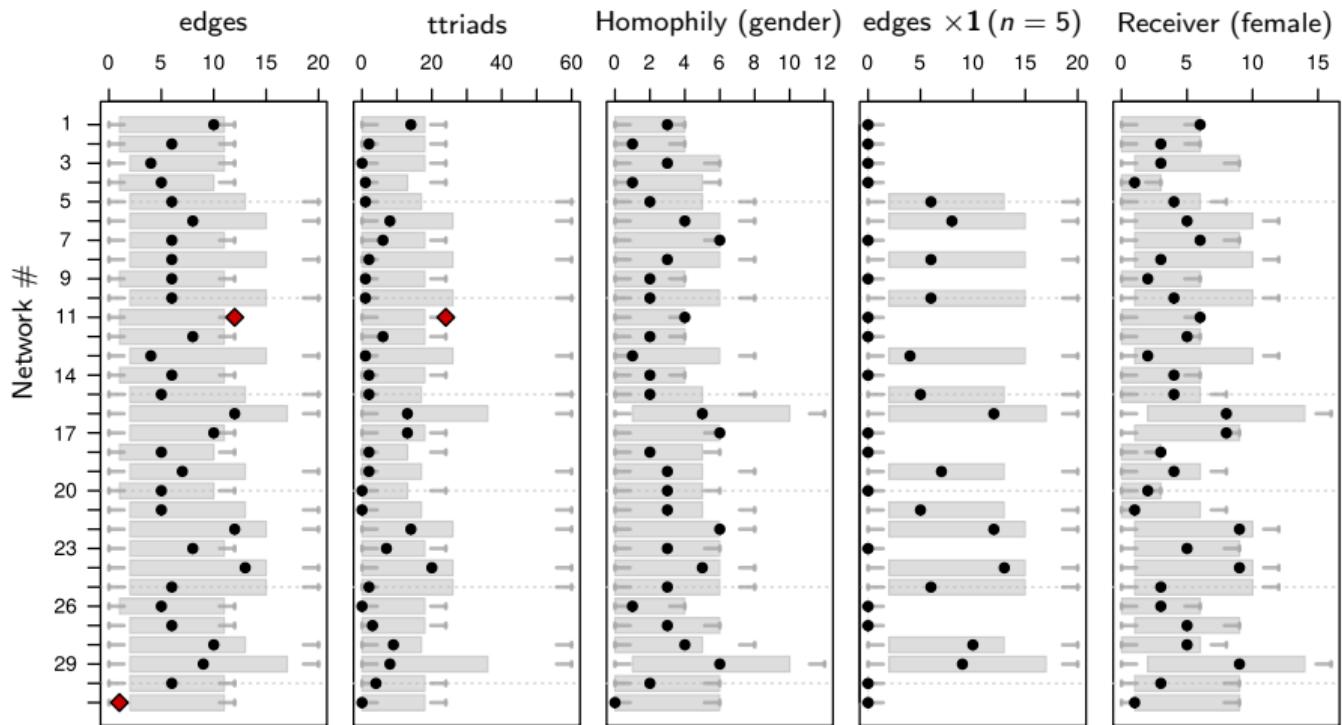
*** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

1. Interaction effects: seemingly included.
2. Transformed variables: also easy to add.
3. Using offset terms, we can constrain the support.
4. Each 1,000 bootstrap replicates took roughly 0.08 secs.
5. No support for gender homophily, but evidence of females sending more ties.

What about goodness-of-fit?

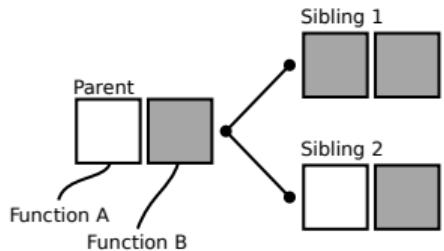
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What About Goodness-of-fit?

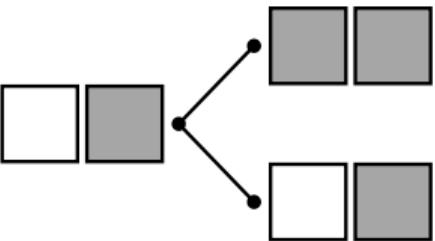
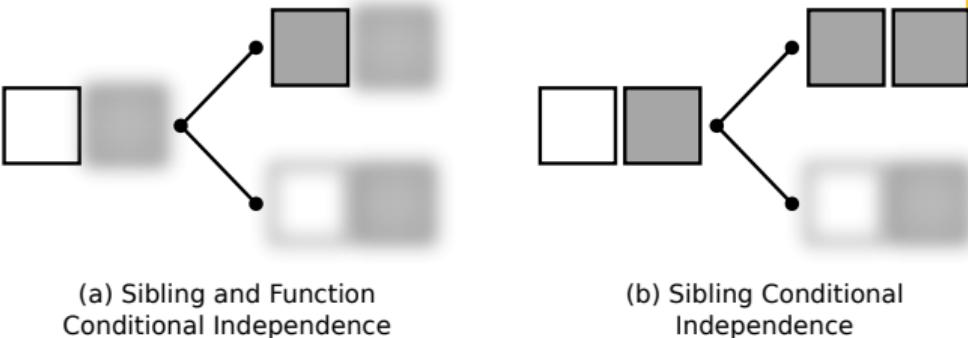
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(1)	(2)	(3)	(4)	(5)	(6)
Size (n)	edges	ttriads	edges \times $\mathbf{1} (n = 5)$	ttriads \times $\mathbf{1} (n = 5)$	edges \times $\log \{1/n\}$
4	10	14	0	0	-13.86
4	6	2	0	0	-8.32
4	4	0	0	0	-5.55
5	6	1	6	1	-9.66
5	8	8	8	8	-12.88
5	6	2	6	2	-9.66
... 25 more rows ...					

Table 4 Example of observed sufficient statistics for the team advice networks. Pooled-data ERGMs have multiple observed sufficient statistics (also known as target statistics). Furthermore, as shown here, we can manipulate common statistics as *edges* (2) and *ttriads* (3) to include, e.g. interaction effects (4) and (5), or more complex transformations, e.g. (6).



Has the function
 Doesn't have the function

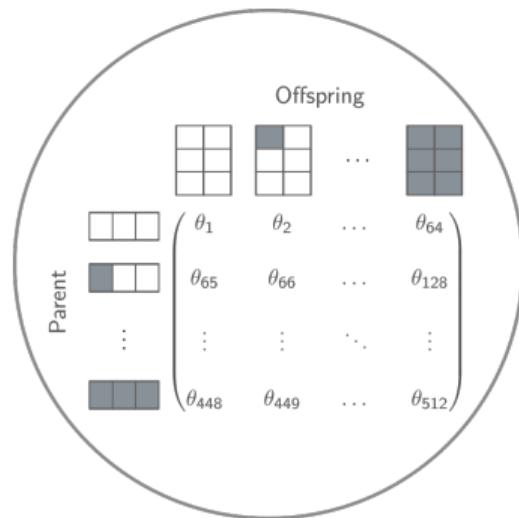


(c) No conditional
independence

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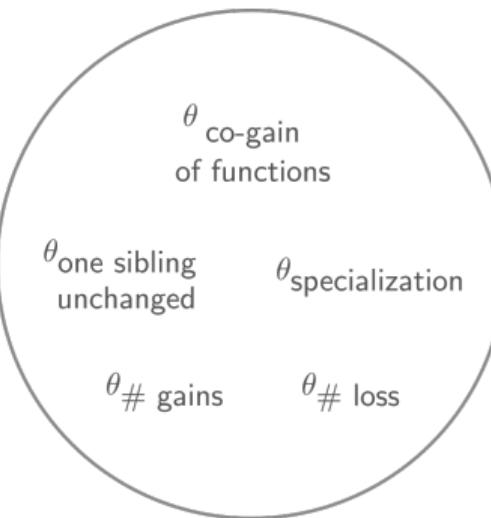
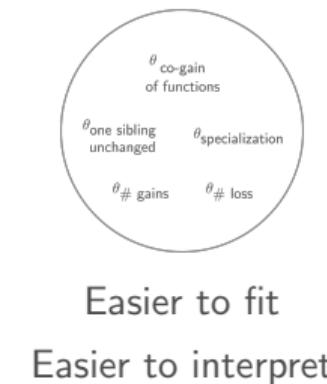
If we wanted to build a model with 3 functions, we would need to estimate...

Full Markov Transition Matrix



512 parameters

Sufficient statistics



5 parameters

◀ numeric example

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](https://USCbiostats.github.io/binaryarrays)

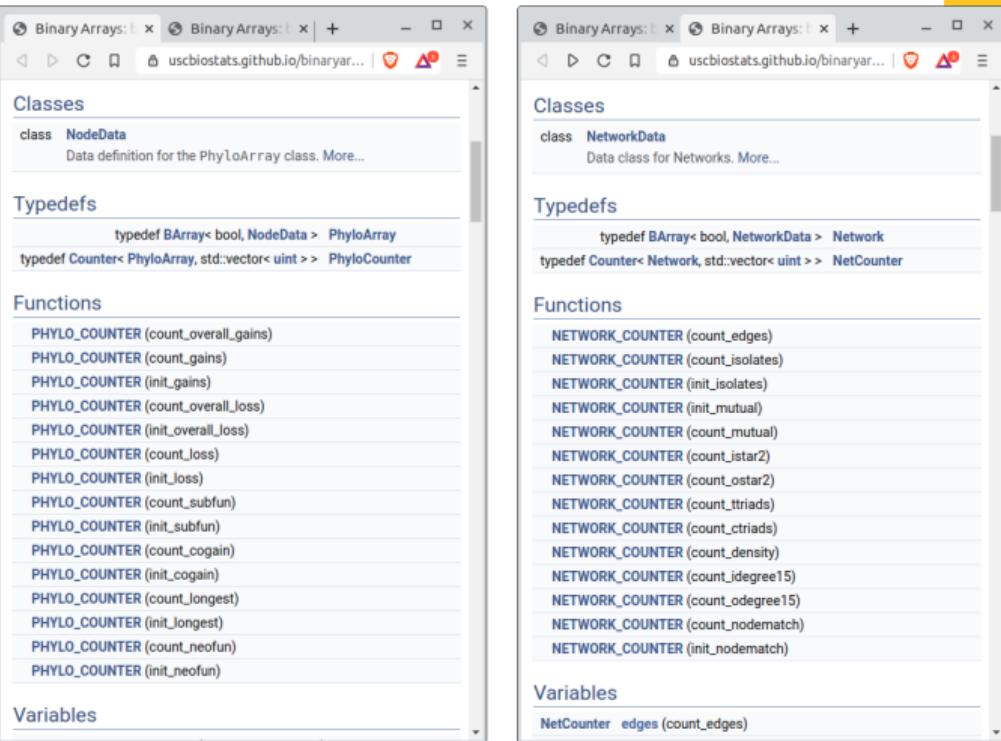


Figure 5 Screenshots from the project's website on GitHub.

What Drives Evolution

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

		Transitions to	
		Case 1	Case 2
Parent	A	$\begin{bmatrix} 0 \\ 1 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \\ 1 & 0 \end{bmatrix}$
	B	$\begin{bmatrix} 1 \\ 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \\ 1 & 1 \end{bmatrix}$
	C	$\begin{bmatrix} 1 \\ 1 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \\ 0 & 1 \end{bmatrix}$

Sufficient statistics

# Gains	1	1
Only one offspring changes (yes/no)	1	0
# Changes (gain+loss)	2	3
Subfunctionalizations (yes/no)	0	1

▶ return

What Drives Evolution: a game changer

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,

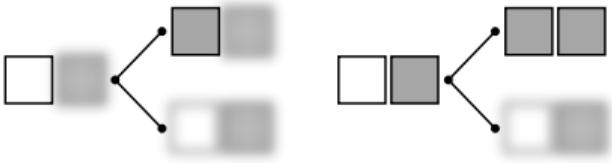
Pairwise Subfunctionalization: 3 terms,

Function specific gain: 3 terms,

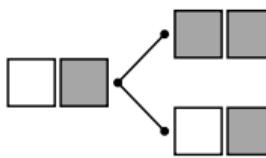
Function specific loss: 3 terms,

Total: 15 parameters.

- ▶ Easier to fit and interpret.



(b) Sibling Conditional Independence



References |

-  Dodd, Diane M. B. (1989). "Reproductive Isolation as a Consequence of Adaptive Divergence in *Drosophila pseudoobscura*". In: Evolution 43.6, pp. 1308–1311. ISSN: 00143820, 15585646. URL: <http://www.jstor.org/stable/2409365>.
-  Handcock, Mark S. (2003). "Assessing Degeneracy in Statistical Models of Social Networks". In: Working Paper No. 39 76.39, pp. 33–50. ISSN: 1936900X. DOI: 10.1.1.81.5086. URL: <http://citeseerx.ist.psu.edu/viewdoc/summary?doi=10.1.1.81.5086>.