Statistical and Computational Methods for Complex Systems

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University of Southern California, Department of Preventive Medicine

Universidad Adolfo Ibáñez

December 10, 2020

Keck School of Medicine of USC

My work sits at the intersection between...

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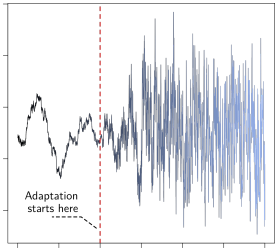
Statistics



Bayesian, Non-parametric, Spatial

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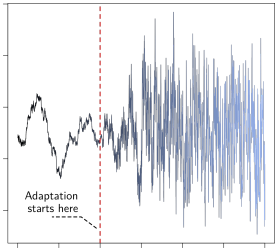
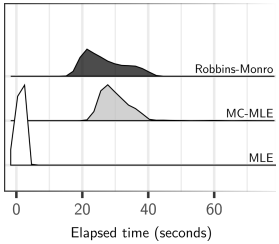


Bayesian, Non-parametric, Spatial

Computer Science



parallel computing, HPC, software

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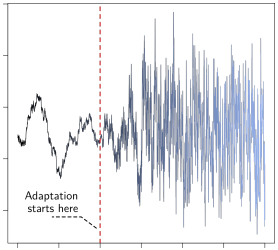

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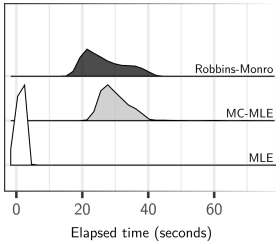

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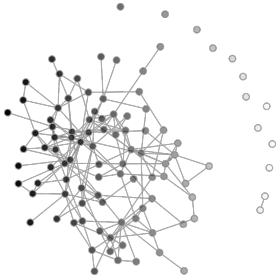
Complex Systems



social, biological, technical

Contents

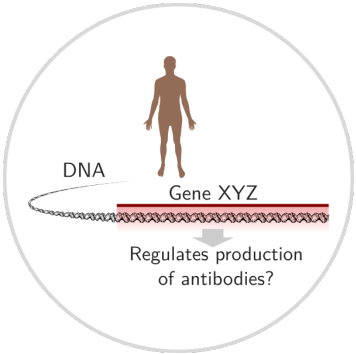
You can download the slides from ggv.cl/slides/uai-fic

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

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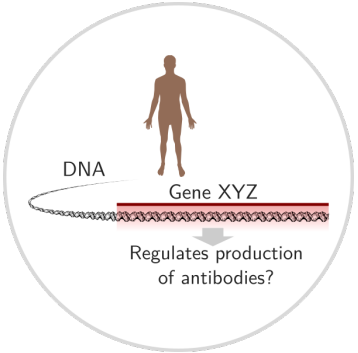

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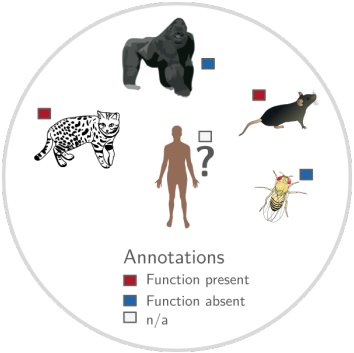

But we may know from other species

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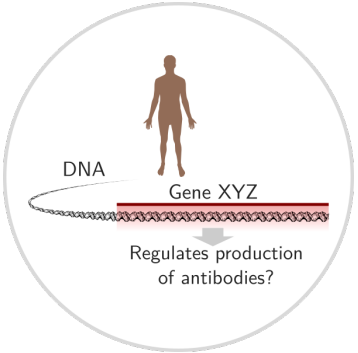

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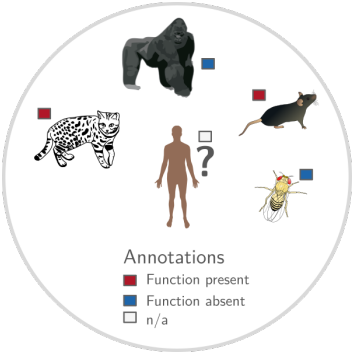

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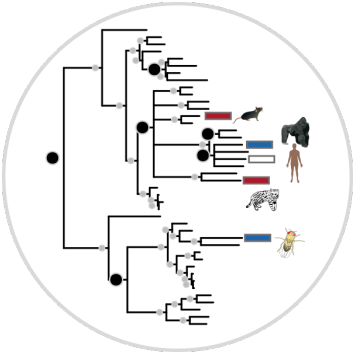

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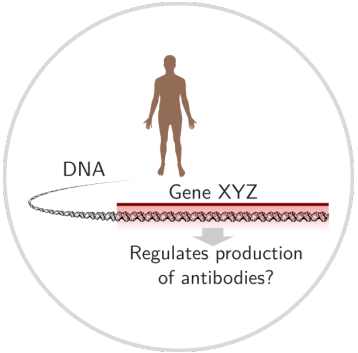

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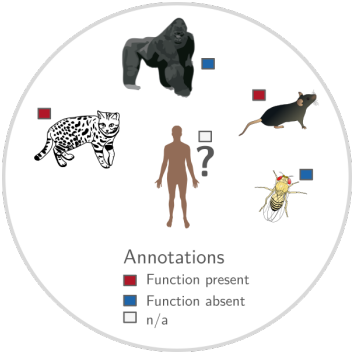

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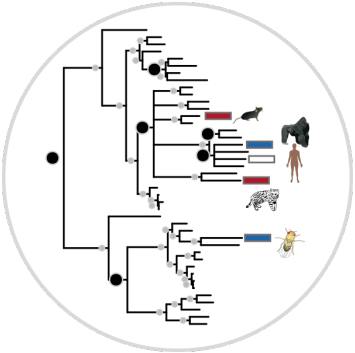
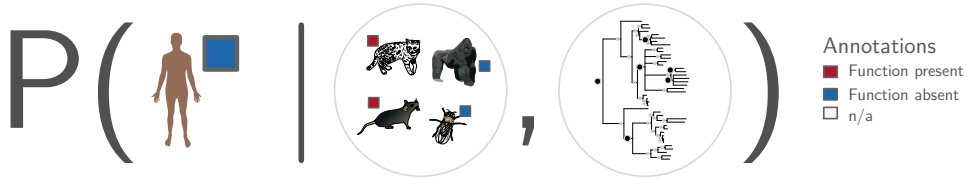


And we further know how these *genetically* connected

... 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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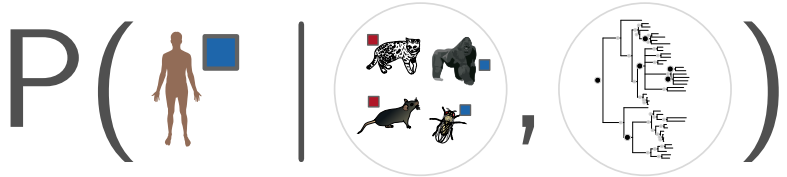

... Where is all this data?

more

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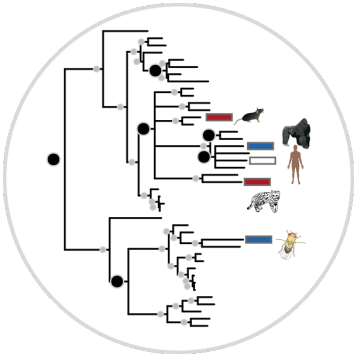

GENEONTOLOGY
Unifying Biology

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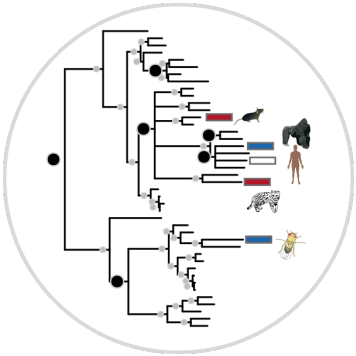

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- $\sim$ 15,000 phylogenetic trees

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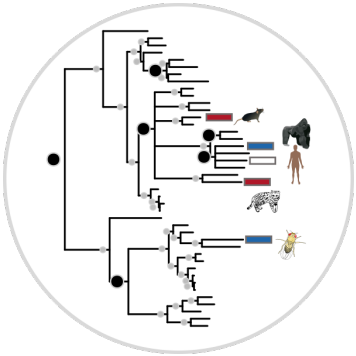

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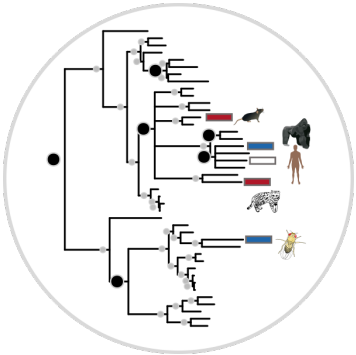

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- $\sim$ 15,000 phylogenetic trees
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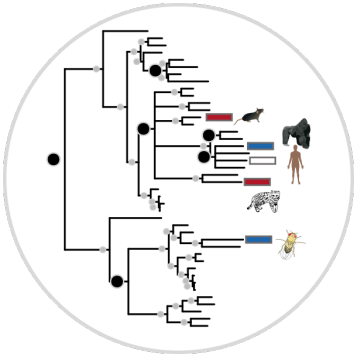

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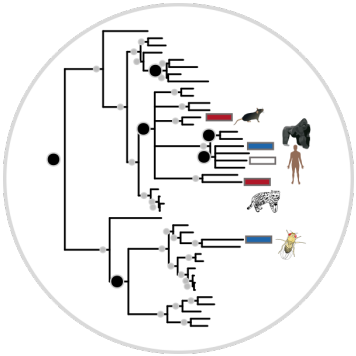

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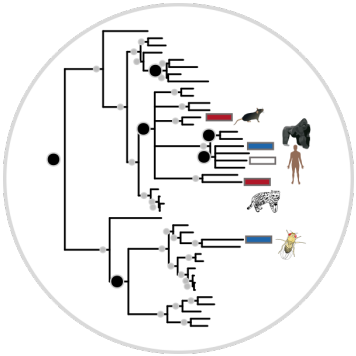

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Only on 2020, 2,000+ COVID-19 papers using the GO (Google Scholar)

more

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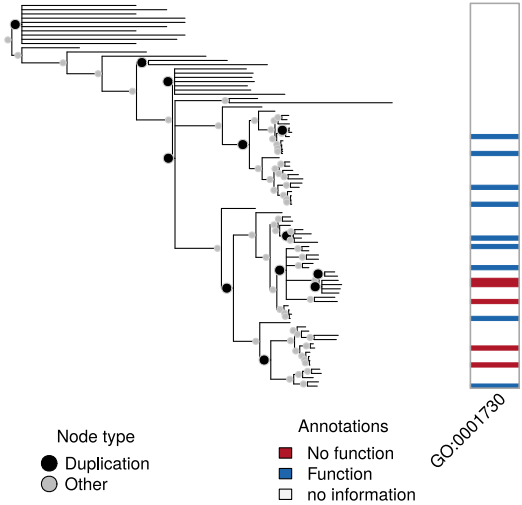
Family: PTHR11258
Type: Molecular Function
Name: 2'-5'-oligoadenylate synthetase activity
Desc: GO:0001730 involved in the process of cellular antiviral activity (wiki on interferon).

see details



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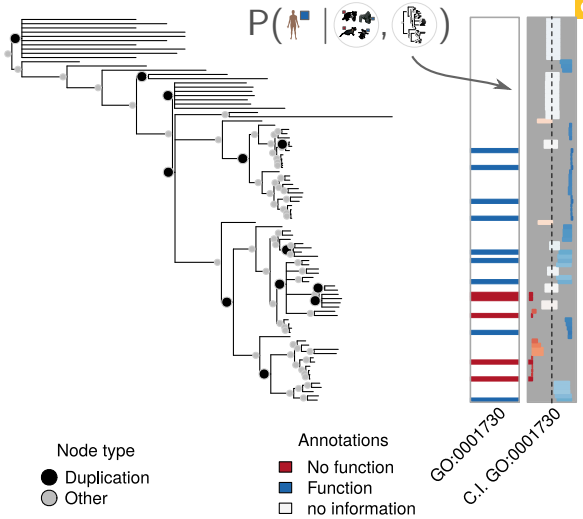

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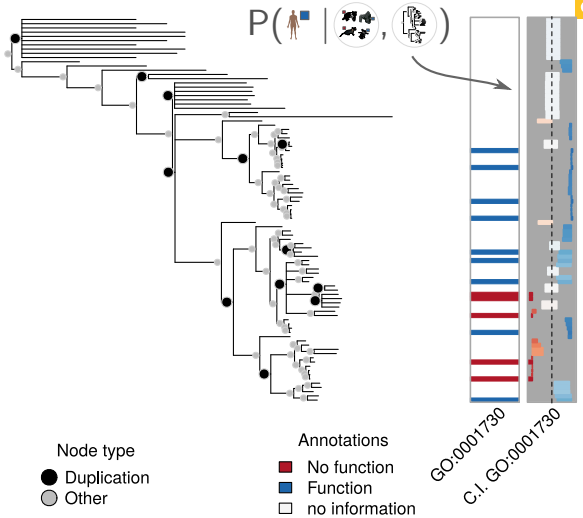
I implemented this model in the **aphylo** R package

see details



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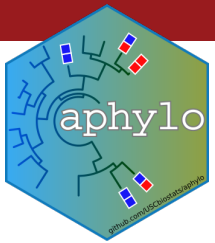
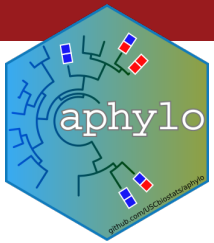
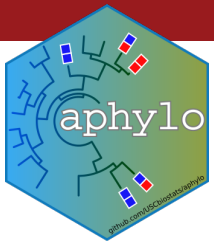


Baseline features



Baseline features

- Parsimony: Conditional independence across functions/siblings.



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- Post-order Tree traversal: Linear complexity $O(|\text{tree}|)$.

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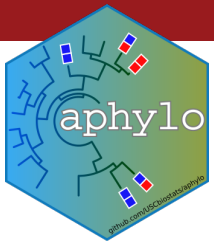

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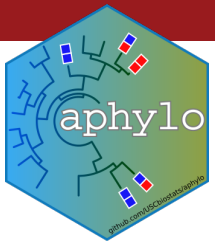

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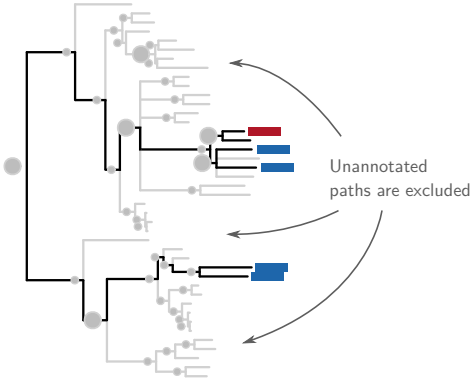

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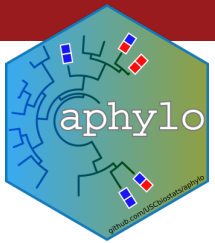

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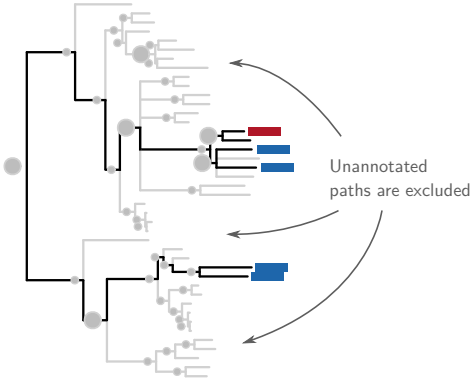
- Implemented in C++ (**pruner** library)



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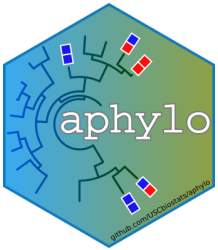

Large scale

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

▸ details

Results: What does aphylo brings to the table?

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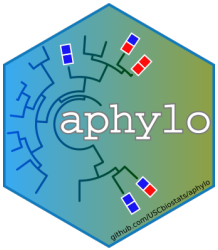

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Pooled-data model provides inference **aligned with theoretical results** (gene duplication is key)

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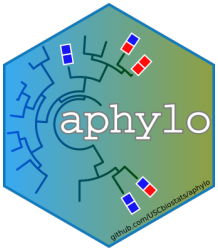

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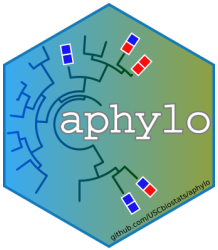

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Accuracy

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*)

Social Networks

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

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- If COVID-19 has taught us something it is that networks matter.

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Social Networks

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- We can study networks using ERGMs.

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Exponential Family Random Graph Models, aka ERGMs are:

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- Statistical models of (social) networks.

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- Statistical models of (social) networks.
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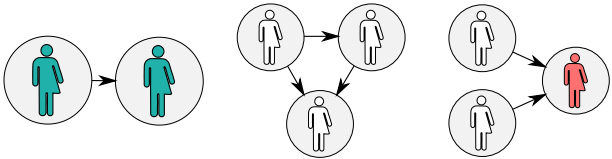

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A vector of model parameters

A vector of sufficient statistics

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

Observed data

The normalizing constant

All possible networks

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... I implemented this in the **ergmito** R package

more theory more terms

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Premise

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- Full enumeration $\neq$ All networks with k ties

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Extra features

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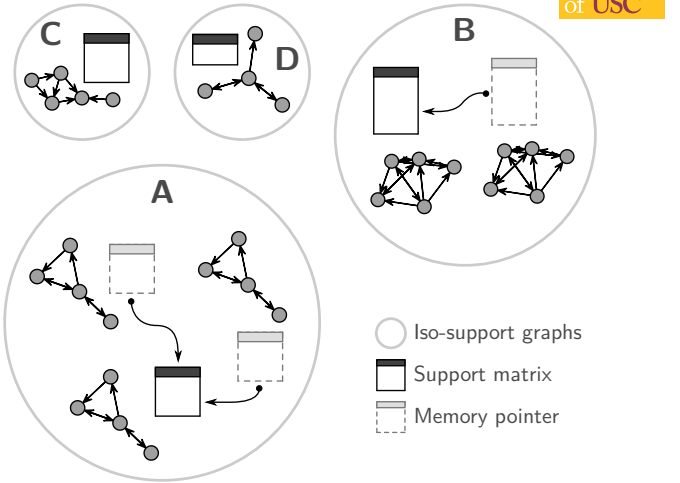
- *Iso-support* structures (model) recycled



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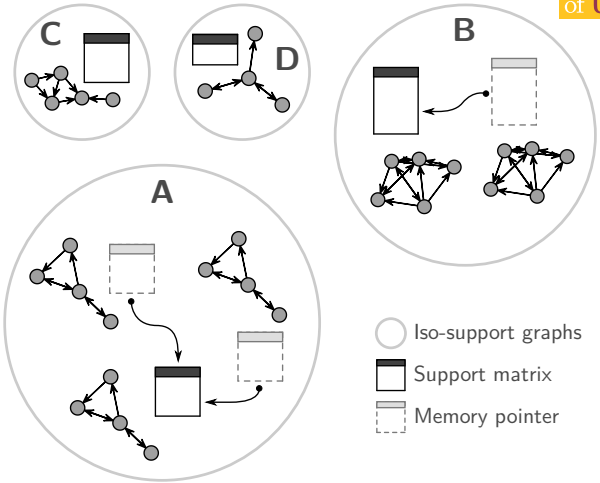

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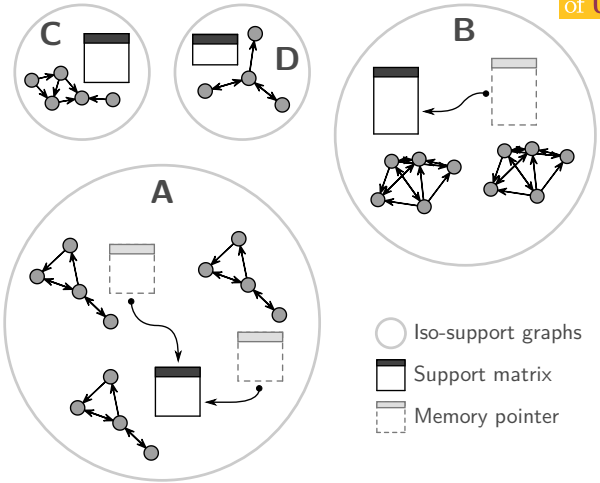
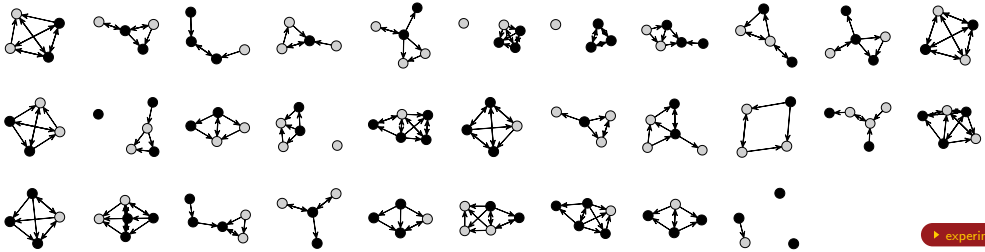
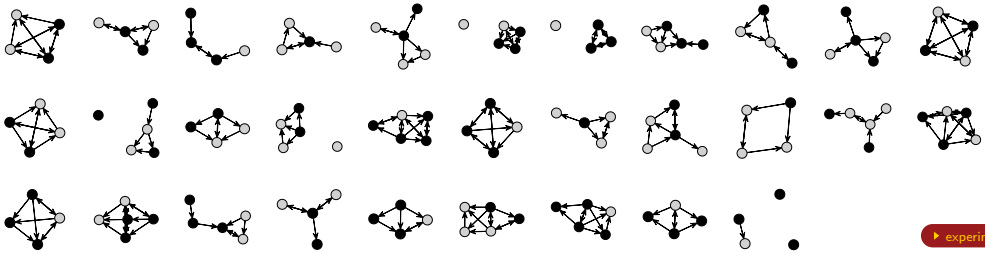


Fitting a pooled-data ERGMito with 80K nodes in 20K small nets $\sim$ 4s

ergmito featured example: Advice seeking networks in small teams (de la Haye et al, 2020)



▸ experiment



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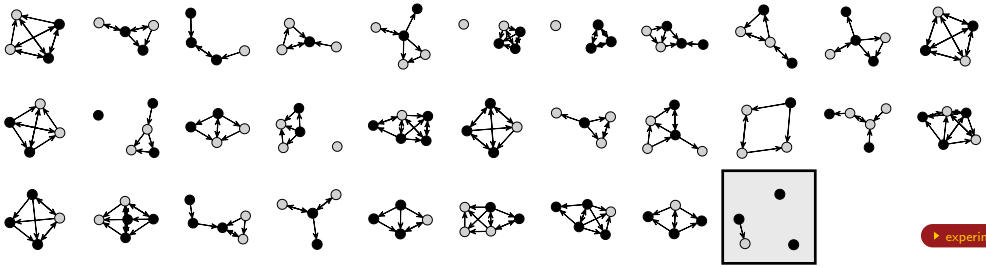

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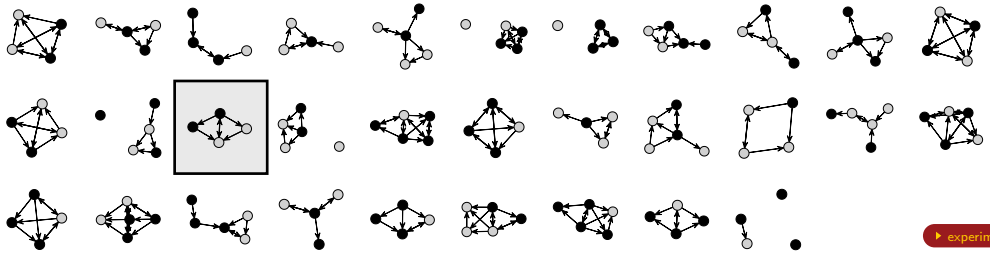

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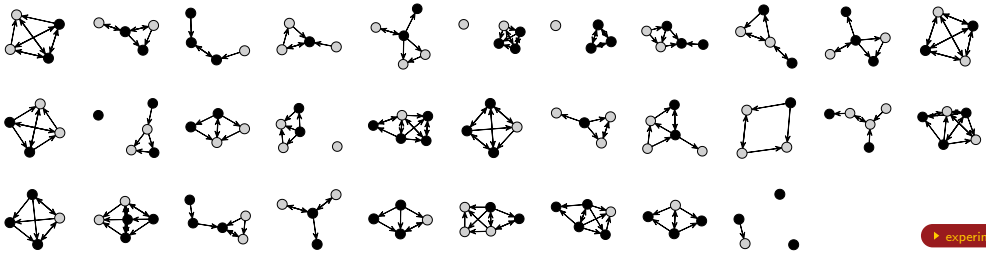

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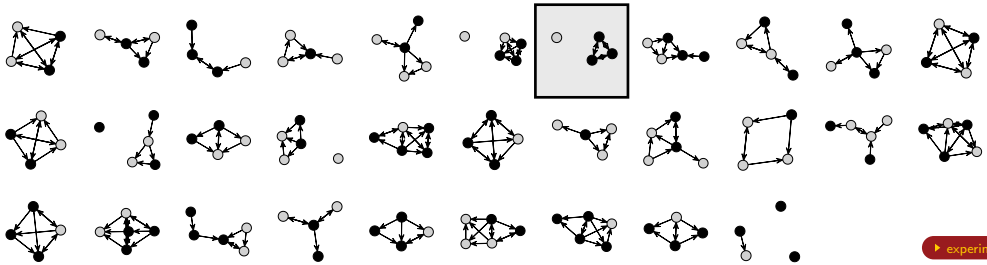

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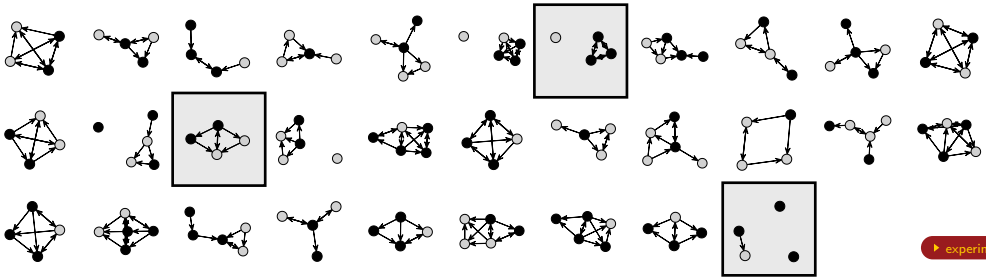

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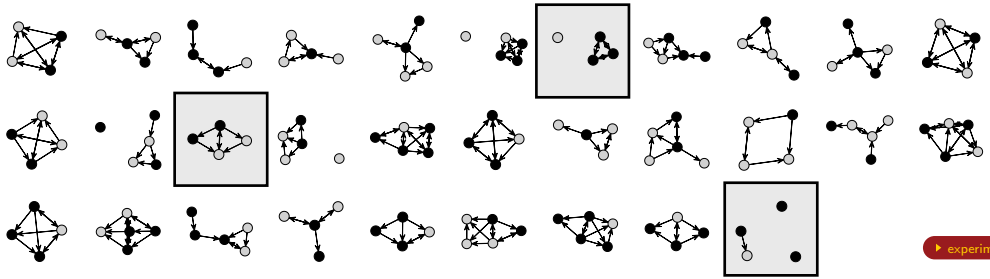

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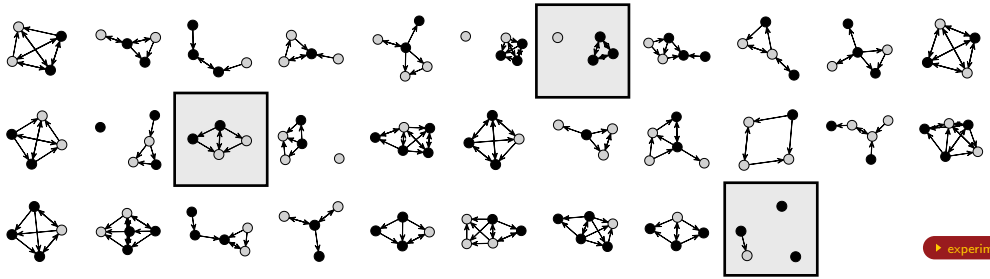

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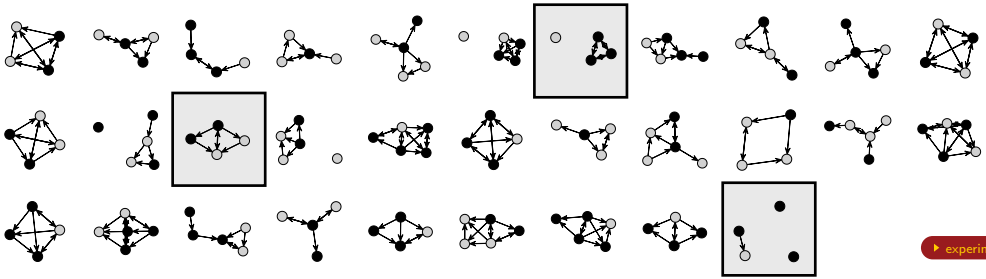

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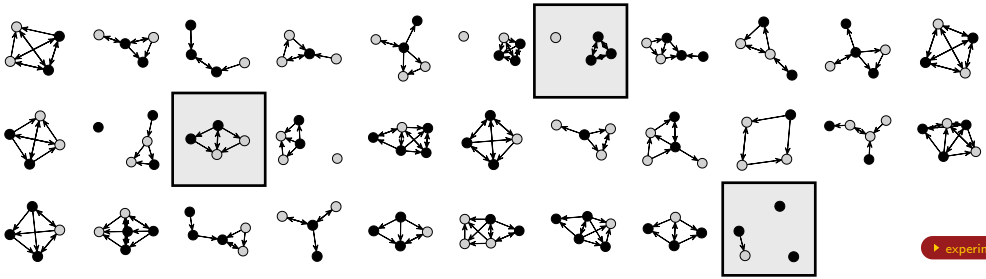

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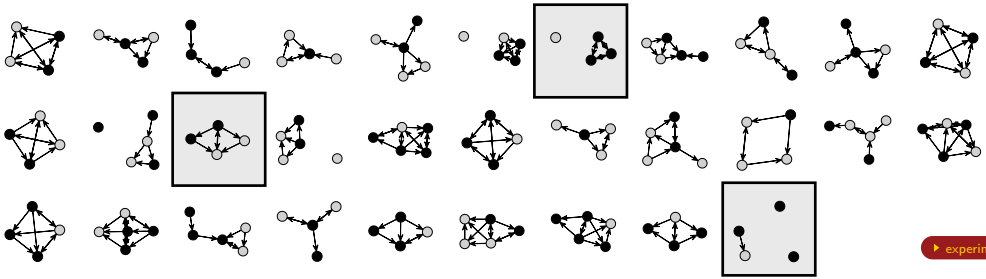

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  ... if you are lucky, using "regular" ERGMs would take you about 5 hours.

▸ details ▸ gof ▸ data

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Theoretical Goodies

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

more

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

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

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The right tool

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

more

Part 3: Current and Future Research

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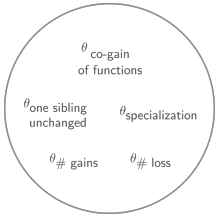
Biology

Extension of gene functional-evolution model using the ERGMs framework



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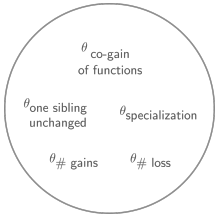

Criminology

The role of social networks on police use of force

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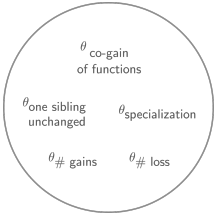

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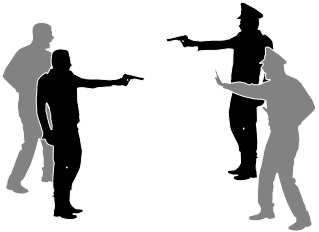
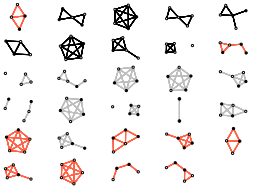


Sociology

Using ERGMitos to model political discussion networks in Romania



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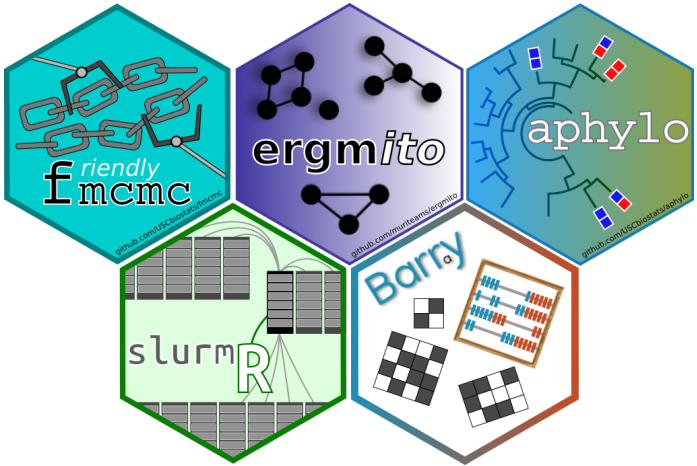
Continue developing scientific software...



The future: Keep building bridges

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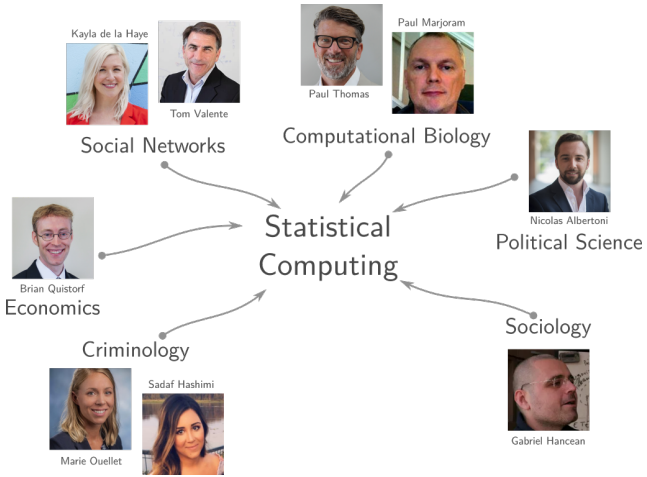

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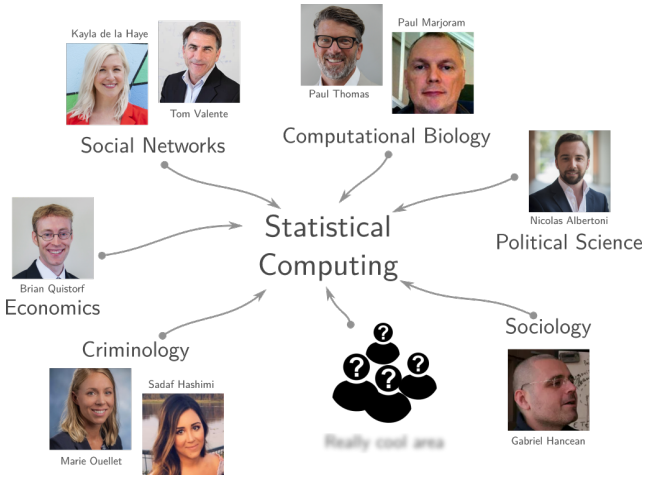

...you could be next!

Statistical and Computational Methods for Complex Systems

George G Vega Yon

https://ggvy.cl

vegayon@usc.edu

Thank you!

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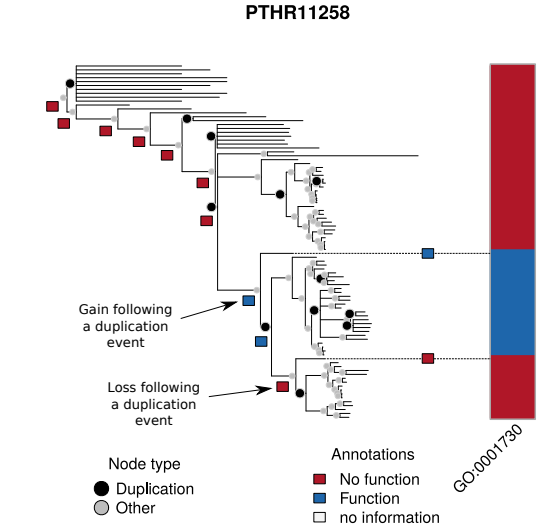

- Starting with the root node (no function in this case).
- Passes the baton to its offspring.
- Possibly without change (on this particular function).
- Or, with some probability, gaining... or loosing the function.
- Until it reaches the end of the tree (modern genes).

more on diplication | alt view | go back

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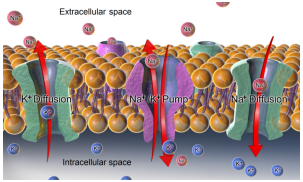
Gene functions can be classified in three types:

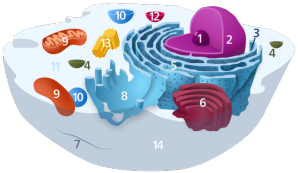
Molecular function

Active transport GO:0005215



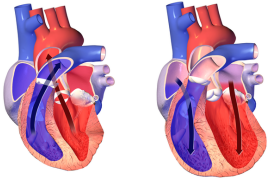
Cellular component

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 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

go back

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Family: PTHR11258

Type: Molecular Function

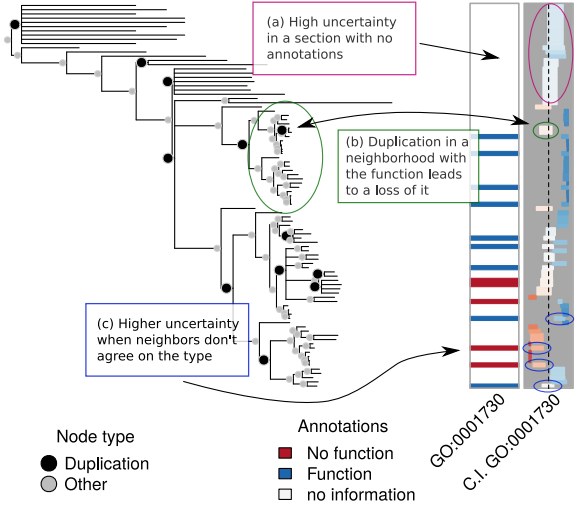
Name: 2'-5'-oligoadenylate synthetase activity

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

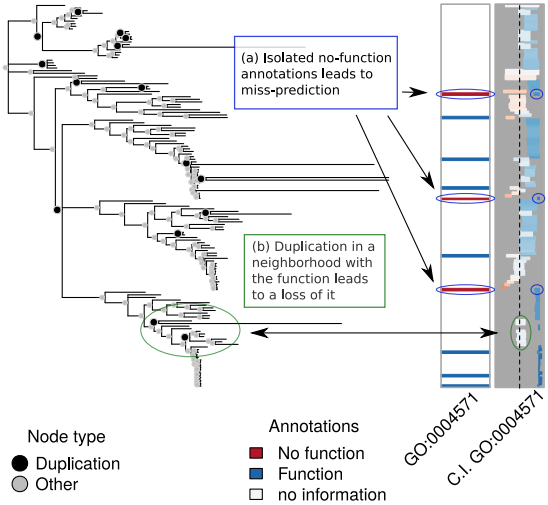
AUC: 0.33

Type: Molecular Function

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

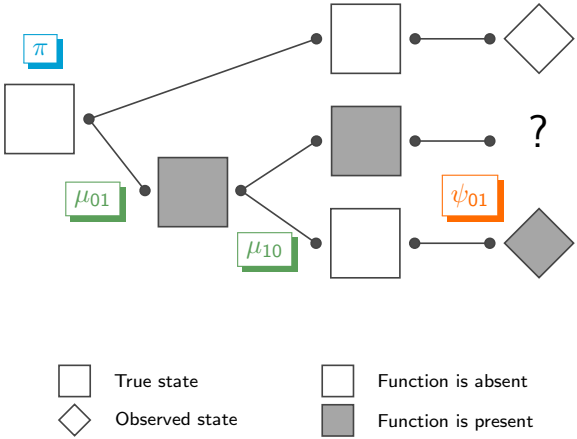
Desc: GO:0004571 involved in synthesis of glycoproteins (wiki and examples).

go back



	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*.



- 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.

go back

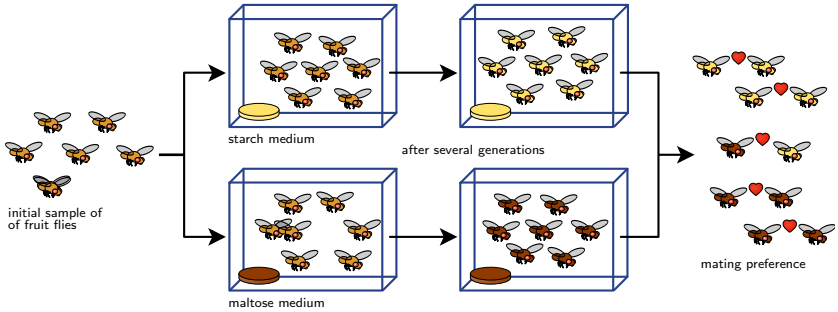


Figure 1 Dodd 1989: After one year of isolation, flies showed a significant level of assortativity in mating (wikimedia)

go back

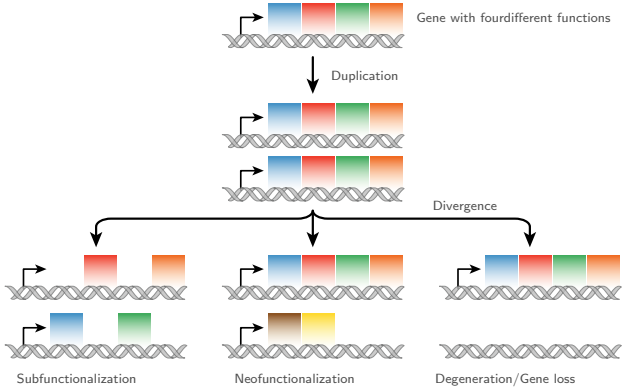


Figure 2 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

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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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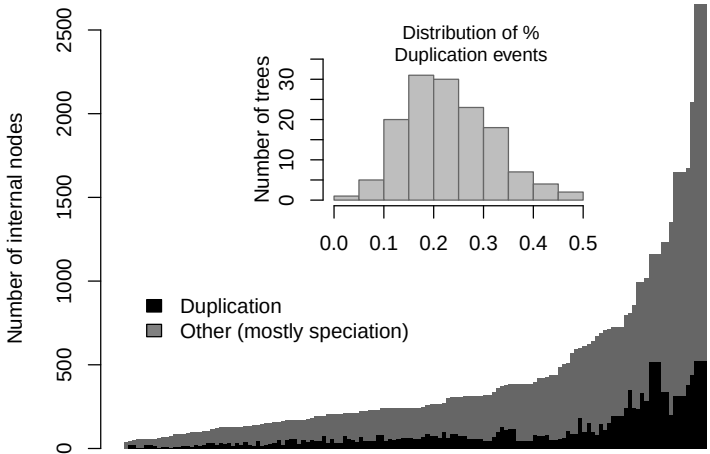

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This is the first 10 of $\sim$ 400,000 experimental annotations used:

	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

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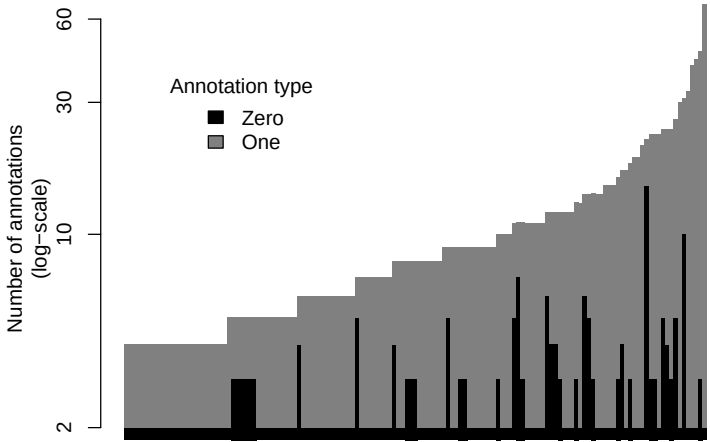

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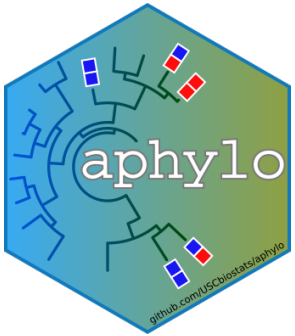
- Simulation, estimation, and prediction: **aphylo** R package.
- Large simulation study (all known trees, about 15,000) on USC's HPC cluster.
- Prediction quality assessment on $\sim$ 1,300 genes involving $\sim$ 130 families... estimation of parameters using a pooled-data model ($<$ 5 min). ◂ modeling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



◂ go back

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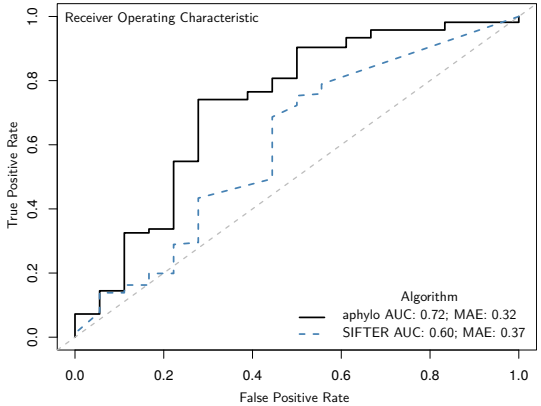
aphylo vs SIFTER (state-of-the-art phylo-based model) on 147 genes.



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).

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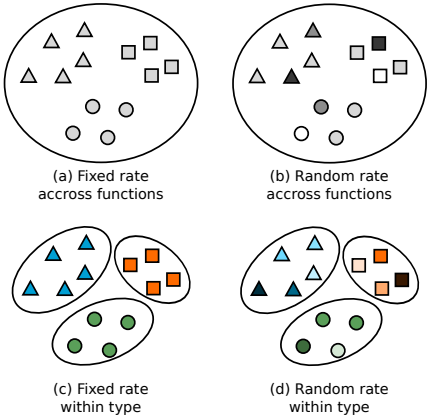

(a) Featured in the first version of the model.

(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`.

go back

Overview of Prediction Results

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	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

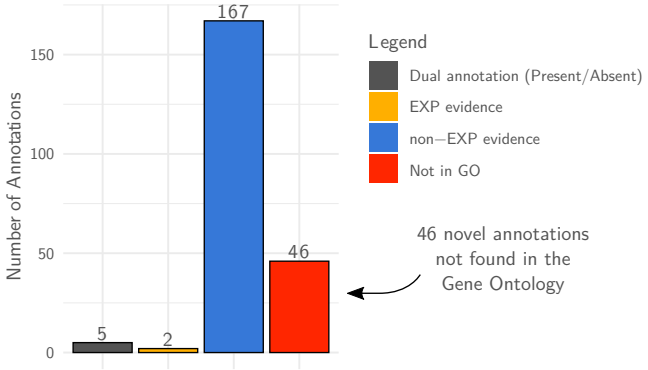

Figure 3 Distribution of predictions

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- In the case that $s_l = s(\mathbf{g}, x)$ is on the boundary: $s_l \to \pm\infty$
- 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:

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

  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

[1] Handcock 2003 briefly mentions this

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- 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.
- $\{\text{CUG}, \text{Rewiring}\} \subset \text{ERGM}$
- We can talk about *Conditional* ERGMs.

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

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 $\sum_{i \neq j} y_{ij} \mathbf{1}\left(x_i = x_j\right)$
	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

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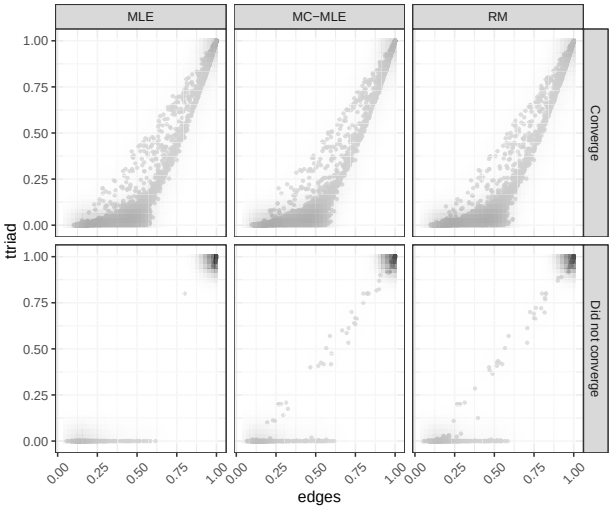
1. **Higher convergence rate**

return



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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

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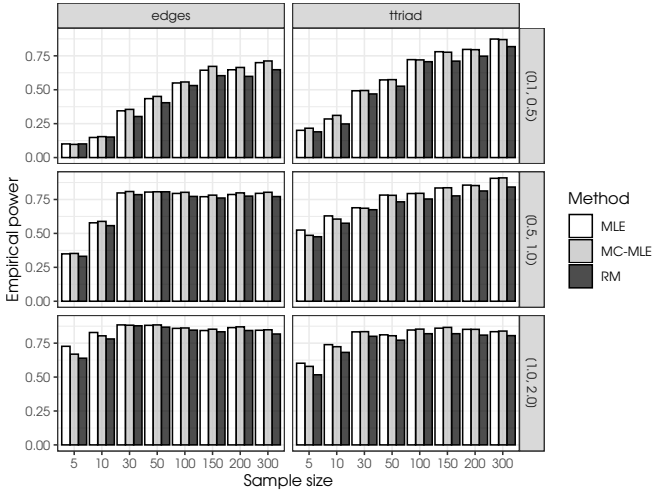
1. Higher convergence rate
2. Smaller bias
3. **Higher power**

return



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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)	
		MLE	MC-MLE	RM	MC-MLE	RM
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

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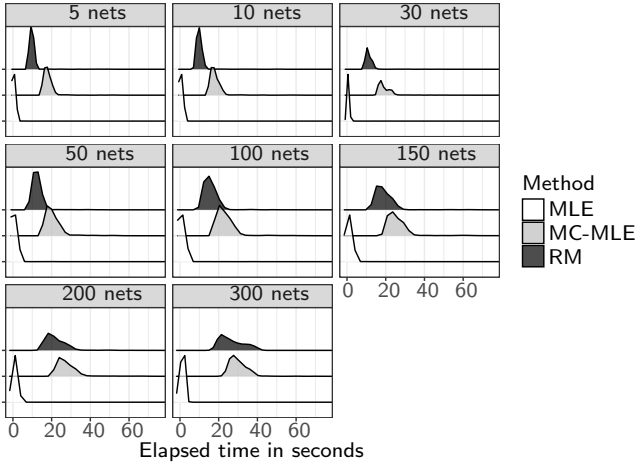
1. Higher convergence rate
2. Smaller bias
3. Higher power
4. Smaller type I error
5. **Elapsed time**

return



Featured Application: Small Teams

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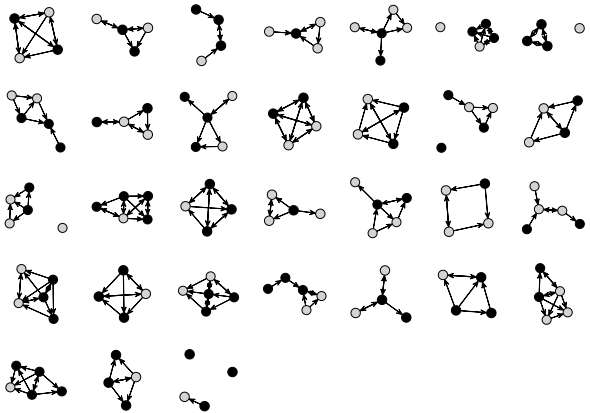
Sample

- 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^{**}	-0.91^{***}	-0.54^{**}	-0.72^{***}	-0.48^{*}	-0.72^{***}
	(0.17)	(0.23)	(0.18)	(0.19)	(0.19)	(0.17)
ttriads	0.36^{***}	0.46^{***}	0.37^{***}	0.36^{***}	0.36^{***}	0.36^{***}
	(0.06)	(0.06)	(0.06)	(0.06)	(0.06)	(0.05)
Homophily (gender)	-0.03	-0.01	-0.20	-0.12	-0.01	-0.12
	(0.20)	(0.21)	(0.46)	(0.20)	(0.20)	(0.20)
edges $\times \mathbf{1}(n = 5)$	-0.53^{***}	-0.47^{**}	-0.52^{***}	-0.53^{***}	-0.53^{***}	-0.53^{***}
	(0.12)	(0.16)	(0.13)	(0.13)	(0.12)	(0.13)
$(\text{Homophily})^{1/2}$			0.54			
			(1.32)			
Sender (female)				0.46^{*}		0.46^{*}
				(0.18)		(0.18)
Receiver (female)					-0.08	
					(0.18)	
Constraint (offset)						
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

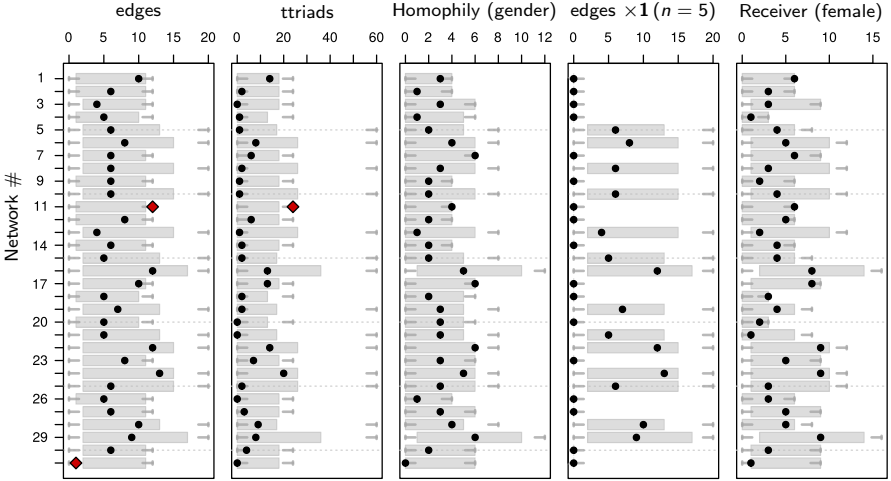
$^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

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?

go back

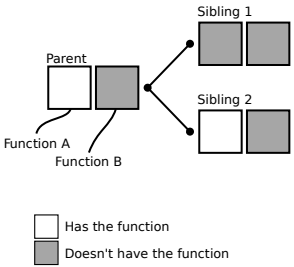
What About Goodness-of-fit?

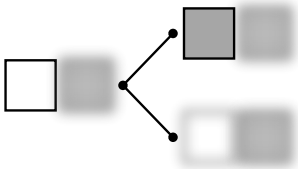


(1) Size (n)	(2) edges	(3) ttriads	(4) edges $\times$ $\mathbf{1}(n = 5)$	(5) ttriads $\times$ $\mathbf{1}(n = 5)$	(6) edges $\times$ $\log\{1/n\}$
4	10	14	0	0	-13.86
4	6	2	0	0	-8.32
4	4	0	0	0	-5.55
5	6	1	6	1	-9.66
5	8	8	8	8	-12.88
5	6	2	6	2	-9.66
			. . . 25 more rows. . .		

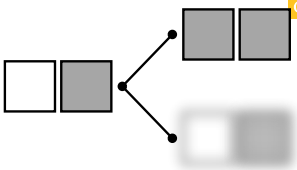
Table 4 Example of observed sufficient statistics for the team advice networks. Pooled-data ERGMs have multiple observed sufficient statistics (also known as target statistics). Furthermore, as shown here, we can manipulate common statistics as *edges* (2) and *ttriads* (3) to include, e.g. interaction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

go back

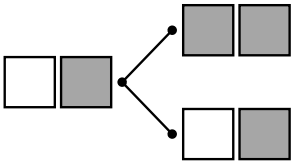




(a) Sibling and Function Conditional Independence



(b) Sibling Conditional Independence

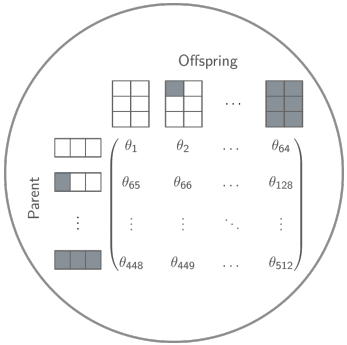


(c) No conditional independence

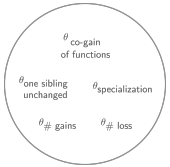
go back

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

Full Markov Transition Matrix



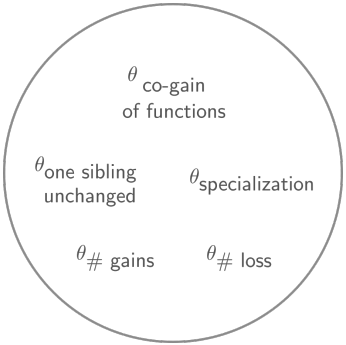
512 parameters



Easier to fit

Easier to interpret

Sufficient statistics



5 parameters

numeric example

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- 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`

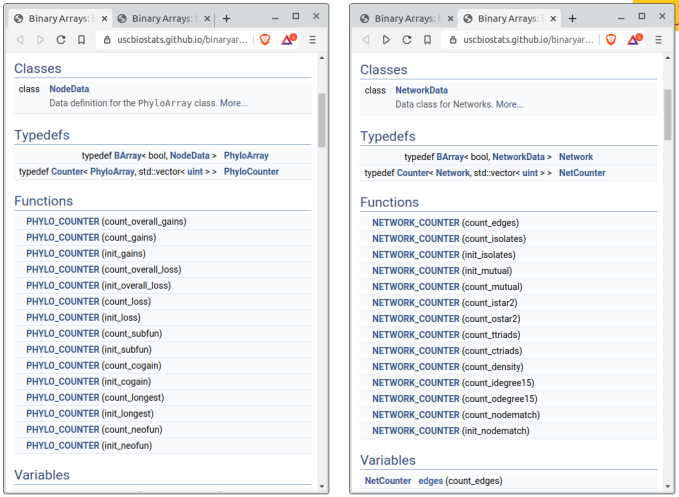

Figure 5 Screenshots from the project's website on GitHub.

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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
	A	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$
Parent	B	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
	C	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 1 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$
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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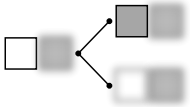
In the model with 3 functions and 2 offspring per node:

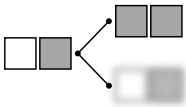
- Full Markov transition matrix: $2^3 \times 2^6 = 512$
- Using sufficient statistics:

  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.

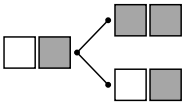
- Easier to fit and interpret.



(a) Sibling and Function Conditional Independence



(b) Sibling Conditional Independence



(c) No conditional independence

return

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