Essays on Bioinformatics and Social Network Analysis

Statistical and Computational Methods for Complex Systems

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November 18, 2019

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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.

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

Paper 2: Exponential Random Graph Models for Small Networks

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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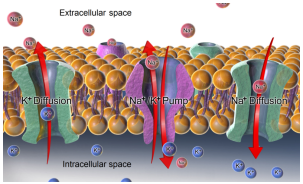
Molecular function

Active transport GO:0005215



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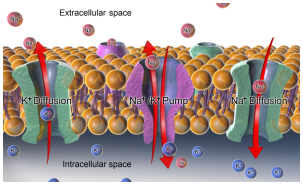
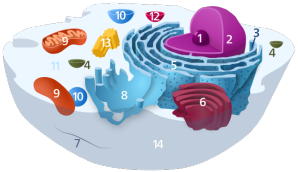


Cellular component

Mitochondria GO:0004016



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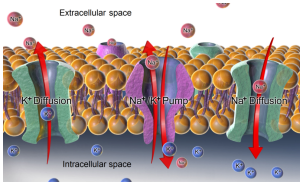

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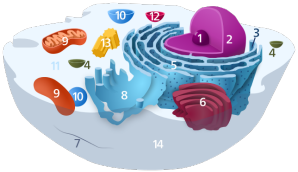
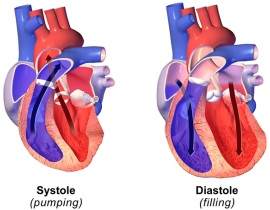


Biological process

Heart contraction GO:0060047



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- $\sim$ 44,700 validated terms more, $\sim$ 7,300,000 annotations on $\sim$ 4,500 species.

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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).

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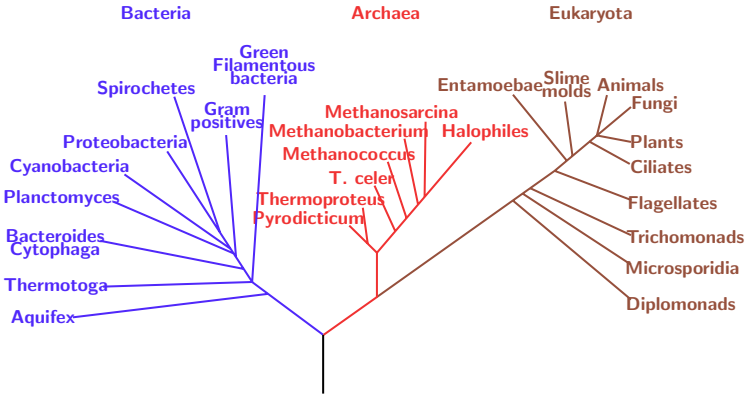

Figure 1 A phylogenetic tree of living things, based on RNA data and proposed by Carl Woese, showing the separation of bacteria, archaea, and eukaryotes (wiki)

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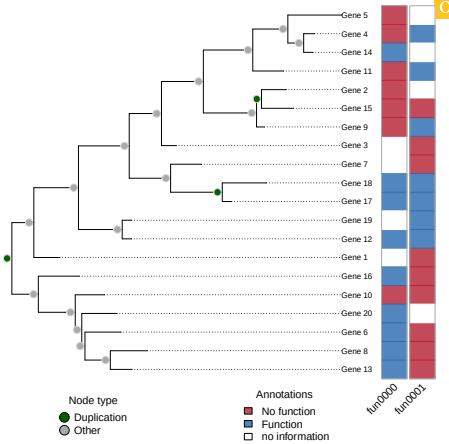

Figure 2 Simulated phylogenetic tree and gene annotations.

We can use

evolutionary trees

to inform a model for predicting

genetic annotations!

An evolutionary model of gene functions

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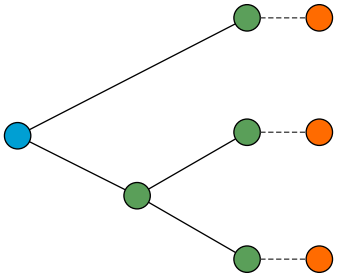

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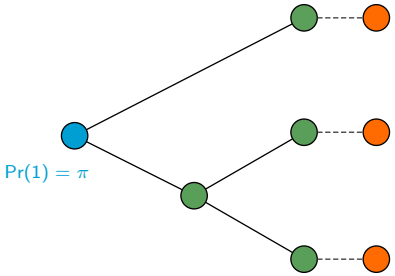
- Initial (spontaneous) gain of function.



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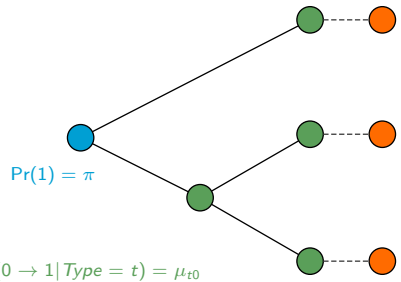
- Initial (spontaneous) gain of function.
- Loss/gain of offspring depends on: (a) the state of their parents (**Markov process**), and (b) the type of node more



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

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

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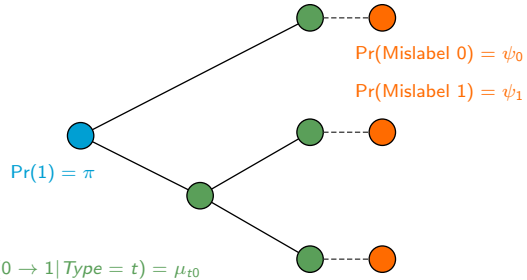

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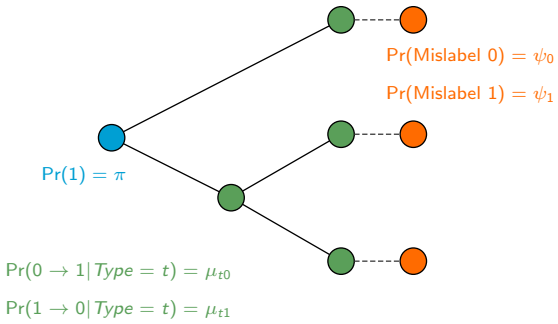

We implemented the model using Felsenstein's' pruning algorithm (linear complexity) in the R package `aphylo` more.

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	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
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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

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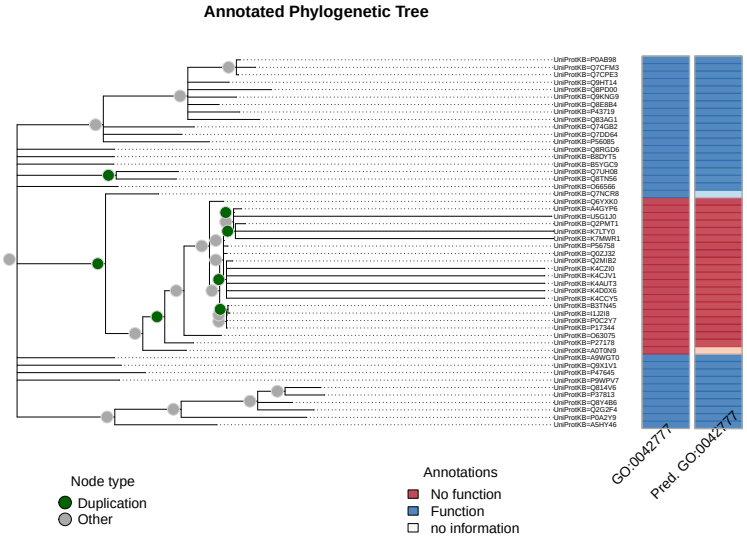

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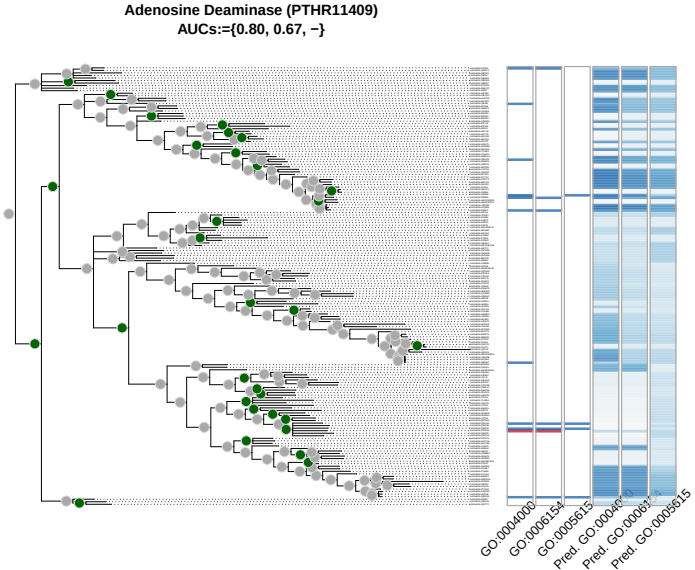

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Key takeaways

- 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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Example 1

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- 2 siblings 2 function involves modelling the following array:

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  - $5 \times 4/2 = 10$ statistics for pairwise correlation.
  - One statistic accounting for longest branch.

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

Paper 2: Exponential Random Graph Models for Small Networks

Exponential Random Graph Models for Small Networks

Joint with: Andrew Slaughter and Kayla de la Haye

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Exponential Family Random Graph Models, aka ERGMs are:

What are Exponential Random Graph Models

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Exponential Family Random Graph Models, aka ERGMs are:

- Statistical models of (social) networks

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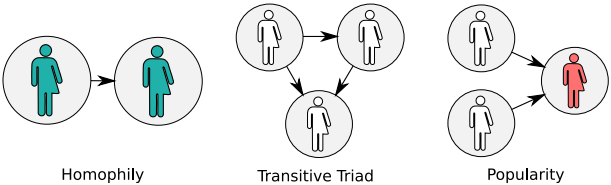
Exponential Family Random Graph Models, aka ERGMs are:

- Statistical models of (social) networks
- 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

$$\Pr(\mathbf{Y} = \mathbf{y} \mid \theta, \mathbf{X}) = \frac{\exp\{\theta^{\mathbf{t}} s(\mathbf{y}, \mathbf{X})\}}{\sum_{\mathbf{y}' \in \mathcal{Y}} \exp\{\theta^{\mathbf{t}} s(\mathbf{y}', \mathbf{X})\}}, \quad \forall \mathbf{y} \in \mathcal{Y}$$

Observed data

The normalizing constant

All possible networks

more on terms

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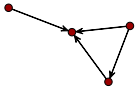
The normalizing constant has $2^{n(n-1)}$ terms!

more on terms

In this network



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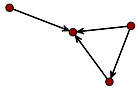

We see 4 **edges**, 1 **transitive triad** and **no mutual ties**.

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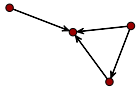

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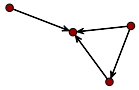

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This model has **MLE parameter estimates** of -0.20 (low density), 0.28 (high chance of ttriads), and -Inf (low chance of mutuality) for the parameters `edges`, `ttriads`, and `mutual` respectively.

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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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- Equilibrium Expectation Algorithm (millions of vertices)

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What about small networks?

Do we care about small networks?

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We see small networks everywhere

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- Families and friends

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- Egocentric networks

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From the methodological point of view, current methods are great, but:

- Possible accuracy issues (error rates)
- Prone to degeneracy problems (sampling and existence of MLE)
- It is not MLE...

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- For example, a network with 5 nodes has 1,048,576 unique configurations.

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- This allow us to directly compute **the normalizing constant**.

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A vector of model parameters

A vector of sufficient statistics

$$\Pr(\mathbf{Y} = \mathbf{y} \mid \theta, \mathbf{X}) = \frac{\exp\{\theta^{\mathsf{t}} s(\mathbf{y}, \mathbf{X})\}}{\sum_{\mathbf{y}' \in \mathcal{Y}} \exp\{\theta^{\mathsf{t}} s(\mathbf{y}', \mathbf{X})\}}, \quad \forall \mathbf{y} \in \mathcal{Y}$$

Observed data

The normalizing constant

All possible networks

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- We implemented this and more in the `ergmito` R package ▸ more

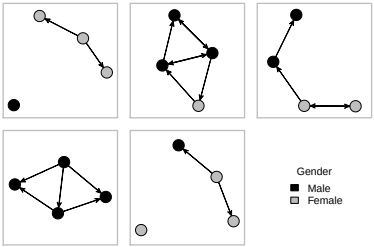

Figure 3 Random sample of 5 networks simulated using the ergmito package

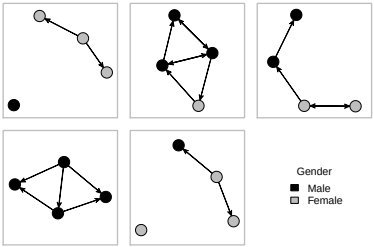

Figure 3 Random sample of 5 networks simulated using the ergmito package

	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.

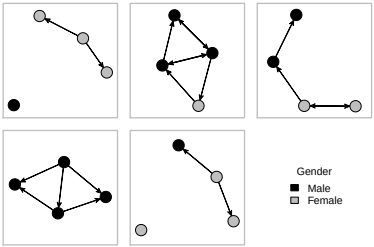

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Table 2 Fitted ERGMitos using the fivenets dataset.

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

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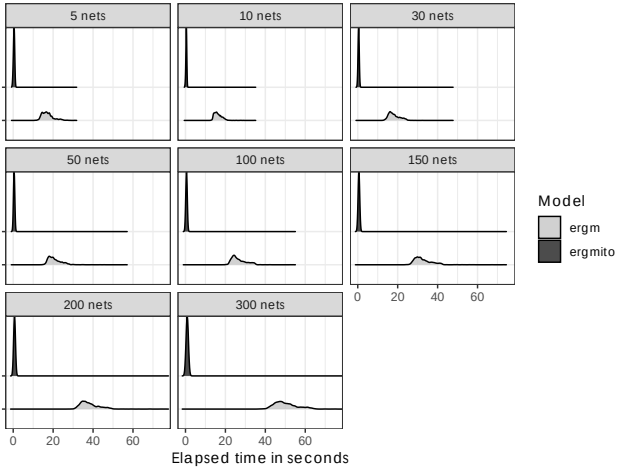
Sample size	N. Simulations	P(Type I error) MC-MLE (`ergm`)	P(Type I error) MLE (`ergmito`)	χ^2
5	2,189	0.084	0.057	11.71 ***
10	2,330	0.070	0.045	12.46 ***
15	2,395	0.084	0.066	5.55 *
20	2,430	0.074	0.060	3.58
30	2,460	0.057	0.052	0.67
50	2,495	0.046	0.044	0.17
100	2,499	0.048	0.048	0.00

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 * $p < 0.05$. The lack of fitted samples in some levels is due to failure of the estimation method.

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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- Opens the door the new methods, e.g. Mixed effects, LRT, etc.

Next steps

- Revisit measurement of goodness-of-fit.
- Explore extending this method for (very) large networks.

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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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!

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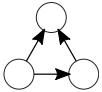
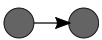
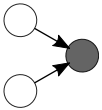
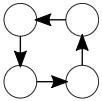
go back

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

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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

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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

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go back

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We performed a simulation study with the following features:

- Draw 20,000 samples of groups of small networks
- Each group had prescribed: (model parameters, number of networks, sizes of the networks)
- Each group could have from 5 to 300 small networks
- We estimated the models using MC-MLE and MLE.

go back

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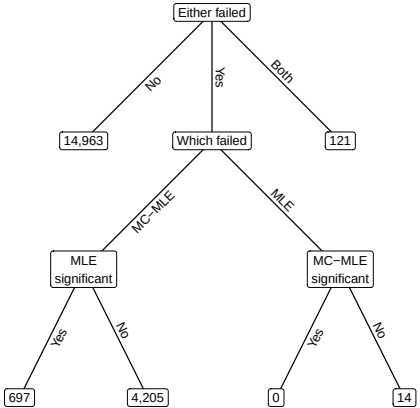
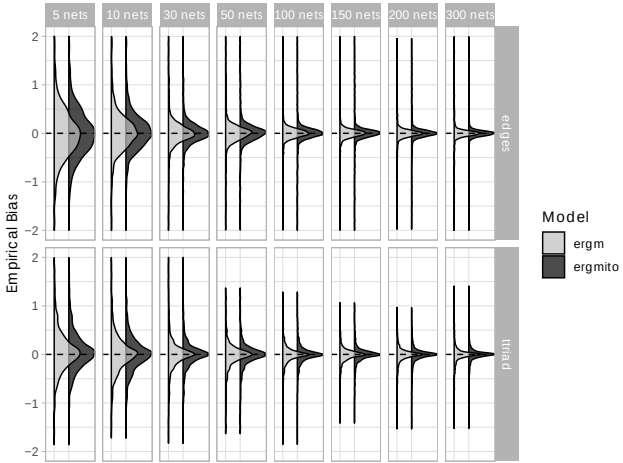


go back

Paper 2 Simulation Studies: Empirical Bias



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 $n \in PostOrder(N)$ **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. $(1 - \mu_1)$;
            else Gain it with prob. μ_0;
    end
    Finally, we allow for mislabeling;
    if n is leaf **then**
        if has the function **then** Mislabel with prob. ψ_1;
        else Mislabel with prob. ψ_0;
end

go back

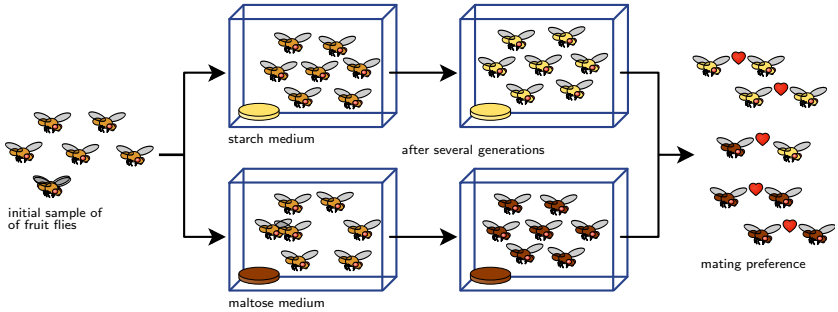

Figure 4 Dodd 1989: After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

go back

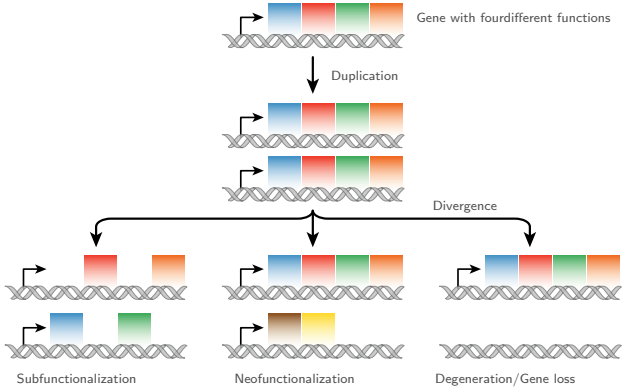

Figure 5 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

go back

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- 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