Statistical and computational methods for bioinformatics and social network analysis

or how did I learn to stop worrying and love the bomb

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Statistical and computational methods for bioinformatics and social network analysis

- We live in a non-*IID* world.
- Some times, looking the whole helps understanding the parts.
- We have the computational tools to do such.

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Paper 1: Exponential Random Graph Models for Small Networks

Paper 2: On the prediction of gene functions using phylogenetic trees

Exponential Random Graph Models for Small Networks

Joint with: Andrew Slaughter and Kayla de la Haye

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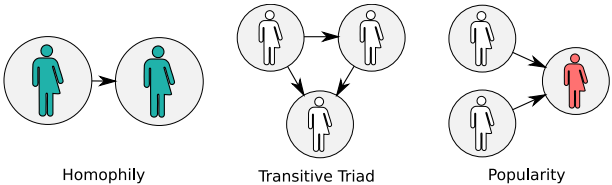
Exponential Family Random Graph Models, aka ERGMs are:

- 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

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

more on terms

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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)

large-huge networks (up to the millions of vertices)

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

What about small networks?

Do we care about small networks?

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We see small networks everywhere

- Families and friends
- Small teams
- Egocentric networks
- Online networks (sometimes)
- etc.

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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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

- In the case of small-enough networks, computation of the likelihood becomes computationally feasible.
- For example, a network with 5 nodes has 1,048,576 unique configurations.
- This allow us to directly compute **the normalizing constant**.
- Using the exact likelihood opens a huge window of methodological-possibilities.
- We implemented this and more in the `ergmito` R package more

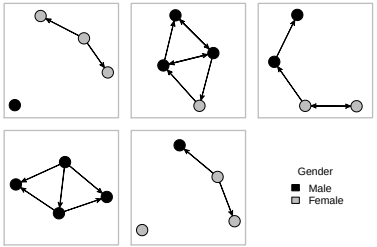

Figure 1 Random sample of 5 networks simulated using the ergmito package

	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 1 Fitted ERGMitos using the fivenets dataset.

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

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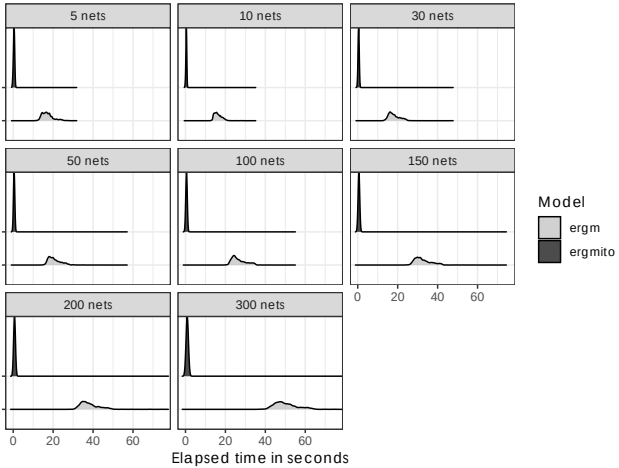
Sample size	N. Simulations	P(Type I error)		χ^2
		MC-MLE (`ergm`)	MLE (`ergmito`)	
5	2,189	0.084	0.057	11.71 ***
10	2,330	0.070	0.045	12.46 ***
15	2,395	0.084	0.066	5.55 *
20	2,430	0.074	0.060	3.58
30	2,460	0.057	0.052	0.67
50	2,495	0.046	0.044	0.17
100	2,499	0.048	0.048	0.00

Table 2 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 1 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.

Next steps

- Revisit measurement of goodness-of-fit.
- Explore extending this method for (very) large 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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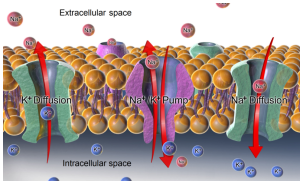
How we organize the information about genes (according to the Gene Ontology Project)

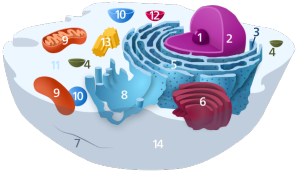
Molecular function

Active transport GO:0005215



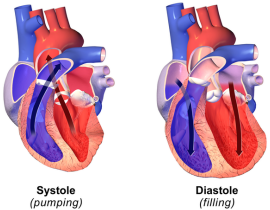
Cellular component

Mitochondria GO:0004016



Biological process

Heart contraction GO:0060047



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- Currently, the Gene Ontology Project has: 44,945 validated terms, $\sim$ 6,400,000 annotations on $\sim$ 1,150,000 species.
- 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 3 Heart Contraction Function. source: amigo.geneontology.org

You know what is interesting about this function?

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

Felis catus pthr10037

Oryzias latipes **pthr11521**

Anolis carolinensis **pthr11521**

Equus caballus pthr24356

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- It can be very general: think of the tree of life
- Nowadays, thanks to gene-sequencing techniques, we are building trees at the gene level.
- A single phylogenetic tree can host multiple species
- The PANTHER project provides information about 15,524 trees w/ 1.7 million genes

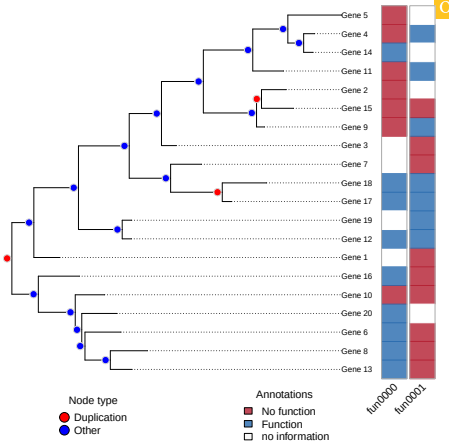

Figure 2 Random annotated phylogenetic tree.

We can use

the evolutionary tree

to infer presence/absence of

gene functions (annotations)!

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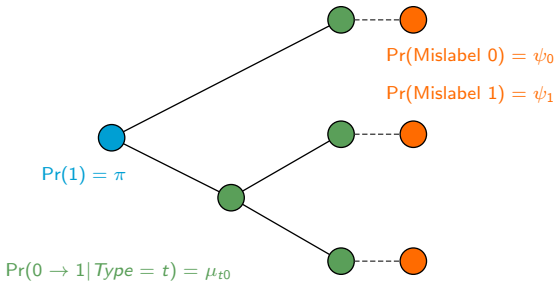
- Initial (spontaneous) gain of function.
- Loss/gain of offspring depends on: (a) the state of its' parents (**Markov process**), and (b) the type of node more
- We control for human error.



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

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	(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
μ_{s1}	0.01	0.02
Root node		
π	0.81	0.45
Prior	Uniform	Beta
AUC (mean)	0.69	0.67
AUC (median)	0.81	0.75

Table 4 Parameter estimates using different priors.

- 141 pooled functions (trees) with 7,388 genes with 0/1 annotations.
- Parameter estiamtes are actually probabilities.
- Data driven results (uninformative prior).
- Biologically meaningful results.
- Took about 5 minutes each.

Prediction with real data: Leave-one-out

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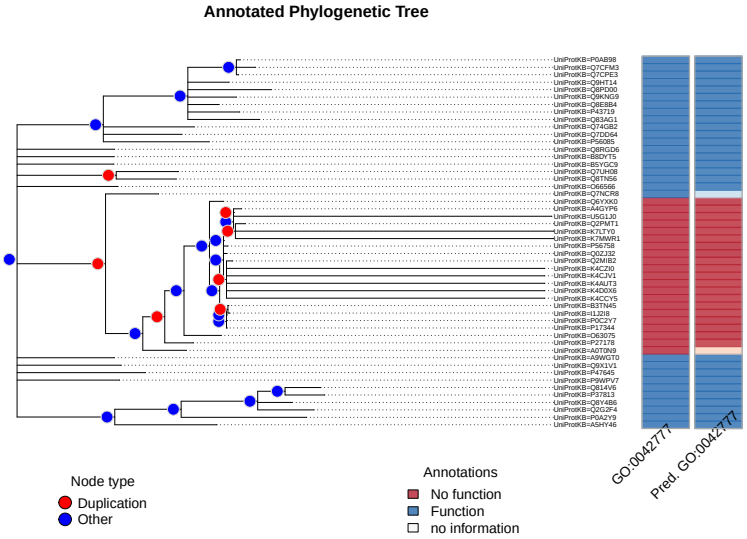

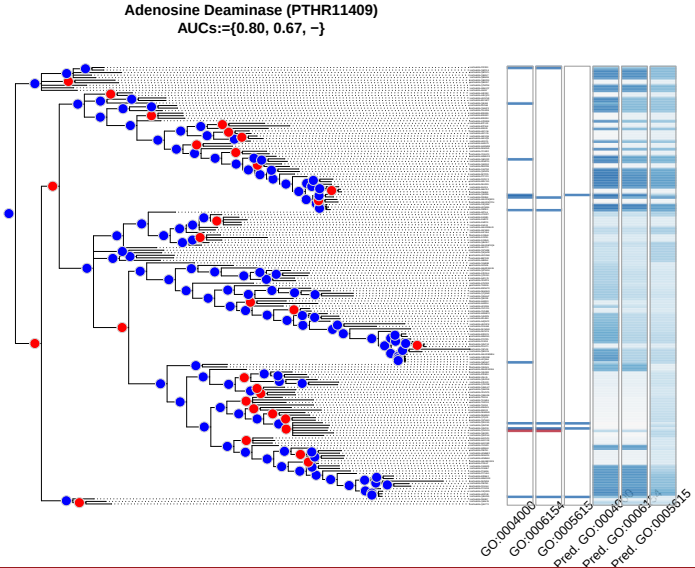
Adenosine Deaminase (PTHR11409)
AUCs:={0.80, 0.67, −}
GO:0004000
GO:0006154
GO:0005615
Pred. GO:0004000
Pred. GO:0006154
Pred. GO:0005615

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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.

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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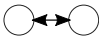
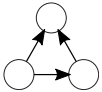
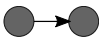
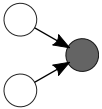
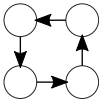
Thanks!

Dodd, D. M. B. (1989). Reproductive isolation as a consequence of adaptive divergence in drosophila pseudoobscura. *Evolution*, *43*(6), 1308–1311. Retrieved from 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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- Implements estimation of ERGMs using exact statistics for small networks
- Meta-programming allows specifying likelihood (and gradient) functions for joint models
- Includes tools for simulating, and post-estimation checks
- Getting ready for CRAN!

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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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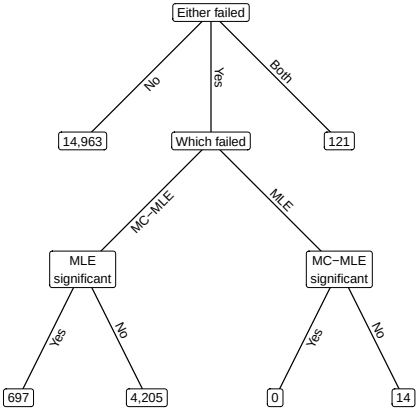

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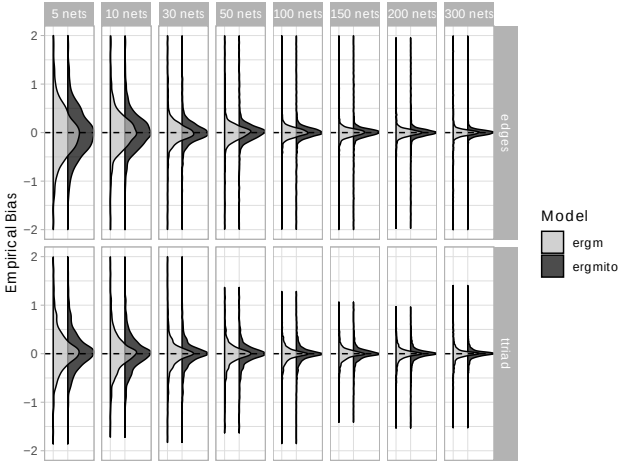
Paper 1 Simulation Studies: Empirical Bias



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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

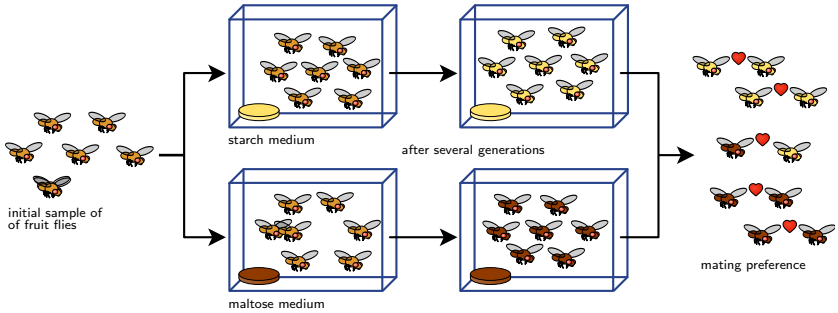

Figure 3 11989DoddDodd (): After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

go back

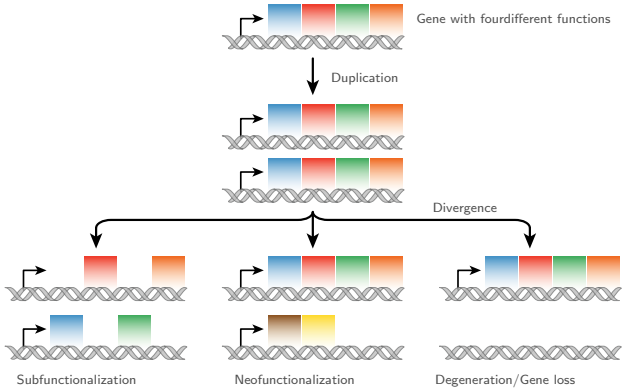

Figure 4 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

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- 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)

go back