Essays on Bioinformatics and Social Network Analysis

Statistical and Computational Methods for Complex Systems

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Statistical and computational methods for bioinformatics and social network analysis

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- In some times, the cannot understand a process unless we look at it as a whole.
- There's a reason why we usually assume *IID*.
- *Modern* (as of today) computational tools help us coping with that.

Contents

On the prediction of gene functions using phylogenetic trees

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

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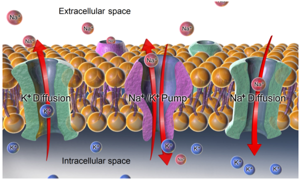
Molecular function

Active transport GO:0005215



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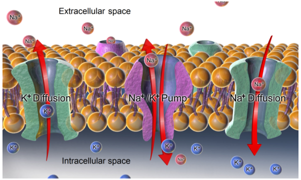
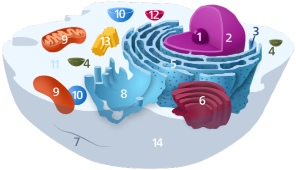


Cellular component

Mitochondria GO:0004016



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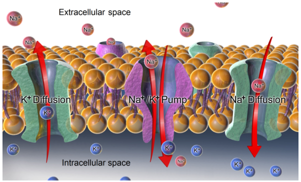

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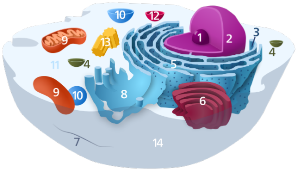
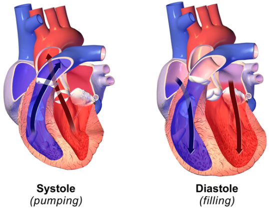


Biological process

Heart contraction GO:0060047



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The Gene Ontology Project

GENEONTOLOGY
Unifying Biology

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- Roughly half of human genes ($\sim$ 10,000 / 20,000) have some form of annotation.
- We know something of less than 10% of known genes (near 1.7M).
- An important effort of the GO has to do with phylogenetics...

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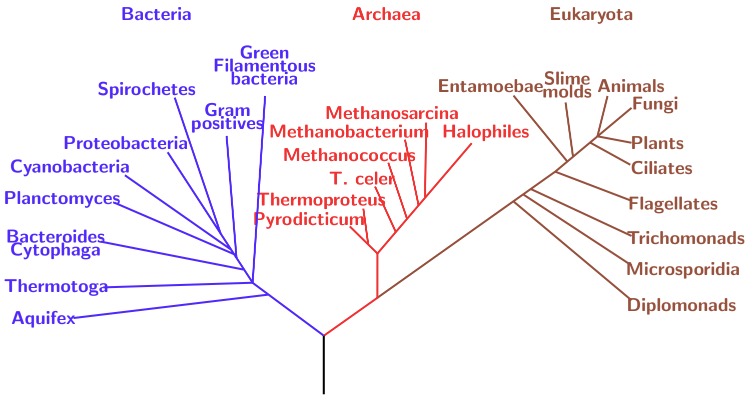

Figure 1 A phylogenetic tree of living things, based on RNA data and proposed by Carl Woese, showing the separation of bacteria, archaea, and eukaryotes (wiki)

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Phylogenetic Trees: The PANTHER classification system

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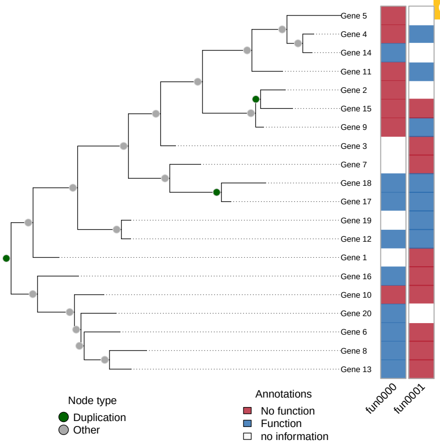


Figure 2 Simulated phylogenetic tree and gene annotations.

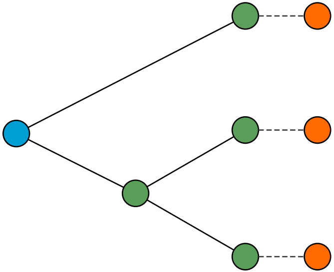
We can use

evolutionary trees

to inform a model for predicting

genetic annotations!

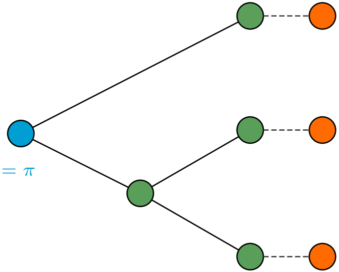
An evolutionary model of gene functions



other models
other view

An evolutionary model of gene functions

- Initial (spontaneous) gain of function.



$\Pr(1) = \pi$

▸ other models ▸ other view

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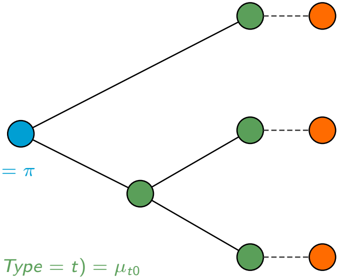

$\Pr(1) = \pi$

$\Pr(0 \to 1 | \mathit{Type} = t) = \mu_{t0}$

$\Pr(1 \to 0 | \mathit{Type} = t) = \mu_{t1}$

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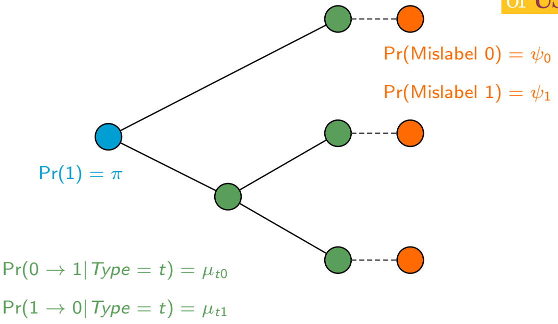

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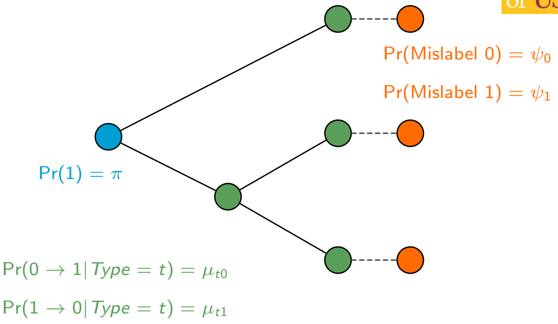

We implemented the model using Felsenstein's' pruning algorithm (linear complexity) in the R package `aphylo` more.

other models other view

Prediction with real data

	Prior	
	Uniform	Beta
Mislab. prob.		
ψ_0	0.23	0.25
ψ_1	0.01	0.01
Gain/Loss at dupl.		
μ_{d0}	0.97	0.96
μ_{d1}	0.52	0.58
Gain/Loss at spec.		
μ_{s0}	0.05	0.06
μ_{s1}	0.01	0.02
Root node		
π	0.81	0.45
Leave-one-out AUC		
Mean	0.69	0.67
Median	0.81	0.75

Table 1 Parameter estimates using different priors.

- 141 pooled functions (trees) with 7,388 genes with 0/1 annotations.

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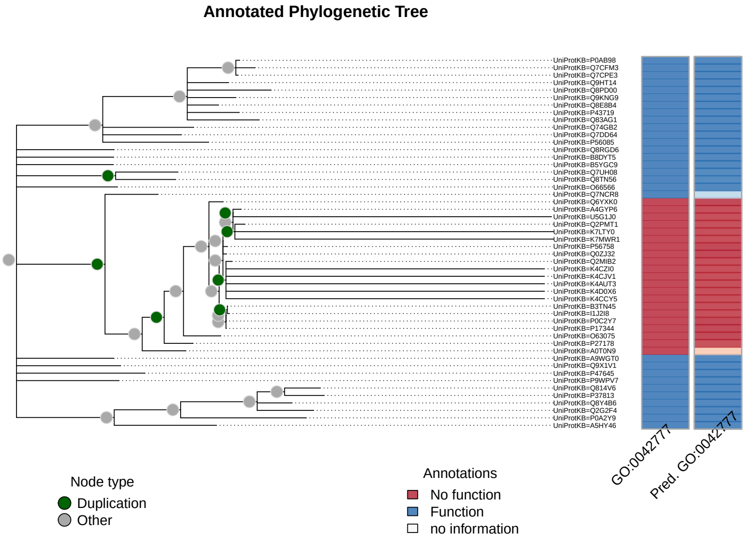
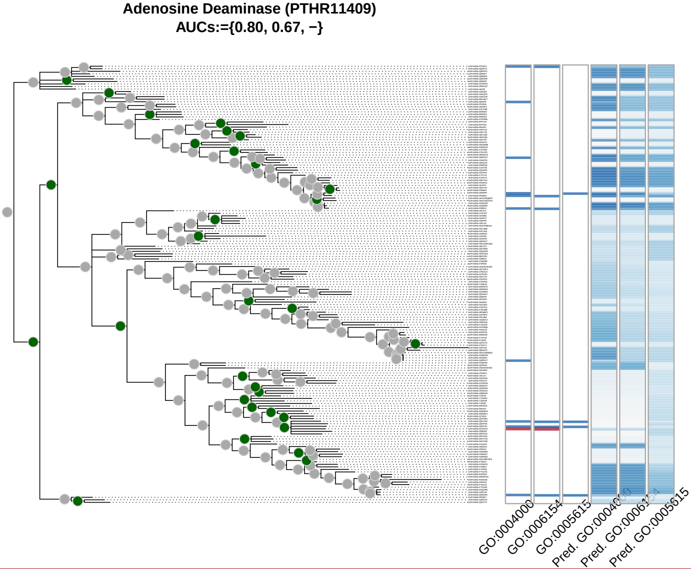
- Biologically meaningful results.
- Took about 5 minutes each.

Prediction with real data: Leave-one-out



Prediction with real data: Out-of-sample prediction



Key takeaways

- A parsimonious model for predicting gene functions using phylogenetics.
- Computationally scalable. SIFTER (our benchmark) would take about 66 years (yes, years) to estimate a model for 100 families of size 300, we take about 5 minutes.
- Meaningful biological results.
- Preliminary accuracy results comparable to state-of-the-art phylo-based models.

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Paper 1: On the prediction of gene functions using phylogenetic trees

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- Offspring are conditional independent on their parent and
- Functions evolve independently. ▸ more

Exponential Random Graph Models for Small Networks

Joint with: Andrew Slaughter and Kayla de la Haye

What are Exponential Random Graph Models

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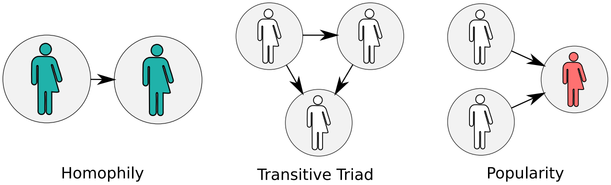
- In simple terms: statistical inference on what network patterns/structures/motifs govern social networks



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A vector of model parameters

A vector of sufficient statistics

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Observed data

The normalizing constant

All possible networks

more on terms

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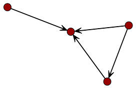
The normalizing constant has $2^{n(n-1)}$ terms!

more on terms

In this network



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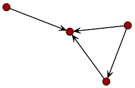

We see 4 **edges**, 1 **transitive triad** and **no mutual ties**.

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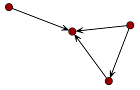

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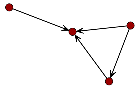

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This model has **MLE parameter estimates** of -0.20 (low density), 0.28 (high chance of ttriads), and -Inf (low chance of mutuality) for the parameters `edges`, `ttriads`, and `mutual` respectively.

ERGMs: State of the Art

Medium-large (dozens to a couple of thousand vertices) networks

- Markov Chain Monte Carlo (MCMC) based approaches like MC-MLE or Robbins-Monro Stochastic Approximation. ▸ details
- Maximum Pseudo Likelihood (MPLE)

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large-huge networks (up to millions of vertices)

- Parametric bootstrap
- Conditional joint estimation (like snowball sampling, a.k.a. divide and conquer)
- Equilibrium Expectation Algorithm (millions of vertices)

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All of these methods are approximations!

Do we care about small networks?

We see small networks everywhere

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- Families and friends

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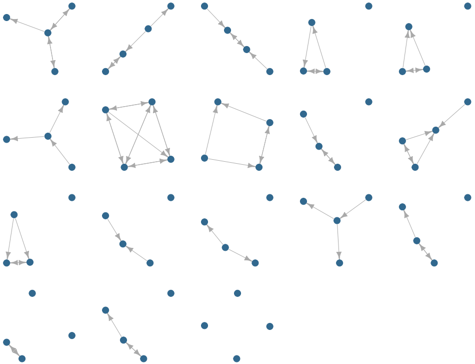
When studying these, network surveys include multiple small networks



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All possible networks

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- Using the exact likelihood opens a huge window of methodological-possibilities.
- We implemented this and more in the `ergmito` R package ▸ more

Sidetrack...

ito, ita: From the latin -*īttus*. suffix in Spanish used to denote small or affection. e.g.:

*¡Qué lindo ese perr***ito***! / What a beautiful little dog!*

*¿Me darías una tac***ita** *de azúcar? / Would you give me a small cup of sugar?*

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Special thanks to George Barnett who proposed the name during the 2018 NASN!

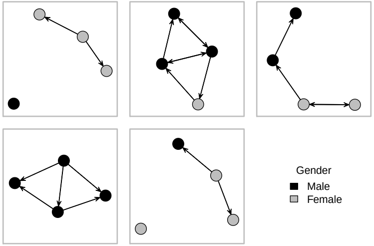

Figure 3 Random sample of 5 networks simulated using the ergmito package

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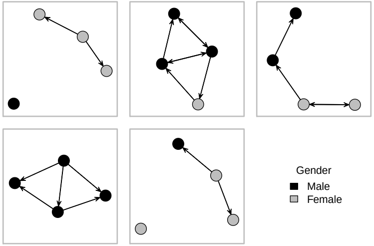

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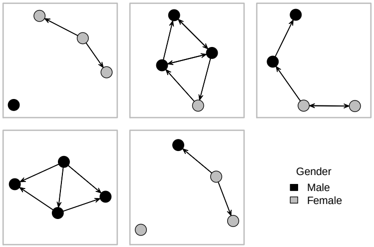
	Bernoulli	Full model
Edge-count	-0.69^{*}	-1.70^{**}
	(0.27)	(0.54)
Homophily (on Gender)		1.59^{*}
		(0.64)
AIC	78.38	73.34
BIC	80.48	77.53
Log Likelihood	-38.19	-34.67
Num. networks	5	5

Standard errors in parenthesis. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 2 Fitted ERGMitos using the fivenets dataset.



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Log Likelihood	-38.19	-34.67
Num. networks	5	5

Standard errors in parenthesis. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$

Table 2 Fitted ERGMitos using the fivenets dataset.

We performed a large simulation study ▸ more comparing MC-MLE (ergm) with MLE (ergmito).

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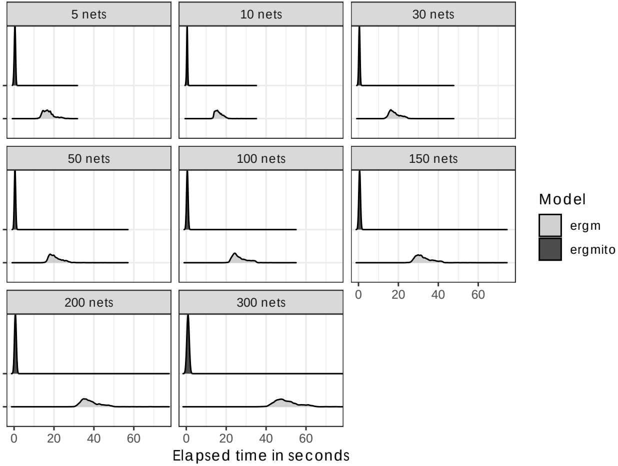
Sample size	P(Type I error) MC-MLE (ergm)	MLE (ergmito)	χ^2
5	0.084	0.057	11.71 ***
10	0.070	0.045	12.46 ***
15	0.084	0.066	5.55 *
20	0.074	0.060	3.58
30	0.057	0.052	0.67
50	0.046	0.044	0.17
100	0.048	0.048	0.00

Table 3 Empirical Type I error rates. The χ^2 statistic is from a 2-sample test for equality of proportions, and the significance levels are given by *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$.

Paper 2 Simulation Studies: Elapsed time



more results

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Key takeaways

- New extension of ERGMs using exact statistics for small networks (families, teams, etc.)
- Performance: Same (un)bias, Lower Type I error rates, (way) faster.
- Opens the door the new methods, e.g. Mixed effects, LRT, etc.

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Challenges

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- Have a good way of assessing goodness-of-fit.
- Explore extending this method for (very) large networks.

Future Research

Future Research: phylogenetic models

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  - Extends to account for joint dist of functions+siblings
  - Can incorporate aditional information such as branch lenghts
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$$
\mathbb{P}\left(\mathbf{X} = \{x_{n1}, x_{n2}, \dots\} \;\middle|\; x_{\mathbf{p}(n1,\dots)}\right) = \frac{\exp\left\{\mu^T s(\mathbf{x}|x_{\mathbf{p}(\cdot)})\right\}}{\sum_{\mathbf{x}'} \exp\left\{\mu^T s(\mathbf{x}'|x_{\mathbf{p}(\cdot)})\right\}}
$$

Future Research: phylogenetic models

Imagine that we have 3 functions and that each node has 2 siblings

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\begin{array}{lccc}
 & & \multicolumn{2}{c}{\textbf{Transitions to}} \\
 & & \text{Case 1} & \text{Case 2} \\
\textbf{Parent} & \begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix} & \begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \end{bmatrix} & \begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 1 & 0 \end{bmatrix}
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In SIFTER, for modelling 3 functions, we need $2^{2\times 3} = 64$ parameters.

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Goodness-of-fit

Future Research: ERGMitos

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Concluding Remarks

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- 11 packages/libraries built (ergmito, similR, gnet, fmcmc, slurmR, aphylo, polygons, pruner, netplot, rphyloxml, jsPhyloSVG)

Essays on Bioinformatics and Social Network Analysis

Statistical and Computational Methods for Complex Systems

George G Vega Yon

University of Southern California, Department of Preventive Medicine

November 18, 2019

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Thanks!

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Yu, Chun et al. (Jan. 2018). "Assessing the Performances of Protein Function Prediction Algorithms from the Perspectives of Identification Accuracy and False Discovery Rate". In: International Journal of Molecular Sciences 19.1, p. 183. ISSN: 1422-0067. DOI: 10.3390/ijms19010183. URL: http://www.mdpi.com/1422-0067/19/1/183.

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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 4 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...

Felis catus pthr10037

Oryzias latipes **pthr11521**

Anolis carolinensis **pthr11521**

Equus caballus pthr24356

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

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go back

There various approaches for this, some to highlight

- Text analysis like in Pesaranghader et al. 2016
- Protein-protein interaction networks like in Oliver 2000; Piovesan et al. 2015.
- Phylogenetic based like SIFTER Barbara E. Engelhardt et al. 2011, 2005.
  - Parameters to estimate: 2^{2P}, where P is the number of functions.

(a nice literature review in Jiang et al. 2016; Yu et al. 2018) go back

An evolutionary model of gene functions (algorithmic view)

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Data: A phylogenetic tree, $\{\pi, \mu, \psi\}$(Model probabilities)
Result: An annotated tree

```
for n ∈ PostOrder(N) do
    Nodes gain/loss function depending on their parent;
    switch class of n do
        case root node do
            Gain function with probability π;
        case interior node do
            if Parent has the function then Keep it with prob. (1 − μ1);
            else Gain it with prob. μ0;
    end
    Finally, we allow for mislabeling;
    if n is leaf then
        if has the function then Mislabel with prob. ψ1;
        else Mislabel with prob. ψ0;
end
```

go back

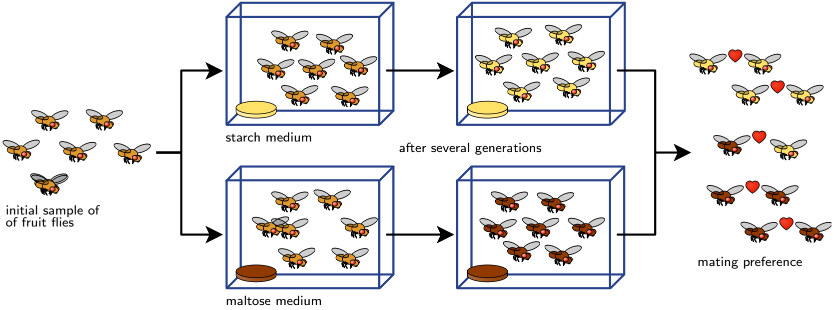


Figure 4 Dodd 1989: After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

go back

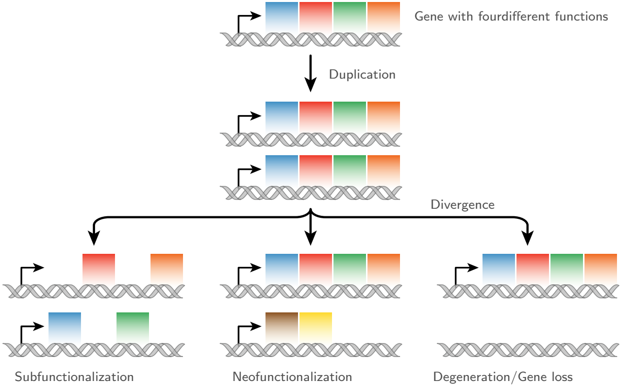


Figure 5 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

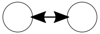
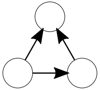
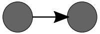
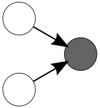
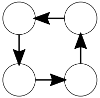
go back

The aphylo R package

- Simulation and visualization of annotated phylogenetic trees.
- Pruning algorithm implemented in C++ using the `pruner` template library (by-product).
- Uses metaprogramming (users can specify different formulas).
- The estimation is done using either Maximum Likelihood, Maximum A Posteriory, or MCMC.
- The MCMC estimation is done via the `fmcmc` R package using adaptive MCMC (also implemented as part of this project):
  - Automatic stop via convergence check.
  - Out-of-the-box parallel chains using parallel computing.
  - User-defined transition kernel (in our case, Adaptive Kernel).

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 $\sum_{i \neq j} y_{ij} \mathbf{1}(x_i = x_j)$
	Covariate Effect for Incoming Ties $\sum_{i \neq j} y_{ij} x_j$
	Four Cycle $\sum_{i \neq j \neq k \neq l} y_{ij} y_{jk} y_{kl} y_{li}$

go back

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One of the most popular methods for estimating ERGMs is the MC-MLE approach (citations here)

This consists on the following steps

1. Start from a sensible guess on what should be the population parameters (usually done using pseudo-MLE estimation)
2. While the algorithm doesn't converge, do:
   2.1 Simulate a stream of networks with the current state of the parameter, θ_t
   2.2 Using the law of large numbers, approximate the ratio of likelihoods based on the parameter θ_t, this is the objective function
   2.3 Update the parameter by a Newton-Raphson step
   2.4 Next iteration

go back

The `ergmito`

In general

- Implements estimation of ERGMs using exact statistics for small networks
- Meta-programming allows specifying likelihood (and gradient) functions for joint models (a function that writes a function)
- Includes tools for simulating, and post-estimation checks
- Getting ready for CRAN!

More specific tricks

- Computes support of Pr using `ergm::ergm.allstats`
- It includes a vectorized function doing the same
- Scales up nice (hundreds of small networks) saving space and computation (when possible)
- Highly tested (90% coverage with more than one hundred tests)

go back

We performed a simulation study with the following features:

- Draw 20,000 samples of groups of small networks

go back

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go back

Paper 2 Simulation Studies

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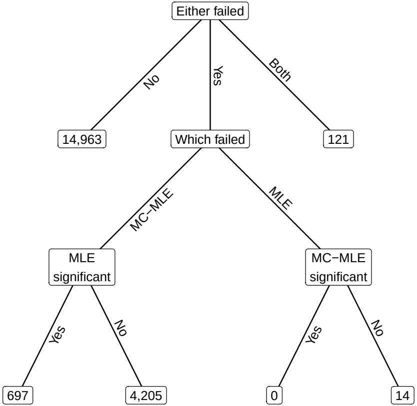
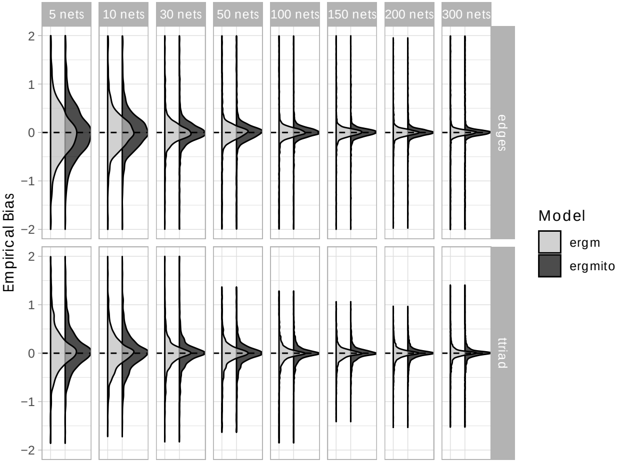
- We estimated the models using MC-MLE and MLE.

go back

Paper 2 Simulation Studies: Error rate



go back


5 nets
10 nets
30 nets
50 nets
100 nets
150 nets
200 nets
300 nets
edges
ttriad
Empirical Bias
2
1
0
−1
−2
Model
ergm
ergmito

go back