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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October 4, 2019

Contents

Paper 1: Exponential Random Graph Models for Small Networks

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

Future directions

Things that are very interesting but I most probably won't have any time to discuss with the attendees

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What are Exponential Random Graph Models

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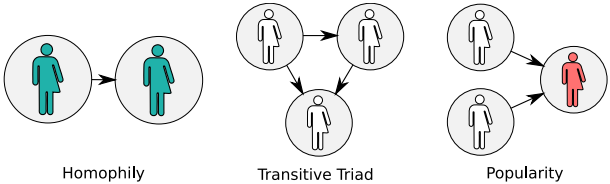

ERGMs (cont'd)

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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

ERGMs: State of the Art

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

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What about tiny to small networks?

A frame with examples of small networks...

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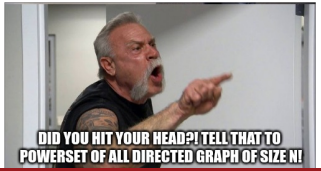

ERGMs for small networks

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

Paper 1 Simulation Studies

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- 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.

Paper 1 Simulation Studies: Empirical Type I error

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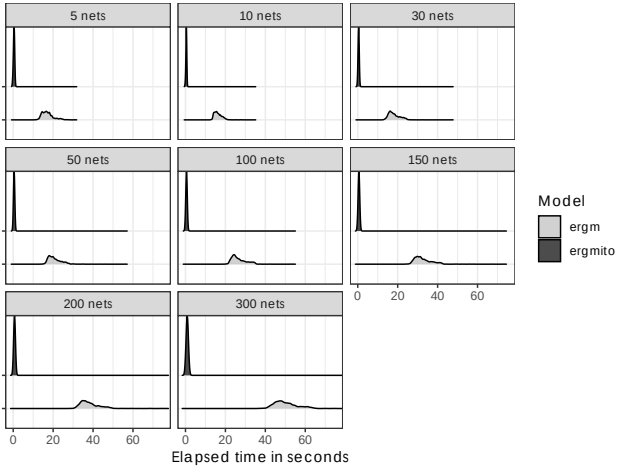
		P(Type I error)		
Sample size	N. Simulations	MC-MLE	MLE	chi2
5	2,189	0.084	0.057	11.71 ***
10	2,330	0.070	0.045	12.46 ***
15	2,395	0.084	0.066	5.55 *
20	2,430	0.074	0.060	3.58
30	2,460	0.057	0.052	0.67
50	2,495	0.046	0.044	0.17
100	2,499	0.048	0.048	0.00

Table 1 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

Paper 1: Key takeaway

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- Performance: Same (un)bias, Lower Type I error rates, (way) faster.

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- Performance: Same (un)bias, Lower Type I error rates, (way) faster.
- Opens the door the new methods.

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Phylogenetic Trees

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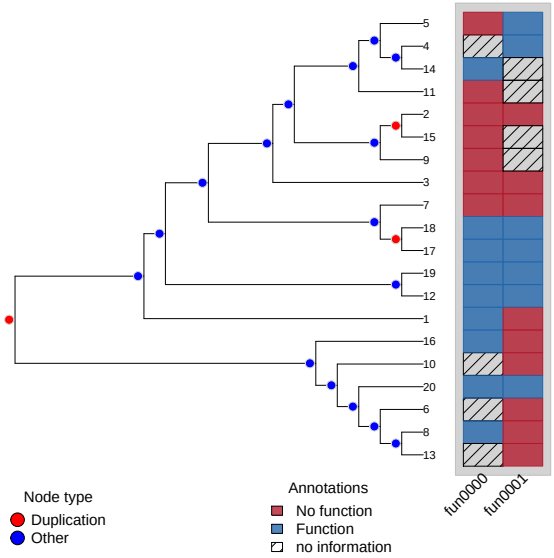
- Nowadays, thanks to gene-sequencing techniques, we are building trees at the gene level (using sequence-alignment methods, i.e. comparing gene sequences to see how much similar/different two genes are between and within species (whattt!)).
- A single phylogenetic tree can host multiple species

Annotated Phylogenetic Tree



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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 2 Heart Contraction Function. source: amigo.geneontology.org

pthr10037

pthr11521

pthr11521

pthr24356

Speciation

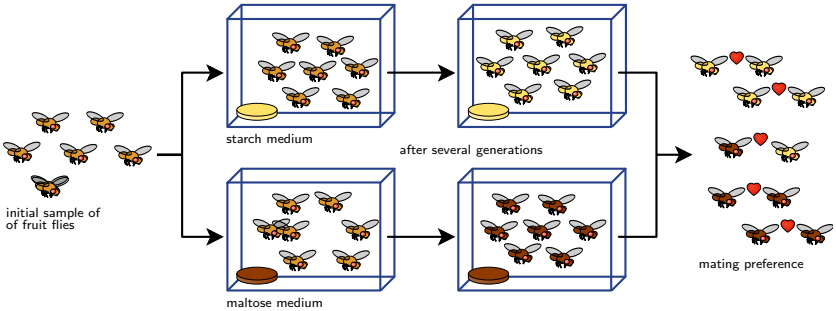

Figure 1 Dodd (1989): After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

Duplication

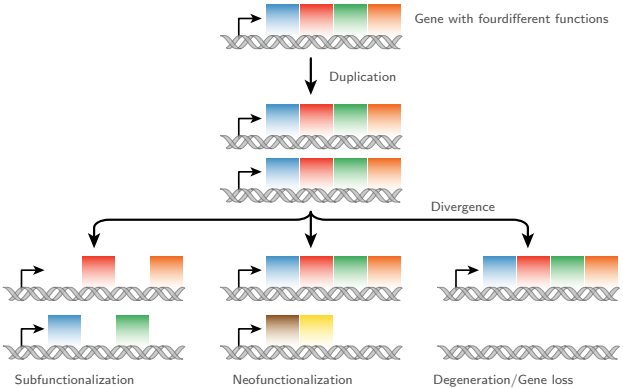

Figure 2 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

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

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An evolutionary model of gene functions: Formal statement

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- The whole is based on the markov-assumption: The current state of the gene can be fully explained by its parent(s).
- For this we use Felsensteins' pruning algorithm (also known as...)
  Formally

$$P(x = 1) = P(x = 1|x_p = 0)P(\text{Gain}) + P(x = 1|x_p = 1)P(\text{No loss})$$

Paper 2: Estimation of the model

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The model has (so far) 7 fixed parameters

ψ_0, ψ_1	Probability of making a mistake (mislabel)
μ_{d0}, μ_{d1}	Probability of functional gain/loss (duplication nodes)
μ_{s0}, μ_{s1}	Probability of functional gain/loss (other nodes)
π	Probability that the root has the function

Paper 2: Estimation of the model (cont'd)

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- We developed a full set of tools (C++ library + R pacakge) for this framework more
- Estimation is done via: MLE, MAP, and MCMC (using an adaptive kernel)
- Posterior probabilities are estimated using the conditional on the observed data.
- To evaluate performance, we used two datasets: manually (fully) annotated (inferred) trees, and experimentally annotated trees

Paper 2: Pooled estimation

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	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
ψ_0	0.00	0.00	0.23	0.25	0.00	0.00	0.21	0.25
ψ_1	0.00	0.00	0.01	0.01	0.00	0.00	0.00	0.01
μ_{d0}	0.01	0.01	0.97	0.96	1.00	0.01	1.00	0.98
μ_{d1}	0.01	0.02	0.52	0.58	0.25	0.02	0.51	0.58
μ_{s0}	0.00	0.00	0.05	0.06	0.07	0.00	0.05	0.06
μ_{s1}	0.01	0.01	0.01	0.02	0.01	0.01	0.01	0.02
π	0.81	0.91	0.78	0.45	0.82	0.91	0.83	0.49
Tree count	88	88	141	141	88	88	141	141
Method	MCMC	MCMC	MCMC	MCMC	MLE	MLE	MLE	MLE
Prior	Uniform	Beta	Uniform	Beta	Uniform	Beta	Uniform	Beta
Inferred	Yes	Yes	No	No	Yes	Yes	No	No
AUC	1.00	1.00	0.69	0.67	0.98	1.00	0.70	0.67
P. Score (obs)	1.00	1.00	0.81	0.81	0.92	1.00	0.81	0.81
P. Score (random)	0.71	0.71	0.61	0.61	0.71	0.71	0.61	0.61

Table 3 Parameter estimates using different estimation methods, priors, and types of annotations.

Paper 2: Pooled estimation (worth it?)

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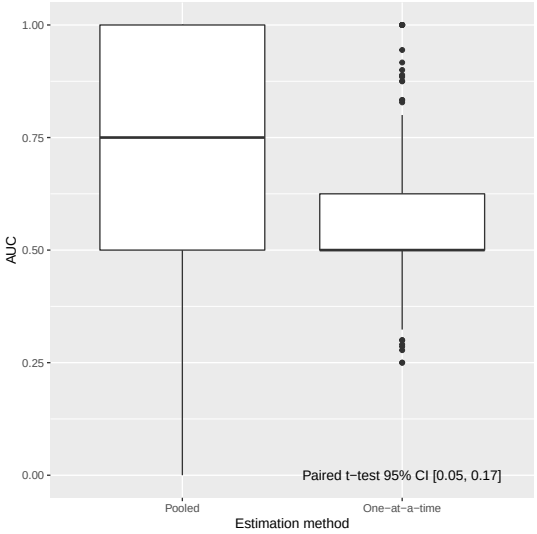

Paper 2: Leave-one-out predictions

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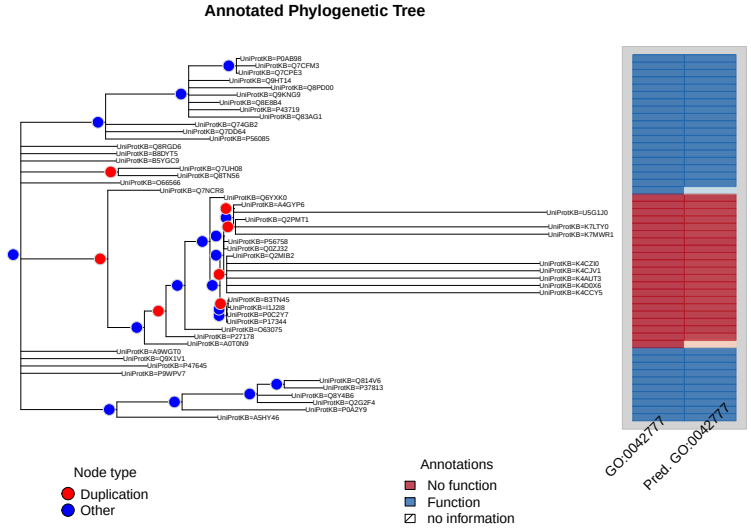

Paper 2: Out-of-sample-predictions

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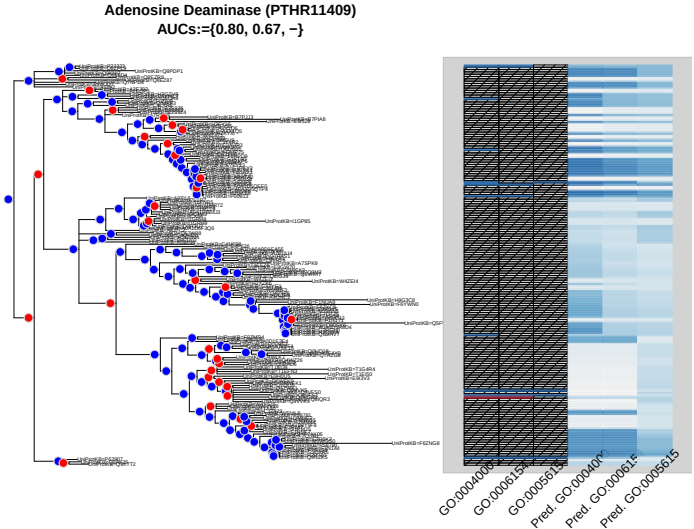

Paper 2: Key takeaways

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- (Yet another) model for predicting gene functions using phylogenetics

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- Big difference... computationally scalable
- Meaningful biological results
- Preliminary accuracy results comparable to state-of-the-art phylo-based models

Future directions: ERGMitos

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Possible venues to continue

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Possible venues to continue

- Identify an adequate test for goodness-of-fit assesment

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Possible venues to continue

- Identify an adequate test for goodness-of-fit assesment
- Extend to estimation of large graphs by splitting the networks in induced-subgraphs

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

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

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

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

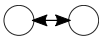
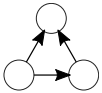
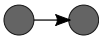
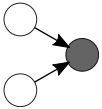
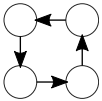
Here are some by-products of my research here at USC

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

References I

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

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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ERGMs: The MC-MLE approach

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

This consists on the folling steps

1. Start from a sensible guess on what should be the population parameters (usually done using pseudo-MLE esimtation)
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

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- Implements estimation of ERGMs using exact statistics for small networks
- Metaprogramming allows specifying likelihood (and gradient) functions for joint models
- Includes tools for simulating, and postestimation checks
- Getting ready for CRAN!

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Paper 1 Simulation Studies: Error rate

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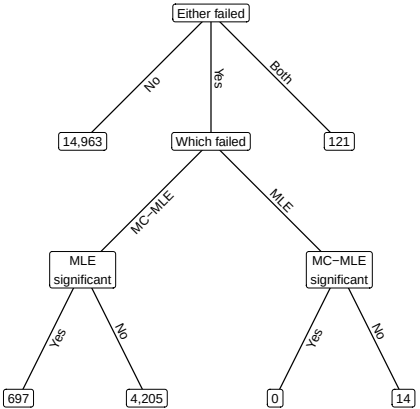

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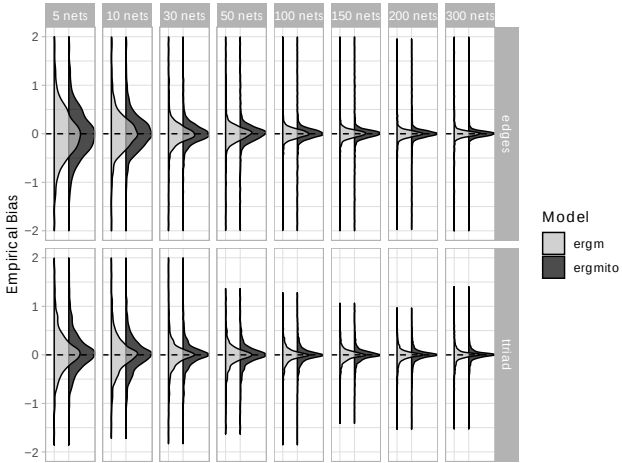
Paper 1 Simulation Studies: Empirical Bias



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