Essays on Bioinformatics and Social Network Analysis

Statistical and Computational Methods for Complex Systems

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University of Southern California, Department of Preventive Medicine

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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

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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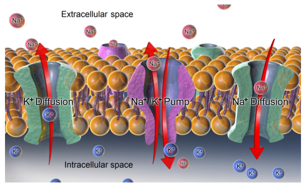
Molecular function

Active transport GO:0005215



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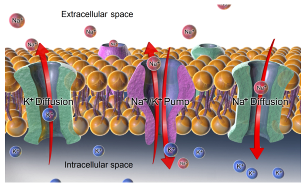
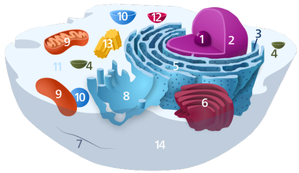
Molecular function	**Cellular component**
Active transport GO:0005215	Mitochondria GO:0004016





Genes

Encode the synthesis of genetic products that ultimately are related to a particular aspect of life, for example

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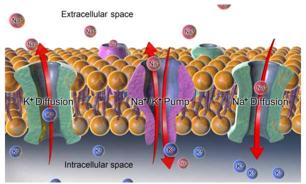

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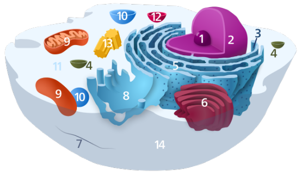
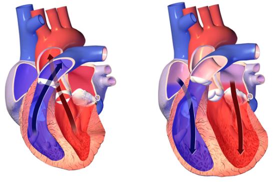


Biological process

Heart contraction GO:0060047



1. Understanding genes means understanding biology
2. Far more than simply persuing knowledge, understanding gene's

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- Of all annotations, about $\sim$ 500,000 are on human genes.
- Knowledge about gene functions can accelerate bio-medical research.

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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

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You know what is interesting about this function?

These four species have a gene with that function...

Felis catus pthr10037

Oryzias latipes **pthr11521**

Anolis carolinensis **pthr11521**

Equus caballus pthr24356

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

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Phylogenetic Trees: The PANTHER classification system

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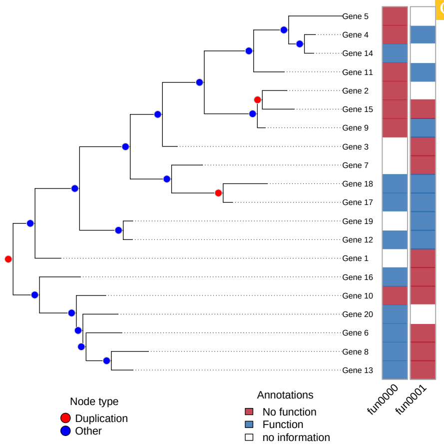


Figure 1 Random annotated phylogenetic tree.

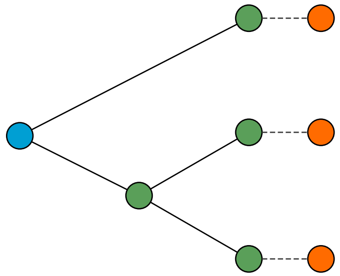
We can use

the evolutionary tree

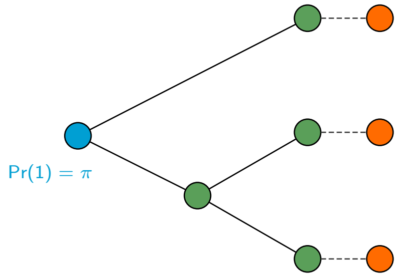
to infer presence/absence of

gene functions (annotations)!

An evolutionary model of gene functions



- Initial (spontaneous) gain of function.



An evolutionary model of gene functions

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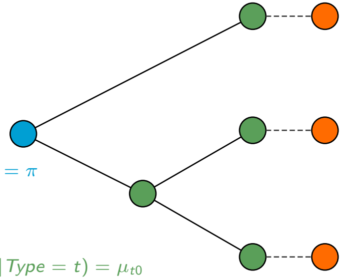
- Initial (spontaneous) gain of function.
- Loss/gain of offspring depends on: (a) the state of its' parents (**Markov process**), and (b) the type of node more



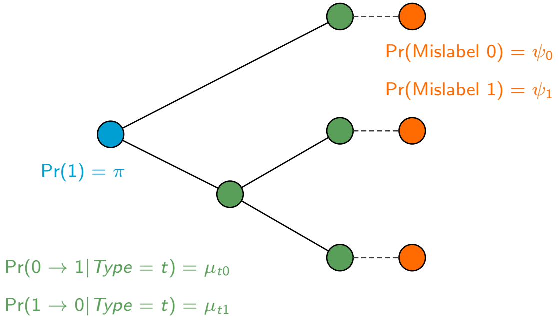
$\Pr(1) = \pi$

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

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

An evolutionary model of gene functions

- Initial (spontaneous) gain of function.
- Loss/gain of offspring depends on: (a) the state of its' parents (**Markov process**), and (b) the type of node ▸ more
- We control for human error.



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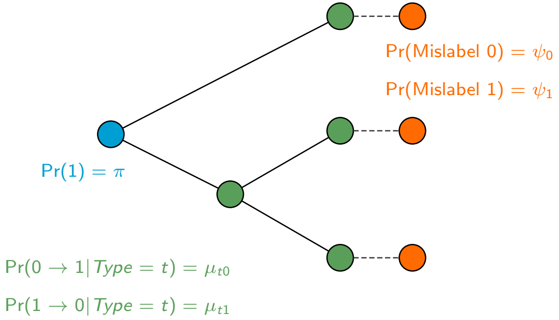

We implemented the model using Felsenstein's' pruning algorithm (linear complexity) in the R package `aphylo` ▸ more.

Prediction with real data

	(1)	(2)
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
Prior	Uniform	Beta
AUC (mean)	0.69	0.67
AUC (median)	0.81	0.75

Table 2 Parameter estimates using different priors.

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

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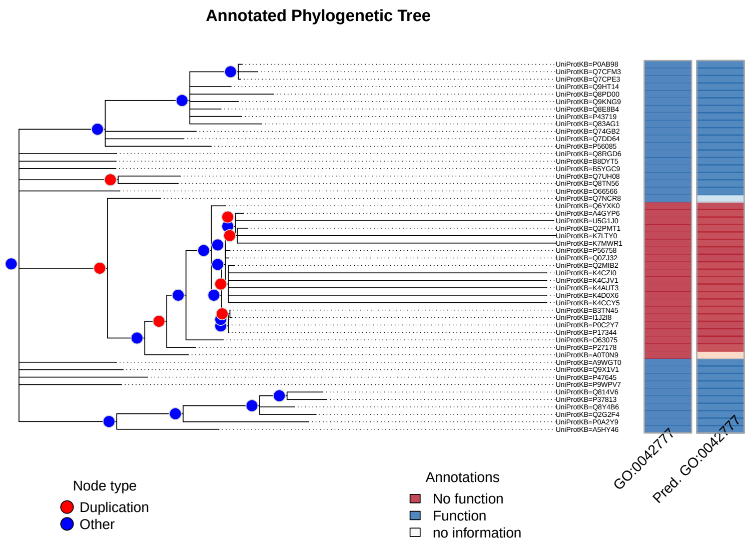
- Biologically meaningful results.
- Took about 5 minutes each.

Prediction with real data: Leave-one-out



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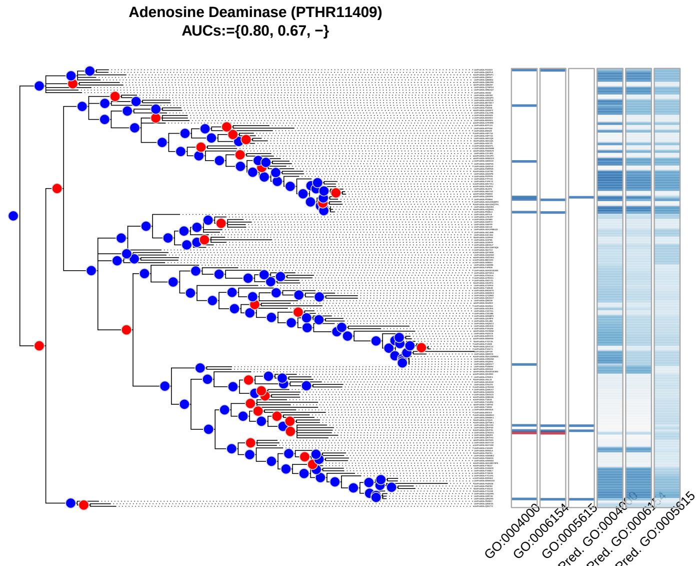

Key takeaways

- Yet another model for predicting gene functions using phylogenetics.
- Big difference, this is 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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Next steps

- Adapt the model to incorporate joint estimation of functions using pseudo-likelihood.

$$P(a, b, c) \approx P(a, b)P(b, c)P(a, c)$$

- Make the model hierarchical when pooling trees: different mutation rates.

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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

Exponential Family Random Graph Models, aka ERGMs are:

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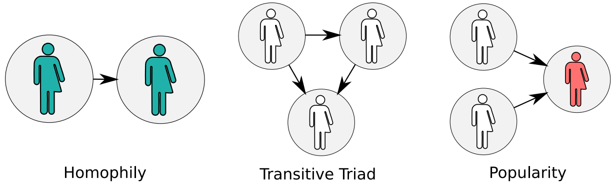
Exponential Family Random Graph Models, aka ERGMs are:

- 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 sufficient statistics

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All possible networks

Observed data

The normalizing constant

more on terms

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

more on terms

ERGMs: State of the Art

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

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What about small networks?

Do we care about small networks?

We see small networks everywhere

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- Families and friends

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- Small teams

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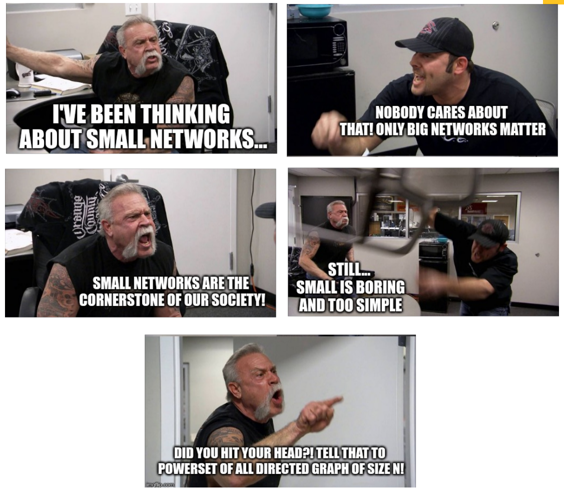

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- Possible accuracy issues (error rates)
- Prone to degeneracy problems (sampling and existence of MLE)
- It is not MLE...

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- Using the exact likelihood opens a huge window of methodological-possibilities.

ERGMs for Small Networks

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$$\Pr\left(\mathbf{Y}=\underbrace{\mathbf{y}\mid\theta,\mathbf{X}}_{\text{Observed data}}\right)=\frac{\exp\left\{\overbrace{\theta}^{\text{A vector of model parameters}}{}^{\mathbf{t}}\overbrace{s\left(\mathbf{y},\mathbf{X}\right)}^{\text{A vector of sufficient statistics}}\right\}}{\underbrace{\sum_{\mathbf{y}'\in\mathcal{Y}}\exp\left\{\theta^{\mathbf{t}}s\left(\mathbf{y}',\mathbf{X}\right)\right\}}_{\text{The normalizing constant}}},\quad\forall\mathbf{y}\in\underbrace{\mathcal{Y}}_{\text{All possible networks}}$$

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- For example, a network with 5 nodes has 1,048,576 unique configurations.
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- We implemented this and more in the `ergmito` R package ▸ more

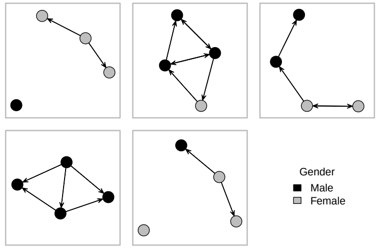
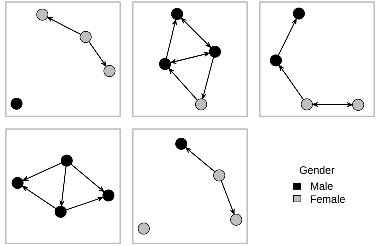


Figure 2 Random sample of 5 networks simulated using the ergmito package



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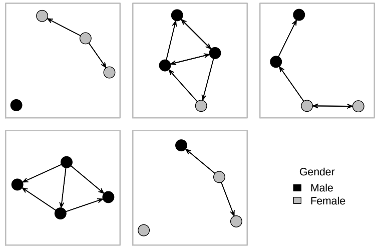
	Bernoulli	Full model
Edge-count	-0.69^{*}	-1.70^{**}
	(0.27)	(0.54)
Homophily (on Gender)		1.59^{*}
		(0.64)
AIC	78.38	73.34
BIC	80.48	77.53
Log Likelihood	-38.19	-34.67
Num. networks	5	5

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

Table 3 Fitted ERGMitos using the fivenets dataset.



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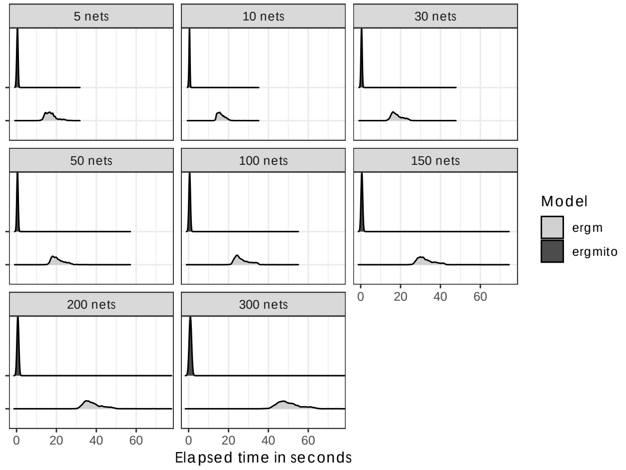
We performed a large simulation study ▸ more comparing MC-MLE (ergm) with MLE (ergmito).

Sample size	N. Simulations	P(Type I error)		χ^2
		MC-MLE (`ergm`)	MLE (`ergmito`)	
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 4 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.



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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Next steps

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

Essays on Bioinformatics and Social Network Analysis

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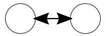
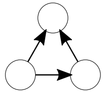
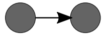
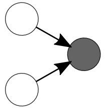
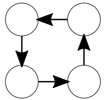
Thanks!

Dodd, Diane M. B. (1989). "Reproductive Isolation as a Consequence of Adaptive Divergence in Drosophila pseudoobscura". In: *Evolution* 43.6, pp. 1308–1311. ISSN: 00143820, 15585646. URL: http://www.jstor.org/stable/2409365.

Here are some by-products of my research here at USC

- The slurmR R package
- The pruner C++ library
- The fmcmc R package

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 $\sum_{i \neq j \neq k \neq l} y_{ij} y_{jk} y_{kl} y_{li}$

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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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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)

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- Draw 20,000 samples of groups of small networks

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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.

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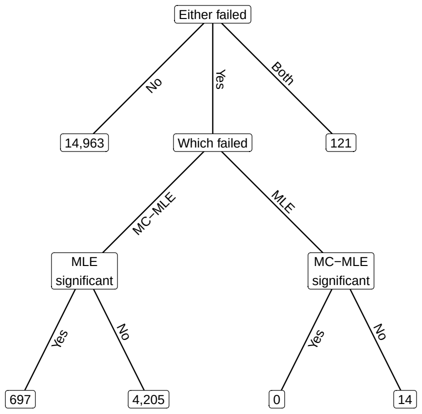

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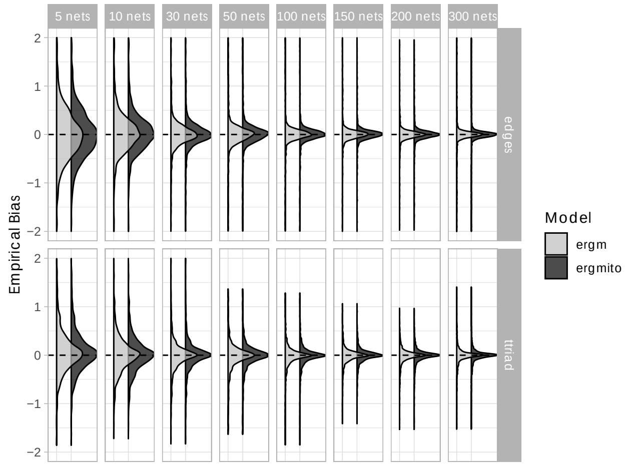

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Data: A phylogenetic tree, $\{\pi, \mu, \psi\}$(Model probabilities)
Result: An annotated tree
for *n* $\in$ *PostOrder*(*N*) **do**
  Nodes gain/loss function depending on their parent;
  switch *class of n* **do**
    case *root node* **do**
      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

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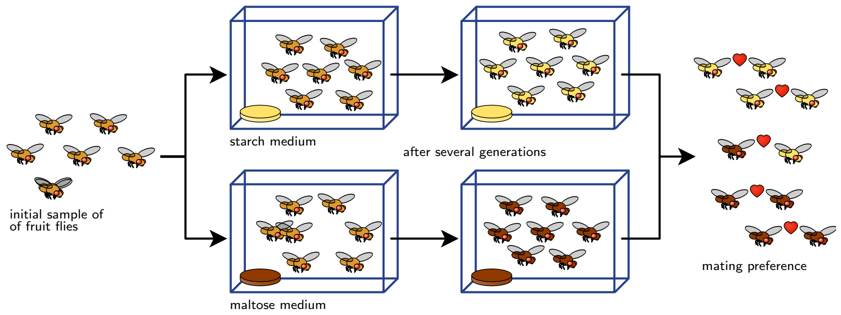

Figure 3 Dodd 1989: After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

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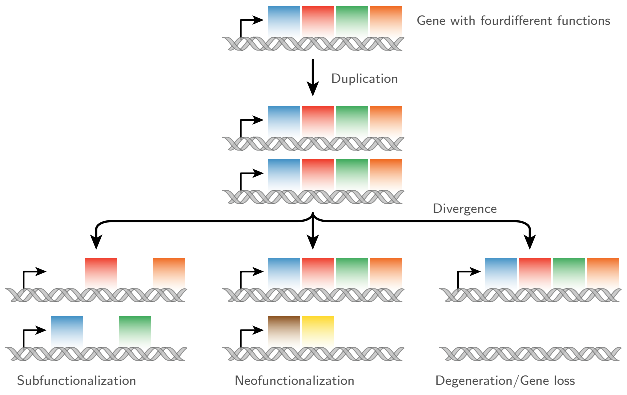

Figure 4 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

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The `aphylo`

- Pruning algorithm implemented in C++ using the `pruner` template library (implemented in this project).
- 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)

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