



## 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.

Paper 1: Exponential Random Graph Models for Small Networks

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

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

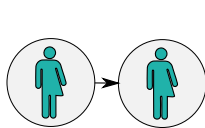
# What are Exponential Random Graph Models

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

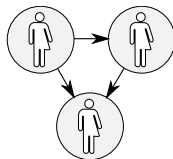
- Statistical models of (social) networks

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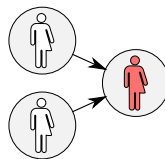
- ▶ Statistical models of (social) networks
- ▶ In simple terms: statistical inference on what network patterns/structures/motifs govern social networks



Homophily



Transitive Triad



Popularity

A vector of  
model parameters

A vector of  
sufficient statistics

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

Observed data

The normalizing  
constant

All possible  
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► more on terms



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Observed data

The normalizing constant

All possible networks

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

► more on terms



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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- ▶ 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?

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We see small networks everywhere

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- Families and friends

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- ▶ Families and friends
- ▶ Small teams



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





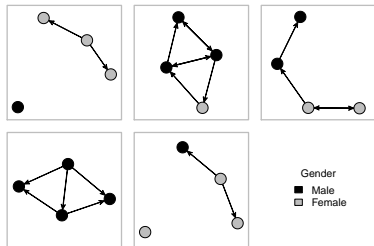
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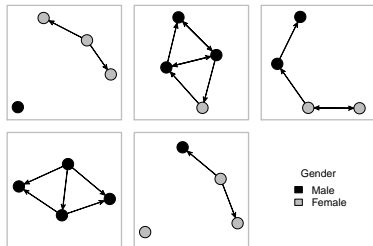
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- ▶ For example, a network with 5 nodes has 1,048,576 unique configurations.
- ▶ This allow us to directly compute **the normalizing constant**.
- ▶ Using the exact likelihood opens a huge window of methodological-possibilities.
- ▶ We implemented this and more in the `ergmito` R package [▶ more](#)



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



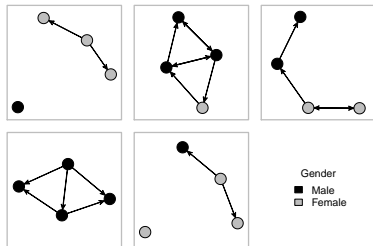
**Figure 1** Random sample of 5 networks simulated using the ergmito package

	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 1** Fitted ERGMitos using the fivenets dataset.





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

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

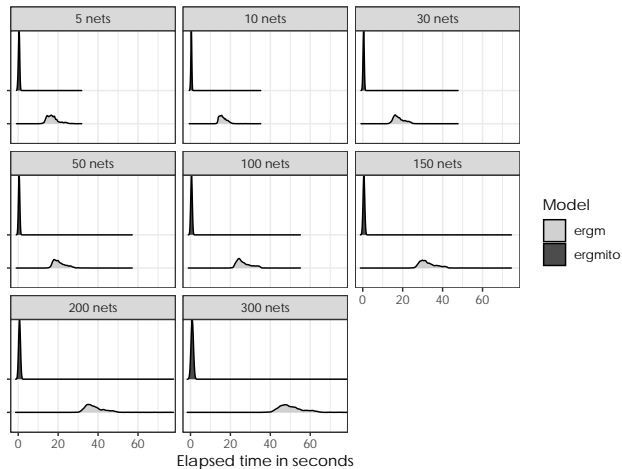
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**Table 1** Fitted ERGMitos using the fivenets dataset.

Sample size	N. Simulations	P(Type I error)		$\chi^2$
		MC-MLE ( <i>ergm</i> )	MLE ( <i>ergmito</i> )	
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  $\chi^2$  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.



## Key takeaways

- ▶ New extension of ERGMs using exact statistics for small networks (families, teams, etc.)
- ▶ Performance: Same (un)bias, Lower Type I error rates, (way) faster.
- ▶ Opens the door the new methods, e.g. Mixed effects, LRT, etc.

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## Next steps

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

Paper 1: Exponential Random Graph Models for Small Networks

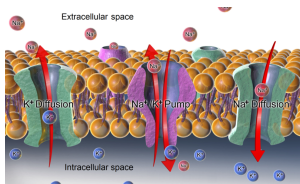
Paper 2: On the prediction of gene functions using phylogenetic trees

How we organize the information about genes (according to the Gene Ontology Project)

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### Molecular function

Active transport GO:0005215

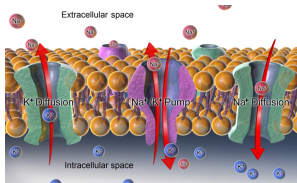




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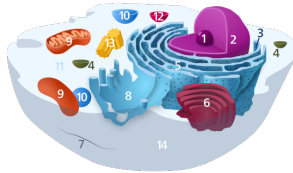
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### Cellular component

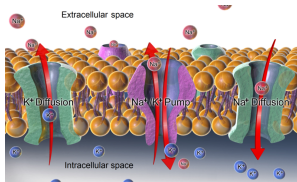
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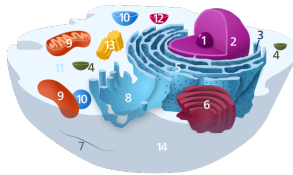
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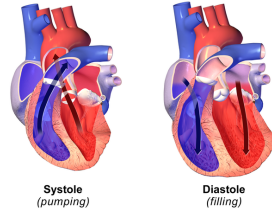
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### Biological process

Heart contraction GO:0060047



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

## Example of GO term

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<b>Accession</b>	GO:0060047
<b>Name</b>	heart contraction
<b>Ontology</b>	biological_process
<b>Synonyms</b>	heart beating, cardiac contraction, hemolymph circulation
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You know what is interesting about this function?

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



*Felis catus* pthr10037



*Oryzias latipes* pthr11521



*Anolis carolinensis* pthr11521



*Equus caballus* pthr24356



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



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- It can be very general: think of the tree of life

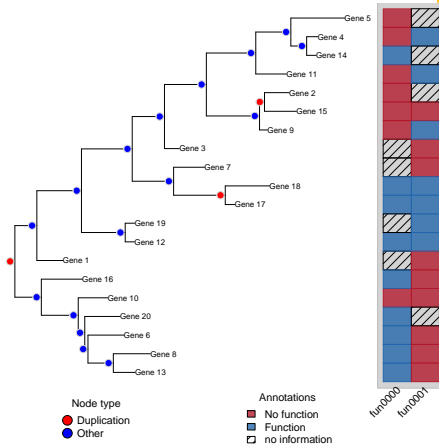
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# Phylogenetic Trees: The PANTHER classification system

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**Figure 2** Random annotated phylogenetic tree.

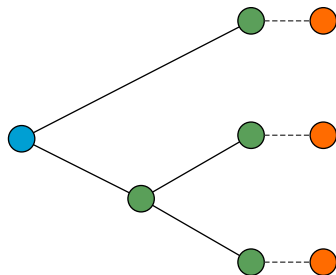
We can use

the evolutionary tree

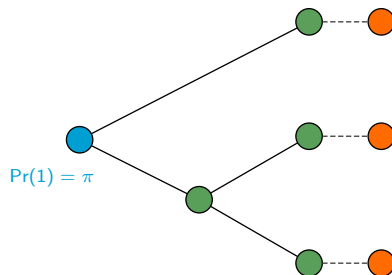
to infer presence/absence of

gene functions (annotations)!



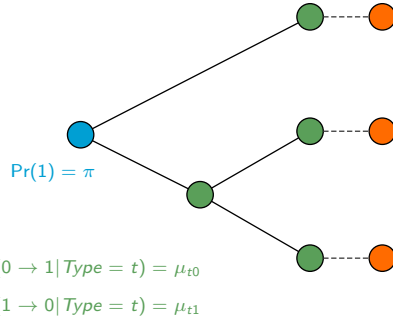


- Initial (spontaneous) gain of function.



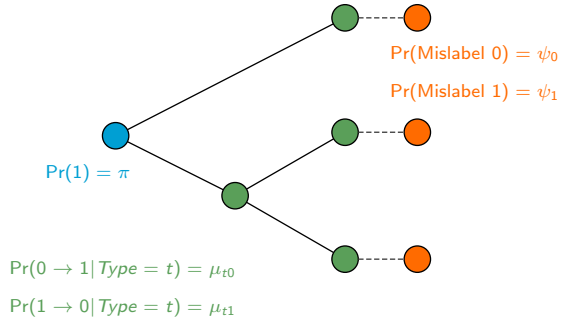
# An evolutionary model of gene functions

- ▶ Initial (spontaneous) gain of function.
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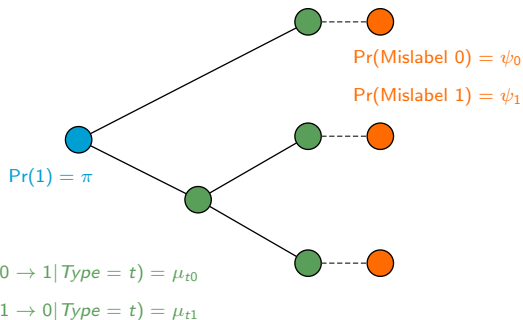
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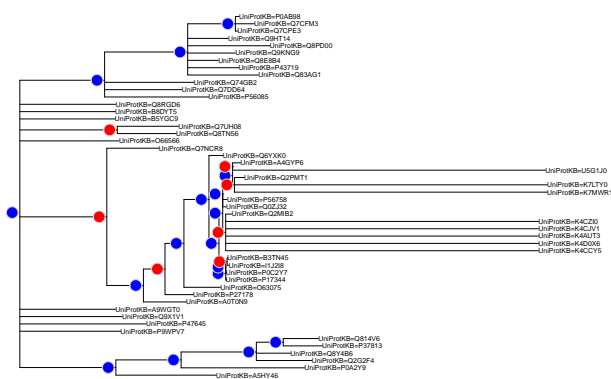


We implemented the model using Felsenstein's' pruning algorithm (linear complexity) in the R package `aphylo` [▶ more](#).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
$\psi_0$	0.00	0.00	<b>0.23</b>	<b>0.25</b>	0.00	0.00	0.21	0.25
$\psi_1$	0.00	0.00	<b>0.01</b>	<b>0.01</b>	0.00	0.00	0.00	0.01
$\mu_{d0}$	0.01	0.01	<b>0.97</b>	<b>0.96</b>	1.00	0.01	1.00	0.98
$\mu_{d1}$	0.01	0.02	<b>0.52</b>	<b>0.58</b>	0.25	0.02	0.51	0.58
$\mu_{s0}$	0.00	0.00	<b>0.05</b>	<b>0.06</b>	0.07	0.00	0.05	0.06
$\mu_{s1}$	0.01	0.01	<b>0.01</b>	<b>0.02</b>	0.01	0.01	0.01	0.02
$\pi$	0.81	0.91	<b>0.78</b>	<b>0.45</b>	0.82	0.91	0.83	0.49
Tree count	88	88	<b>141</b>	<b>141</b>	88	88	141	141
Method	MCMC	MCMC	<b>MCMC</b>	<b>MCMC</b>	MLE	MLE	MLE	MLE
Prior	Uniform	Beta	<b>Uniform</b>	<b>Beta</b>	Uniform	Beta	Uniform	Beta
Inferred	Yes	Yes	<b>No</b>	<b>No</b>	Yes	Yes	No	No
AUC	1.00	1.00	<b>0.69</b>	<b>0.67</b>	0.98	1.00	0.70	0.67
P. Score (obs)	1.00	1.00	<b>0.81</b>	<b>0.81</b>	0.92	1.00	0.81	0.81
P. Score (random)	0.71	0.71	<b>0.61</b>	<b>0.61</b>	0.71	0.71	0.61	0.61

**Table 4** Parameter estimates using different estimation methods, priors, and types of annotations.

Annotated Phylogenetic Tree

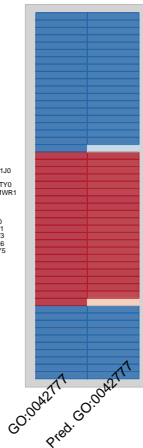


Node type

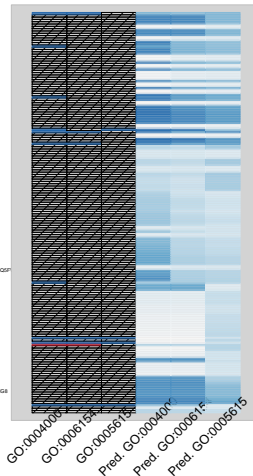
- Duplication
- Other

Annotations

- No function
- Function
- no information



**AUCs:={0.80, 0.67, -}**





### Key takeaways

- ▶ (Yet another) model for predicting gene functions using phylogenetics.
- ▶ Big difference... computationally scalable.
- ▶ Meaningful biological results.
- ▶ Preliminary accuracy results comparable to state-of-the-art phylo-based models.

### Key takeaways

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### Next steps

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

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

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

# 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 10, 2019




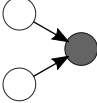

# Thanks!

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

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,  $\theta_t$
  - 2.2 Using the law of large numbers, approximate the ratio of likelihoods based on the parameter  $\theta_t$ , this is the objective function
  - 2.3 Update the parameter by a Newton-Raphson step
  - 2.4 Next iteration

◀ go back

- ▶ 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!

◀ go back



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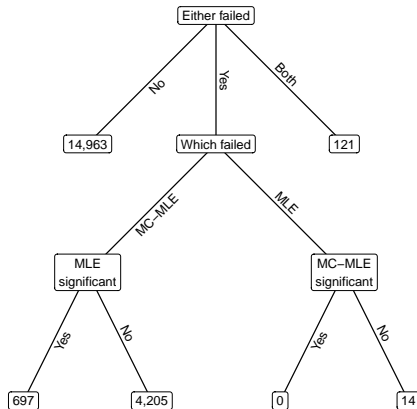
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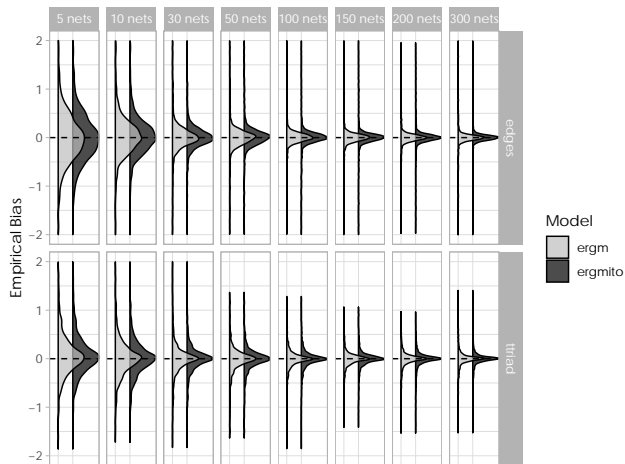
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- ▶ We estimated the models using MC-MLE and MLE.

◀ 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  $\pi$ ;

        case *interior node* do

            if *Parent has the function* then Keep it with prob.  $(1 - \mu_1)$ ;

            else Gain it with prob.  $\mu_0$ ;

    end

**Finally, we allow for mislabeling;**

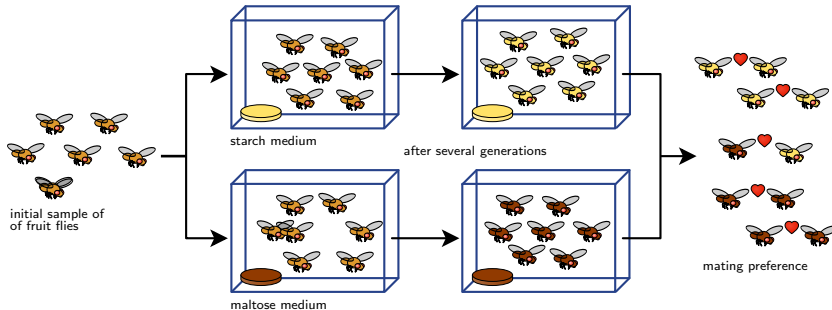
    if *n is leaf* then

        if *has the function* then Mislabel with prob.  $\psi_1$ ;

        else Mislabel with prob.  $\psi_0$ ;

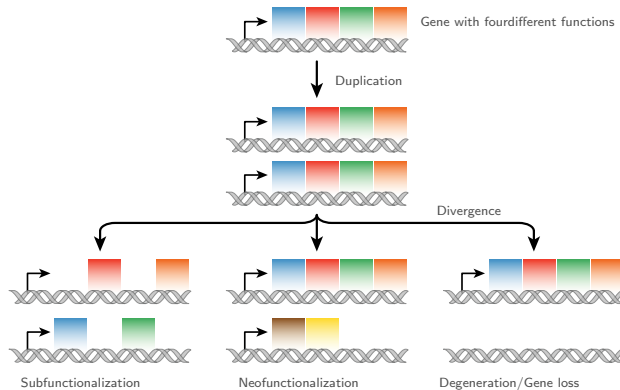
end

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





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

- ▶ Pruning algorithm implemented in C++ using the `pruner` template library (implemented in this project).
- ▶ The estimation is done using either Maximum Likelihood, Maximum A Posteriory, or MCMC.
- ▶ The MCMC estimation is done via the `fmcmc` R package using adaptive MCMC (also implemented as part of this project)

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