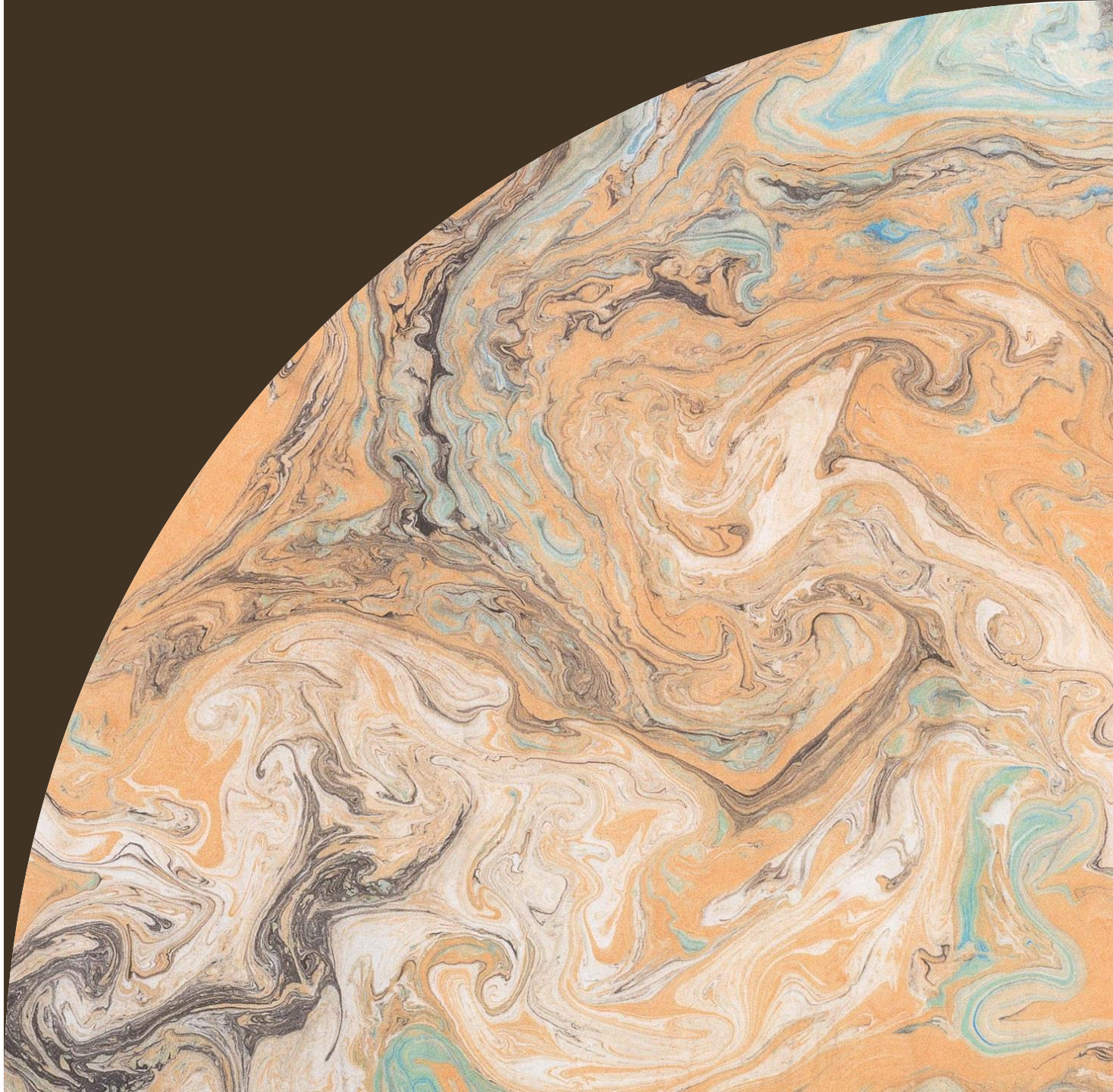
Application of Amino Acid Property Grouping Technique to Predict Protein Function Using Natural Language Processing Algorithms

By: Ritwik Katiyar



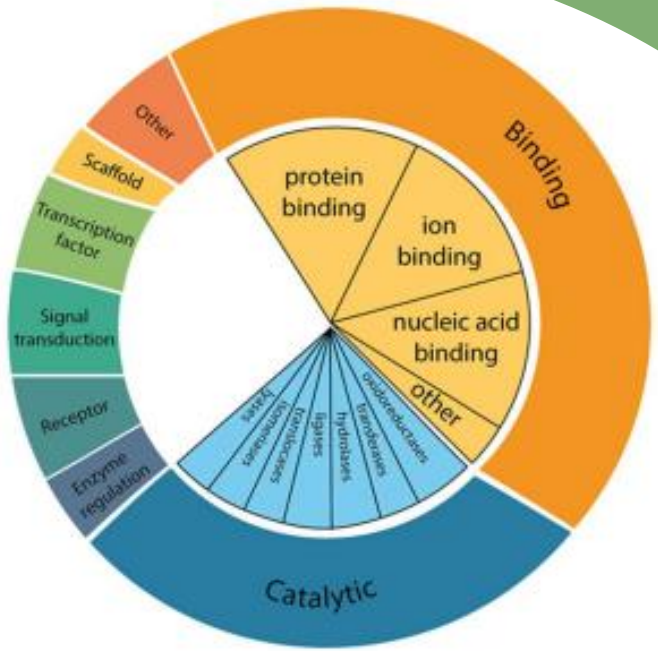
Purpose

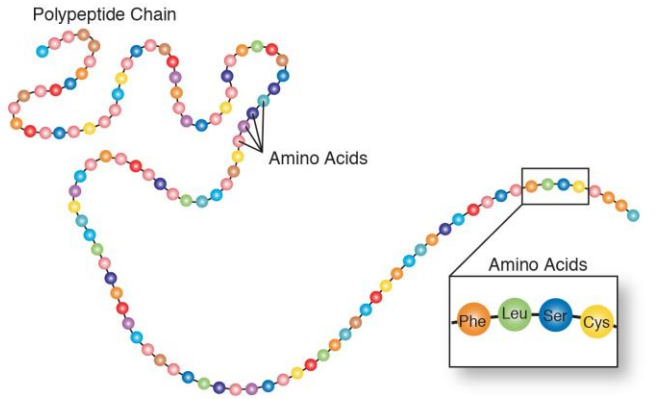
- Testing Amino Acid property grouping technique against some of the more common techniques and methodologies applied in the field of protein as a language.
- To test the viability of this technique and if it shows potential for future applications and testing.

Introduction

Proteins and Functions

- Life's fundamental building blocks consist of sequences of amino acids at the molecular level.
- Proteins exhibit a wide array of functions ranging from facilitating biochemical reactions to providing essential structural support.
- The functionality of proteins denotes their distinct biological roles within an organism.
- Further granularity exists within protein functions, as they can be subdivided into specific sub-functions.
- Proteins often serve multiple functions, showcasing their adaptability and versatility in biological processes.





Amino Acids

Ala: Alanine	Gln: Glutamine	Leu: Leucine	Ser: Serine
Arg: Arginine	Glu: Glutamic acid	Lys: Lysine	Thr: Threonine
Asn: Asparagine	Gly: Glycine	Met: Methionine	Trp: Tryptophane
Asp:Aspartic acid	His: Histidine	Phe: Phenylalanine	Tyr: Tyrosisne
Cys:Cysteine	Ile: Isoleucine	Pro: Proline	Val: Valine

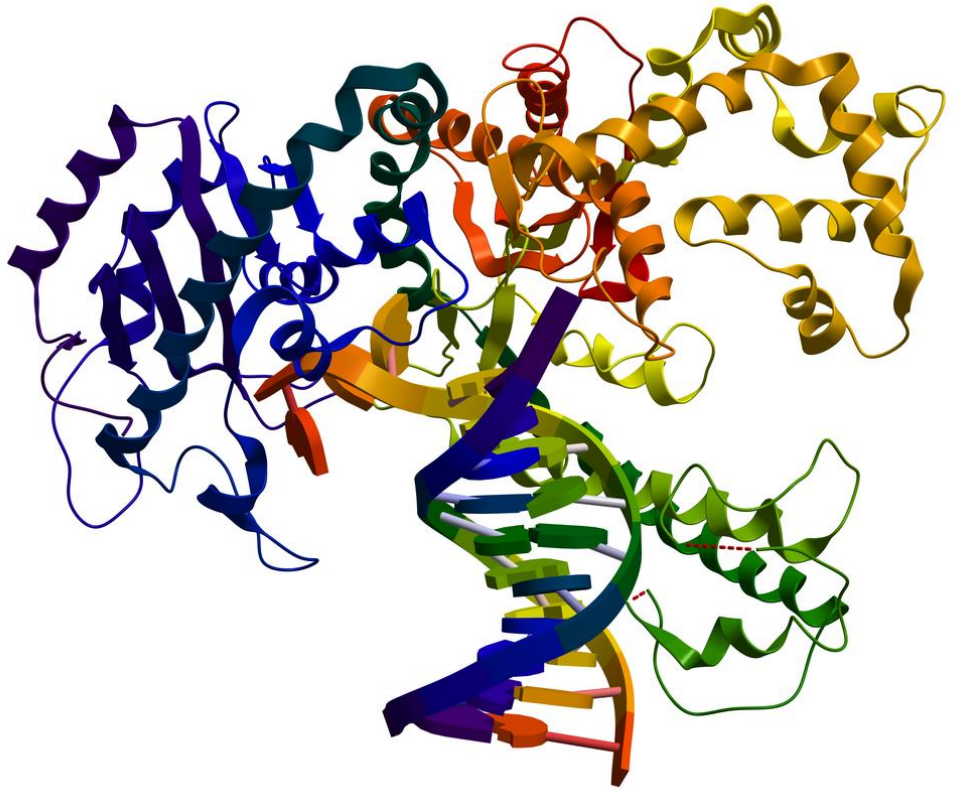
Various Methods of Protein Function Determination

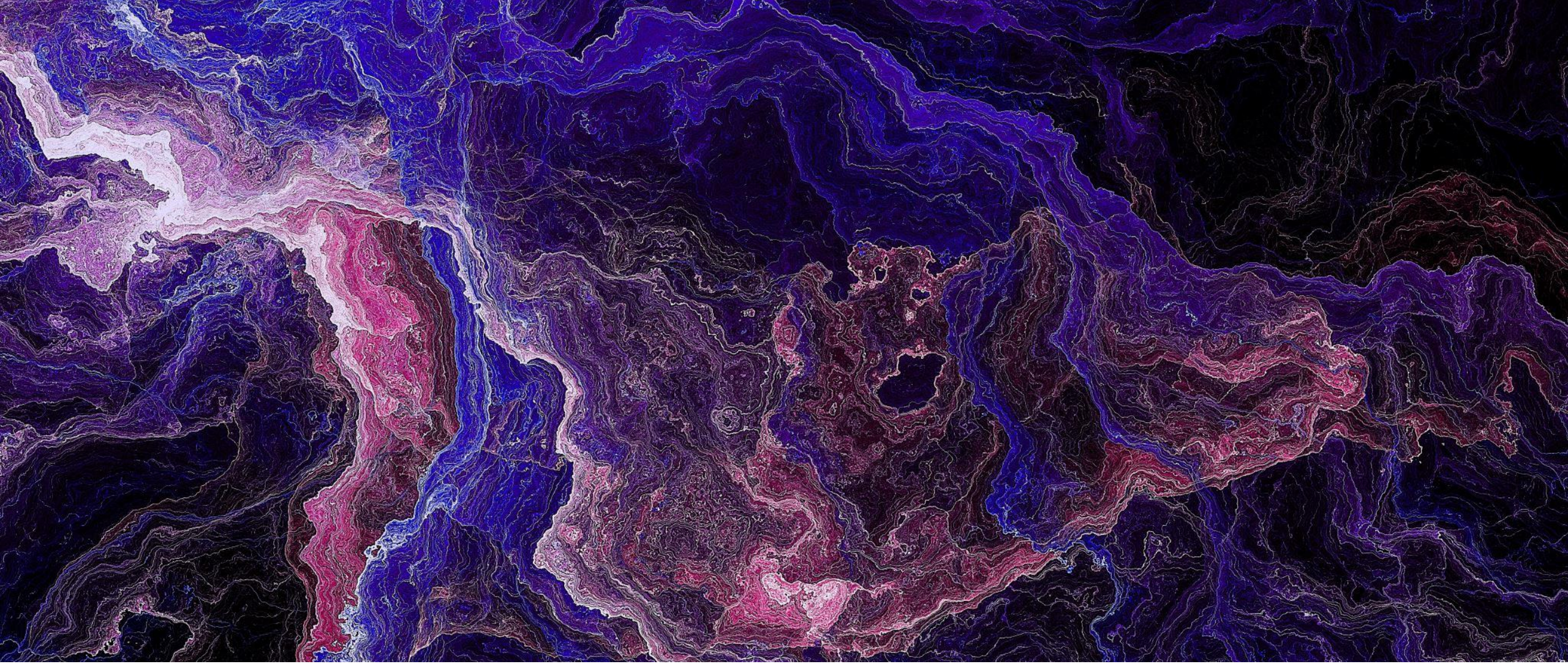
Various Approaches that can be used to obtain the function of the protein via the sequence. Some of the more popular techniques are:

- Conventional Methods via the use of experimental assays.
- Homology or Similarity Based Approaches (BLAST).
- Feature Embedding or Information Based.
- As a Language Approach.

Importance of Discovering Protein Function

- Facilitate and Streamline Drug Discovery processes.
- Enhance the understanding of biological systems
- Design of more targeted and effective therapeutic interventions.
- Protein engineering
- Bio-Manufacturing

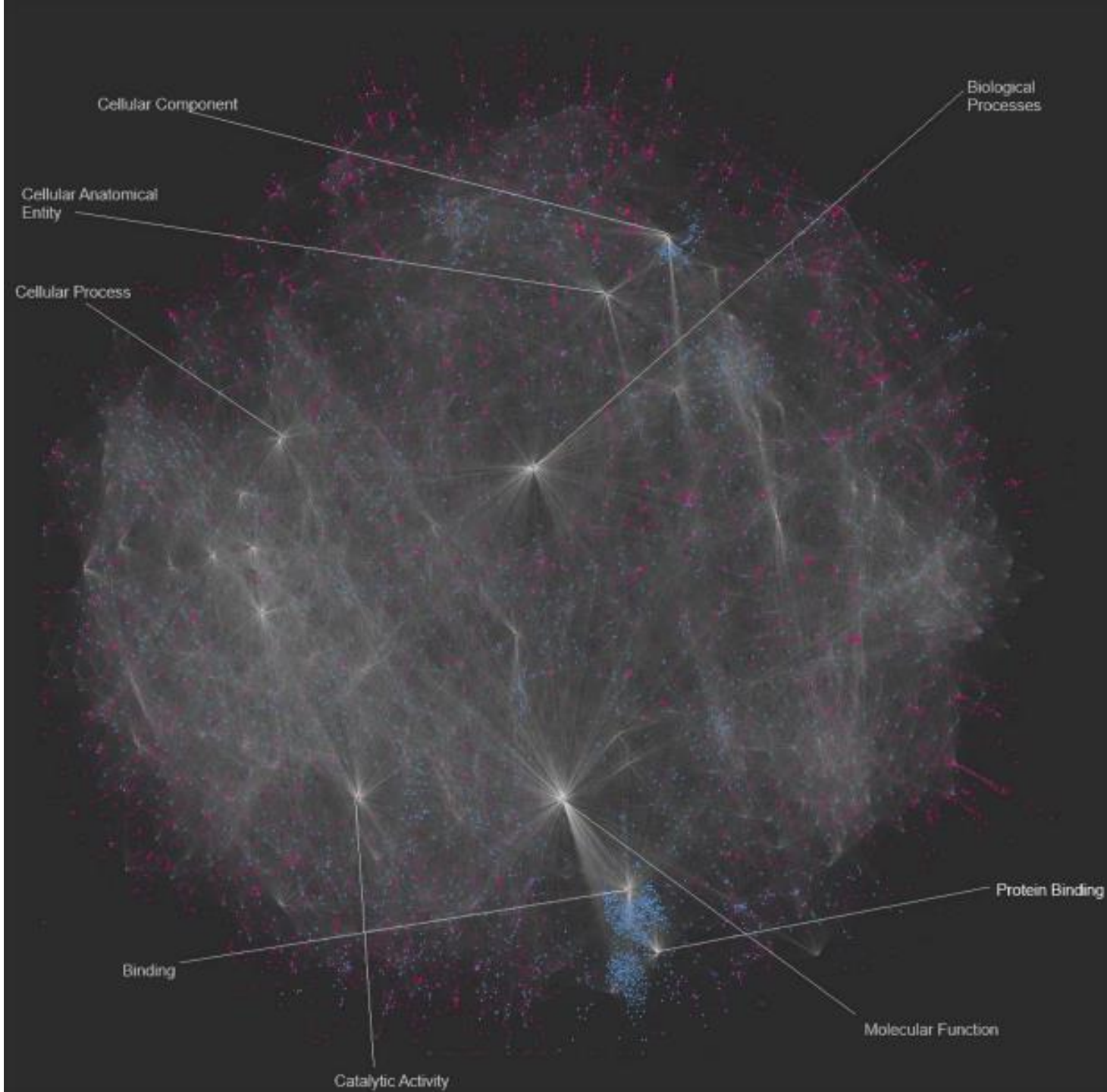




Background

Complexity of the Relation Between Proteins and Functions.

The Bi-Partite Network showcases the complex relation between proteins (blue) and their respective functions (red) within our sample data of just 3131 proteins sequences.

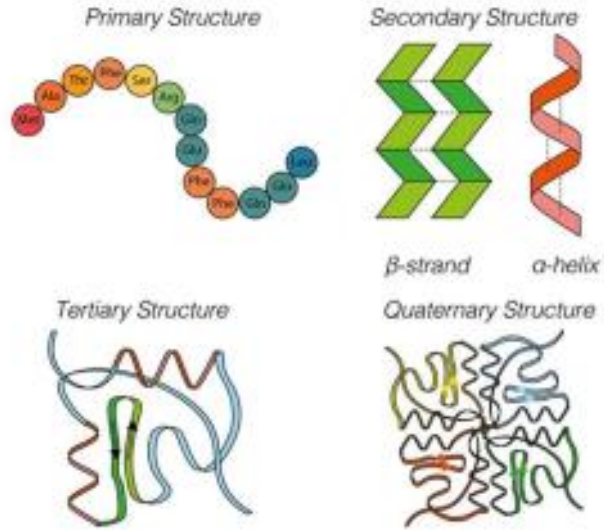


Feature Embedding – Common Features

- Early applications employing the Term Frequency - Inverse Document Frequency to obtain the number of times an amino acid appears in a sequence [3]

$$tfidf(t, d, D) = tf(t, d) * idf(t, D)$$

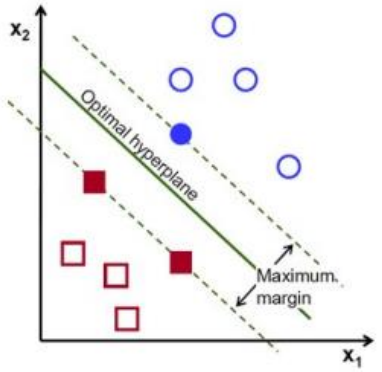
- Predicted secondary Structures (Elongated coils, Helixes, and Beta sheets)
- Tertiary structures (Domains and Motifs)
- pKa (Acidity of the amino acid)
- Hydrophobicity (Repealed by water molecules)



Support Vector Machine (SVM)

- SVM is a supervised machine learning algorithm that is used for binary classification.
- SVM attempts to classify the data by finding the best possible hyperplane that classifies the data points.
- A standard SVM is designed to work best with liner data
- Polynomial Kernel traditionally used for DNA and Protein applications.
- The polynomial kernel uses a polynomial function to redefine the data into a higher dimension.

$$K(x_1, x_2) = (x_1^{\top} x_2 + c)^{d}$$



Decision Tree & Random Forest

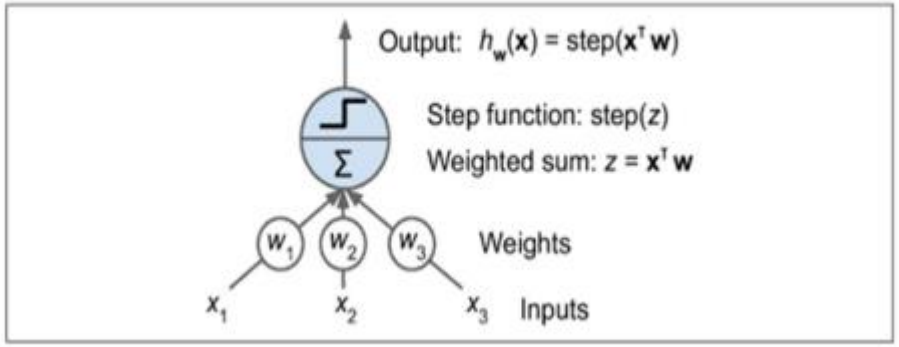
- Decision trees are non-parametric supervised learning methods that are commonly used for classification and regression.
- Most decision trees use the Gini index to determine the nodes it needs to select.
- The Gini score is a measure of the impurity of the node
- A node is considered pure if all training instances it applies to belong to the same class.

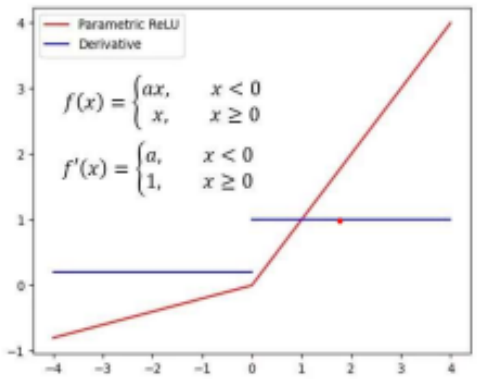
$$G_i = 1 - \sum_{k=1}^{n} P_{i,k}^2$$

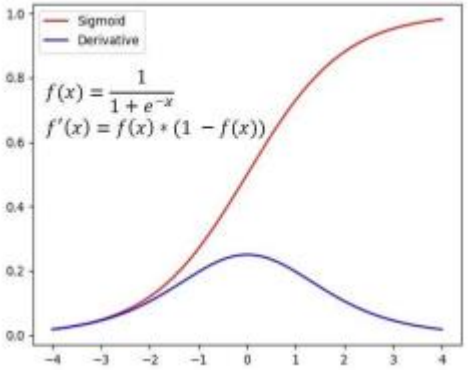
- Random Forest is largely considered over decision trees, as a random forest algorithm is simply a collection or an ensemble of decision trees

Deep Neural Network (DNN)

- A neural network aims to mimic the human brain and how the neurons interact with one another
- Like neurons the neural networks are made up of perceptron's. Invented in 1957 by Frank Rosenblatt, perception uses a weighted sum to generate output from an input.
- The ReLU activation function primarily assists with the performance of the neural network by replacing negative values with 0 and only keeping only the positive value.
- The sigmoidal function restricts the values between 0 and 1. Essentially generating a probability.

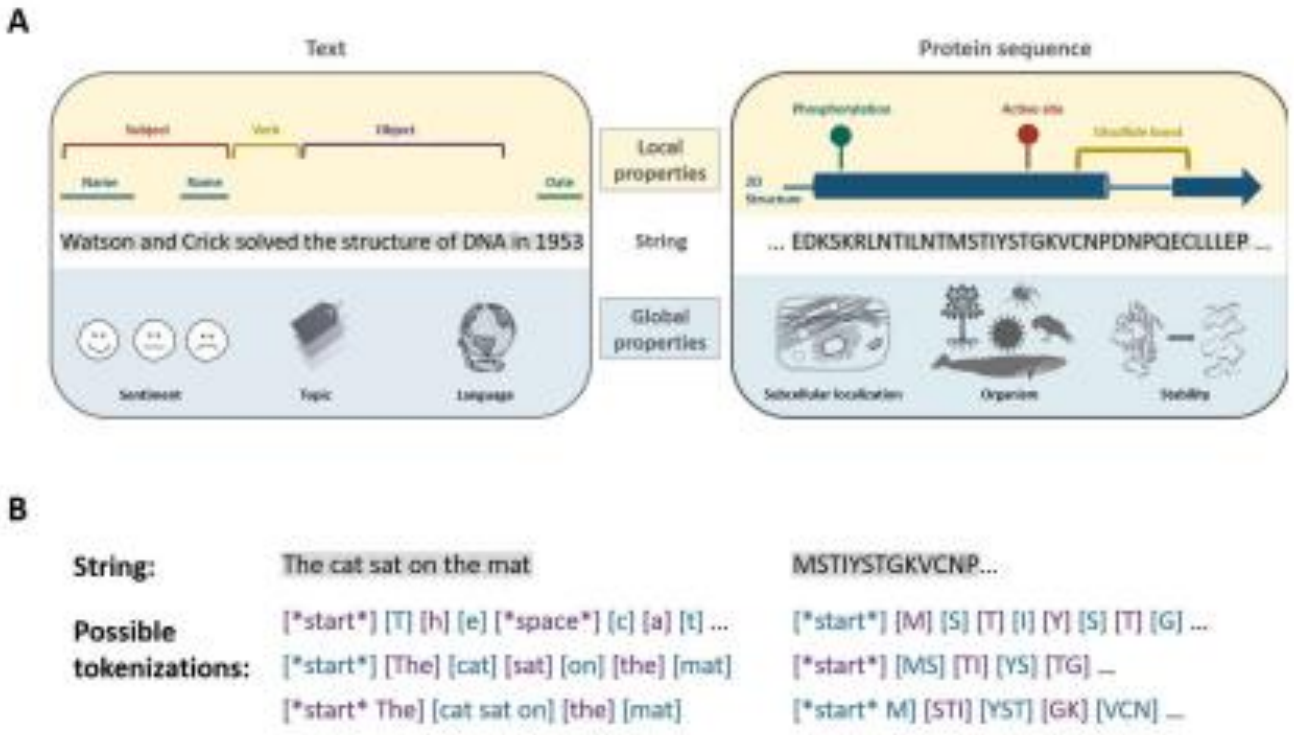






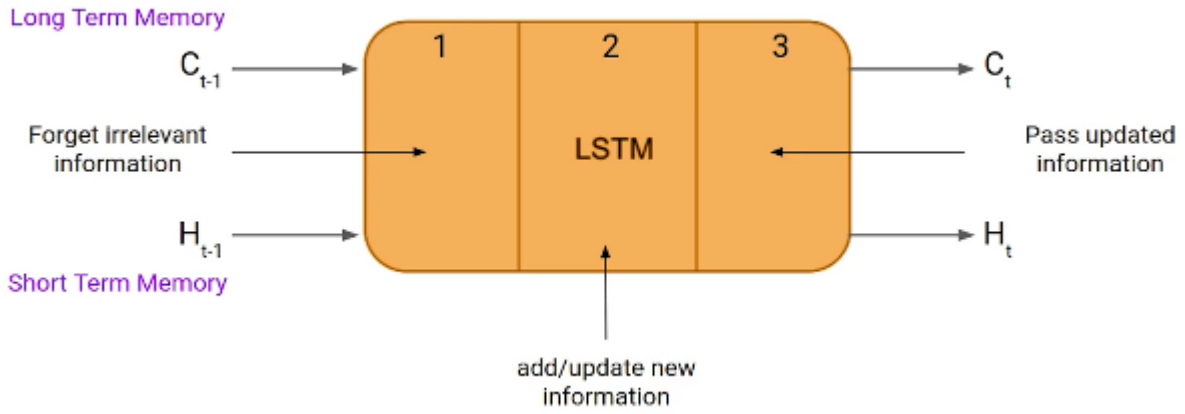
A Shift From Feature Embedding

- Improved Computational Algorithms Resulting in the use of language within the need for embedding.
- Tokenization or Bag of Words technique.
- As a language approach.



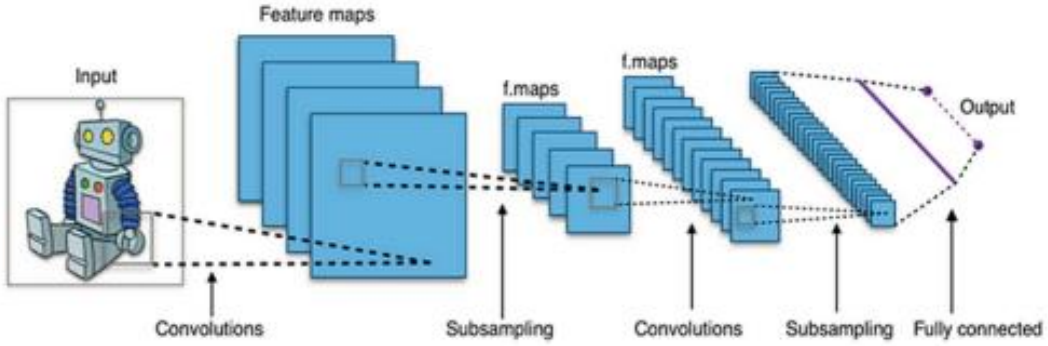
Recurrent Neural Network (RNN)

- RNN's can account for the sequential nature of language and process language while accounting for context.
- Fundamentally, an RNN comprises of Long Short-Term Memory (LSTM) layers.
- At each iteration, the LSTM meticulously evaluates the current word, the carry, and the cell state
- ProLanGo [4]



Convolutional Neural Network (CNN)

- The application of CNNs to textual data becomes feasible through tokenization and the conversion of language into two-dimensional numerical arrays.
- CNN architectures encompass convolutional layers comprising specialized perceptrons, which can be either pooled or fully connected
- ProtConv [9]



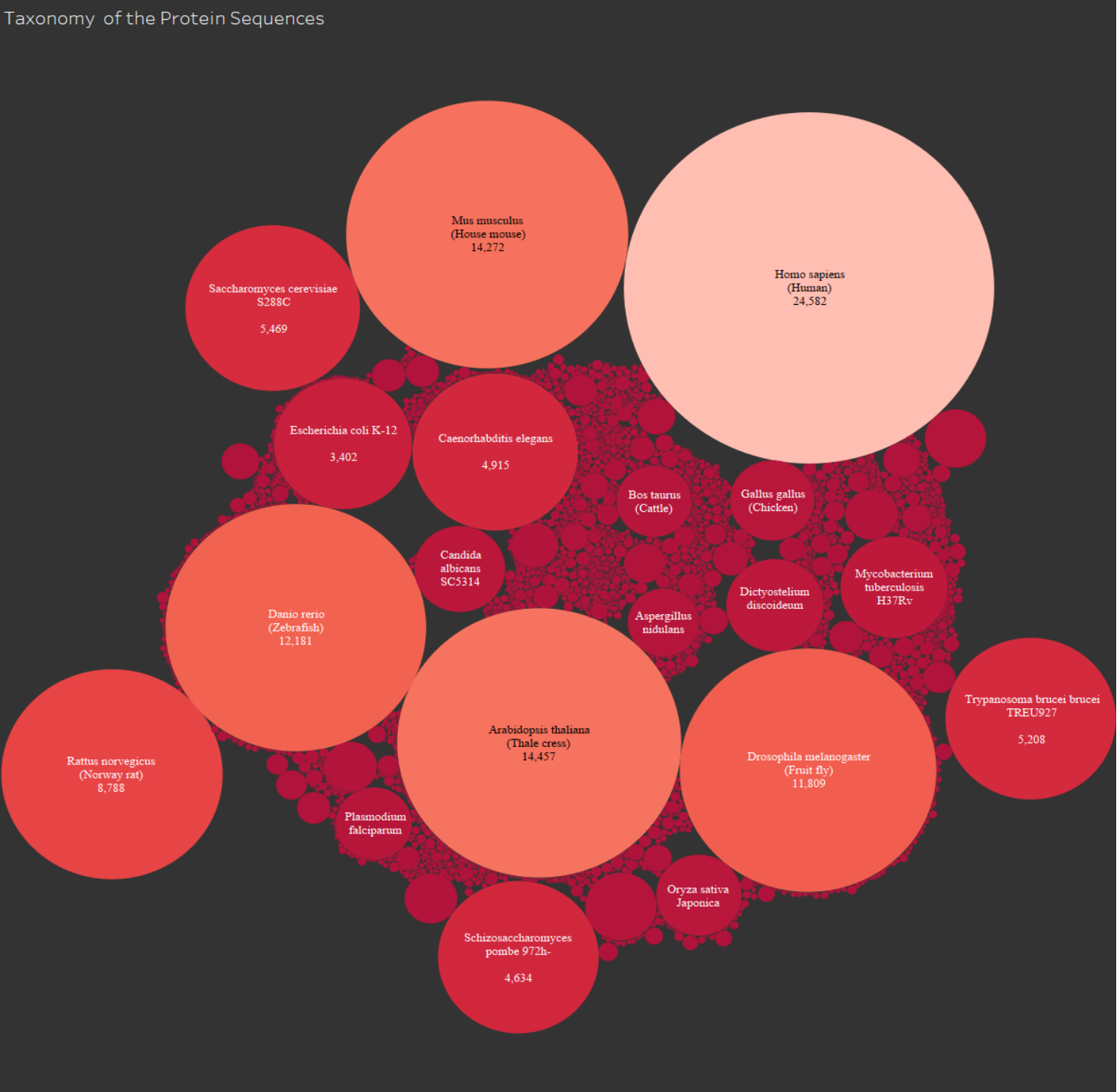
Data Background, Exploratory Data Analysis, and Methodology

Data Background

- The Gene Ontology knowledgebase provides a computational representation of our current scientific knowledge about the functions of genes.
- The GO ontology: The logical structure describing the full complexity of the biological functions of various kinds.
- Includes experimental findings from over 150,000 published papers and 700,000 experimentally supported annotations. [5]
- Join over 16M+ machine learners to share, stress test, and stay up-to-date on all the latest ML techniques and technologies
- The data itself was obtained from Kaggle referred to as CAFA-5 [2]

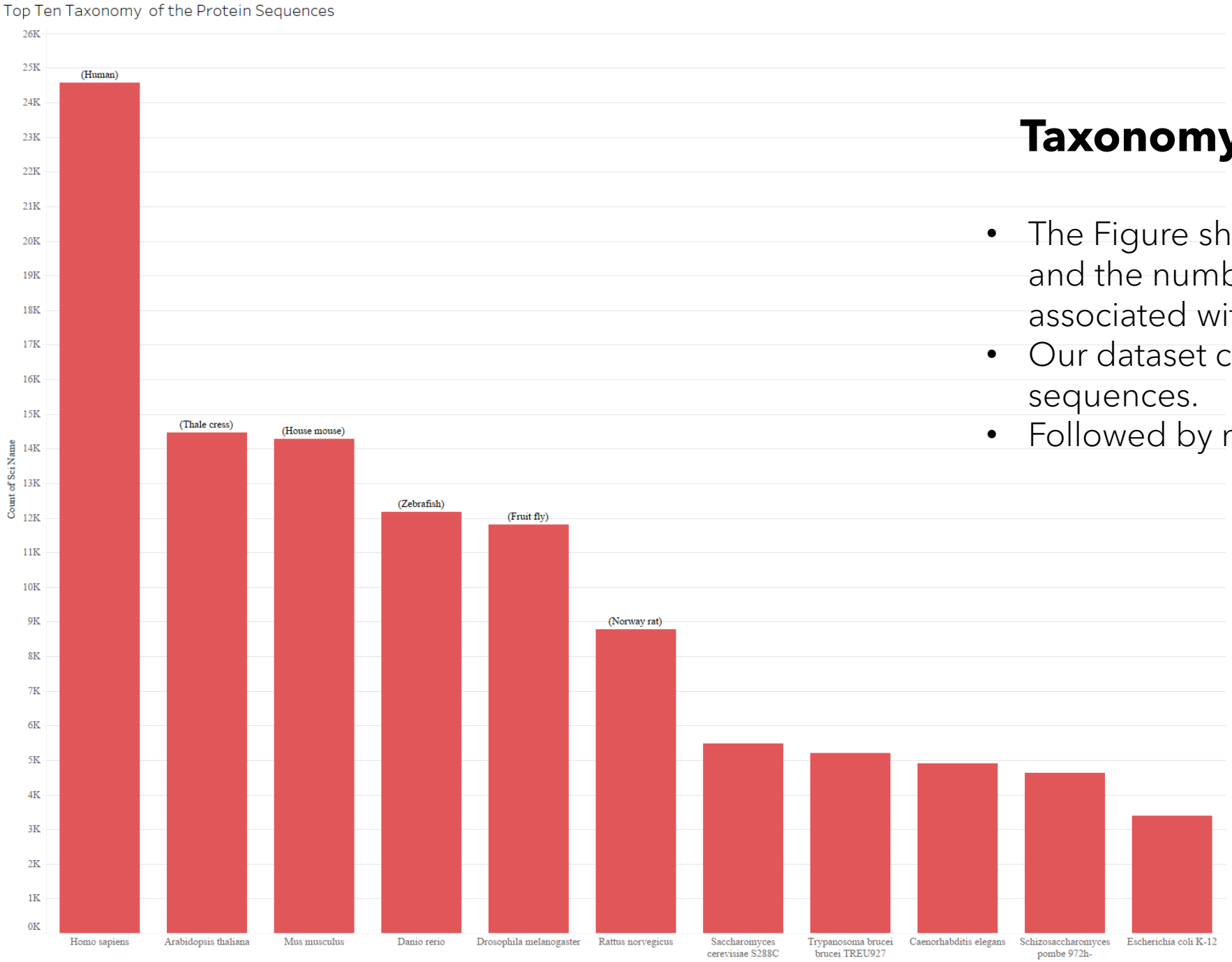
kaggle

GENEONTOLOGY
Unifying Biology



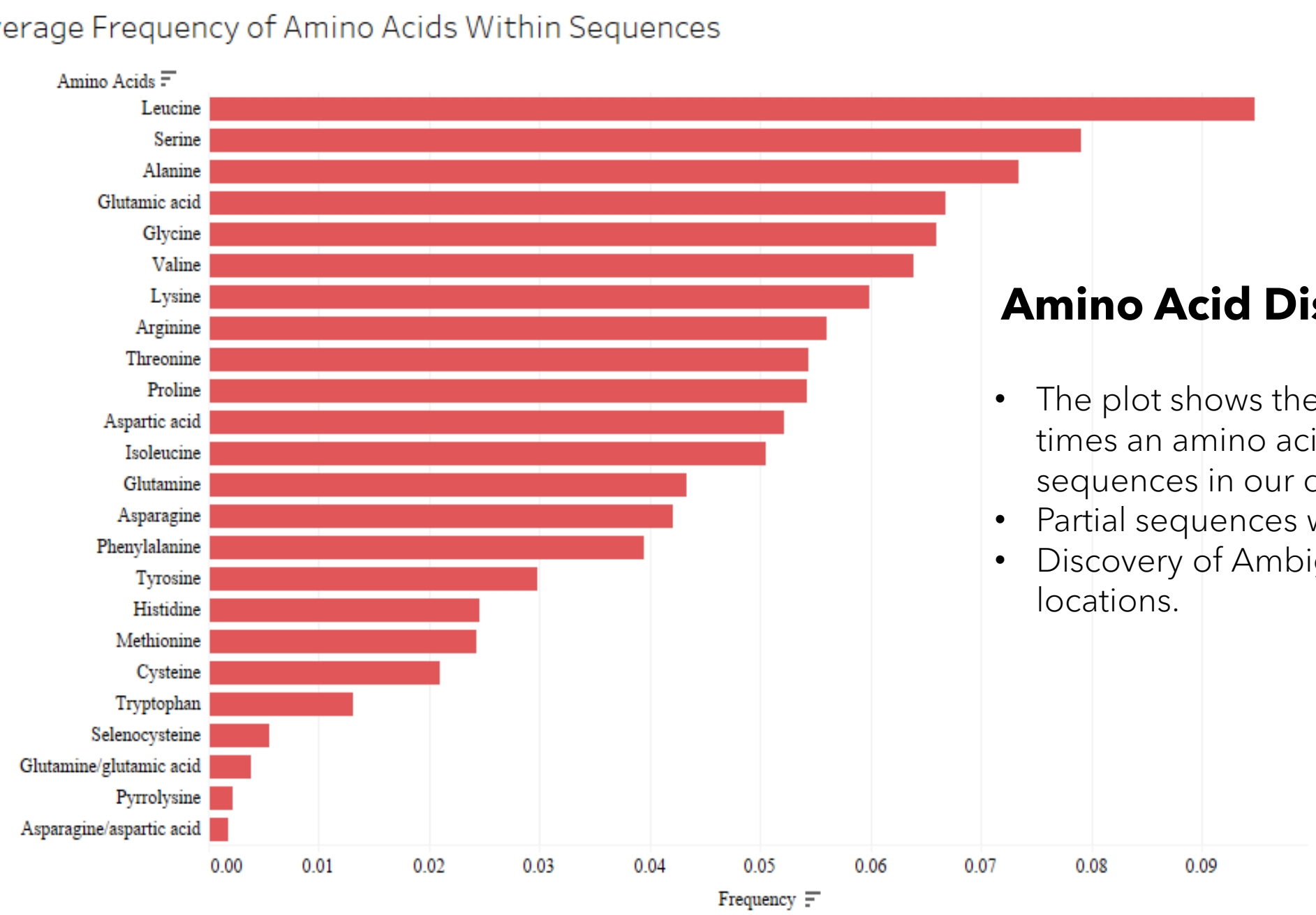
Represented Taxonomies

- 140674 Sequences
- Average Sequence Length 553.56
- Max Sequence Length 35375 (This complex protein is from the Norway rat. The protein seems to be responsible for the deployment of muscle)
- Min Sequence Length 3 (The protein sequence is from a type of a mushroom. The protein is generally responsible for regulation and inhibition)
- 3131 protein sequences obtained from plants, animals, and micro-organisms (bacteria and viruses)
- Removed Partial Sequences



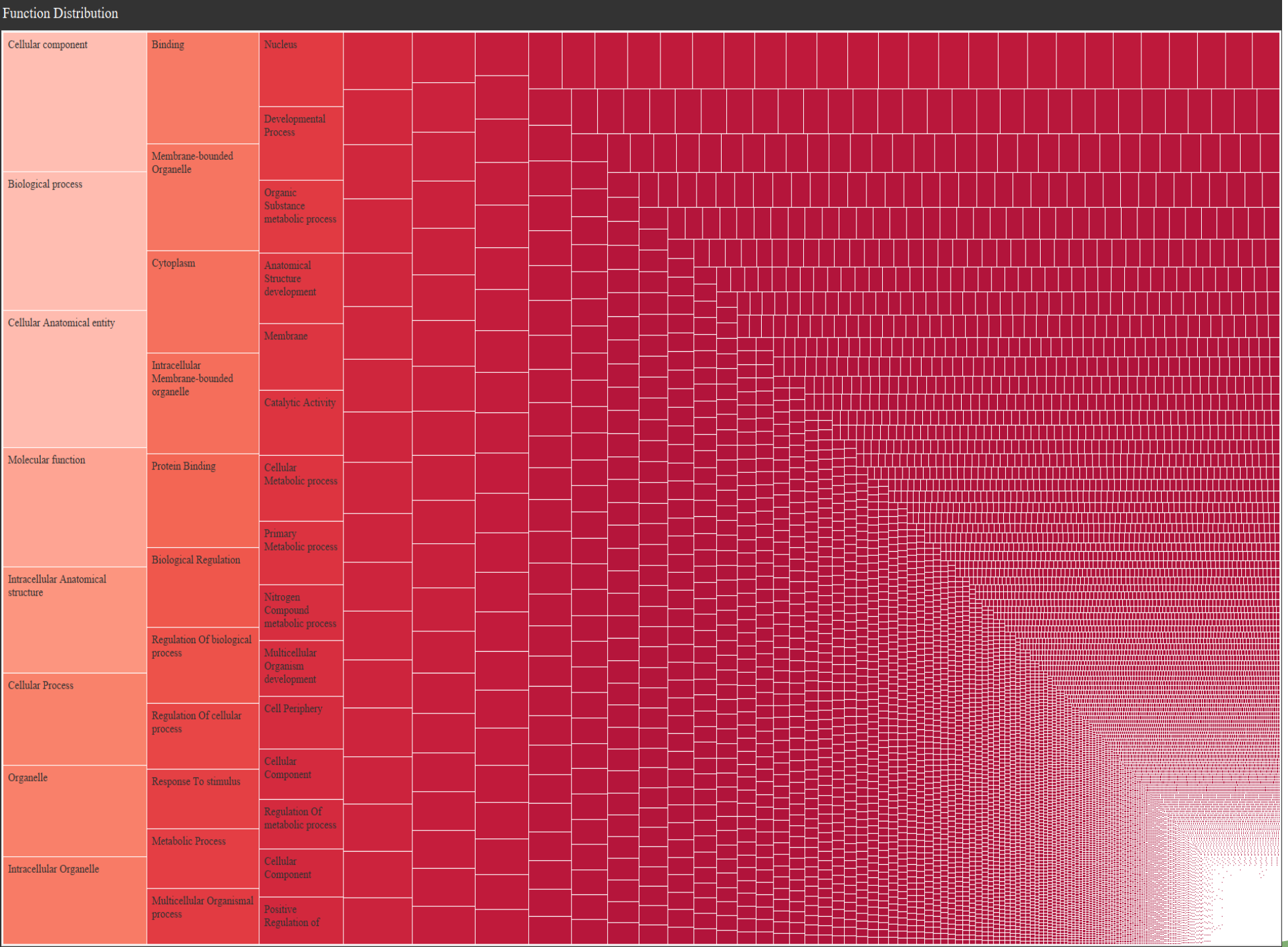
Taxonomy Distribution

- The Figure shows the top ten taxonomies and the number protein sequences associated with them.
- Our dataset contains primarily human sequences.
- Followed by novel organisms.



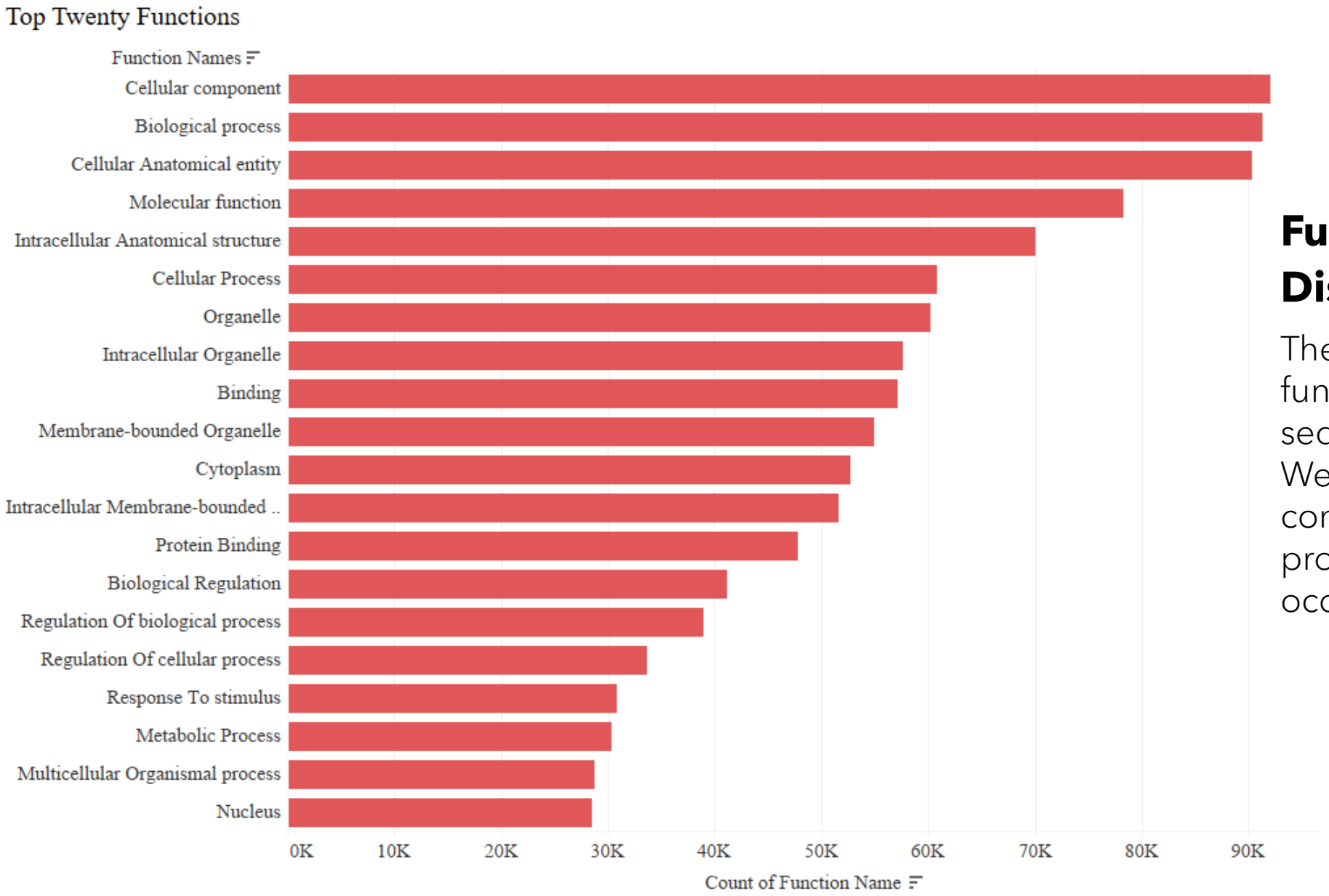
Amino Acid Distribution

- The plot shows the average number of times an amino acid occurs within the sequences in our data set
- Partial sequences were removed
- Discovery of Ambiguous Amino Acid locations.



Function Distribution

- This visualization illustrates the vast magnitude of various functions within our data set.
- There are over all a 43,248 Different Functions

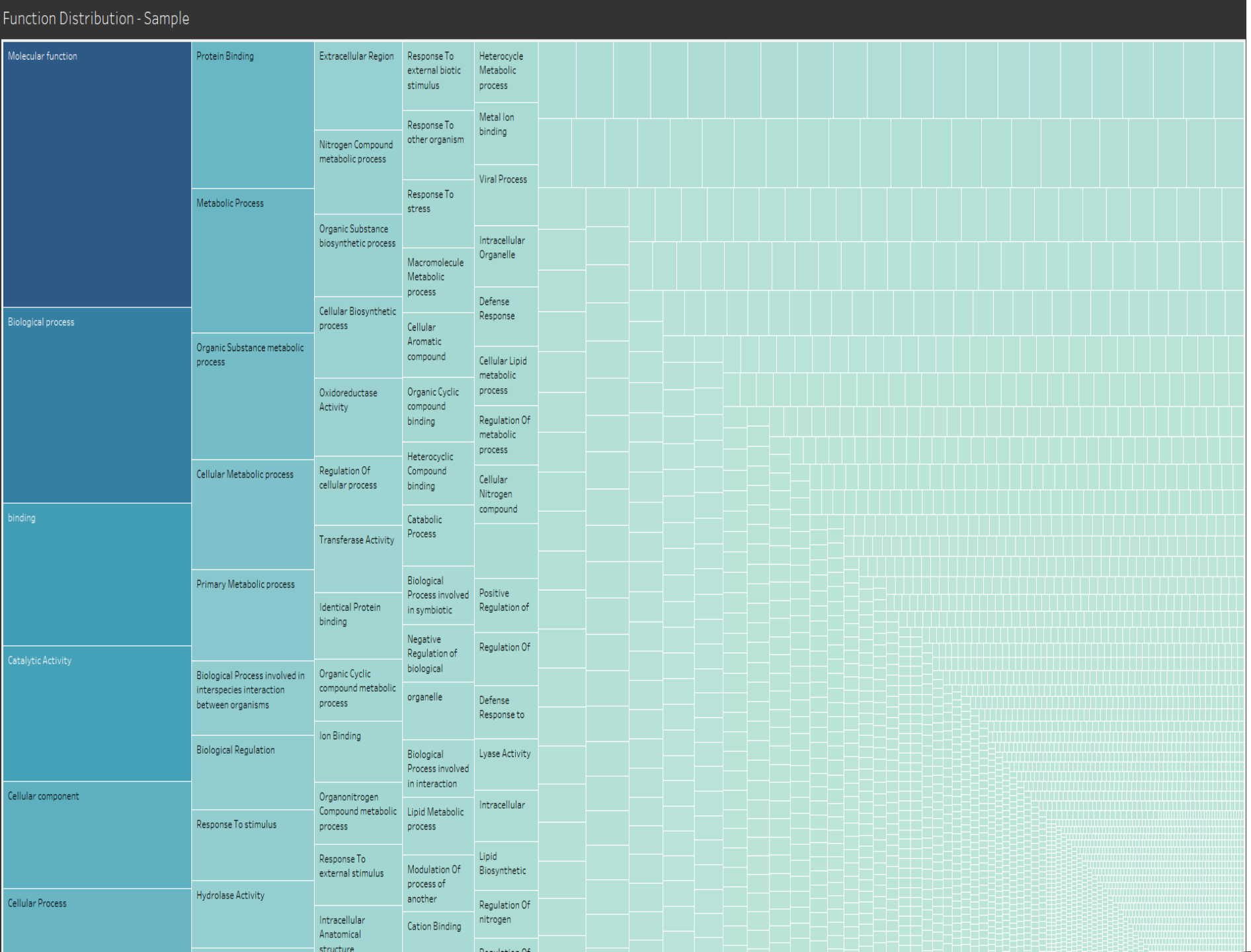


Function Distribution

The Bar plot shows the top 20 functions that the protein sequences are associated with. We can note that Cellular components and Biological processes have the highest occurrences.

Sampling

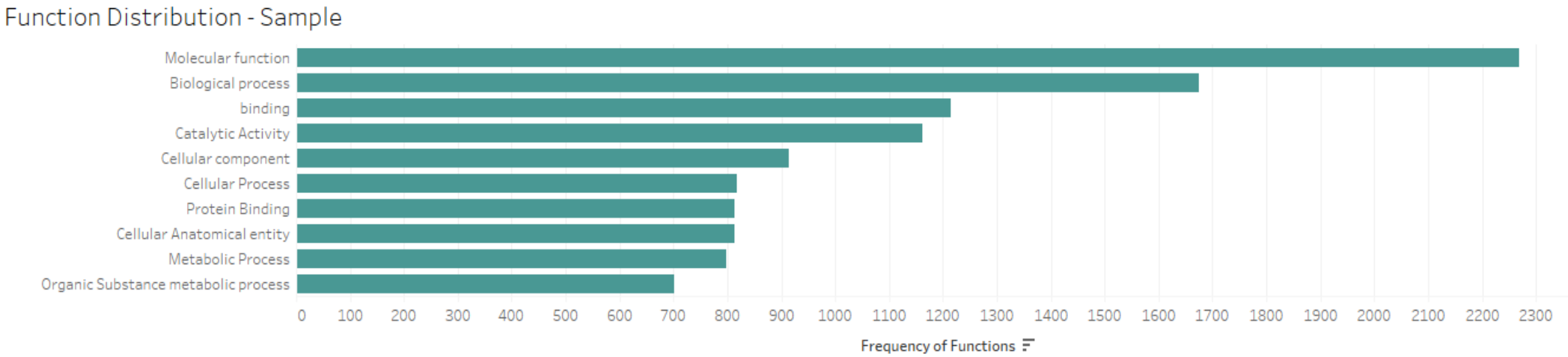
- SMOTE Technique or Synthetic Minority Oversampling Technique: Such a single sequence form every single taxon is represented even taxon that may have only one sequence.
- SMOTE was utilized since it provides a diverse number of proteins with unique functions. However, this could influence the accuracy of our model.
- SMOTE was chosen specifically to have a high variation in our sample data. A high variation.
- Sampled 3131 Sequences. One for each Taxonomy.



Sample Function Distribution

- A similar Representation of the magnitude of functions. However, this visualization uses our sample data.
- We can note that our sample has a lot less functions than our original data set
- 5206 Different Functions

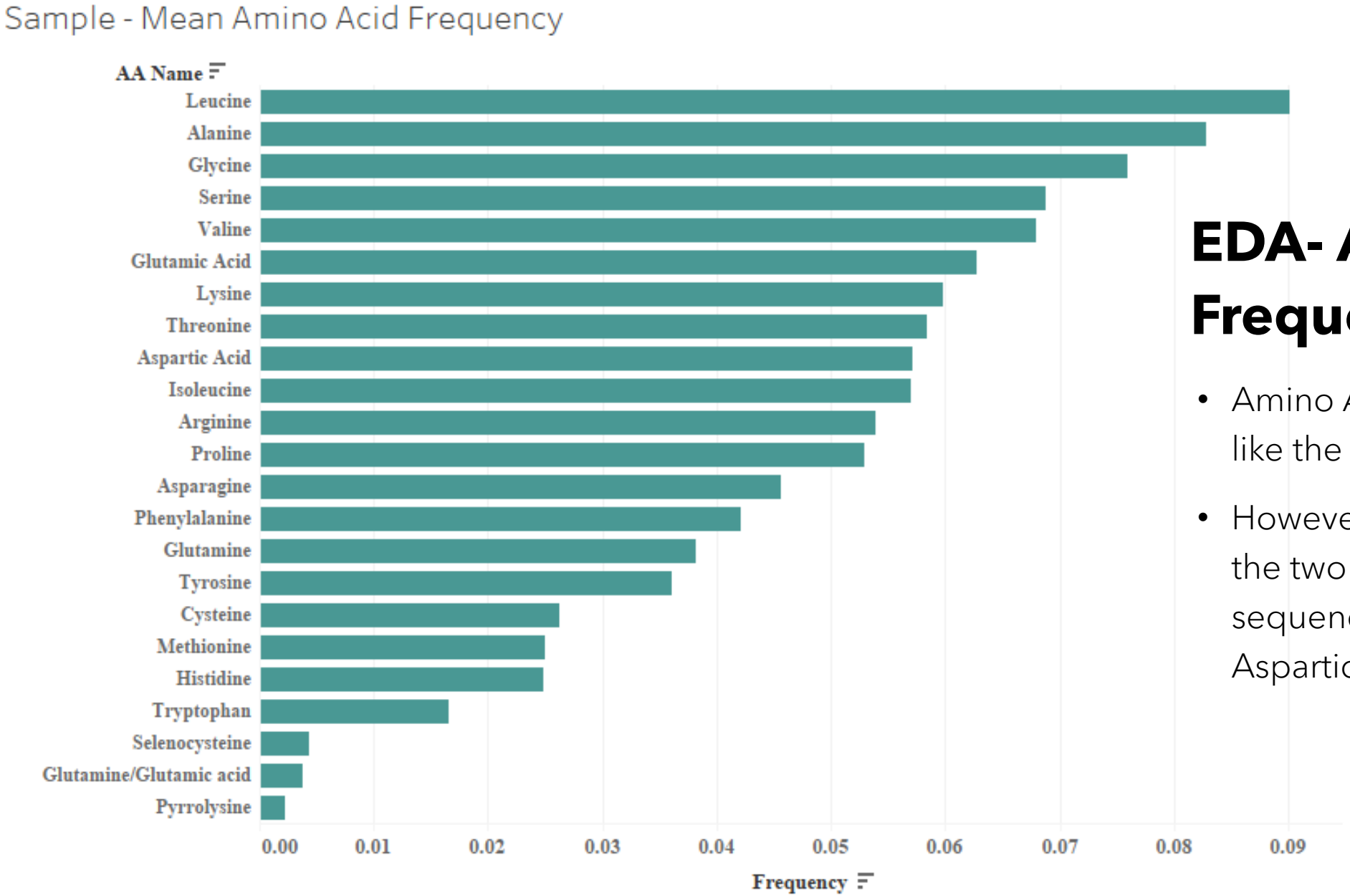
Sample Functions – Top Ten



- The minimum sequence length within this dataset remains three (pertaining to sequences from the same fungal species discussed earlier).
- The maximum sequence length has extended to 6,872 amino acids.
- The average sequence length stands at 474 amino acids.
- The plot shows the top 10 functions within the now sampled data. We can note that now cellular component is no longer the most dominant function
- The Distribution has changed. However, the goal is to test accuracy of our model. These changes shouldn't be a cause for concern.
- However, we can note that our data is highly imbalanced.

Functions Explained

- Molecular Function - Molecular - level activities performed by gene products such as catalysis or transportation as opposed to non-gene product activities.
- Biological Process - A proteins involvement in a larger multimolecular activity
- Binding & catalytic activity - Border terms used to describe proteins that perform said functions
- Cellular Component - The protein belongs to a specific or a larger cellular component.
- Cellular Anatomical entities - Implies gene product proteins involved in cellular structures.
- Protein binding & Metabolic Processes - Proteins which bind with other proteins or are involved with the metabolic pathways
- Organic Substance Metabolic Processes - Proteins that are involved in chemical reactions and pathways which require organic acids



EDA- Amino Acid Frequency

- Amino Acid Frequency is a lot like the over all data set.
- However, we have lost one of the two ambiguous sequences. (Asparagine / Aspartic Acid)

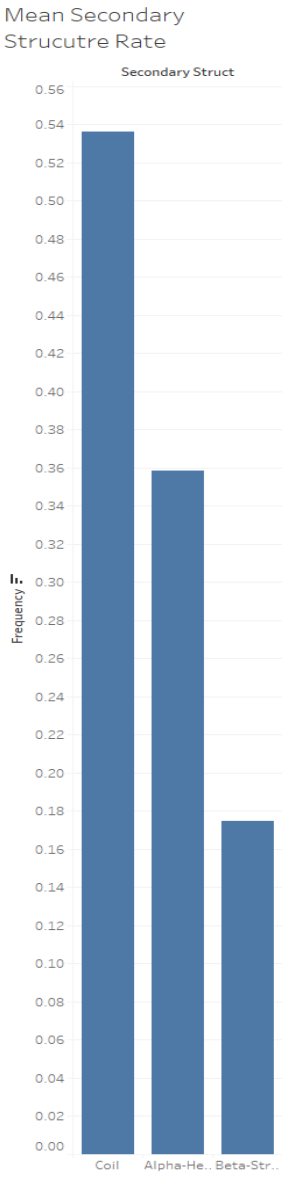
Sample – Secondary Structure Prediction

- S4pred is a prediction tool that uses the sequence to predict secondary structure. [8]
- The tool uses a deep semi-supervised learning framework to obtain its results
- The tool boasts an about 75% accuracy on predictions. And is regarded as one of the top secondary structure prediction tools.
- The tool is also open source can be downloaded from git-hub

sec_seq_id	sec_seq
O87540	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCEEEEEEEEEEEEECCCCEEEEEEEEECCCCCCEEEEECCCECCCEECCCCCCCCCCCCCC
B8ZV93	CCCCCEECCCCCCCCCHHHHHHHHHHHHHHHCCCCCCCCCCCECCCCCCHEEEECCHHHHHHHHHHHHHHHHHCCCCCCCCHHHHHHHHHHHHHHHH
Q1JUQ0	CCCCCCCCCCCCCCCCCCCCCCCCCCCHHHHHHHHHHHHHHHCCCEEEEECCCCCHCCCCHHHHHHHHHHHHHHHHCCCCCEEEECCCCHHHHHHHHHH
P17452	CCCCCCCCCCCCCCCCCHHHHHHHHHHHHCCCCCCCCCHHHHHHHHHHHHHHHCCCCHHHHHHHHHHHHHHHHHCCCCCCCCCCCCEECCCCCCCCCC
P19508	CCCCCCCCCCCCCCCCCHHHHHHHHHHHHHHHHHHHHHHHHCCCHHHHHHHHHHHHHHHHHHHHCCCCCHHHHHHHHHHHHHHHHHHHCCCCCCCCCC
P31621	CCCCCCCCCCCCCHHHCCCHHHHHHHCCCCCCCCCCCCHHHHHHHCCCCHCCCCCCCCCCHHHHHHHHHHHHHHHHHCCCCCEEEEECCCCHHHHHC
P10271	CCCCCCHHHHHHHHHHHHHHHHHCCCCCCHHHHHHHHHHHHHHHHCCCCCCCCCCHHHHHHHHHHHHHHHHHHHHCCCCCCCHHHHHHHHHHHHHH
Q8UN00	CCCCCCCCCCCCHCCHHHHHHHHHHCCCCCCCCCCEEEECCCCCCCCCCCCCCCCCHCCCCEEEEEEECCCCCCCCCCCEEEEEEECCCCCCCCCCCC
P07567	CCCCCCHHHHHHHHHHHHHHHHHCCCCCCHHHHHHHHHHHHHHHHCCCCCCCCCCHHHHHHHHHHHHHHHHHHHHCCCCCCCHHHHHHHHHHHHHHHC
P17863	CCCCCCCCCCCCCCCCCHHHHHHHCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCEEEEEEECCCCECCHHHHHHHHHHHCCCHH
P25020	CCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCCEECCCCCCCCCCCCCHCCCCCCCCEEEEEEECCCCCCCCCC
P03354	CCHHHHHHHHHHHHHHCCCCCCCHHHHHHHHHHHHHHHCCCCCCHHHCCCCCCCCHHHHHHHHHHHHHHHCCCCHHHHHHHHHHHHHHHHHHHCCCCHHH
P25058	CCCCCCCCCCCCCHHHHHHHHHHHHHHHCCCCCCCCCHHHHHHHHHHHHHHHHCCCCCCCCCCCCCCCCCCCCCCHHHHHHHHHHHHHHCCCCCCCCCCC
O39198	CCCEEEECCCCCCCEECCCCCCEEEEEEECCCCEEEECCCCCEEEECCCCCEECHHHHHHCCCCCCCCCCCCCCCCCC

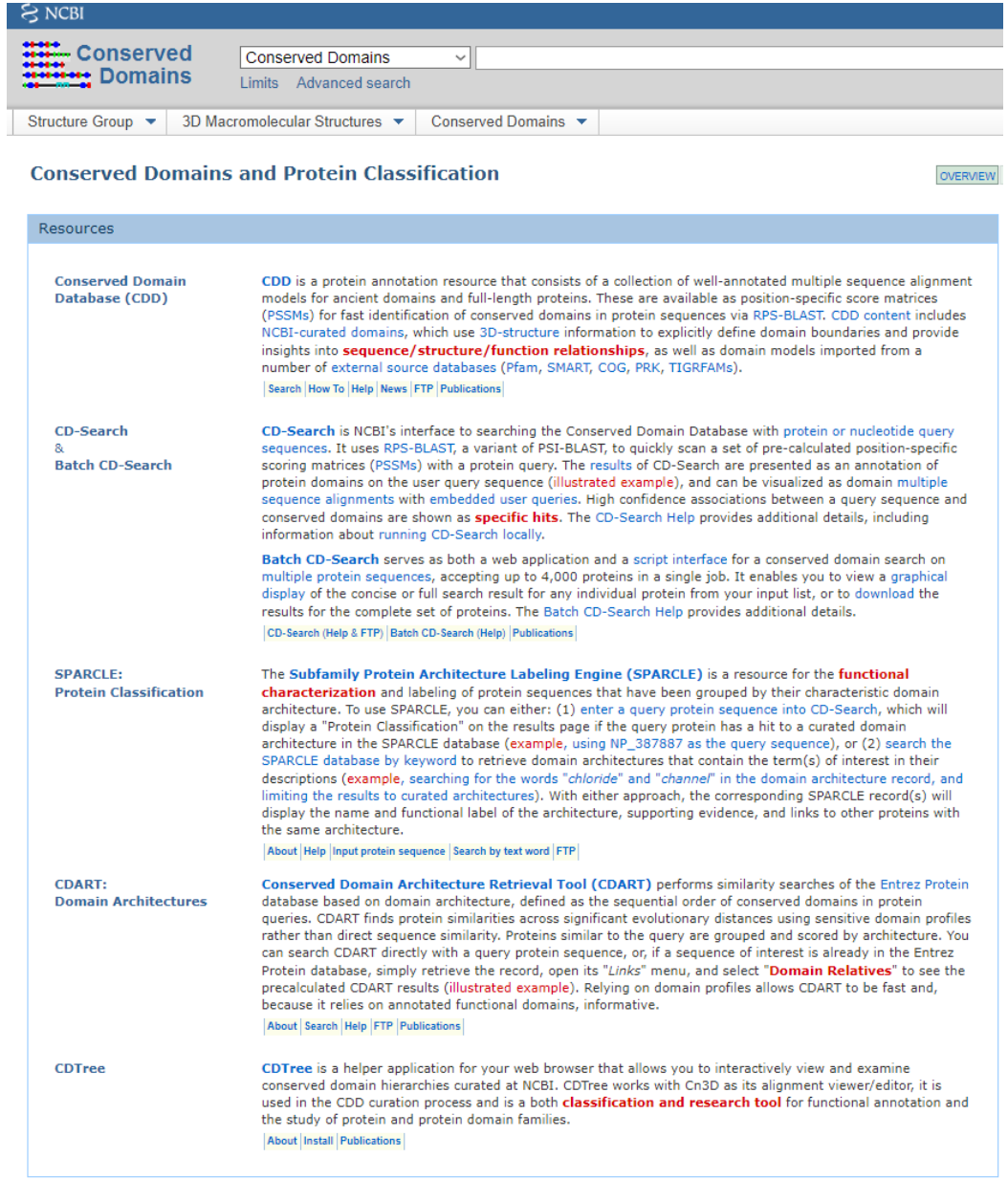
EDA – Secondary Structure

- alpha-helix, which is a regular state denoted by an ‘H’.
- beta-strand, which is a regular state denoted by an ‘E’.
- coil region, which is an irregular state denoted by a ‘C’.



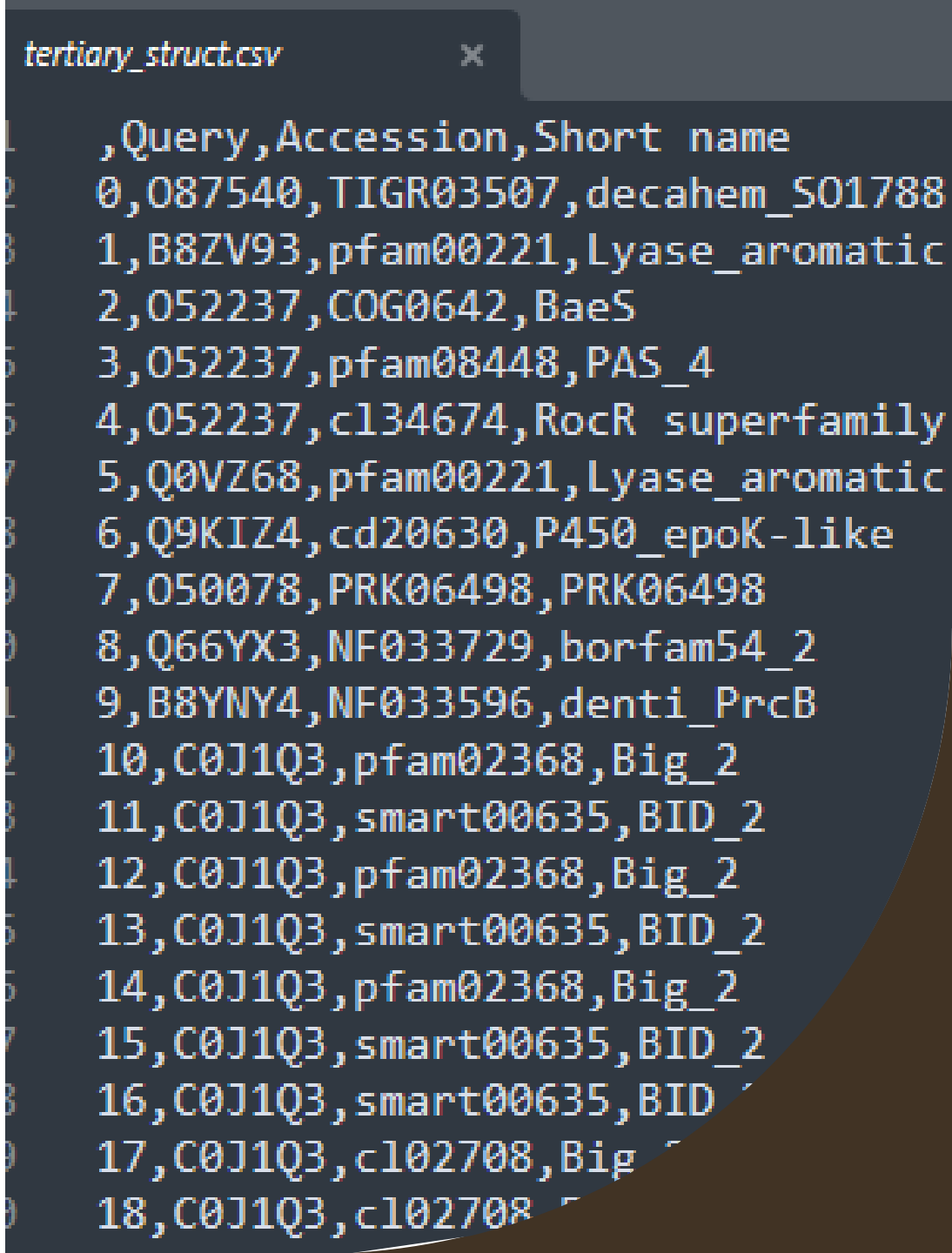
Sample – Tertiary Structure

- Tertiary structure information was obtained from Conserved domains database (CDD) [10]
- CDD uses RPS-BLAST a variation on the PSI-BLAST algorithm to find regions of similarity and obtain hits.
- Only the concise hits with values higher than 0.0001 E-values were selected. To Guarantee the best results
- Due to high traffic the limit was set to 1000 sequence per run.
- Average run time was around thirty minutes to an hour.



Tertiary Structure - Data

- We can observe various motifs and domains discovered within a protein sequence.
- A motif refers to a conserved pattern associated with distinct functions.
- Domain is a 3-D structure, Hence a larger pattern associated with a function.
- A specific Motif can occur multiple times within a sequence.



Single letter code for Amino Acids

Amino acid	1 letter code	3 letter code
Alanine	A	Ala
Arginine	R	Arg
Asparagine	N	Asn
Aspartic acid	D	Asp
Cysteine	C	Cys
Glutamic acid	E	Glu
Glutamine	Q	Gln
Glycine	G	Gly
Histidine	H	His
Isoleucine	I	Ile
Leucine	L	Leu
Lysine	K	Lys
Methionine	M	Met
Phenylalanine	F	Phe
Proline	P	Pro
Serine	S	Ser
Threonine	T	Thr
Tryptophan	W	Trp
Tyrosine	Y	Tyr
Valine	V	Val
Selenomethionine*	X	SeM

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BACUCBARBPAPCACPPAPPBPPCRACUBUBUBAARPBAABPABPAPBARUBCPBAU
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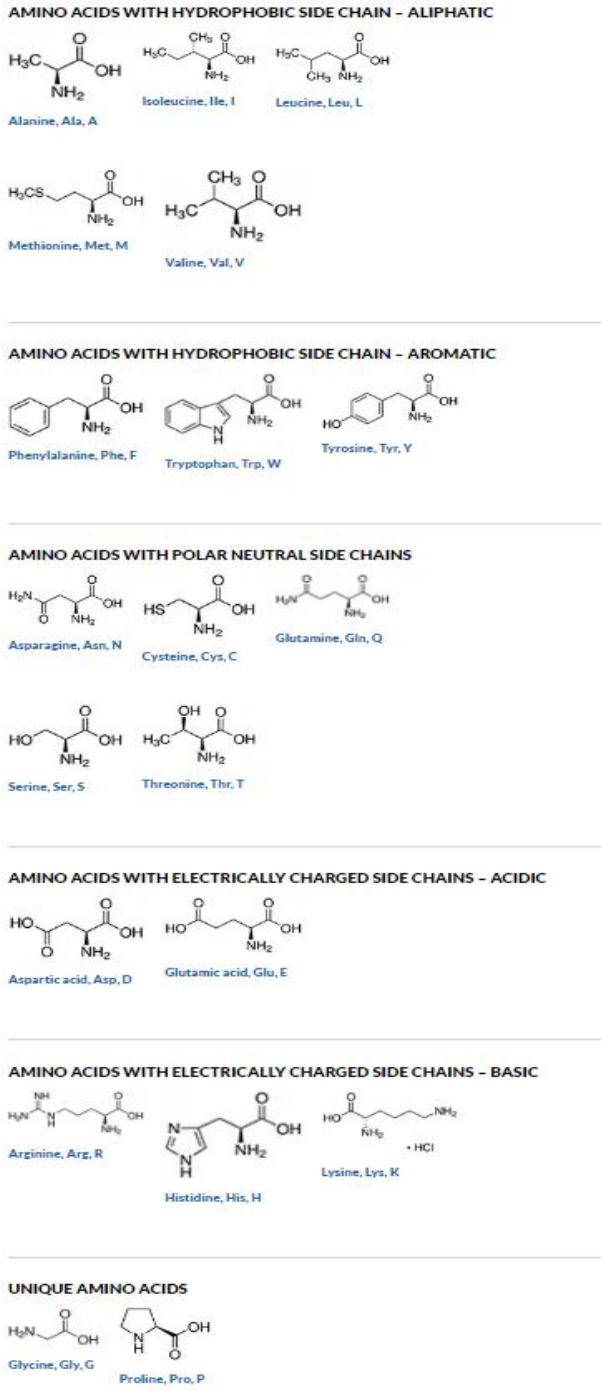
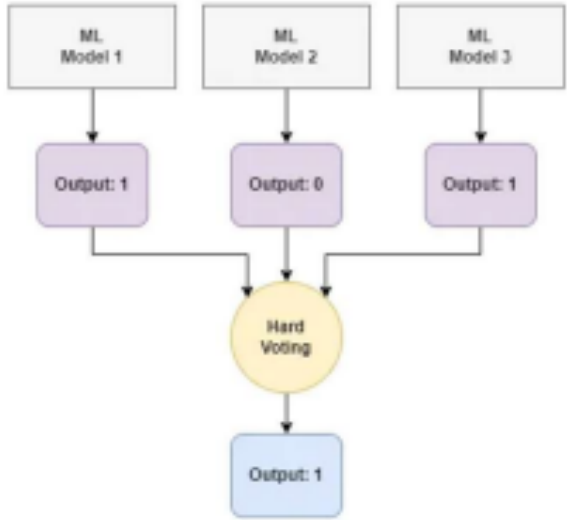


Amino Acid - Properties

- Changed the amino acid sequence and grouped amino acids based on their properties
- Sigma Aldrich. [1]
- (A,I,L,M,V) → Aliphatic Amino Acids (A)
- (F,W,Y) → Aromatic (R)
- (N,C,Q,S,T) → Polar Neutral (P)
- (D,E) → Acidic (C)
- (R,H,K) → Basic (B)
- (G,P) → Unique (U)
- (O,U,Z) → Rare (S)

Ensemble Techniques

- Hard and Soft Voting
- In hard voting, a majority voting mechanism among multiple algorithms is employed to determine the final predictions.
- Soft voting leverages the probability estimates from each algorithm to formulate its predictions.



Standard RNN Language Encoder

AILRST

↓

[1, 8, 10,14, 16, 17]

↓

[[1],[8],[10], [14], [16],[17]]

↓

$$\begin{bmatrix} 0 & 0 & 0 & 0 & 0 & 1 \\ 0 & 0 & 0 & 0 & 1 & 8 \\ 0 & 0 & 0 & 1 & 8 & 10 \\ 0 & 0 & 1 & 8 & 10 & 14 \\ 0 & 1 & 8 & 10 & 14 & 16 \\ 1 & 8 & 10 & 14 & 16 & 17 \end{bmatrix}$$

Amino Acid Grouping RNN Encoder

AILRST

↓

[1, 8, 10,14, 16, 17]

↓

[[1, 8, 10], [14], [16,17]]

↓

$$\begin{bmatrix} 0 & 0 & 0 & 1 & 8 & 10 \\ 0 & 0 & 1 & 8 & 10 & 14 \\ 1 & 8 & 10 & 14 & 16 & 17 \end{bmatrix}$$

Singular Value Decomposition (SVD)

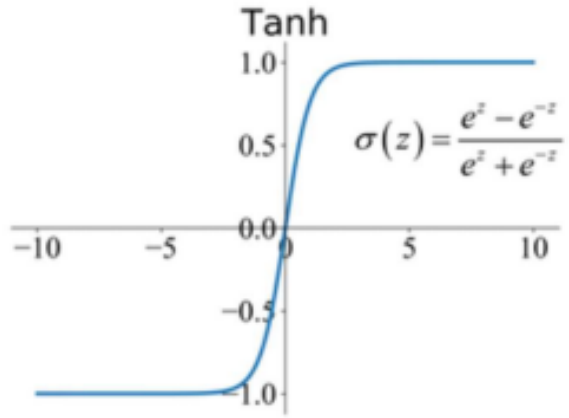
- Dimensionality reduction algorithm
- Condense the sparse array to a size of 28x28.
- The SVD is a matrix can be interpreted as the factorization of a matrix of three other matrices.

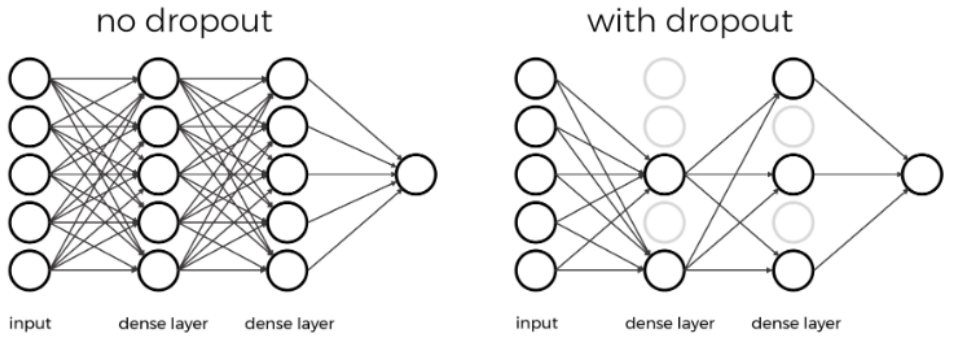
$$A = U \sum V^T$$

- U is the mxm matrix of the orthonormal eigenvectors of AA^T
- V^T is the transpose of nxn matrix containing the orthonormal eigenvectors of A^TA
- **Σ** is the diagonal matrix with r elements equal to the root of the positive eigenvalues AA^T or A^TA

RNN Application

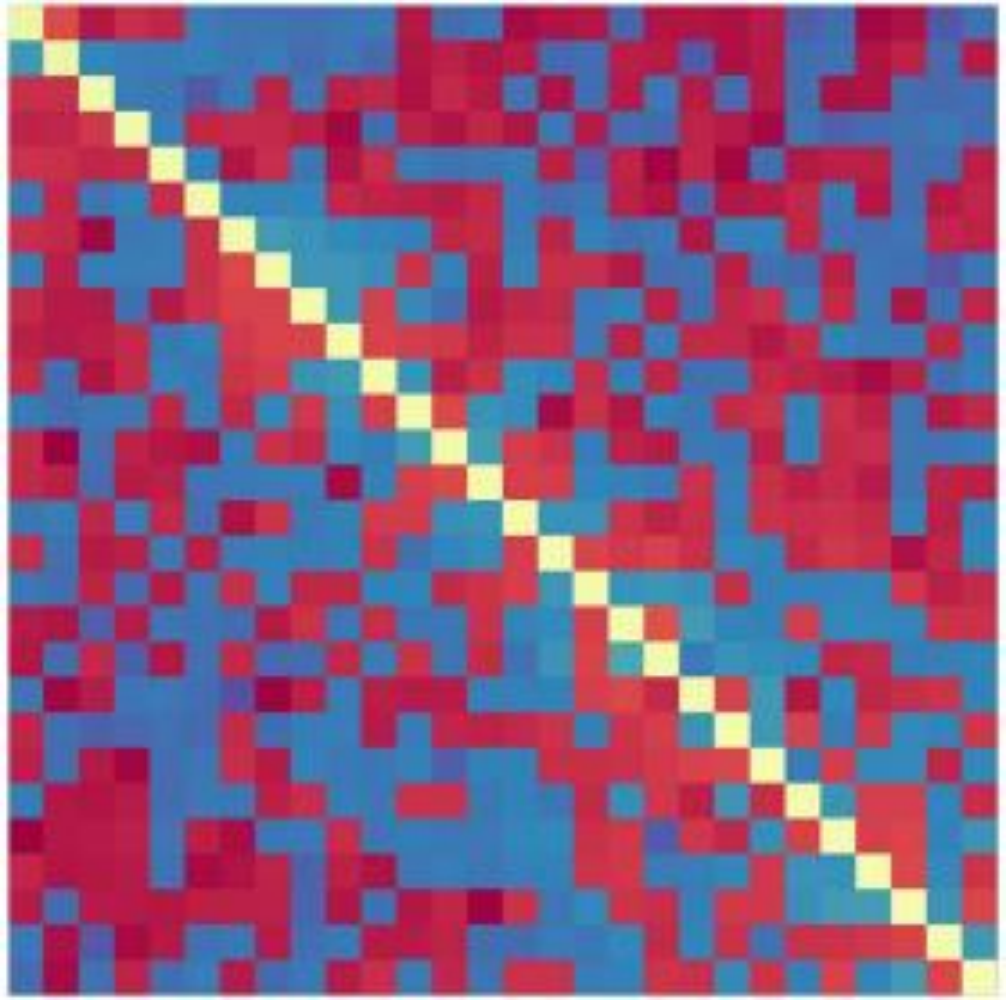
- RNNs are computationally intensive, rendering them more efficient when executed on a Graphics Processing Unit.
- Sequences exceeding 500 amino acids, truncation to the first 500 amino acids was necessary due to computational intensity
- For GPU execution, the activation function is modified from Rectified Linear Unit (ReLU) to Hyperbolic Tangent (Tanh)
- Drop Out layers





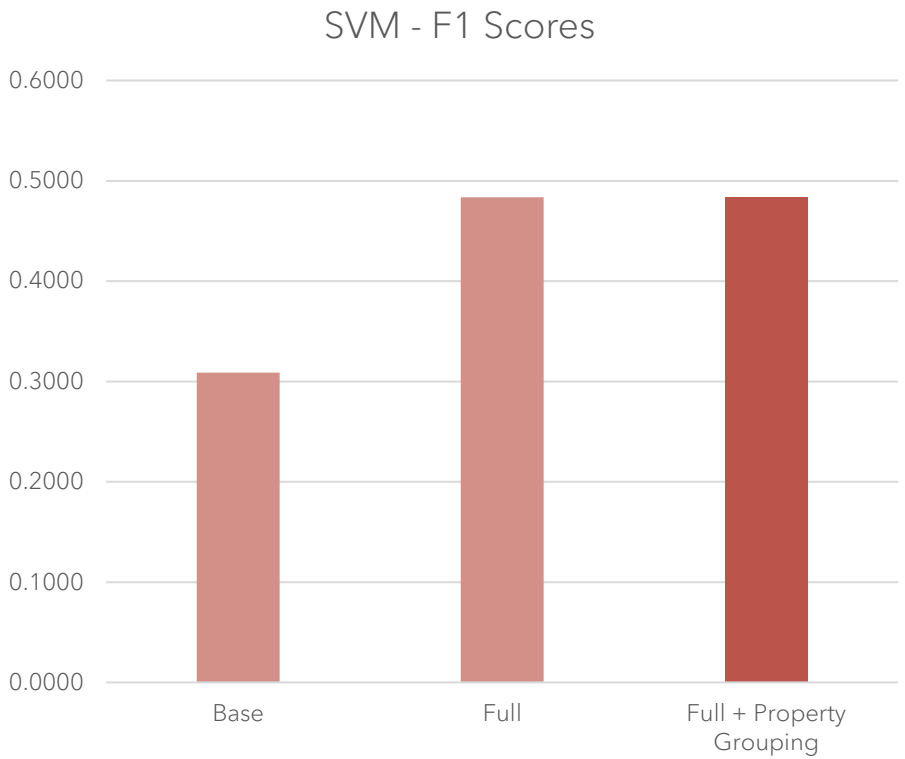
CNN – QR Code of Life

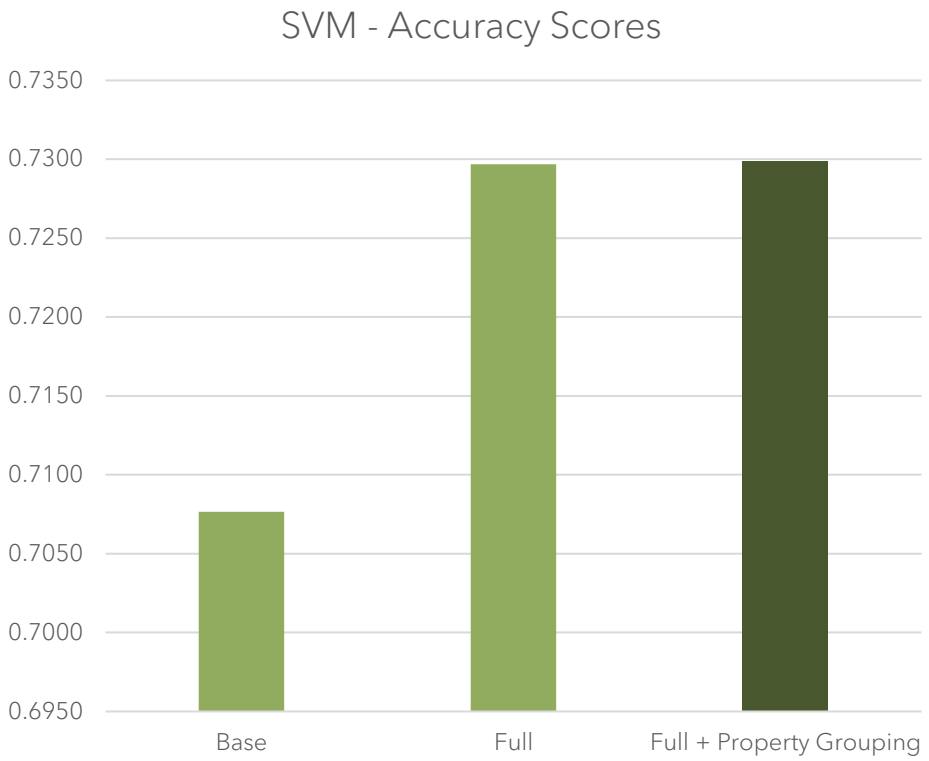
- A heatmap represents the matrix as an image
- Enhance data visualization, natural logarithm transformation is applied
- ColorNet: Investigating the importance of color spaces for image classification. In *Computer Vision–ACCV 2018:* RGB coloring was used as the study dictates that RGB yielded better results compared to other color formats. [6]
- Ada-Delta optimizer [7]
- Pooling Layers



Results

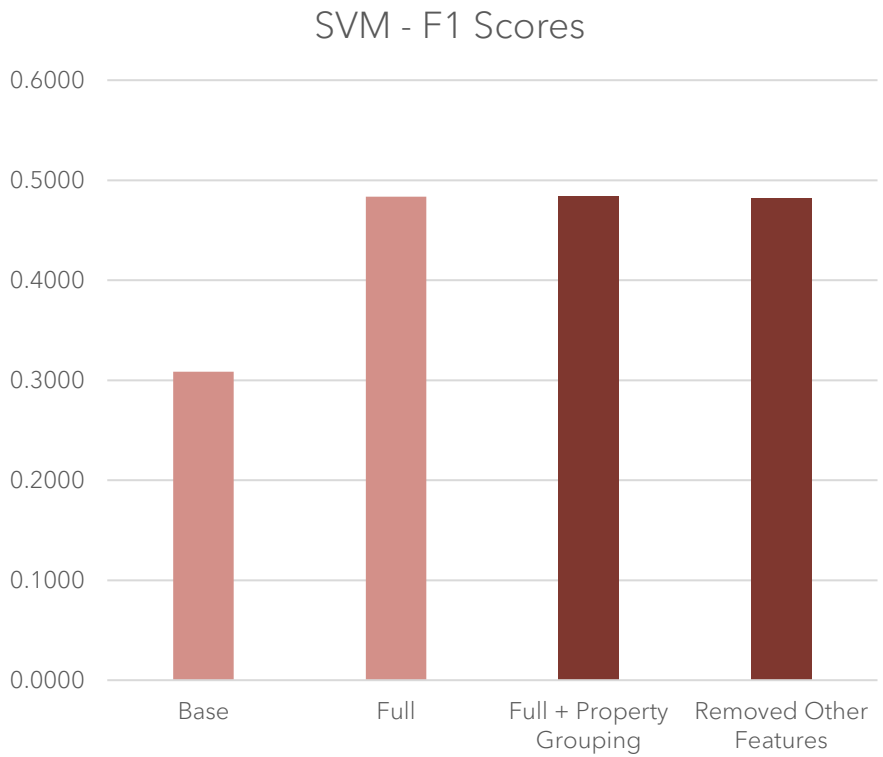
SVM Results

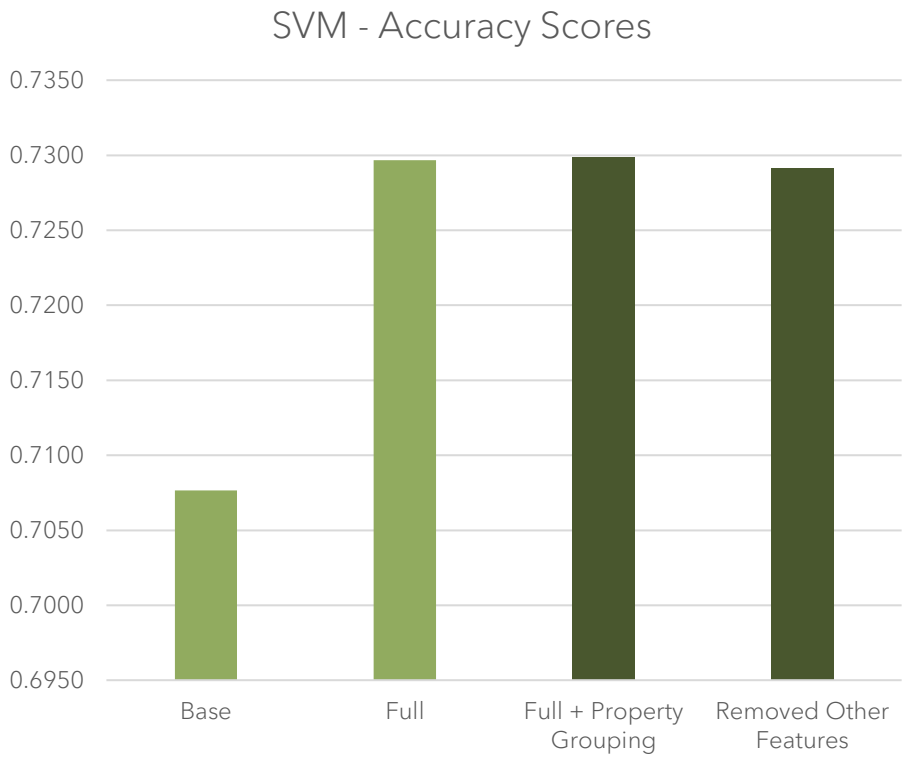




- Base - Amino Acid Counts
- Full – pKa, Amino Acid TFIDF, Secondary Structure TFIDF, Tertiary Structures, Hydrophobicity
- Full + Property Grouping - Addition of Property grouping to the previous data set

SVM Results

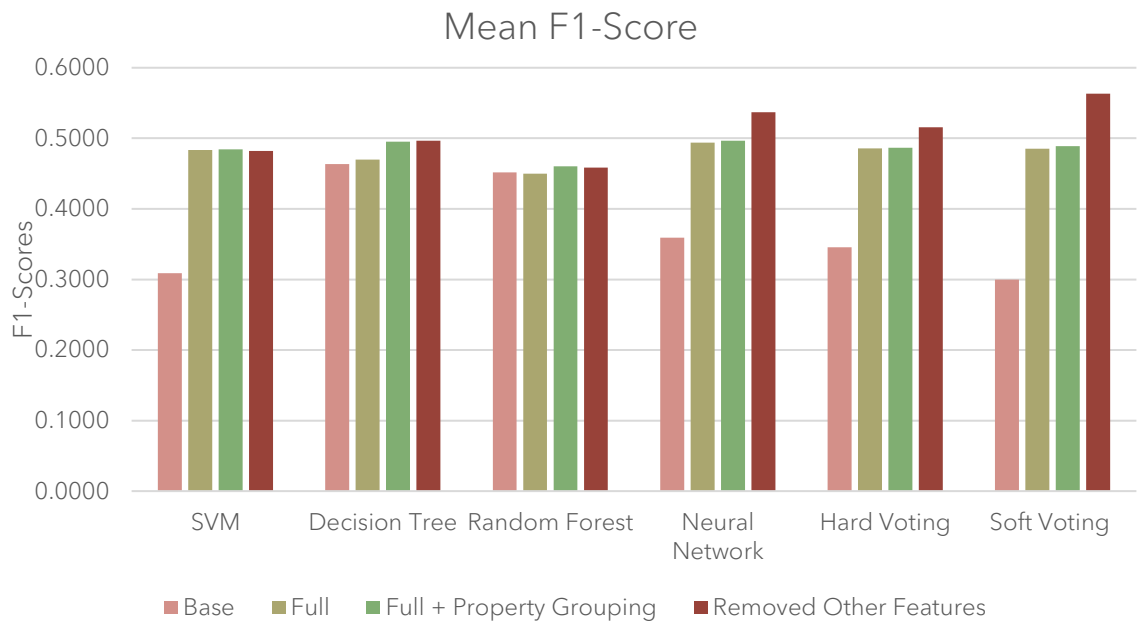


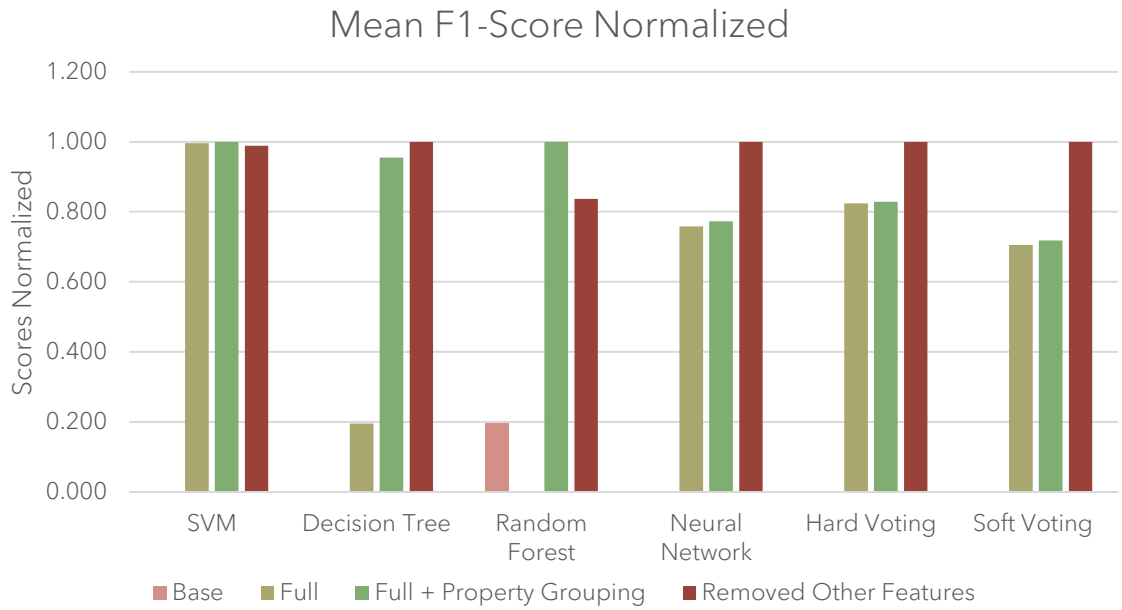


- Base - Amino Acid Counts
- Full – pKa, Amino Acid TFIDF, Secondary Structure TFIDF, Tertiary Structures, Hydrophobicity
- Full + Property Grouping - Addition of Property grouping to the previous data set.
- Removed – Amino Acid TFIDF, Tertiary Structures, and Property Grouping

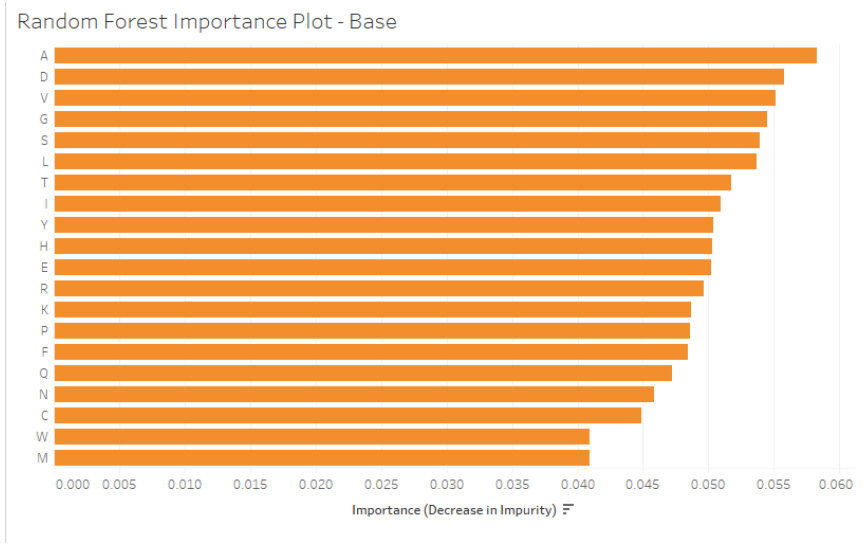
Mean F1- Scores

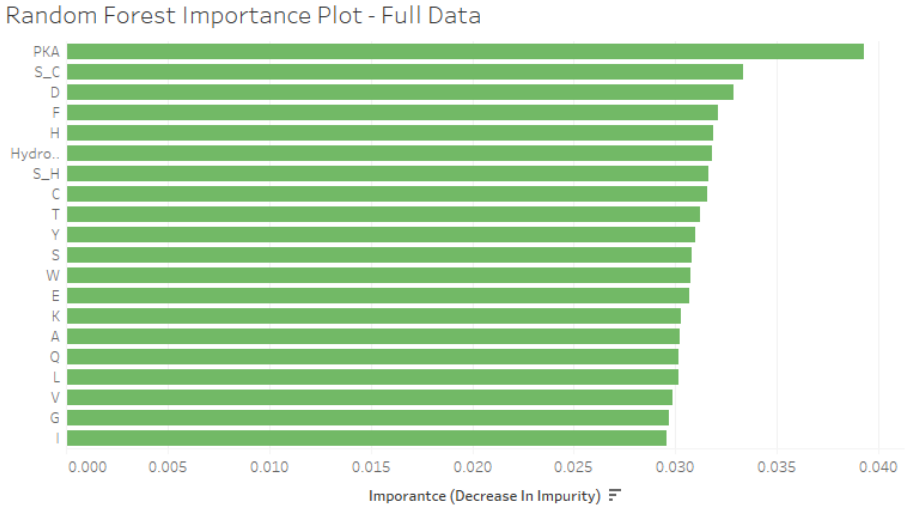
- We can observe the min-max normalization was applied to the scores for each algorithm, facilitating a clearer visualization
- SVM and Random Forest were the sole algorithms that exhibited improved performance with the full dataset and property grouping
- Other algorithms exhibited a stronger preference for the removed features

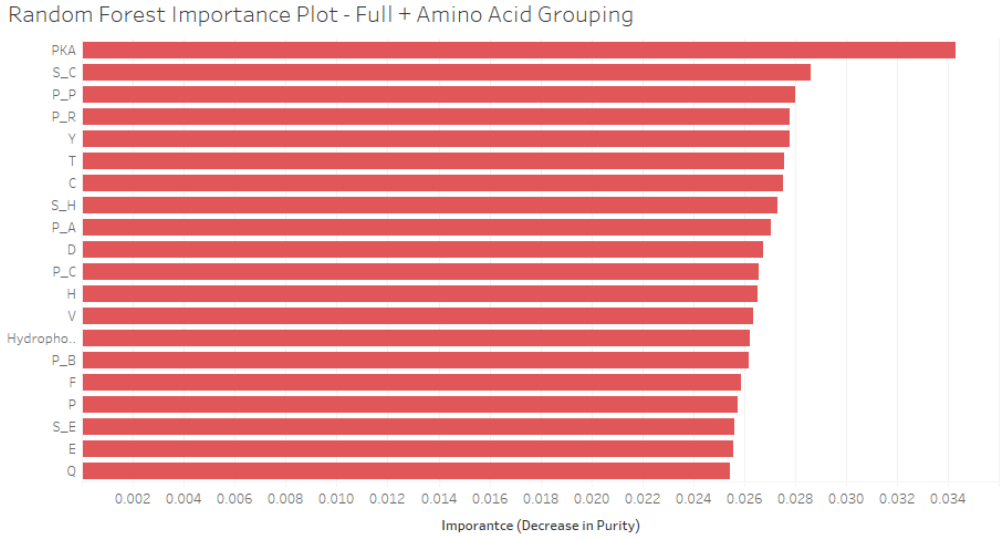


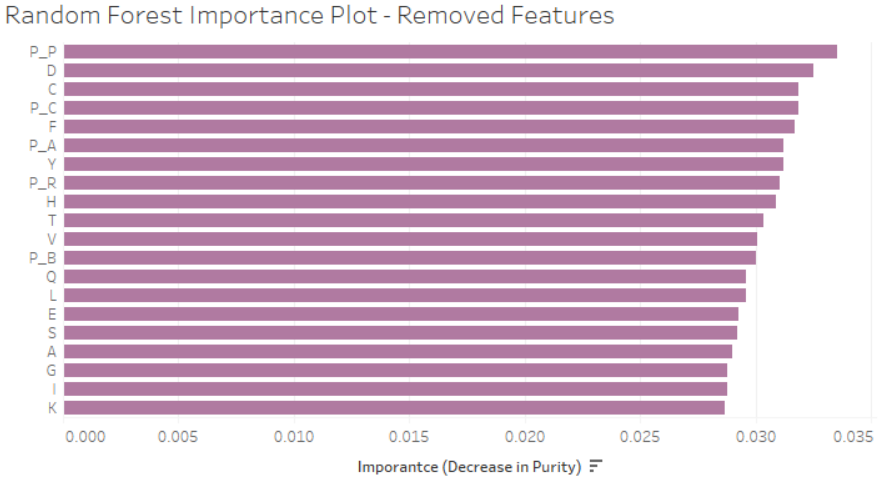


Random Forest Importance Plots



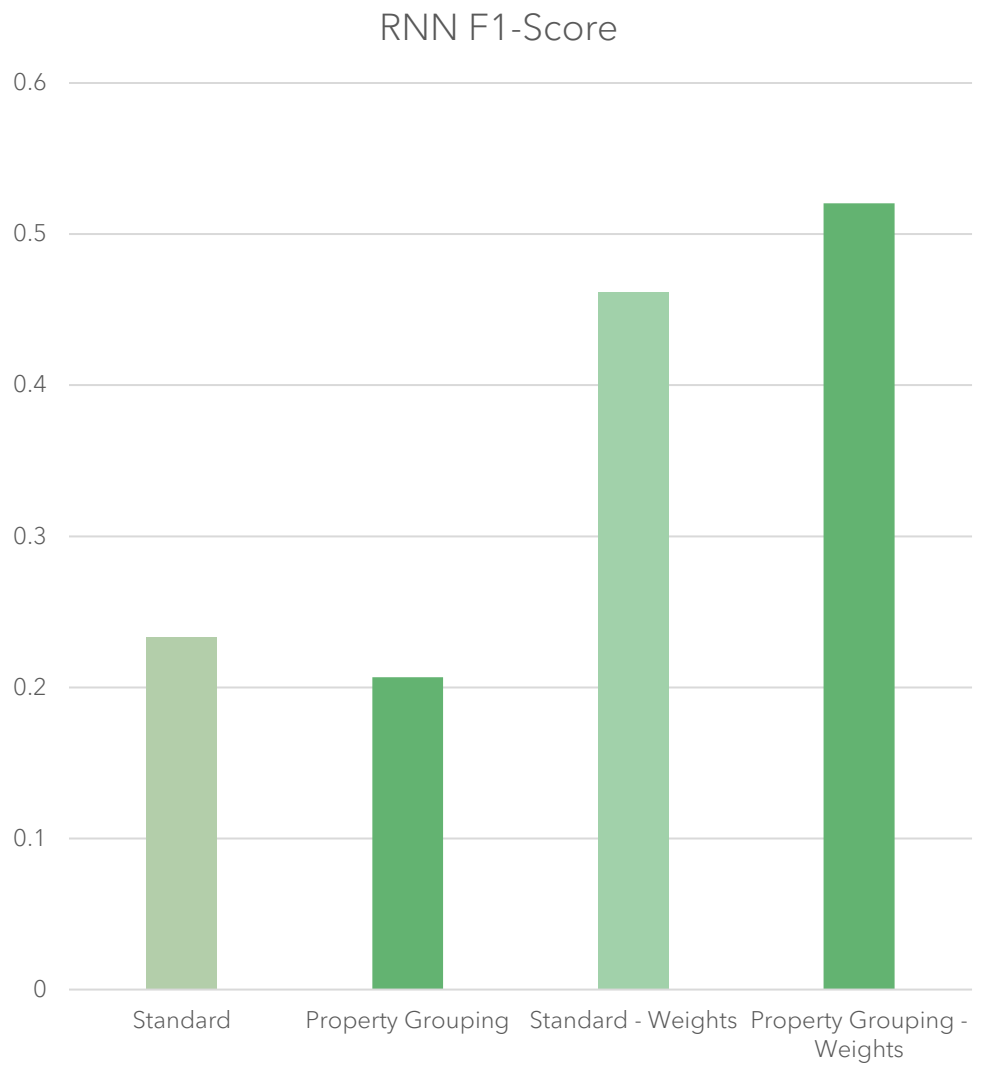






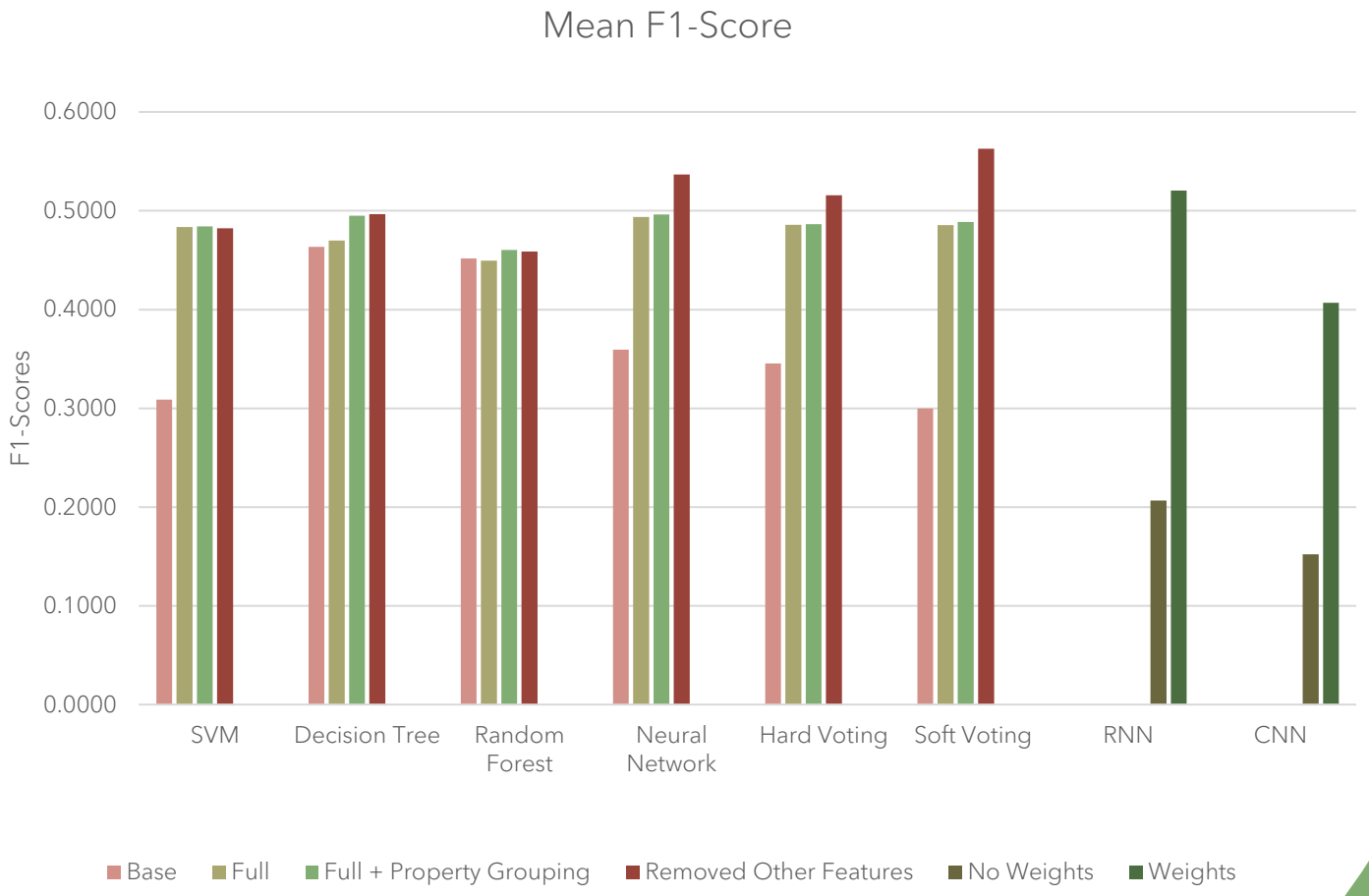
Standard Encoder

- We can observe that our Property Grouping Encoder outperformed the standard encoder.
- Hence, the property encoder was used for the CNN.
- Addition of weights helped obtain better F1-Scores.



Mean Scores For RNN and CNN

- F1-scores indicated suboptimal performance, potentially attributed to overgeneralization and insufficient data for neural network training.
- Considering the imbalance in our dataset, class weights were introduced to enhance balance and consistency
- The assertion that the imbalanced dataset contributed to performance disparities F1-scores for each protein function. For example, Molecular function consistently achieved the highest accuracy and F1-scores across all algorithms (0.86).



Conclusion and Future Work

Conclusions

- Amino acid property grouping technique shows promise for predicting protein sequence function.
- Deliberate introduction of high variance in sample data is crucial, impacting the significance of each feature.
- Despite intentional variance, property grouping technique demonstrates minimal loss in predictive power.
- SVM and decision tree algorithms exhibit capacity for property grouping without substantial decline in predictive ability.
- Neural network and voting algorithms show improved scores with the introduction of amino acid property grouping.
- Recurrent neural networks (RNN) and convolutional neural networks (CNN) achieve comparable F1-scores to feature-embedded algorithms with class weights, but technical constraints may contribute to suboptimal performance.

Future Work

- Further analyses are needed before confirming the significance of this property grouping.
- Alternative sampling techniques should be explored to assess model performance under reduced sequence variance.
- Sampling strategies ensuring a balanced distribution of functions could provide additional insights.
- High-performance computation can be leveraged to utilize the entire dataset, mitigating concerns about data imbalance.
- The Transformer algorithm, with its multidirectional processing and attention mechanisms, holds promise for protein function prediction. [11]
- Recent publications explore Transformer architectures for protein sequences, but none align with the concept of amino acid property grouping.
- A specialized encoder based on amino acid grouping could be integrated into a Transformer encoder for enhanced protein function prediction.

Motivation and Inspiration

- Background in Bioinformatics
- A unique look at a problem
- This work was inspired by several researches within the field
- An attempt to try and make a difference in an immerging field of research.
- Still a lot more work to be done. However, through our preliminary work we have shown that there is some promise to the property binning technique which requires further investigation.


Thank you

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