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

January 30, 2020

Keck School of Medicine of USC

On the prediction of gene functions using phylogenetic trees

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

Genes

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

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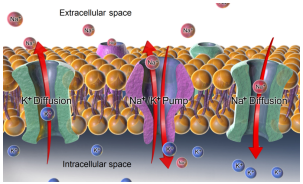
Molecular function

Active transport GO:0005215



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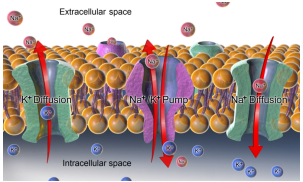
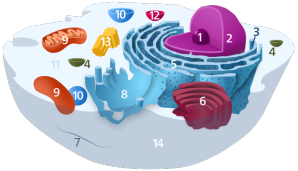


Cellular component

Mitochondria GO:0004016



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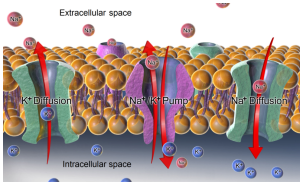

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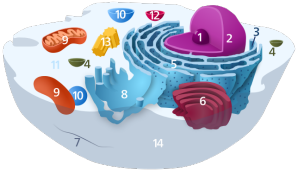
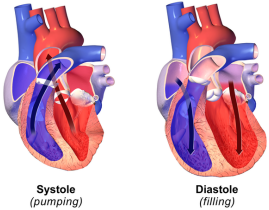


Biological process

Heart contraction GO:0060047



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GENEONTOLOGY
Unifying Biology

- The GO project has $\sim$ 44,700 validated terms more, $\sim$ 7.3M annotations on $\sim$ 4,500 species.

source: Statistics from `pantherdb.org` and `geneontology.org`

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The Gene Ontology Project

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- 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 across species).

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

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

go back

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

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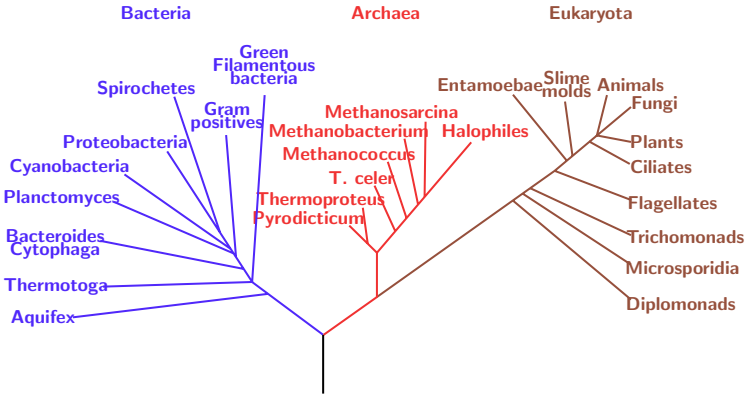

Figure 1 A phylogenetic tree of living things, based on RNA data and proposed by Carl Woese, showing the separation of bacteria, archaea, and eukaryotes (wiki)

Phylogenetic Trees: The PANTHER classification system

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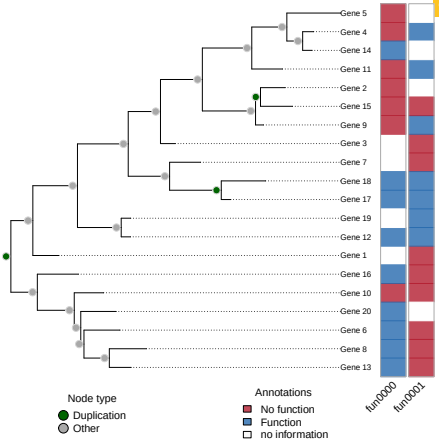


Figure 2 Simulated phylogenetic tree and gene annotations.

Speciation

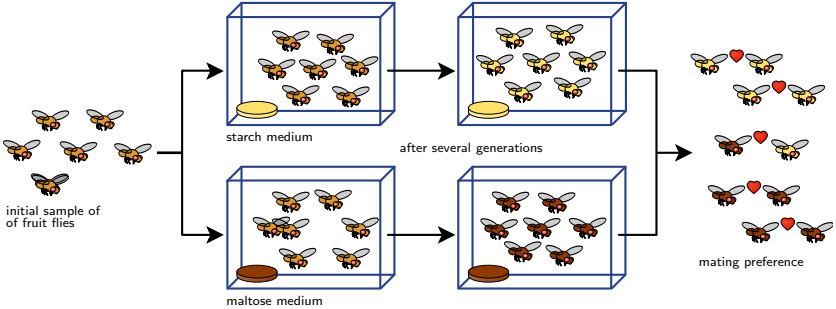


Figure 3 Dodd 1989: After one year of isolation, flies showed a significant level or assortativity in mating (wikimedia)

go back

Duplication

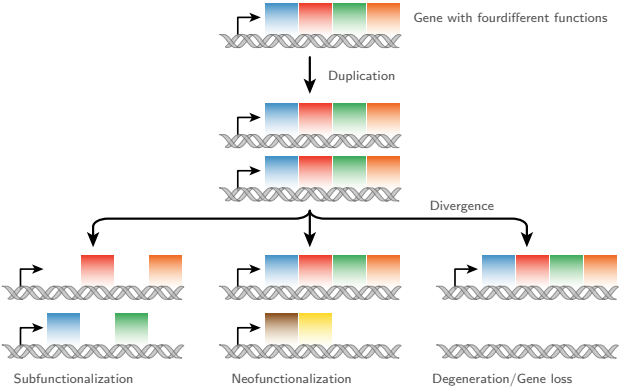


Figure 4 A key part of molecular innovation, gene duplication provides opportunity for new functions to emerge (wikimedia)

go back

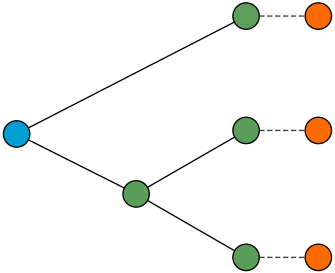
We can use

evolutionary trees

to inform a model for predicting

genetic annotations!

An evolutionary model of gene functions



other models

other view

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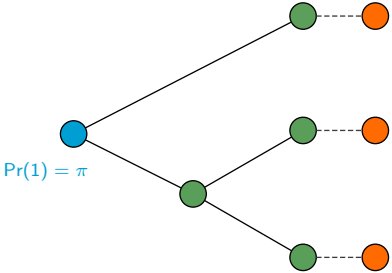

other models | other view

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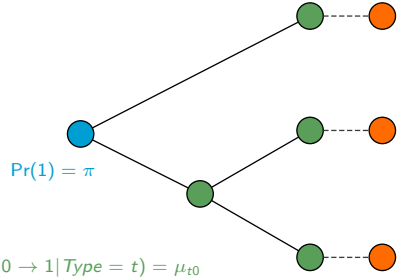

$\Pr(0 \to 1 | \mathit{Type} = t) = \mu_{t0}$

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

other models
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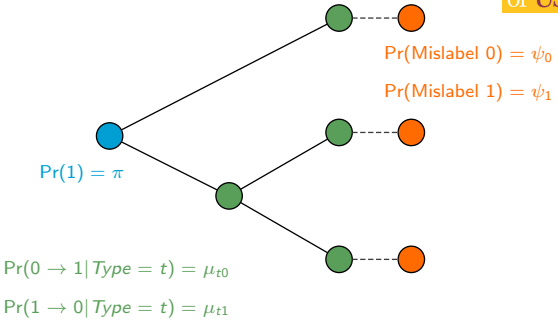

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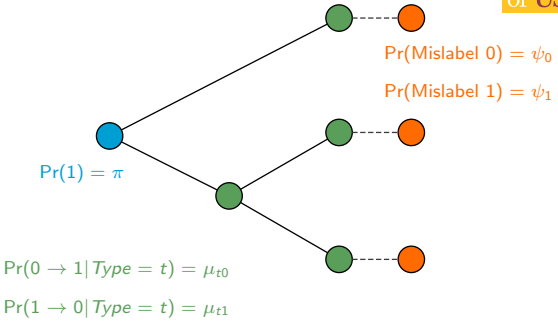

We implemented the model using Felsenstein's' pruning algorithm (linear complexity) in the R package `aphylo`.

other models
other view

The `aphylo` R package

- Simulation and visualization of annotated phylogenetic trees.

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  - User-defined transition kernel (in our case, Adaptive Kernel).

Some preliminary results

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

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
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Root node		
π	0.81	0.45
Leave-one-out AUC		
Mean	0.69	0.67
Median	0.81	0.75

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

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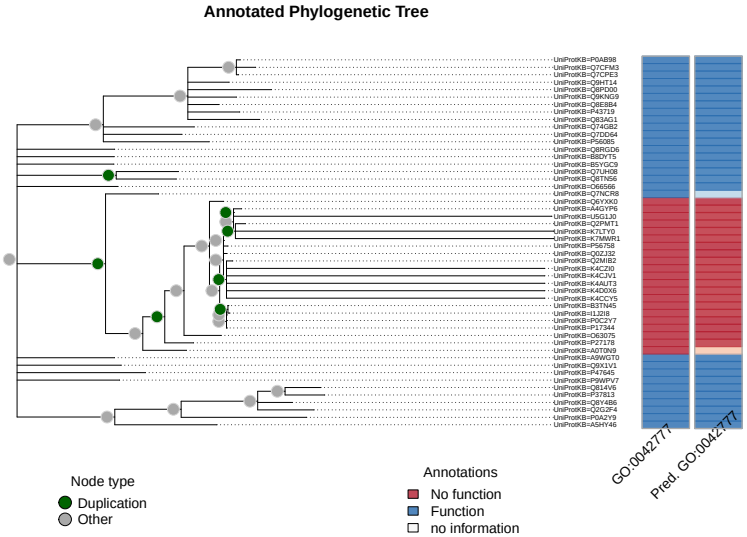
- Took about 5 minutes each.

Prediction with real data: Leave-one-out



Prediction with real data: Out-of-sample prediction

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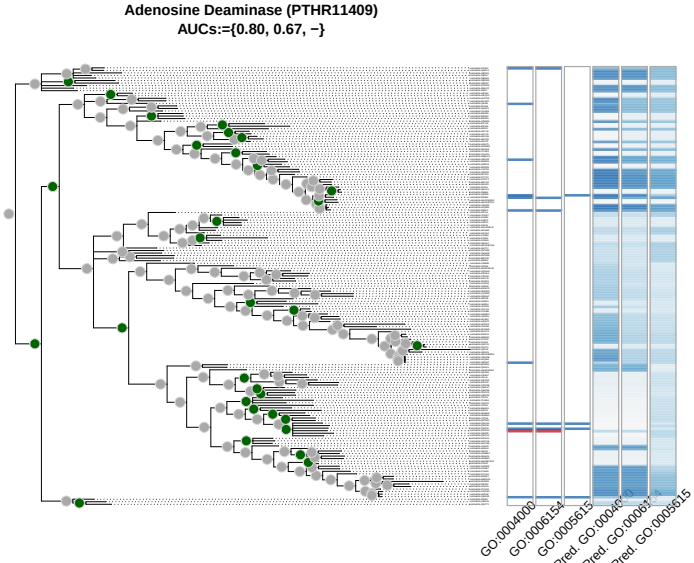

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Key takeaways

- 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.

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Future Research: phylogenetic models

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$$\mathbb{P}\left(\mathbf{X} = \{x_{n1}, x_{n2}, \ldots\} \;\middle|\; x_{\mathbf{p}(n1,\ldots)}\right) = \frac{\exp\left\{\mu^T s(\mathbf{x}|x_{\mathbf{p}(\cdot)})\right\}}{\sum_{\mathbf{x}'} \exp\left\{\mu^T s(\mathbf{x}'|x_{\mathbf{p}(\cdot)})\right\}}$$

  - 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 (finite number of parameters).

Future Research: phylogenetic models

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

			Transitions to	
			Case 1	Case 2
	A	$\begin{bmatrix} 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$
Parent	B	$\begin{bmatrix} 1 \end{bmatrix}$	$\begin{bmatrix} 1 & 0 \end{bmatrix}$	$\begin{bmatrix} 0 & 0 \end{bmatrix}$
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In SIFTER, for modelling 3 functions, we need $2^{2\times 3} = 64$ parameters.

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Thanks!

References I

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Predicting gene functions

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)

Keck School of Medicine of USC

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

Result: An annotated tree

```
for n ∈ 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 − μ1);
            else Gain it with prob. μ0;
    end
    Finally, we allow for mislabeling;
    if n is leaf then
        if has the function then Mislabel with prob. ψ1;
        else Mislabel with prob. ψ0;
end
```

go back

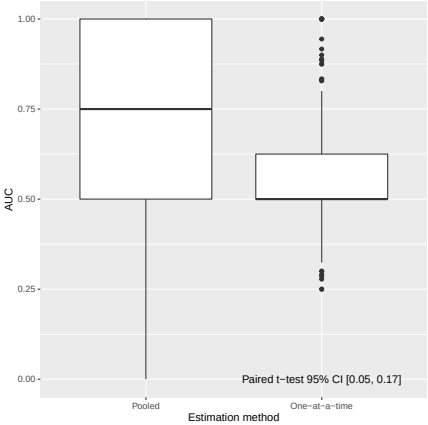

Figure 5 Comparing LOOCV AUC when performing predictions using either the estimates from the pooled model or each trees' own set of estimates obtained when fitting the model individually go back.