

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:

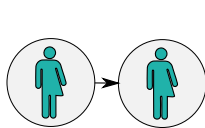
What are Exponential Random Graph Models

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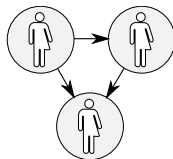
- Statistical models of (social) networks

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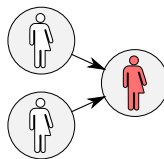
- ▶ Statistical models of (social) networks
- ▶ In simple terms: statistical inference on what network patterns/structures/motifs govern social networks



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 networks

► more on terms

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The normalizing constant

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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)
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What about small networks?

Do we care about small networks?

We see small networks everywhere

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We see small networks everywhere

- 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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- ▶ 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](#)

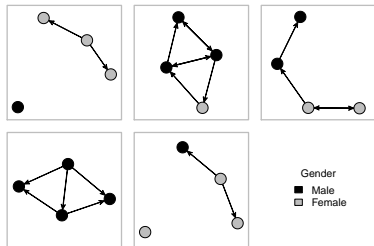


Figure 1 Random sample of 5 networks simulated using the ergmito package

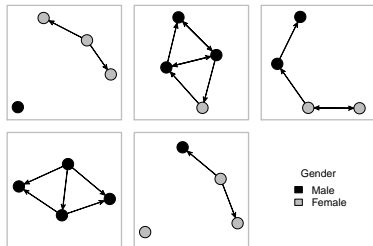


Figure 1 Random sample of 5 networks simulated using the ergmito package

	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.

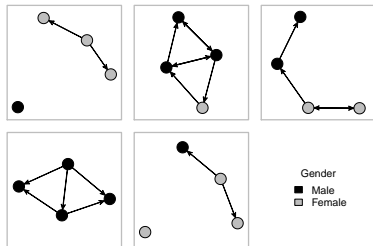


Figure 1 Random sample of 5 networks simulated using the ergmito package

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

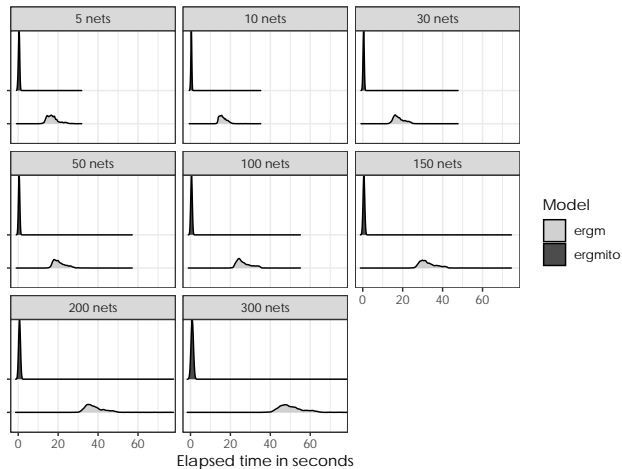
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Table 1 Fitted ERGMitos using the fivenets dataset.

Sample size	N. Simulations	P(Type I error)		χ^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 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.



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

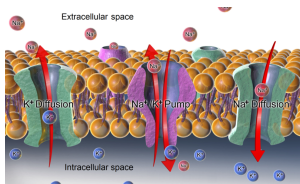
Paper 2: On the prediction of gene functions using phylogenetic trees

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

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Molecular function

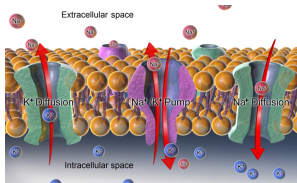
Active transport GO:0005215



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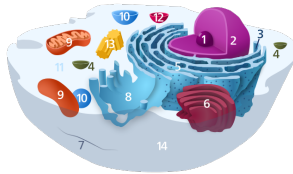
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Cellular component

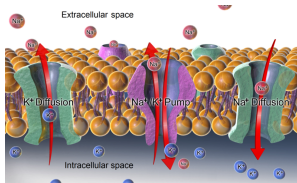
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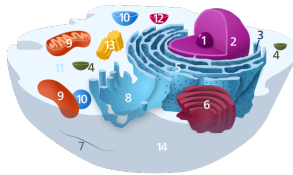
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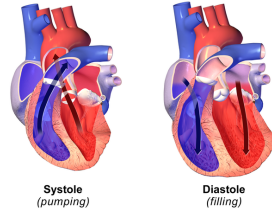
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Biological process

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

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

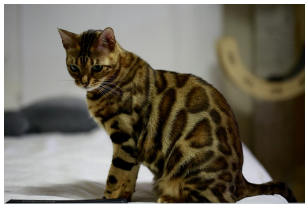
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You know what is interesting about this function?

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



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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Phylogenetic Trees: The PANTHER classification system

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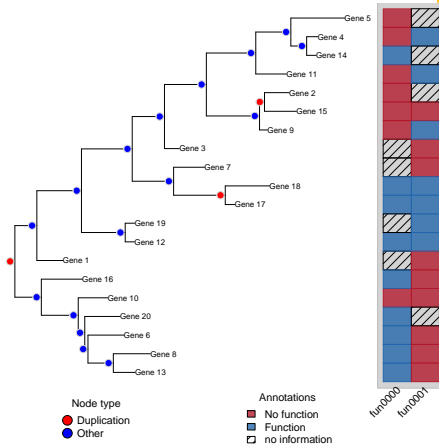
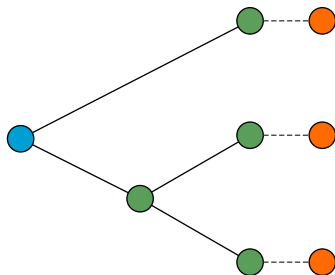
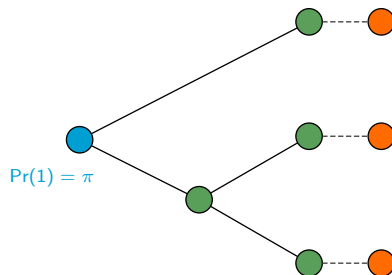


Figure 2 Random annotated phylogenetic tree.

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

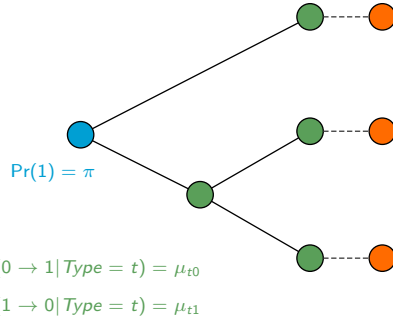


- Initial (spontaneous) gain of function.



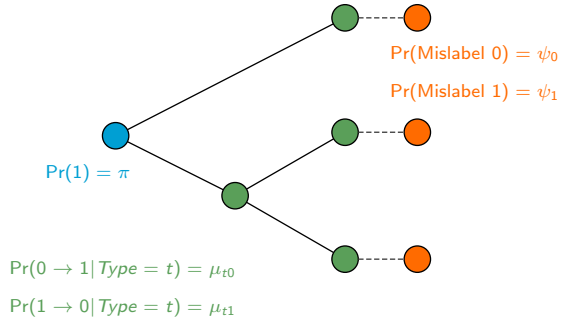
An evolutionary model of gene functions

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- ▶ Loss/gain of offspring depends on: (a) the state of its' parents (**Markov process**), and (b) the type of node [▶ more](#)



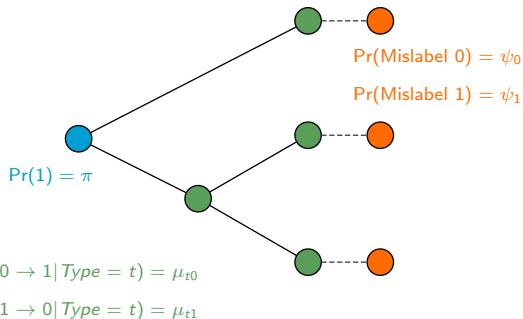
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We implemented the model using Felsenstein's' pruning algorithm (linear complexity) in the R package `aphylo` [▶ more](#).

	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
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.

UniProtKB=Q0A98
UniProtKB=Q7CFM3
UniProtKB=Q7CPE3
UniProtKB=Q9HT14
UniProtKB=Q8PDD0
UniProtKB=Q9KNG9
UniProtKB=Q8E8B4
UniProtKB=P43719
UniProtKB=Q83AG1

UniProtKB=Q74GB2
UniProtKB=Q7DC64
UniProtKB=P360B5

UniProtKB=Q8RGD6
UniProtKB=B8DYT5
UniProtKB=B5YGC3

UniProtKB=Q7UH08
UniProtKB=Q8TN56
UniProtKB=C66566

UniProtKB=Q7NCR8

UniProtKB=Q6YXK0
UniProtKB=A4GY6
UniProtKB=Q2PMT1

UniProtKB=U5GJ10
UniProtKB=K7LTY0
UniProtKB=K7MWVR

UniProtKB=P56758
UniProtKB=Q0ZJ32
UniProtKB=Q2MB2

UniProtKB=K4CZ10
UniProtKB=K4CJV1
UniProtKB=K4AULT3
UniProtKB=K4CX6
UniProtKB=K4CCY5




UniProtKB=B3TN45
UniProtKB=L1228
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UniProtKB=C63075
UniProtKB=P22778
UniProtKB=AOTN09

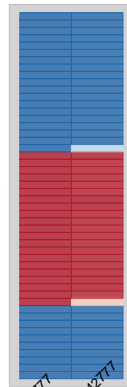
UniProtKB=A9WGTO
UniProtKB=G0K1V1
UniProtKB=P47645
UniProtKB=P9WPV7

UniProtKB=Q814V6
UniProtKB=P37813
UniProtKB=C8Y4B6
UniProtKB=Q2G2F4
UniProtKB=P0AZY9

UniProtKB=ASHY46

● Duplication
● Other

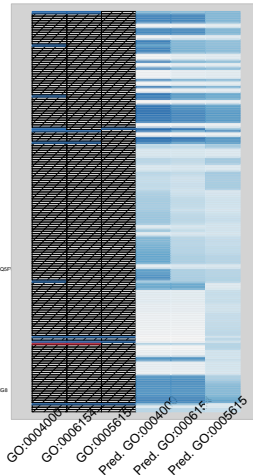
-  No function
-  Function
-  no information



GO:0042777

Pred. GO:0042777

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.

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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




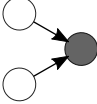

Thanks!

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, 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

◀ 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

We performed a simulation study with the following features:

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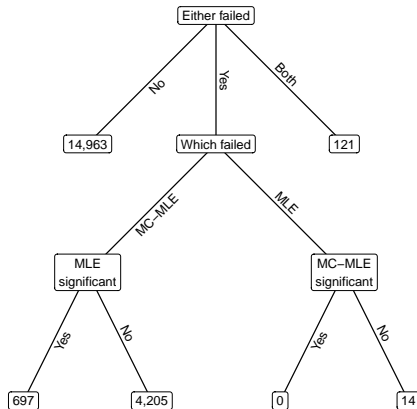
- ▶ Draw 20,000 samples of groups of small networks
- ▶ Each group had prescribed: (model parameters, number of networks, sizes of the networks)
- ▶ Each group could have from 5 to 300 small networks

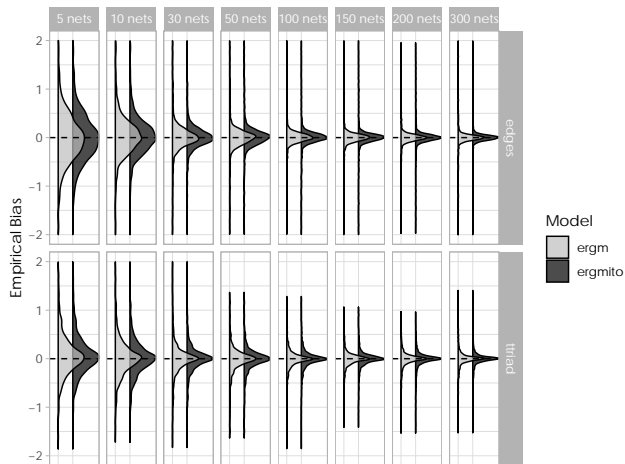
◀ go back

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





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

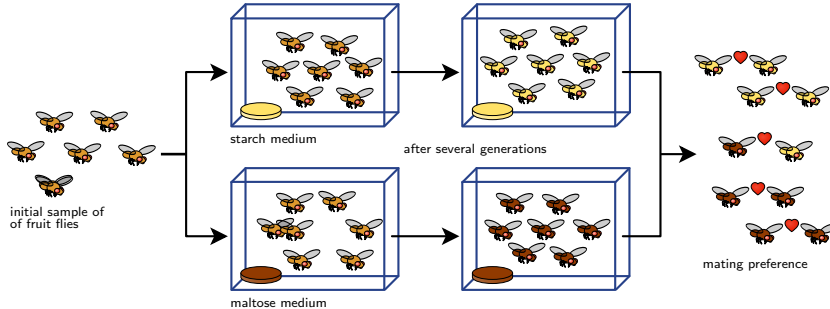


Figure 3 11989DoddDodd (): After one year of isolation, flies showed a significant level of assortativity in mating (wikimedia)

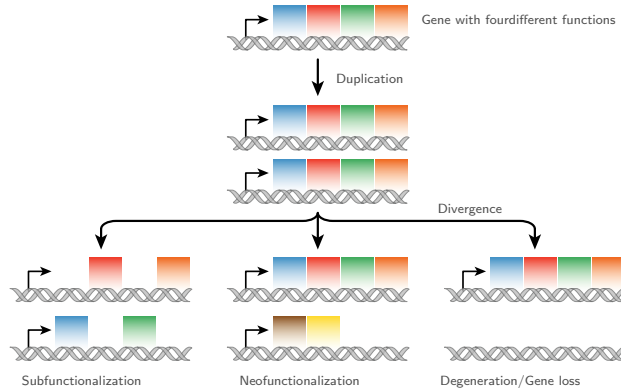


Figure 4 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

- ▶ Pruning algorithm implemented in C++ using the `pruner` template library (implemented in this project).
- ▶ The estimation is done using either Maximum Likelihood, Maximum A Posteriori, 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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