

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

Statistical and computational methods for bioinformatics and social network analysis

- We live in a non-*IID* world.

Statistical and computational methods for bioinformatics and social network analysis

- ▶ We live in a non-*IID* world.
- ▶ In some times, the cannot understand a process unless we look at it as a whole.

Statistical and computational methods for bioinformatics and social network analysis

- ▶ We live in a non-*IID* world.
- ▶ 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*.

Statistical and computational methods for bioinformatics and social network analysis

- ▶ We live in a non-*IID* world.
- ▶ 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.

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

Paper 2: Exponential Random Graph Models for Small Networks

Future Research

On the prediction of gene functions using phylogenetic trees

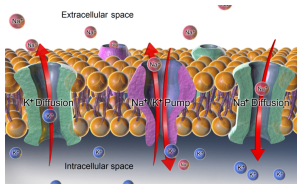
Joint with: Paul D Thomas, Paul Marjoram, Huaiyu Mi, Duncan Thomas, and John Morrison

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

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

Molecular function

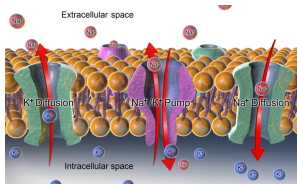
Active transport GO:0005215



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

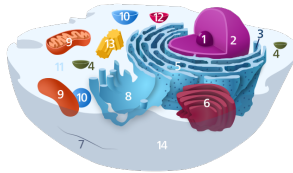
Molecular function

Active transport GO:0005215



Cellular component

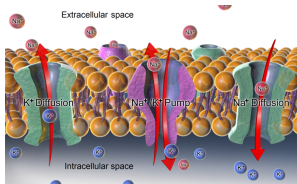
Mitochondria GO:0004016



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

Molecular function

Active transport GO:0005215



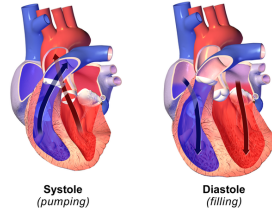
Cellular component

Mitochondria GO:0004016



Biological process

Heart contraction GO:0060047





- ▶ The GO project has $\sim 44,700$ validated terms [▶ more](#), $\sim 7.3\text{M}$ annotations on $\sim 4,500$ species.

source: Statistics from pantherdb.org and geneontology.org



- ▶ The GO project has $\sim 44,700$ validated terms [▶ more](#), $\sim 7.3\text{M}$ annotations on $\sim 4,500$ species.
- ▶ About $\sim 500,000$ are on human genes.

source: Statistics from pantherdb.org and geneontology.org



- ▶ The GO project has $\sim 44,700$ validated terms [▶ more](#), $\sim 7.3\text{M}$ annotations on $\sim 4,500$ species.
- ▶ About $\sim 500,000$ are on human genes.
- ▶ Roughly half of human genes ($\sim 10,000 / 20,000$) have some form of annotation.

source: Statistics from pantherdb.org and geneontology.org



- ▶ The GO project has $\sim 44,700$ validated terms [▶ more](#), $\sim 7.3\text{M}$ annotations on $\sim 4,500$ species.
- ▶ About $\sim 500,000$ are on human genes.
- ▶ 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).

source: Statistics from pantherdb.org and geneontology.org



- ▶ The GO project has $\sim 44,700$ validated terms [▶ more](#), $\sim 7.3\text{M}$ annotations on $\sim 4,500$ species.
- ▶ About $\sim 500,000$ are on human genes.
- ▶ 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...

source: Statistics from pantherdb.org and geneontology.org

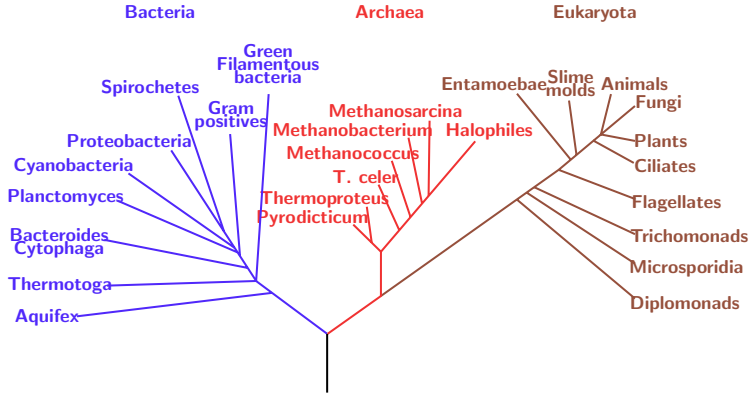


Figure 1 A phylogenetic tree of living things, based on RNA data and proposed by Carl Woese, showing the separation of bacteria, archaea, and eukaryotes (wiki)

- ▶ The PANTHER project (part of GO)
provides information about evolutionary
structure of 1.7 million genes

- ▶ The PANTHER project (part of GO) provides information about evolutionary structure of 1.7 million genes
- ▶ These genes are grouped in 15,524 phylogenetic trees (families)

- ▶ The PANTHER project (part of GO) provides information about evolutionary structure of 1.7 million genes
- ▶ These genes are grouped in 15,524 phylogenetic trees (families)
- ▶ A single family can host multiple species

Phylogenetic Trees: The PANTHER classification system

- The PANTHER project (part of GO) provides information about evolutionary structure of 1.7 million genes
- These genes are grouped in 15,524 phylogenetic trees (families)
- A single family can host multiple species

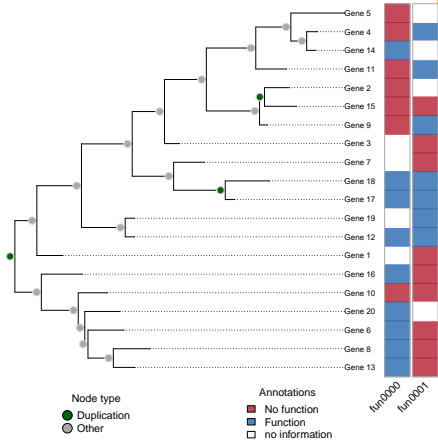


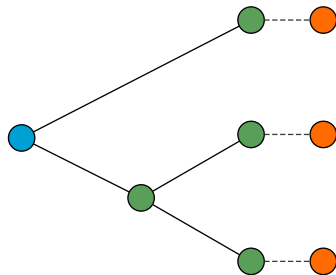
Figure 2 Simulated phylogenetic tree and gene annotations.

We can use

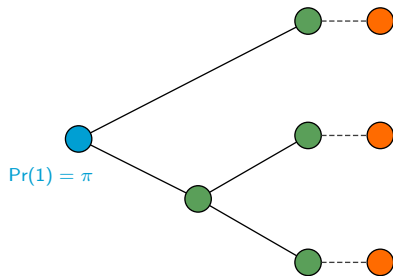
evolutionary trees

to inform a model for predicting

genetic annotations!



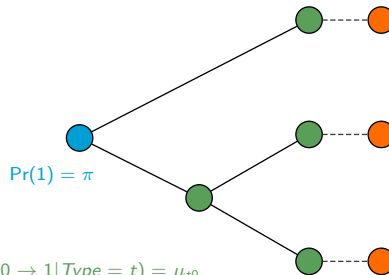
- Initial (spontaneous) gain of function.



► other models

► other view

- ▶ 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](#)

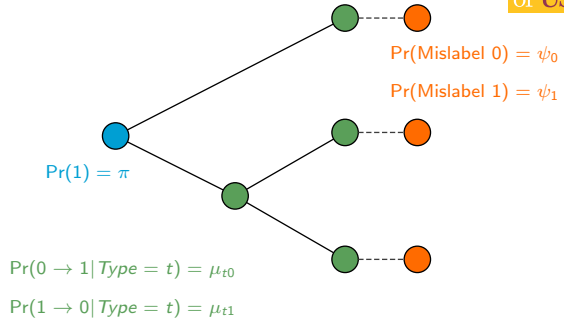


$$\Pr(0 \rightarrow 1 | Type = t) = \mu_{t0}$$

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

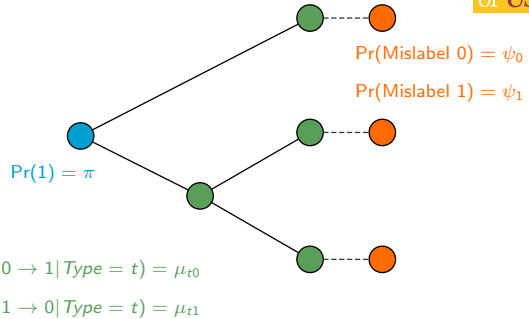
An evolutionary model of gene functions

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



An evolutionary model of gene functions

- ▶ 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](#)
- ▶ We control for human error.



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

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

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

Table 1 Parameter estimates using different priors.

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

- ▶ 141 pooled functions (trees) with 7,388 genes with 0/1 annotations.
- ▶ Parameter estimates are actually probabilities.

Table 1 Parameter estimates using different priors.

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

- ▶ 141 pooled functions (trees) with 7,388 genes with 0/1 annotations.
- ▶ Parameter estimates are actually probabilities.
- ▶ Data driven results (uninformative prior).

Table 1 Parameter estimates using different priors.

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.
- ▶ Parameter estimates are actually probabilities.
- ▶ Data driven results (uninformative prior).
- ▶ **Biologically meaningful results.**

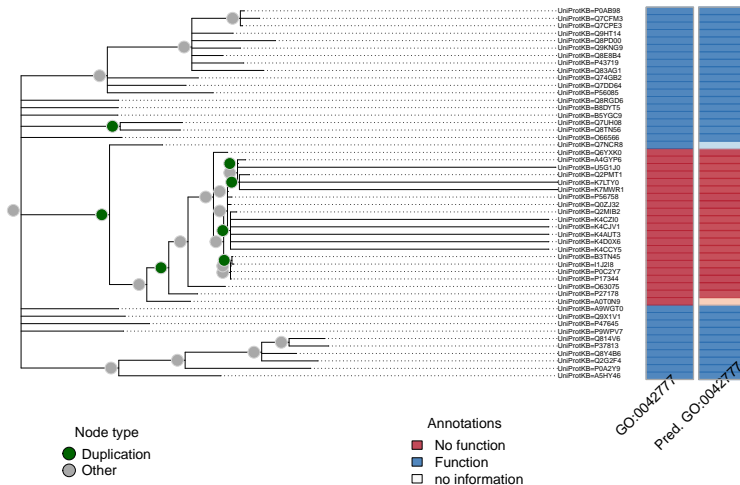
Prediction with real data

	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.
- ▶ Parameter estimates are actually probabilities.
- ▶ Data driven results (uninformative prior).
- ▶ **Biologically meaningful results.**
- ▶ Took about 5 minutes each.

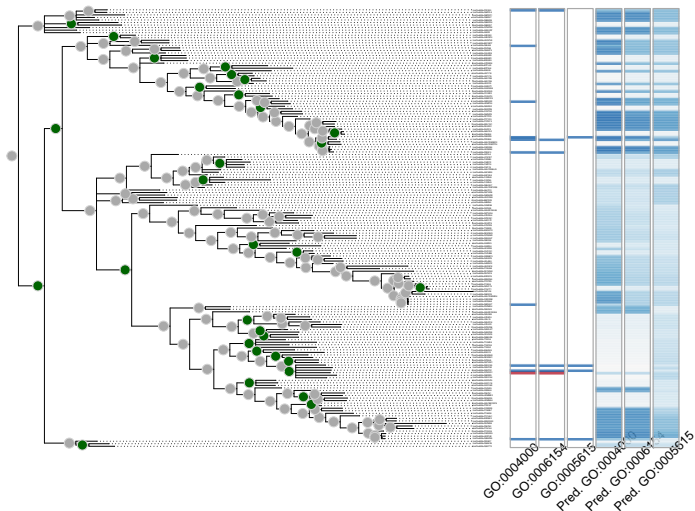
Annotated Phylogenetic Tree



Prediction with real data: Out-of-sample prediction

Adenosine Deaminase (PTHR11409)

AUCs:={0.80, 0.67, -}



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.

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.

Challenges

- ▶ Offspring are conditional independent on their parent and

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.

Challenges

- ▶ 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

Exponential Family Random Graph Models, aka **ERGMs** are:

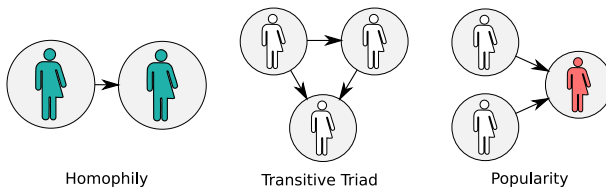
What are Exponential Random Graph Models

Exponential Family Random Graph Models, aka **ERGMs** are:

- Statistical models of (social) networks

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



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

A vector of
model parameters A vector of
sufficient statistics

Observed data The normalizing
constant All possible
networks




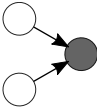

$$\Pr(\mathbf{Y} = \mathbf{y} \mid \theta, \mathbf{X}) = \frac{\exp\{\theta^t \mathbf{s}(\mathbf{y}, \mathbf{X})\}}{\sum_{\mathbf{y}' \in \mathcal{Y}} \exp\{\theta^t \mathbf{s}(\mathbf{y}', \mathbf{X})\}}, \quad \forall \mathbf{y} \in \mathcal{Y}$$

A vector of model parameters A vector of sufficient statistics

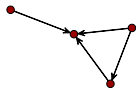
Observed data The normalizing constant All possible networks

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

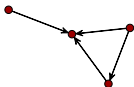
Sufficient statistics have various forms

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

In this network

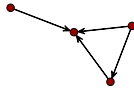


In this network



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

In this network



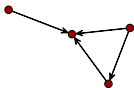
We see 4 **edges**, 1 **transitive triad** and **no mutual ties**.

The probability function of this model would be

$$\mathbb{P}(\mathbf{G} = \mathbf{g} \mid \theta) = \frac{\exp \{4\theta_{edges} + \theta_{ttriads} + 0\theta_{mutual}\}}{\sum_{\mathbf{g}' \in \mathcal{G}} \exp \{\theta^t s(\mathbf{g}')\}}$$

with $\theta = [\theta_{edges} \quad \theta_{ttriads} \quad \theta_{mutual}]^t$

In this network



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

The probability function of this model would be

$$\mathbb{P}(\mathbf{G} = \mathbf{g} \mid \theta) = \frac{\exp \{4\theta_{edges} + \theta_{ttriads} + 0\theta_{mutual}\}}{\sum_{\mathbf{g}' \in \mathcal{G}} \exp \{\theta^t s(\mathbf{g}')\}}$$

$$\text{with } \theta = [\theta_{edges} \quad \theta_{ttriads} \quad \theta_{mutual}]^t$$

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.

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)

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 millions of vertices)

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

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 millions of vertices)

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

All of these methods are approximations!

Do we care about small networks?

We see small networks everywhere

Do we care about small networks?

We see small networks everywhere

- Families and friends

We see small networks everywhere

- ▶ Families and friends
- ▶ Small teams

We see small networks everywhere

- ▶ Families and friends
- ▶ Small teams
- ▶ Egocentric networks

We see small networks everywhere

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

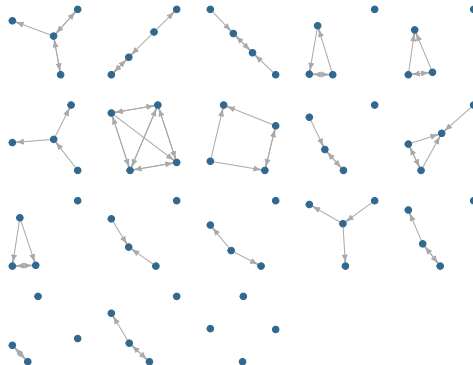
We see small networks everywhere

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

We see small networks everywhere

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

Small networks come in samples



- In the case of small-enough networks, computation of the likelihood becomes computationally feasible.

- ▶ In the case of small-enough networks, computation of the likelihood becomes computationally feasible.
- ▶ This allow us to directly compute **the normalizing constant**.

- ▶ In the case of small-enough networks, computation of the likelihood becomes computationally feasible.
- ▶ This allow us to directly compute **the normalizing constant**.

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

A vector of model parameters A vector of sufficient statistics

Observed data The normalizing constant All possible networks

- ▶ In the case of small-enough networks, computation of the likelihood becomes computationally feasible.
- ▶ This allow us to directly compute **the normalizing constant**.
- ▶ Using the exact likelihood opens a huge window of methodological-possibilities.

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

A vector of model parameters A vector of sufficient statistics

Observed data The normalizing constant All possible networks

- ▶ In the case of small-enough networks, computation of the likelihood becomes computationally feasible.
- ▶ 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](#)

Sidetrack...

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

¡Qué lindo ese perrito! / What a beautiful little dog!

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

Sidetrack...

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

¡Qué lindo ese perrito! / What a beautiful little dog!

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

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

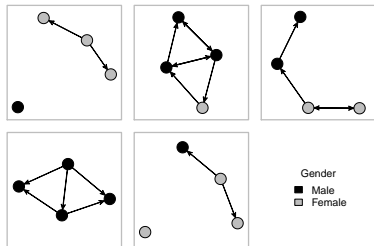


Figure 3 Random sample of 5 networks simulated using the ergmito package

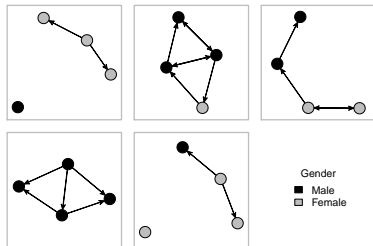


Figure 3 Random sample of 5 networks simulated using the ergmito package

	Bernoulli	Full model
Edge-count	-0.69* (0.27)	-1.70** (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.

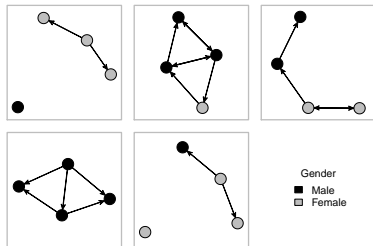


Figure 3 Random sample of 5 networks simulated using the ergmito package

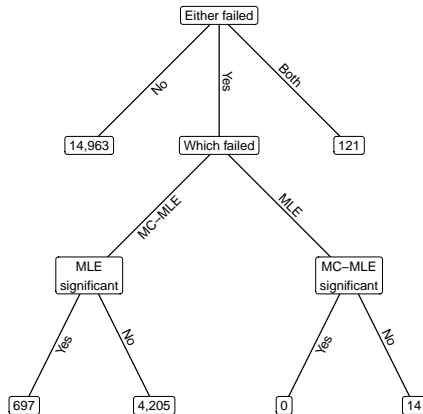
We performed a large simulation study [▶ more](#) comparing MC-MLE (ergm) with MLE (ergmito).

	Bernoulli	Full model
Edge-count	-0.69* (0.27)	-1.70** (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

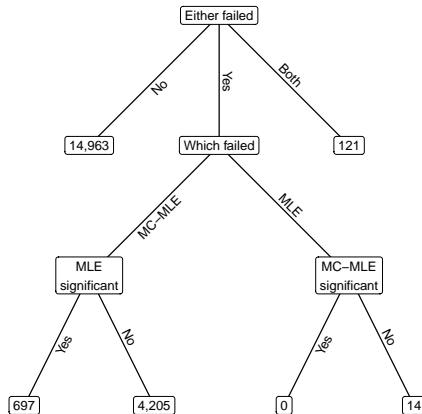
Standard errors in parenthesis. *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$

Table 2 Fitted ERGMitos using the fivenets dataset.

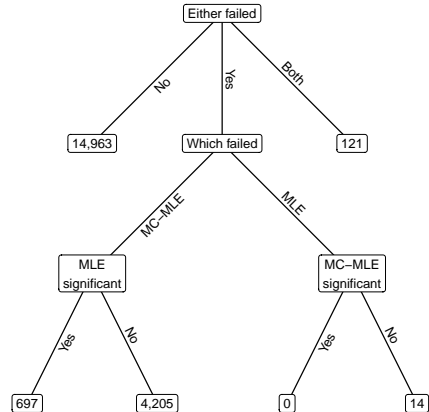
- The MC-MLE implementation failed \sim 5,000/20,000 times



- ▶ The MC-MLE implementation failed $\sim 5,000/20,000$ times
- ▶ In ~ 700 of those cases ergmito (MLE) reported a significant effect

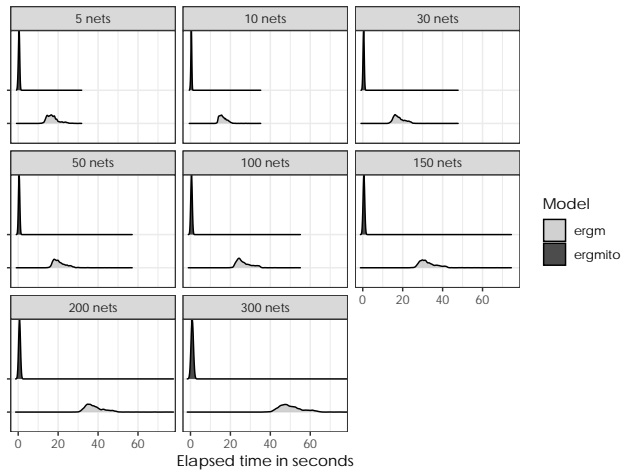


- ▶ The MC-MLE implementation failed $\sim 5,000/20,000$ times
- ▶ In ~ 700 of those cases ergmito (MLE) reported a significant effect
- ▶ I no case that MLE failed MC-MLE reported an effect.



Sample size	P(Type I error)		χ^2
	MC-MLE (ergm)	MLE (ergmito)	
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 * $p < 0.05$.



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.

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.

Challenges

- ▶ Computationally, we can do better in terms of speed/memory.

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.

Challenges

- ▶ Computationally, we can do better in terms of speed/memory.
- ▶ Have a good way of assessing goodness-of-fit.

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.

Challenges

- ▶ Computationally, we can do better in terms of speed/memory.
- ▶ Have a good way of assessing goodness-of-fit.
- ▶ Explore extending this method for (very) large networks.

Future Research

- Make the model hierarchical when pooling trees

Future Research: phylogenetic models

- ▶ Make the model hierarchical when pooling trees
 - ▶ Different mutation rates per class of tree/function
 - ▶ Can be complicated to fit (how many classes?)

Future Research: phylogenetic models

- ▶ Make the model hierarchical when pooling trees
 - ▶ Different mutation rates per class of tree/function
 - ▶ Can be complicated to fit (how many classes?)
- ▶ Use a framework similar to Exponential Random Graph Models:

Future Research: phylogenetic models

- ▶ Make the model hierarchical when pooling trees
 - ▶ Different mutation rates per class of tree/function
 - ▶ Can be complicated to fit (how many classes?)
- ▶ Use a framework similar to Exponential Random Graph Models:
 - ▶ A generalization of the model
 - ▶ Extends to account for joint dist of functions+siblings
 - ▶ Can incorporate additional information such as branch lengths
 - ▶ Yet computationally more compact compared to SIFTER (iso-statistics)

Future Research: phylogenetic models

- ▶ Make the model hierarchical when pooling trees
 - ▶ Different mutation rates per class of tree/function
 - ▶ Can be complicated to fit (how many classes?)
- ▶ Use a framework similar to Exponential Random Graph Models:
 - ▶ A generalization of the model
 - ▶ Extends to account for joint dist of functions+siblings
 - ▶ Can incorporate additional information such as branch lengths
 - ▶ Yet computationally more compact compared to SIFTER (iso-statistics)

$$\mathbb{P}(\mathbf{X} = \{x_{n1}, x_{n2}, \dots\} \mid x_{\mathbf{p}(n1, \dots)}) = \frac{\exp\{\mu^T s(\mathbf{x} \mid x_{\mathbf{p}(\cdot)})\}}{\sum_{\mathbf{x}'} \exp\{\mu^T s(\mathbf{x}' \mid x_{\mathbf{p}(\cdot)})\}}$$

Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

		Transitions to			
		Case 1		Case 2	
Parent	A	$\begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	
	B	$\begin{bmatrix} 1 \\ 0 \\ 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$	
	C	$\begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	

Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

			Transitions to			
			Case 1		Case 2	
Parent	A	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$		$\begin{bmatrix} 1 & 0 \end{bmatrix}$	
	B	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$		$\begin{bmatrix} 0 & 0 \end{bmatrix}$	
	C	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$		$\begin{bmatrix} 1 & 0 \end{bmatrix}$	

Sufficient statistics

Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

		Transitions to				
		Case 1		Case 2		
Parent	A	$\begin{bmatrix} 0 \\ 1 \\ 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \\ 1 & 0 \\ 0 & 1 \end{bmatrix}$		$\begin{bmatrix} 1 & 0 \\ 0 & 0 \\ 1 & 0 \end{bmatrix}$	
	B					
	C					
Sufficient statistics						
# Gains		1		2		

Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

			Transitions to	
			Case 1	Case 2
Parent	A	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
	B	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$
	C	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$

Sufficient statistics

# Gains	1	2
# only one offspring changes	1	0

Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

			Transitions to	
			Case 1	Case 2
Parent	A	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
	B	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$
	C	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
Sufficient statistics				
# Gains			1	2
# only one offspring changes			1	0
# Swaps ($0 \rightarrow 1, 1 \rightarrow 0$)			2	4

Imagine that we have 3 functions (rows) and that each node has 2 siblings (columns)

			Transitions to	
			Case 1	Case 2
Parent	A	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
	B	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$
	C	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
Sufficient statistics				
# Gains			1	2
# only one offspring changes			1	0
# Swaps (0→1, 1→0)			2	4

In SIFTER, for modelling 3 functions, we need $2^{2 \times 3} = 64$ parameters.

Goodness-of-fit

Goodness-of-fit

- Is something that will need to be addressed at some point.

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.
- ▶ Two key questions: What sufficient statistic to look at? what test?

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.
- ▶ Two key questions: What sufficient statistic to look at? what test?

ERGMs for large networks

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.
- ▶ Two key questions: What sufficient statistic to look at? what test?

ERGMs for large networks

- ▶ There is still no standard way to estimate ERGMs for large networks.

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.
- ▶ Two key questions: What sufficient statistic to look at? what test?

ERGMs for large networks

- ▶ There is still no standard way to estimate ERGMs for large networks.
- ▶ Most attempts are still depending on simulation methods.

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.
- ▶ Two key questions: What sufficient statistic to look at? what test?

ERGMs for large networks

- ▶ There is still no standard way to estimate ERGMs for large networks.
- ▶ Most attempts are still depending on simulation methods.
- ▶ We could use the Snowball Sampling framework together with ERGMitos.

Goodness-of-fit

- ▶ Is something that will need to be addressed at some point.
- ▶ The problem is not easy as we need to deal a discrete distribution.
- ▶ Two key questions: What sufficient statistic to look at? what test?

ERGMs for large networks

- ▶ There is still no standard way to estimate ERGMs for large networks.
- ▶ Most attempts are still depending on simulation methods.
- ▶ We could use the Snowball Sampling framework together with ERGMitos. (... I would call this ERGMote)

- ▶ Paper 1: Phylogenetic models of gene functional evolution

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.
- ▶ Paper 2: ERGMs for small networks

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.
- ▶ Paper 2: ERGMs for small networks
 - ▶ An extension to a well studied models for social networks.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.
- ▶ Paper 2: ERGMs for small networks
 - ▶ An extension to a well studied models for social networks.
 - ▶ Small size allows exact calculations.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.
- ▶ Paper 2: ERGMs for small networks
 - ▶ An extension to a well studied models for social networks.
 - ▶ Small size allows exact calculations.
 - ▶ Opens the door to a large set of methodological innovations.

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.
- ▶ Paper 2: ERGMs for small networks
 - ▶ An extension to a well studied models for social networks.
 - ▶ Small size allows exact calculations.
 - ▶ Opens the door to a large set of methodological innovations.
 - ▶ **Next steps:** GOF or extensions to large networks?

Concluding Remarks

- ▶ Paper 1: Phylogenetic models of gene functional evolution
 - ▶ Parsimonious and biologically meaningful.
 - ▶ Computationally scalable.
 - ▶ Performance comparable to state-of-the-art alternatives.
 - ▶ **Next steps:** Use ERGMs framework to break assumptions.
- ▶ Paper 2: ERGMs for small networks
 - ▶ An extension to a well studied models for social networks.
 - ▶ Small size allows exact calculations.
 - ▶ Opens the door to a large set of methodological innovations.
 - ▶ **Next steps:** GOF or extensions to large networks?

Accomplishments during the development of this work

- ▶ 6 journal publications (Journal of Open Source Software, Stata Journal, Journal of health and social behavior, Translational behavioral medicine, Social Science & Medicine)
- ▶ 11 packages/libraries built (ergmito, similR, gnet, fmcmm, 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



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>.
-  Engelhardt, Barbara E. et al. (2011). "Genome-scale phylogenetic function annotation of large and diverse protein families". In: Genome Research 21.11, pp. 1969–1980. ISSN: 10889051. DOI: 10.1101/gr.104687.109.
-  Engelhardt, Barbara E et al. (2005). "Protein Molecular Function Prediction by Bayesian Phylogenomics". In: PLOS Computational Biology 1.5. DOI: 10.1371/journal.pcbi.0010045. URL: <https://doi.org/10.1371/journal.pcbi.0010045>.
-  Jiang, Yuxiang et al. (Dec. 2016). "An expanded evaluation of protein function prediction methods shows an improvement in accuracy". In: Genome Biology 17.1, p. 184. ISSN: 1474-760X. DOI: 10.1186/s13059-016-1037-6. URL: <http://genomebiology.biomedcentral.com/articles/10.1186/s13059-016-1037-6>.



Oliver, Stephen (Feb. 2000). “Guilt-by-association goes global”. In: Nature 403.6770, pp. 601–602. ISSN: 0028-0836. DOI: 10.1038/35001165. URL: <http://www.nature.com/articles/35001165>.



Pesaranghader, Ahmad et al. (May 2016). “simDEF: definition-based semantic similarity measure of gene ontology terms for functional similarity analysis of genes”. In: Bioinformatics 32.9, pp. 1380–1387. ISSN: 1367-4803. DOI: 10.1093/bioinformatics/btv755. URL: <https://academic.oup.com/bioinformatics/article-lookup/doi/10.1093/bioinformatics/btv755>.



Piovesan, Damiano et al. (July 2015). “INGA: protein function prediction combining interaction networks, domain assignments and sequence similarity”. In: Nucleic Acids Research 43.W1, W134–W140. ISSN: 0305-1048. DOI: 10.1093/nar/gkv523. URL: <https://academic.oup.com/nar/article-lookup/doi/10.1093/nar/gkv523>.



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>.

Example of GO term

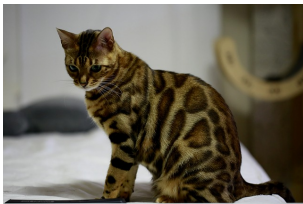
Accession	GO:0060047
Name	heart contraction
Ontology	biological_process
Synonyms	heart beating, cardiac contraction, hemolymph circulation
Alternate	IDs None
Definition	The multicellular organismal process in which the heart decreases in volume in a characteristic way to propel blood through the body. 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

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

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)

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

Result: An annotated tree

for $n \in \text{PostOrder}(N)$ 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

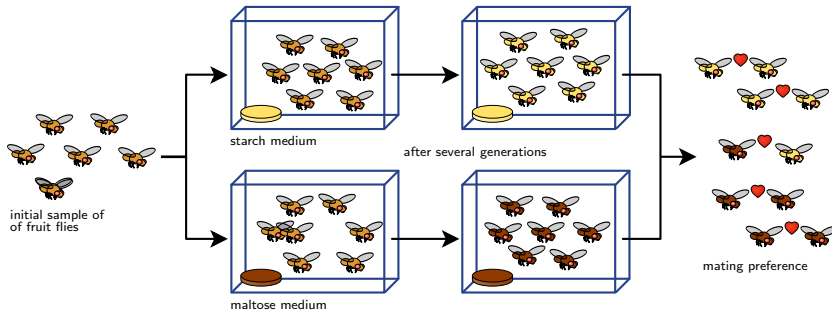


Figure 4 Dodd 1989: After one year of isolation, flies showed a significant level of assortativity in mating (wikimedia)

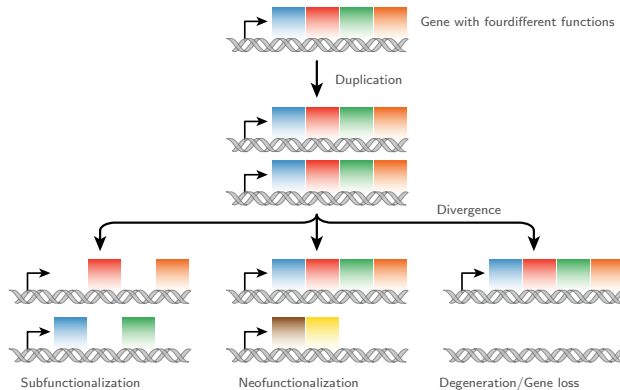


Figure 5 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

- ▶ 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 Posteriori, 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

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

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)

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

