Statistical and computational methods for bioinformatics and social network analysis

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

George G Vega Yon

University of Southern California, Department of Preventive Medicine

October 9, 2019

Motivation

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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.

Contents

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What are Exponential Random Graph Models

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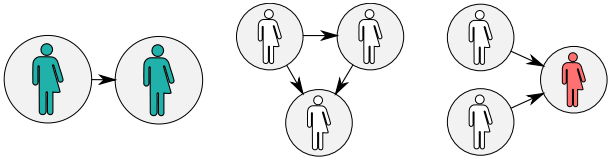
- Statistical models of (social) networks

What are Exponential Random Graph Models

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 the data-generating process



ERGMs (cont'd)

A vector of model parameters

A vector of sufficient statistics

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

Observed data

The normalizing constant

All possible networks

more on terms

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

more on terms

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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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)

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

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

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- 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

ergmito example

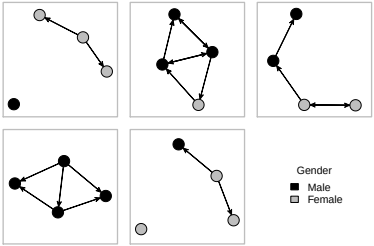

Figure 1 Random sample of 5 networks simulated using a negative

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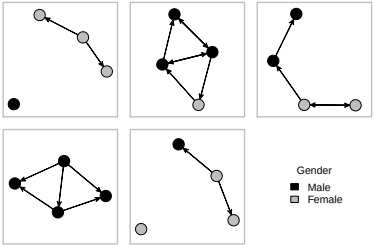

Figure 1 Random sample of 5 networks simulated using a negative

	Edgecount	Full model
Edgecount	-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.

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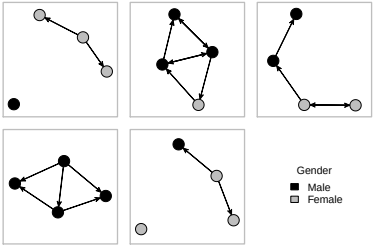

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We performed a large simulation study ▸ more comparing MC-MLE (ergm) with MLE (ergmito).

Paper 1 Simulation Studies: Empirical Type I error

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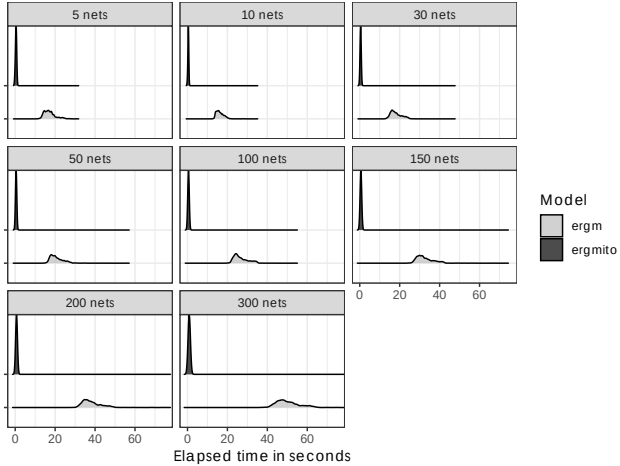
		P(Type I error)		
Sample size	N. Simulations	MC-MLE	MLE	chi2
5	2,189	0.084	0.057	11.71 ***
10	2,330	0.070	0.045	12.46 ***
15	2,395	0.084	0.066	5.55 *
20	2,430	0.074	0.060	3.58
30	2,460	0.057	0.052	0.67
50	2,495	0.046	0.044	0.17
100	2,499	0.048	0.048	0.00

Table 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

Paper 1: Exponential Random Graph Models for Small Networks

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Key takeaways

- New extension of ERGMs using exact statistics for small networks (families, teams, ego-centered, etc.)

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- Revisit measurment of goodness-of-fit.

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

Contents

Gene functions

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The Gene Ontology

- Three domains: Cellular component, molecular function, biological process.

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

Gene Functional Annotations: The Gene Ontology Project

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

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You know what is interesting about this function?

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

pthr10037

pthr11521

pthr11521

pthr24356

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

pthr10037

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Phylogenetic Trees

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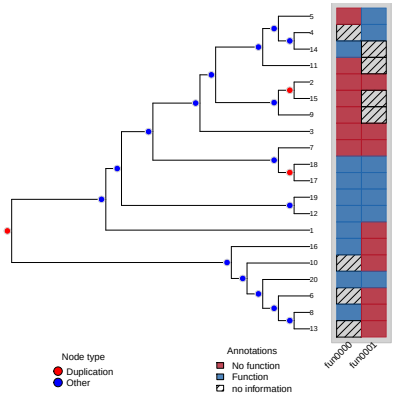

Figure 2 Random annotated phylogenetic tree.

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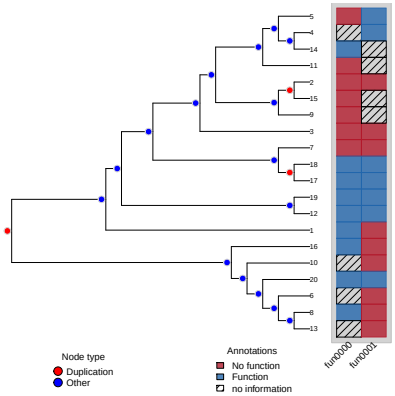
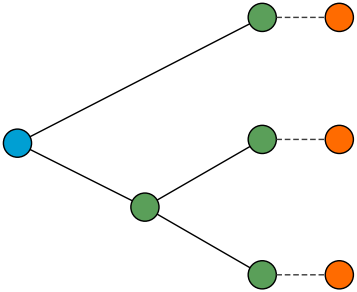


Figure 2 Random annotated phylogenetic tree.

We can use the evolutionary tree to infer presence/absence of gene functions!

An evolutionary model of gene functions



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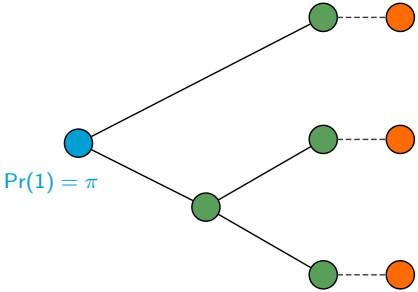

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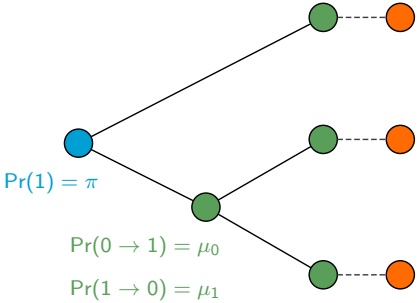

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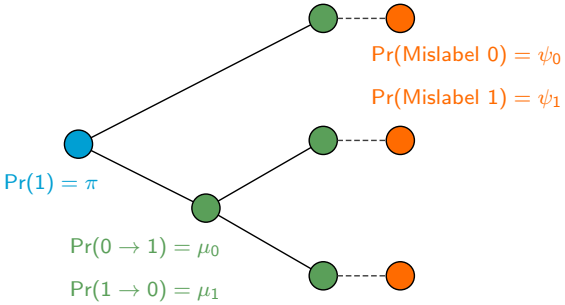
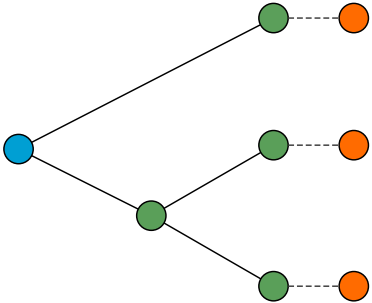
- There's a chance of error.



An evolutionary model of gene functions (cont'd)



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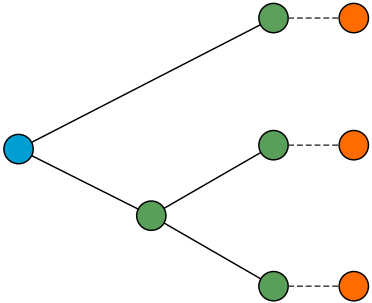

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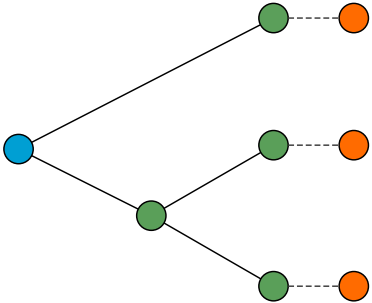

- Gain and loss also depend on the type of the parent node speciation vs duplication
- We use Felsensteins' pruning algorithm ▸ algorithmic view (linear complexity)
- Full framework has been implemented in the `aphylo` R package ▸ more.

Prediction with real data

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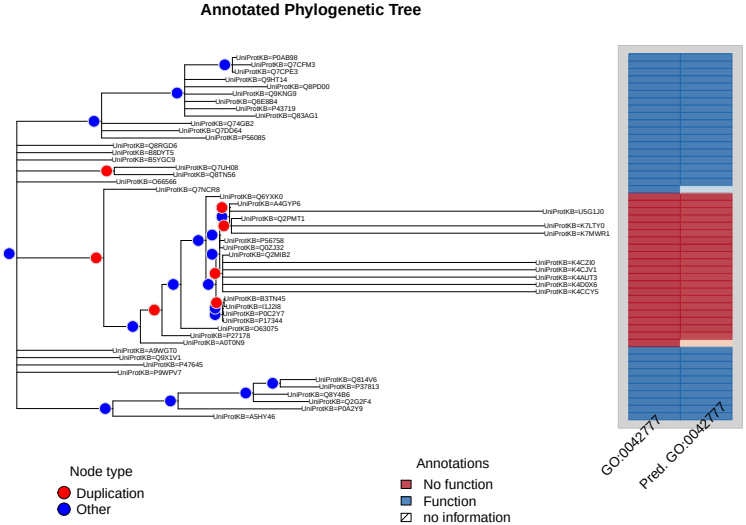
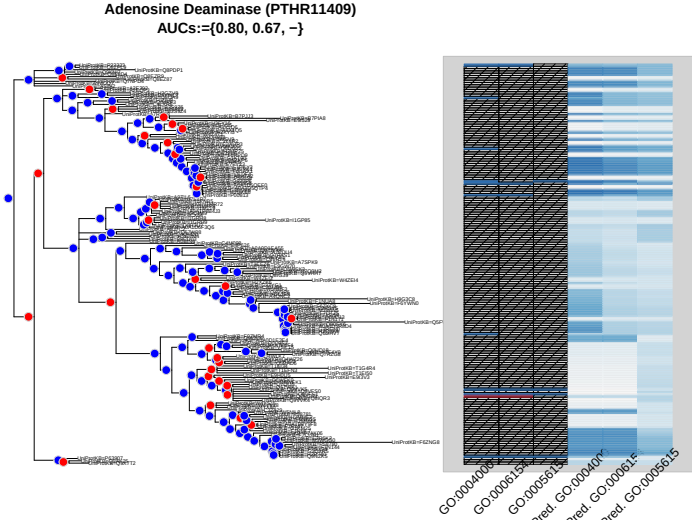
	(1)	(2)	**(3)**	**(4)**	(5)	(6)	(7)	(8)
ψ_0	0.00	0.00	**0.23**	**0.25**	0.00	0.00	0.21	0.25
ψ_1	0.00	0.00	**0.01**	**0.01**	0.00	0.00	0.00	0.01
μ_{d0}	0.01	0.01	**0.97**	**0.96**	1.00	0.01	1.00	0.98
μ_{d1}	0.01	0.02	**0.52**	**0.58**	0.25	0.02	0.51	0.58
μ_{s0}	0.00	0.00	**0.05**	**0.06**	0.07	0.00	0.05	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 4 Parameter estimates using different estimation methods, priors, and types of annotations.

Prediction with real data: Leave-one-out



Prediction with real data: Out-of-sample prediction



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

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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.

Statistical and computational methods for bioinformatics and social network analysis

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University of Southern California, Department of Preventive Medicine

October 9, 2019

Thanks!

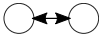
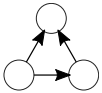
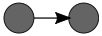
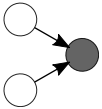
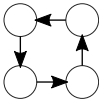
Here are some by-products of my research here at USC

- 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

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

- 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

We performed a simulation study with the following features:

- Draw 20,000 samples of groups of small networks

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- Each group could have from 5 to 300 small networks
- We estimated the models using MC-MLE and MLE.

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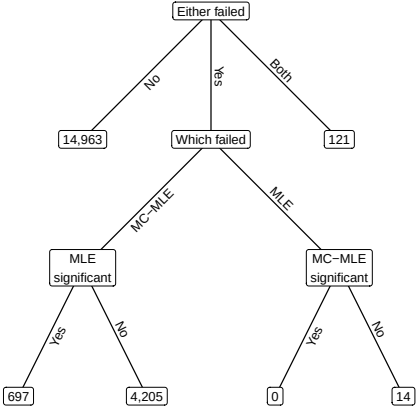
Paper 1 Simulation Studies: Error rate



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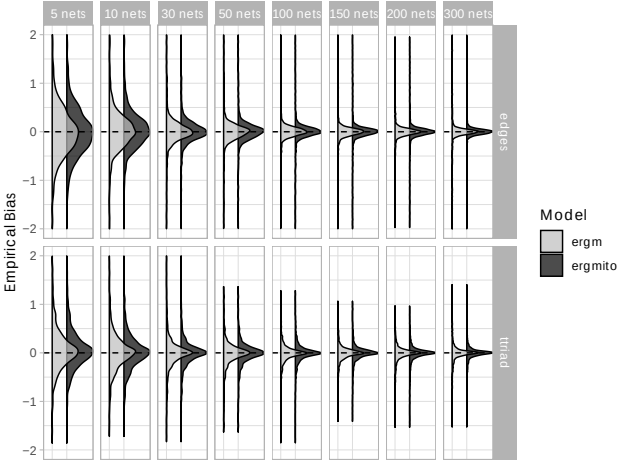
Paper 1 Simulation Studies: Empirical Bias



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An evolutionary model of gene functions (algorithmic view)

Keck School of Medicine of USC

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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Speciation

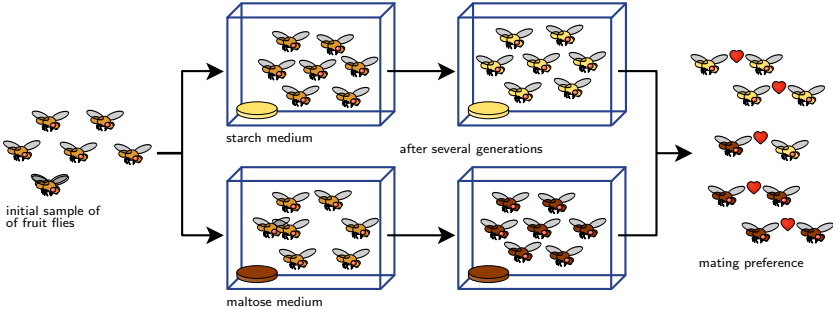

Figure 3 Dodd (1989): After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

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Duplication

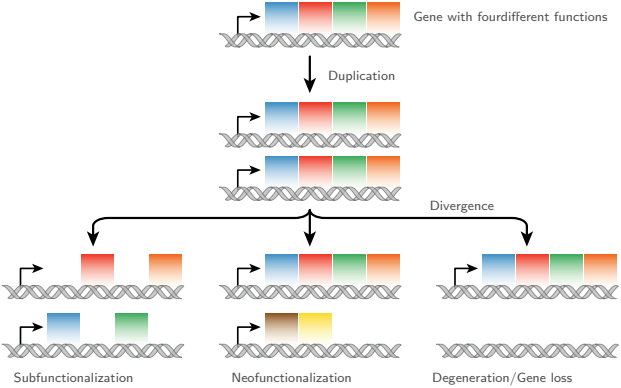

Figure 4 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

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The aphylo

Keck School of Medicine of USC

- Pruning algorithm implemeted in C++ using the `pruner` template library (implemeted 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 implemeted as part of this project)

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