Predicting of Gene Functions by Leveraging Biological Insights with Mechanistic Machine Learning

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Division of Epidemiology @ University of Utah

Jan 11th, 2023 @ Data Science Seminar

Collaborators: Paul Thomas, Paul Marjoram, Huaiyu Mi, Christopher Williams (USC), Alun Thomas (UofU)

Table of Contents

You can download the slides from `https://ggv.cl/UofUDS2023`

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But first...

whoami

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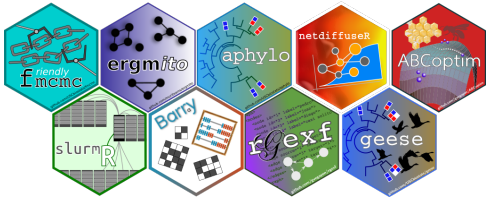

George G. Vega Yon's GitHub Stats

Total Stars Earned:	247
Total Commits (2022):	2.4k
Total PRs:	111
Total Issues:	228
Contributed to:	33

A++

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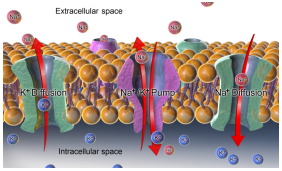
- Scientific software developer (R/C++) with (¿ 500K downloads + 9 CRAN packages).

Table of Contents

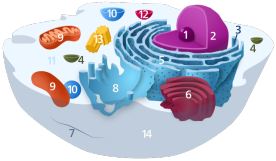
Gene Function

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

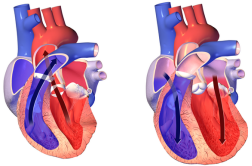
Molecular function
Active transport
GO:0005215



Cellular component
Mitochondria GO:0004016



Biological process
Heart contraction
GO:0060047



Systole *(pumping)*

Diastole *(filling)*

Gene Function: the Gene Ontology Project

- The GO project has $\sim$ 43,000 validated terms, $\sim$ 7.4M annotations on $\sim$ 5,200 species.

source: Statistics from `http://pantherdb.org/panther/summaryStats.jsp` and `http://geneontology.org/stats.html`

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- About $\sim$ 173,000 publications have used the GO.

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Predicting Gene Function: State-of-the-art

Sequences, phylogenomics, and ML.

- **BLAST**:[2] Prediction by sequence homology ($\sim$ 105,000 citations).

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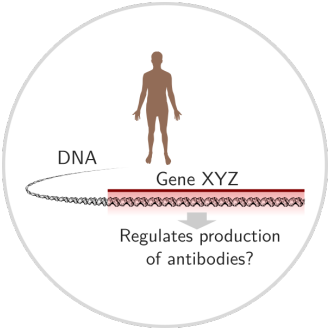
In the latest CAFA, **none** of the top-performing methods scored an AUC above 0.60, and most were outperformed by BLAST,[19] which annotates using homology based on sequence similarity.

Table of Contents

Is gene *XYZ* involved in process *ABC*?



Complex to directly assess

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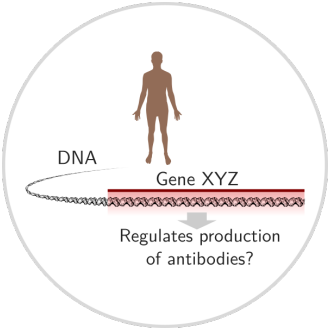

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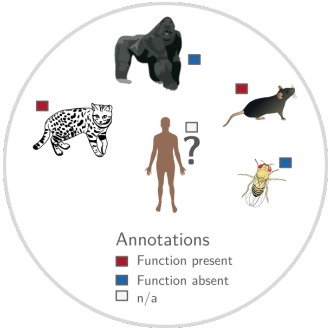

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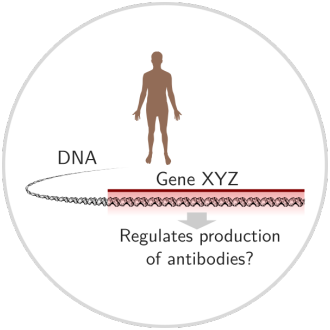

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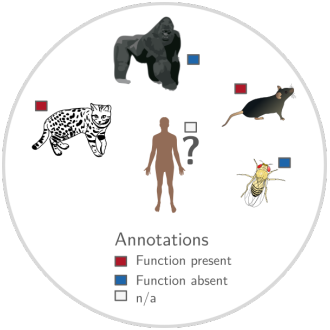

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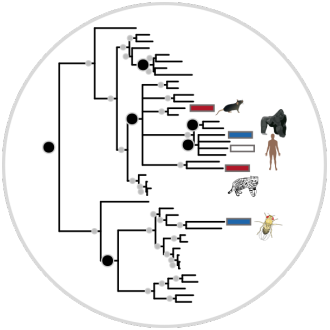


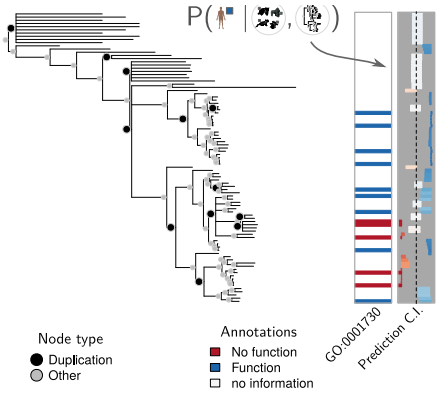
And we further know how these are *evolutionary* connected

Is the human gene **XYZ** involved in process **ABC**, given what we know about that for other *related* species?

Evolution of Gene function (of one function)

Built a big model (lots of trees and annotations) called aphylo:

- Only two sources of data: Phylogenetic tree (`pantherdb.org`) and functional annotations (`geneontology.org`).



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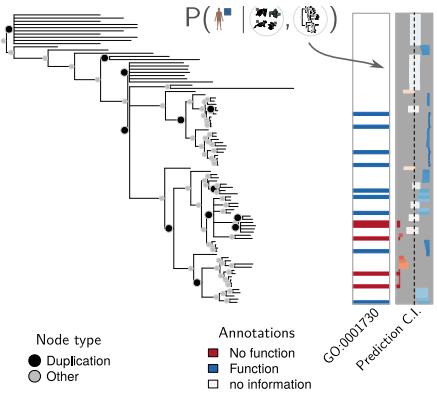

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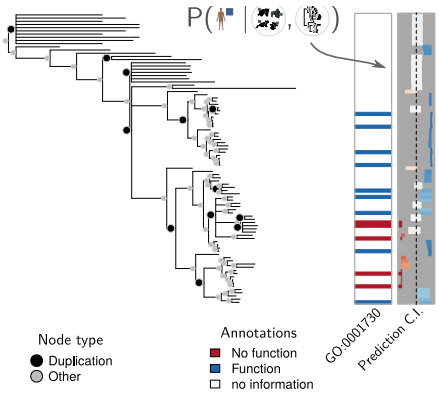

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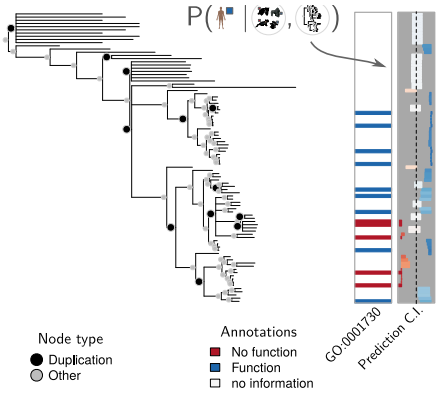
- Fit pooled models featuring thousands of annotations in hundreds of trees (with split-second prediction capability).



... But what if we wanted to deal with multiple functions?

Evolution of Gene function (multiple functions)

Tapping into Evol. Theory

- A fundamental part of Fun. Evol. is Duplication Events.

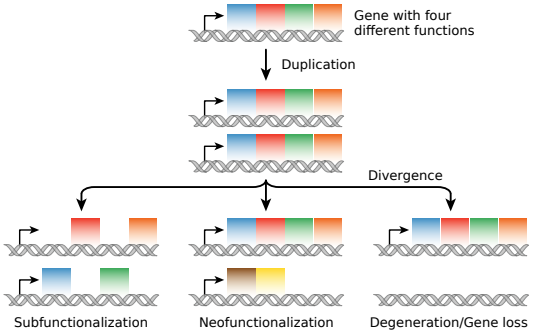


Figure: A key part of molecular innovation, gene duplication provides an opportunity for new functions to emerge (wikimedia)

Evolution of Gene function (multiple functions)

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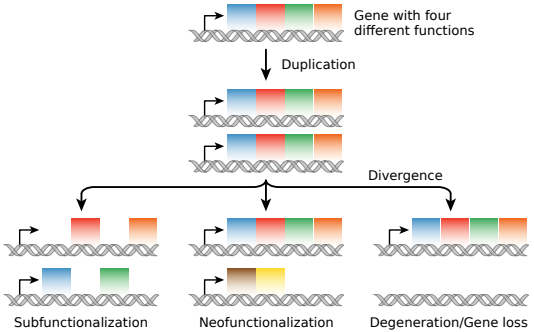
- Furthermore, knowing what happened to gene A (*e.g.*, neofunctionalization) is highly informative to learn about the functional state of B.



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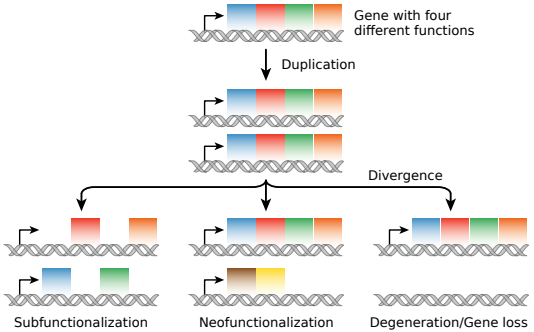
- A fundamental part of Fun. Evol. is Duplication Events.
- Furthermore, knowing what happened to gene A (*e.g.*, neofunctionalization) is highly informative to learn about the functional state of B.
- One way to model this is using a Markov Transition Model (as in SIFTER).



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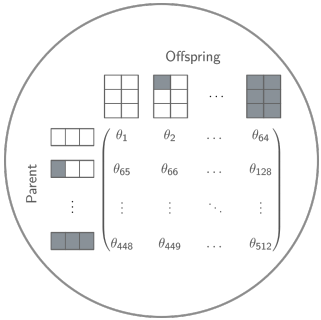
Evolution of Gene function (multiple functions)

If we wanted to build a model with 3 functions, we would need to estimate...

Full Markov Transition Matrix



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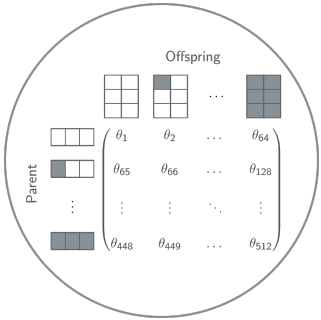

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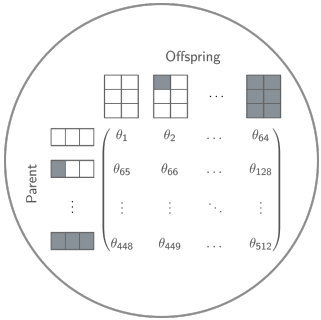

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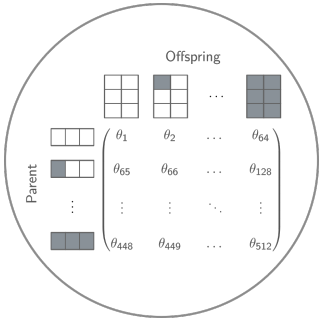

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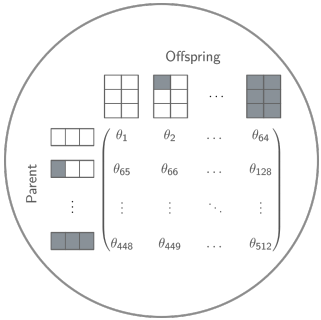

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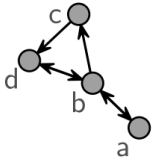
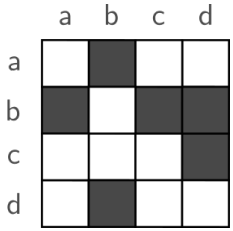
Social Network Analysis may help us...

Exponential Random Graph Models (ERGMs)

Social Network





Exponential Random Graph Models (ERGMs)

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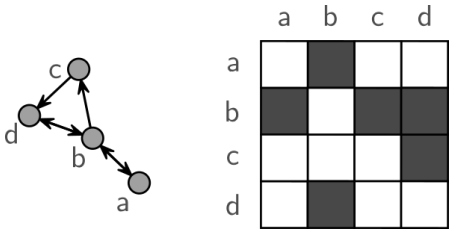

- Not about individual ties.

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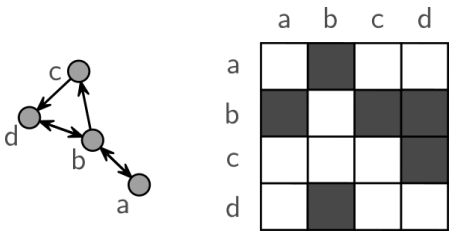

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- Statistical inference on *motifs* (triangles, dyads, homophily, etc.)

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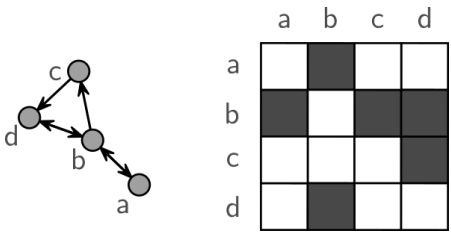

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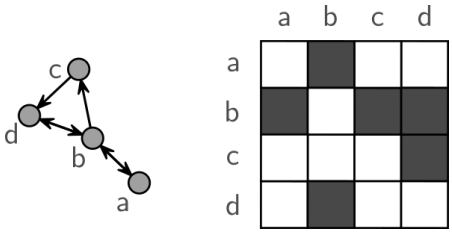

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Ultimately...

ERGM $\equiv$ Modeling binary arrays

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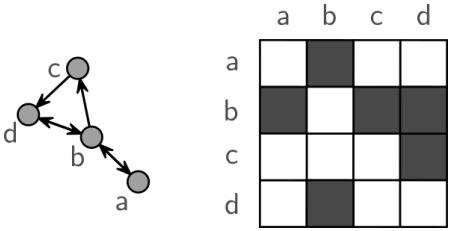
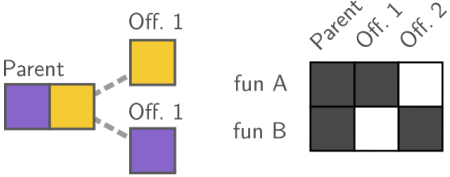


Evolutionary Event



Social Networks are usually represented as **adjacency matrices**, and so can evolutionary events!

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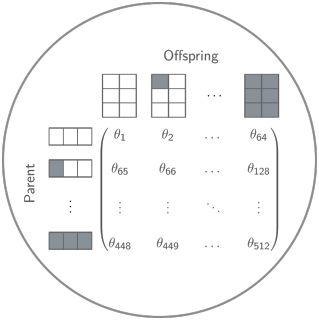
Full Markov Transition Matrix

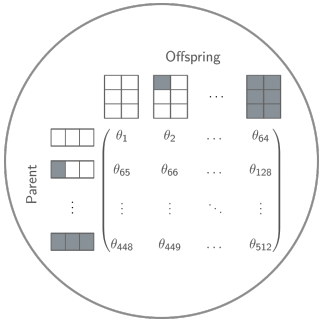


512 parameters

Evolution of Gene function (multiple functions) (cont.)

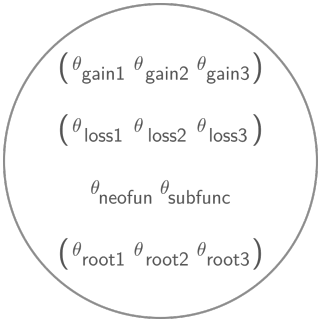
If we wanted to build a model with 3 functions, we would need to estimate...

Full Markov Transition Matrix



512 parameters

Sufficient statistics



11 parameters (for example)

Evolution of Gene function (multiple functions) (cont.)

If we wanted to build a model with 3 functions, we would need to estimate...

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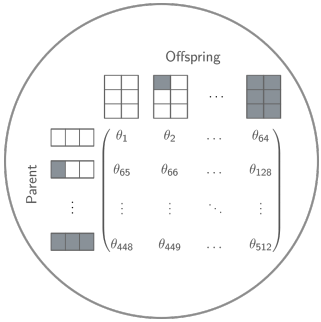

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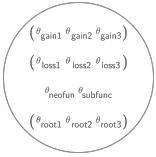
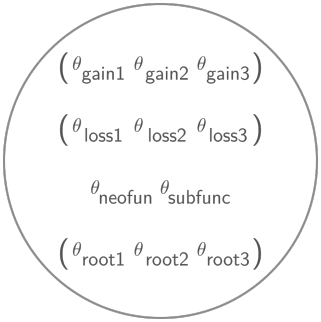


Easier to fit
Easier to interpret

Sufficient statistics



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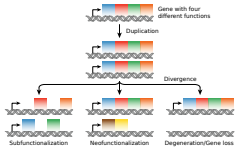

Rep.	Description	Definition
	Gain of function	$(1-x_p)\sum_{n:n\in Off} x_n$
	Loss of function	$x_p \sum_{n:n\in Off}(1-x_n)$
	Subfunctionalization	$x_p^k x_p^j \sum_{n\neq m} x_n^k(1-x_n^j)(1-x_m^k)x_m^j$
	Neofunctionalization	$x_p^k(1-x_p^j)\sum_{n\neq m} x_n^k(1-x_n^j)(1-x_m^k)x_m^j$
	Longest branch gains	$(1-x_p^k)\mathbf{1}\left(x_m^k : m = \text{argmax}_n \text{blength}_n\right)$

Table: Example of sufficient statistics for evolutionary transitions.

GEESE: **GE**ne functional **E**volution using **S**ufici**E**ncy

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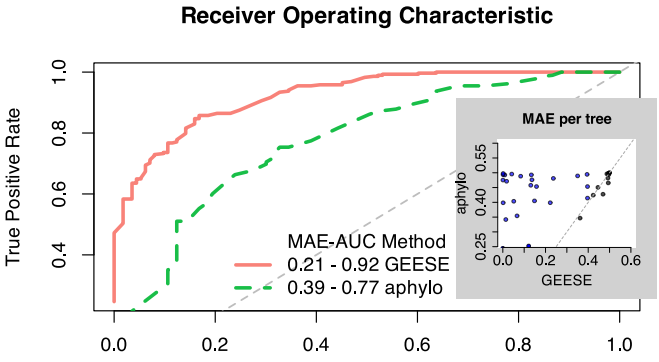
- Fitted both of them using MCMC.
- Used LOO cross-validation to compute aggregated AUCs and MAE.

GEESE for predicting gene function (cont.)

How much can we gain from a joint dist. model?



Phylogenetic models predicting 401 GO annotations.

Just controlling for preservation (having only one duplicate changing) significantly improves our predictions.

Table of Contents

Mechanistic Machine Learning: State-of-the-art

- After all the data pouring, attention to causal inference and mechanistic models is coming back[3,14]
- Applications in Physics, Chemistry, Biomedical Imaging, and Biology[16,11,7,1] show the benefits of combining the two approaches.

Mechanistic Models

- Inference driven (causality)
- Great for small datasets
- Not the most accurate

Machine Learning Models

- Data-driven (prediction)
- Lots of points to "learn"
- Great for big data

Important: Mechanistic Machine Learning **is not** domain-knowledge aided feature engineering. You need a whole other model to complement the ML algorithm.

Three strategies

Figure: "A van Gogh-style painting of an android holding a large biology book in one hand and a computer in another, examining an evolutionary tree that, instead of leaves, have genes."–DALL-E's interpretation of my description (link)

Three strategies

a. **ML Correction**: Use machine learning to learn the errors of a mechanistic model.

Figure: "A van Gogh-style painting of an android holding a large biology book in one hand and a computer in another, examining an evolutionary tree that, instead of leaves, have genes."–DALL-E's interpretation of my description (link)

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a. **ML Correction**: Use machine learning to learn the errors of a mechanistic model.
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a. **ML Correction**: Use machine learning to learn the errors of a mechanistic model.
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c. **Mechanistic Penalty**: Add constraints to the ML algorithm based on a mechanistic model.

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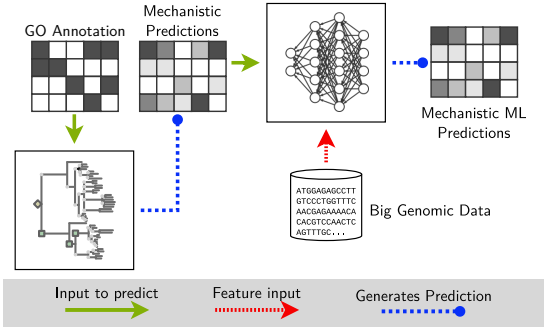
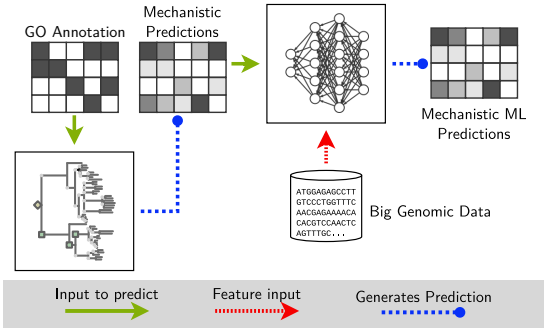


Three strategies

a. ML Correction

1. Fit the mechanistic model using GEESE
2. Generate the mechanistic-based predictions, $\hat{\mathbf{y}}^{GEESE}$,



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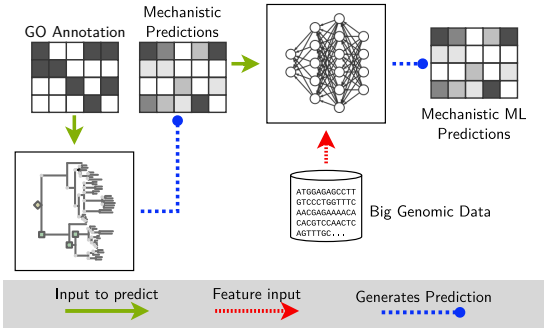
a. ML Correction

1. Fit the mechanistic model using GEESE
2. Generate the mechanistic-based predictions, $\hat{\mathbf{y}}^{GEESE}$,
3. fit an ML model $f(X, \Omega)$ to predict $\varepsilon \equiv (\mathbf{y} - \hat{\mathbf{y}}^{GEESE})$,



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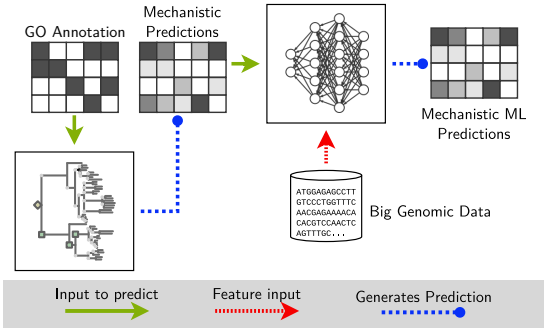

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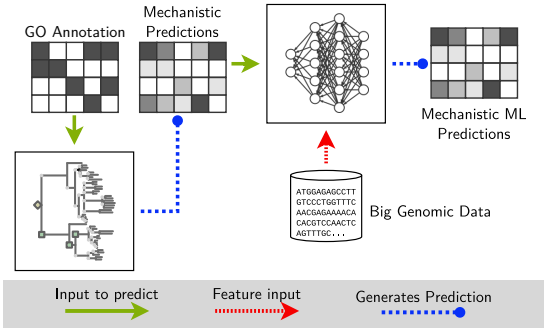
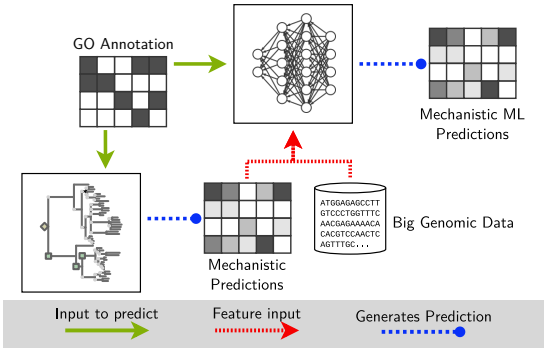
3. fit an ML model $f(X, \Omega)$ to predict $\varepsilon \equiv (\mathbf{y} - \hat{\mathbf{y}}^{GEESE})$,
4. generate the predictions of $\hat{\varepsilon}$, and
5. Compute the Mechanistic-ML predictions as $\hat{\mathbf{y}}^{MML1} \equiv \hat{\mathbf{y}}^{GEESE} + \hat{\varepsilon}$



Three strategies

b. Mechanistic Feature

1. Fit the mechanistic model using GEESE,



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b. Mechanistic Feature

1. Fit the mechanistic model using GEESE,
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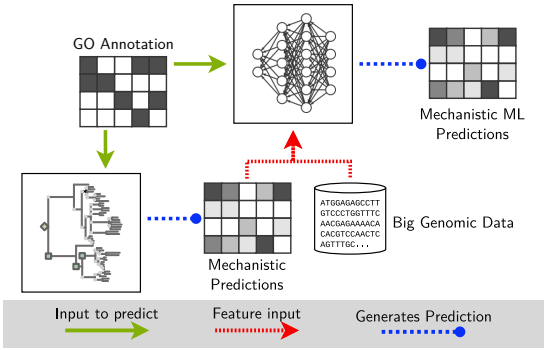

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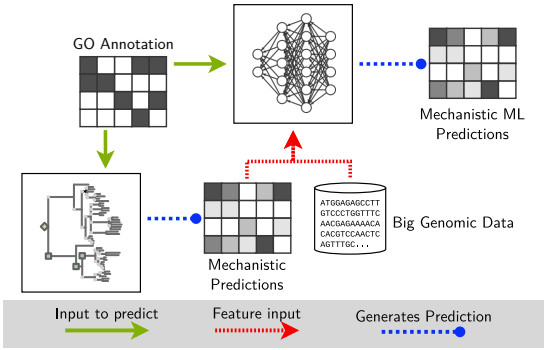
b. Mechanistic Feature

1. Fit the mechanistic model using GEESE,
2. generate the mechanistic-based predictions, $\hat{\mathbf{y}}^{GEESE}$,
3. fit an ML model that uses the mechanistic predictions as features, $f(X, \Omega, \hat{\mathbf{y}}^{GEESE})$, and



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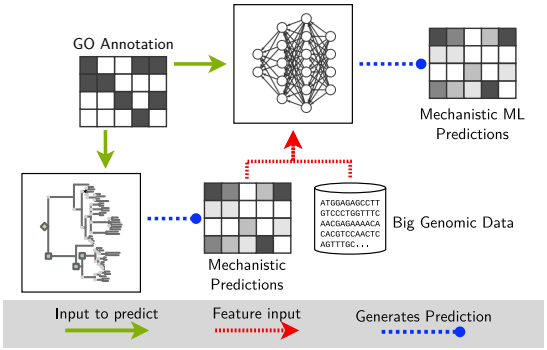
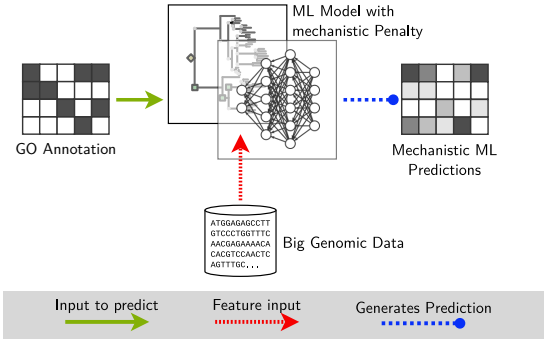
3. fit an ML model that uses the mechanistic predictions as features, $f(X, \Omega, \hat{\mathbf{y}}^{GEESE})$, and
4. Compute the Mechanistic-ML predictions as $\hat{\mathbf{y}}^{MML2} \equiv f(X, \Omega, \hat{\mathbf{y}}^{GEESE})$



Three strategies

c. Mechanistic Penalty

1. Fit the mechanistic model using GEESE and store the parameter estimates $\hat{\theta}$,



Three strategies

c. Mechanistic Penalty

1. Fit the mechanistic model using GEESE and store the parameter estimates $\hat{\theta}$,
2. minimize the following loss function:

$$L(y_{\cdot}^{obs} X, \Omega) - \mathcal{L}\left(f(y_{\cdot}^{obs} X, \Omega)\right)_{GEESE},$$

where $\mathcal{L}(\cdot)$ is the likelihood function under GEESE.

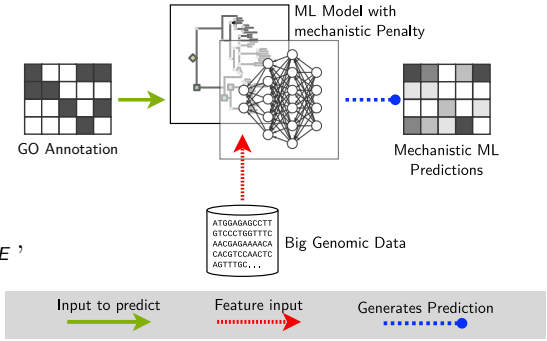


Table of Contents

Beyond GO and Trees... Bgee

The Bgee project "is a **database** for retrieval and **comparison of gene expression** patterns **across multiple animal species**. It provides an intuitive answer to the question 'where is a gene expressed?' and supports research in cancer and agriculture as well as evolutionary biology." – Bastian et al. [4]

- Raw expression annotations.
- Standardized expression scores (so can compare across species/tissues).
- And also yes/no expression annotations based on the standardized scores.

Beyond GO and Trees... Bgee (cont.)

Divergence across species in gene expression levels has been linked to evolutionary events,[13,9] *i.e.*, expression levels clustered phylogenies.

Thinking of different ways to use it as:

- As an additional feature for our model: "Given the phylo, observed annotations, **and expression levels in *n* tissues**, ..."
- As 0/1 variable (expression is present/absent) to predict in our model: "Model the evolution of gene function **and expression**."
- As part of a prediction model in, say, a Machine Learning Model.

What went into the blender

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Data Feats

- Bgee 15 dataset: approx 7 billion annotations for 1.5 million genes.
- Our dataset: 1,484 predictions for 1,318 genes.
- Search by Gene name: 9,923,427 Bgee annotations.

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Final model

- 10 GO terms (in a full-Markov model, this is 1 MM params).
- 278 annotations for 256 genes.
- 10 GEESE predictions for each gene.
- 46 Bgee score for gene expression computed as **mean expression score by gene-genus**

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GO terms: GO:0004672, GO:0004713, GO:0004867, GO:0005730, GO:0005829, GO:0005886, GO:0006468, GO:0009408, GO:0015020, GO:0060070

Genus: Anguilla, Anolis, Astatotilapia, Astyanax, Bos, Branchiostoma, Caenorhabditis, Callithrix, Canis, Capra, Cavia, Cercocebus, Chlorocebus, Danio, Drosophila, Equus, Esox, Felis, Gadus, Gallus, Gasterosteus, Gorilla, Heterocephalus, Homo, Latimeria, Lepisosteus, Macaca, Manis, Meleagris, Microcebus, Monodelphis, Mus, Neolamprologus, Nothobranchius, Ornithorhynchus, Oryctolagus, Oryzias, Ovis, Pan, Papio, Poecilia, Rattus, Salmo, Scophthalmus, Sus, Xenopus

Mechanistic ML

We are comparing three models:

GEESE

Phylogenetic based predictions (evolution of gene function)

Mechanistic ML

We are comparing three models:

GEESE

Phylogenetic based predictions (evolution of gene function)

Bgee

Linear Prob. model using expression as predictors.

Mechanistic ML

We are comparing three models:

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Phylogenetic based predictions (evolution of gene function)

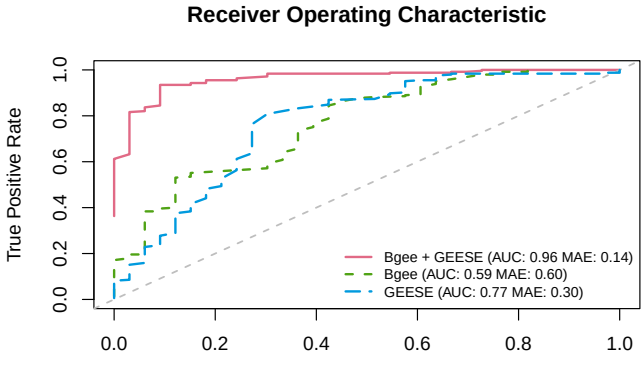
Bgee

Linear Prob. model using expression as predictors.

GEESE + Bgee

Linear Prob. model using expression as predictors **and** predictions made by GEESE.

Mechanistic ML (prelim res.)



Linear probability models predicting 278 GO annotations.

Both AUC and MAE were computed only using predictions for which we knew the true value.

Discussion

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Gene function

- We are racing to discover what genes do.
- Experimental assessment is expensive (money and time,) $\rightarrow$ automatic annotations.
- Many ways to do it (seq. homology, evolutionary theory, ML, etc.)
- The best methods use ML (pattern discovery)... but none (AFAIK) are based on bio. theory.

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- We showed it really helps.

Mechanistic ML

- Mechanistic Machine Learning (mixing theory-based models with ML) promises improved predictions.
- I showed an application using gene expression (Bgee).
- Adding our mechanistic predictions (based on GEESE) boosted quality

Thank you!

Predicting of Gene Functions by Leveraging Biological Insights with Mechanistic Machine Learning

George G. Vega Yon, Ph.D.
george.vegayon@utah.edu
Division of Epidemiology @ University of Utah

Jan 11th, 2023 @ Data Science Seminar

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Tree likelihoods: Felsenstein's Pruning algorithm

All possible transitions from $\mathbf{x}_n$

Transition Probability (ERGM)

$$\mathbb{P}\left(\tilde{D}_n \,\middle|\, \mathbf{x}_n, \Theta\right) = \sum_{\mathbf{x}} \mathbb{P}\left(\mathbf{x} \mid \mathbf{x}_n\right) \prod_{m \in \mathbf{O}(n)} \mathbb{P}\left(\tilde{D}_m \,\middle|\, \mathbf{x}_m\right)$$

Tree likelihoods: Felsenstein's Pruning algorithm

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Model Parameters

Vector of Sufficient Statistics

$$\mathbb{P}\left(\mathbf{x} \mid \mathbf{x}_n\right) = \frac{\exp\left\{\Theta^t s(\mathbf{x}, x_n)\right\}}{\sum_{\mathbf{x}'} \exp\left\{\Theta^t s(\mathbf{x}', x_n)\right\}}$$

Normalizing Constant

the ***lingua franca*** of SNA

... I implemented this (and more) on **barry**

Some computational features of **barry**