TEAM: The Phospho Force

Protein Function Prediction

(Differentiating Kinases for Targeted Drug Discovery)

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Data science Boot Camp: Spring 2023

Why Kinases?

- Central Role in Cell Signalling
- Abundance and Diversity
- Druggability
- Potential for Combination Therapies
- Biomarkers and Pharmacodynamics
- Versatility and Adaptability

Stakeholders

- Pharmaceutical & Biotechnology Companies
- Academic and Research Institutions
- Regulatory Bodies
- Investors and Funding Agencies
- Government and Policy Makers
- Ethics Committees

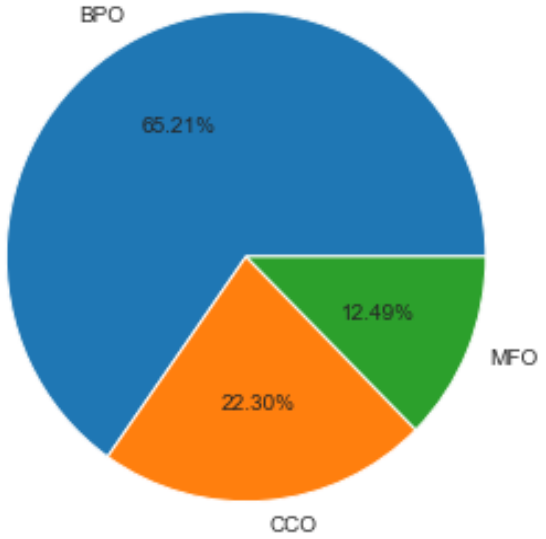
Objective

- **Predict the GO term based on the sequence**
- **A classification problem**

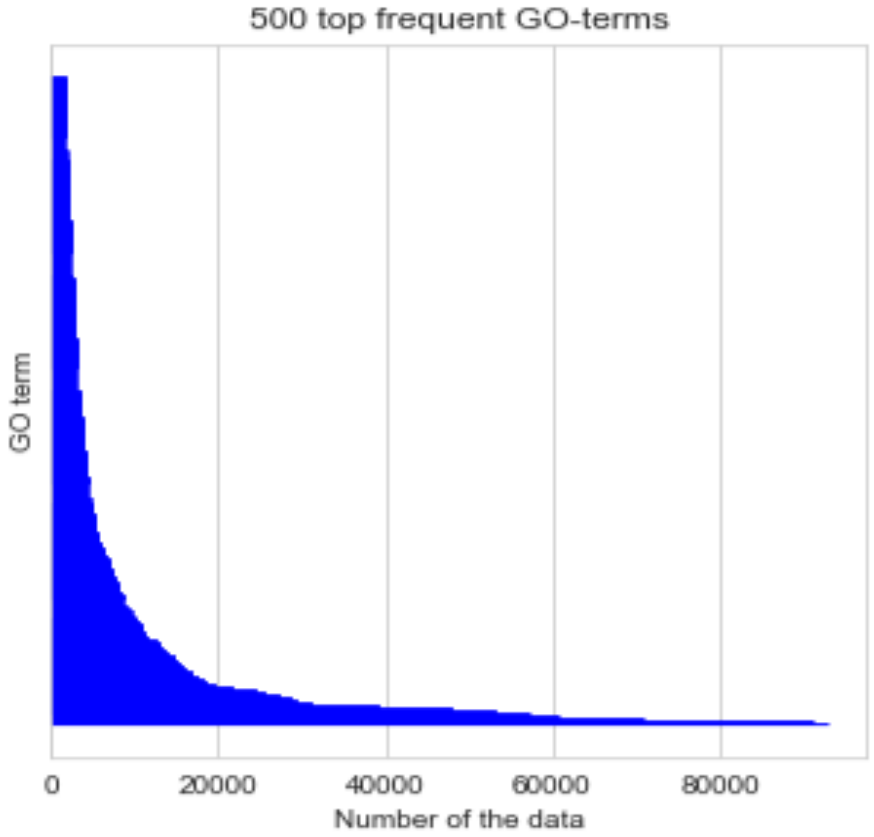
Data

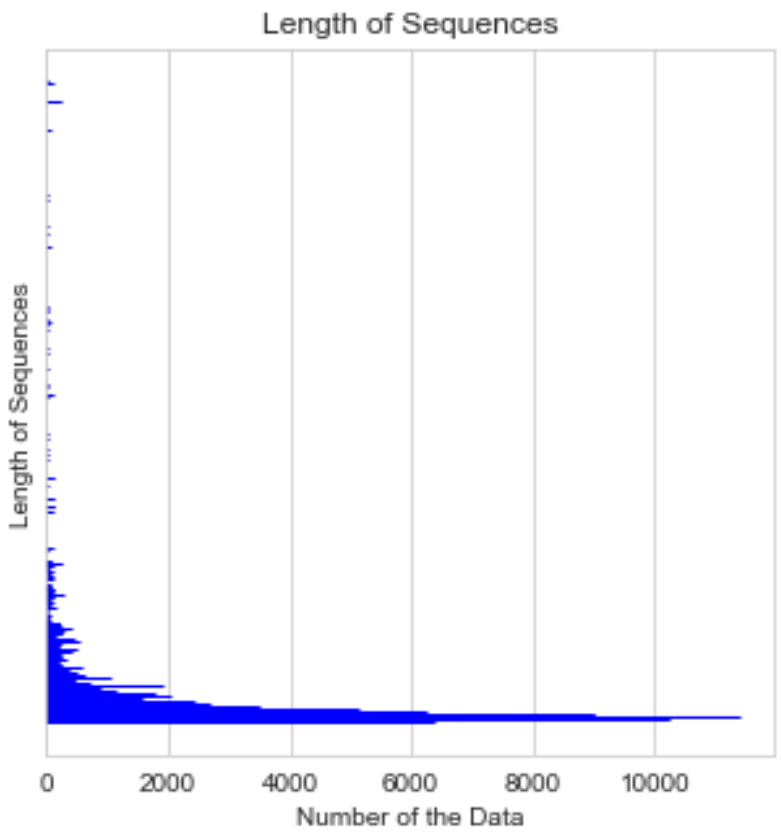
- **5,363,863 proteins (= # of rows)**
- **Length of sequence ranges from 3 to 11391 with a focus under 1500.**
- **31,466 different GO terms (classes)**

	seq_id	sequence	term	aspect
0	P20536	MNSVTVSHAPYTITYHDDWEPVMSQLVEFYNEVASWLLRDETSPIP...	0008152	BPO
1	P20536	MNSVTVSHAPYTITYHDDWEPVMSQLVEFYNEVASWLLRDETSPIP...	0071897	BPO
2	P20536	MNSVTVSHAPYTITYHDDWEPVMSQLVEFYNEVASWLLRDETSPIP...	0044249	BPO
3	P20536	MNSVTVSHAPYTITYHDDWEPVMSQLVEFYNEVASWLLRDETSPIP...	0006259	BPO
4	P20536	MNSVTVSHAPYTITYHDDWEPVMSQLVEFYNEVASWLLRDETSPIP...	0009059	BPO



Exploratory Data Analysis





Data Setup

term	name	namespace	EntryID	aspect	sequence
GO:0033549	MAP kinase phosphatase activity	molecular_function	P35182	MFO	MSNHSEILERPETPYDITYRVGVAENKNSKFRRTMEDVHTYVKNFA...
GO:1990439	MAP kinase serine/threonine phosphatase activity	molecular_function	P35182	MFO	MSNHSEILERPETPYDITYRVGVAENKNSKFRRTMEDVHTYVKNFA...
GO:0004672	protein kinase activity	molecular_function	Q0KHV6	MFO	MSVRLLTVRLIKHGRYILRSYCKRDIHANILDQNQLKTRSKRGFPL...
GO:0004674	protein serine/threonine kinase activity	molecular_function	Q0KHV6	MFO	MSVRLLTVRLIKHGRYILRSYCKRDIHANILDQNQLKTRSKRGFPL...
GO:0016301	kinase activity	molecular_function	Q0KHV6	MFO	MSVRLLTVRLIKHGRYILRSYCKRDIHANILDQNQLKTRSKRGFPL...

Pre-processing:

- Random subsample (n=2000, 10000, 60000)
- Select 100 most frequent GO terms
- Filter for kinases

Classification Models:

- Random Forest
- SVM
- Keras Neural Network

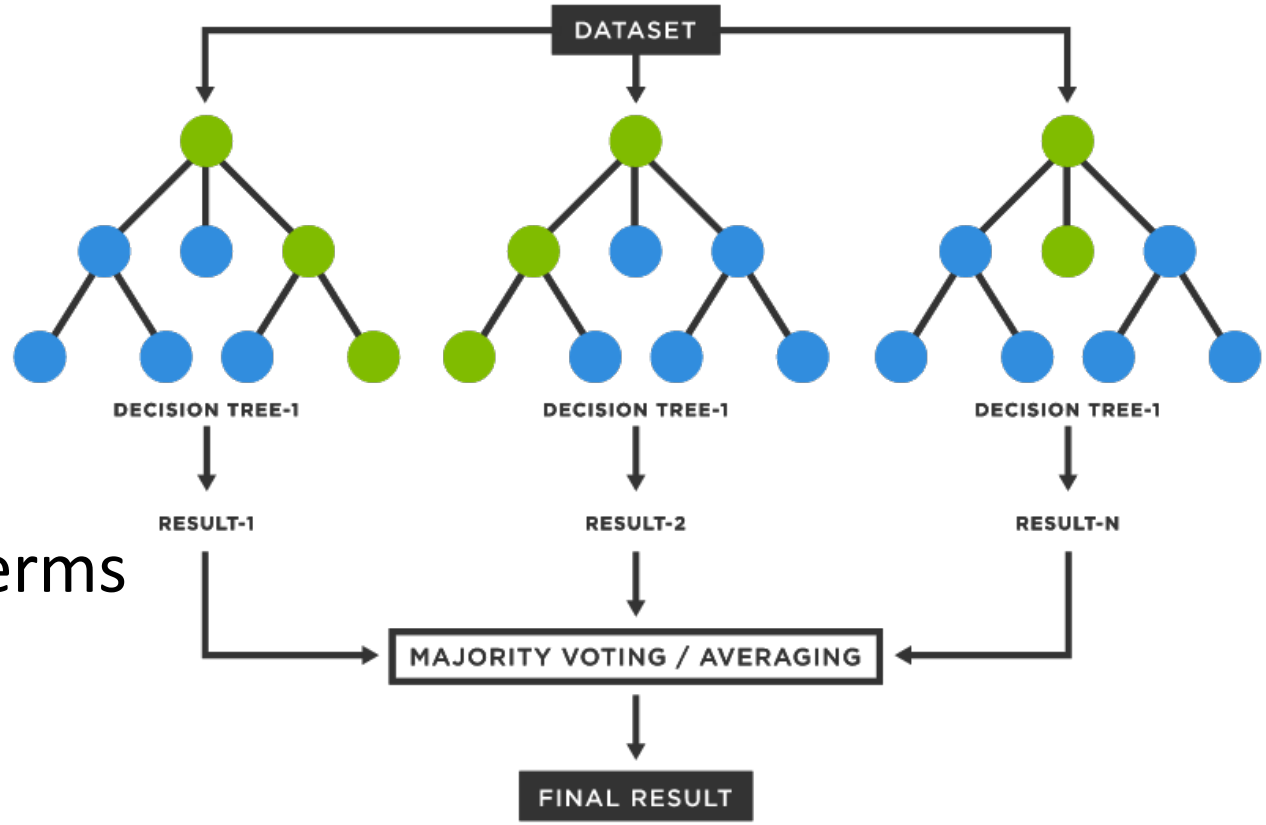
Random Forest

Limitations:

- Computational resources
- Time

Solution:

- Select 100 most frequent GO terms
- Truncate sequence
- Encode target labels with Label_Encoder()
- Accuracy = 2.1%



https://www.tibco.com/reference-center/what-is-a-random-forest

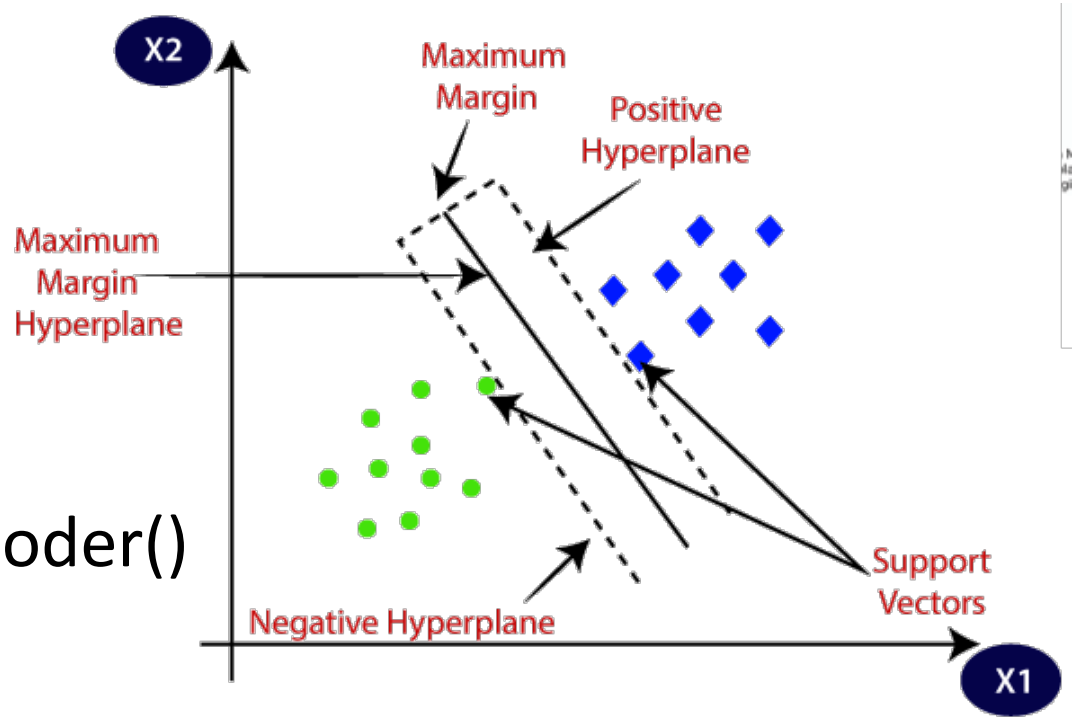
SVM

Limitations:

- Computational resources
- Time

Solution 1:

- Select 100 most frequent GO terms
- Truncate sequence
- Encode target labels with Label_Encoder()
- Accuracy = 2.1%



Solution 2:

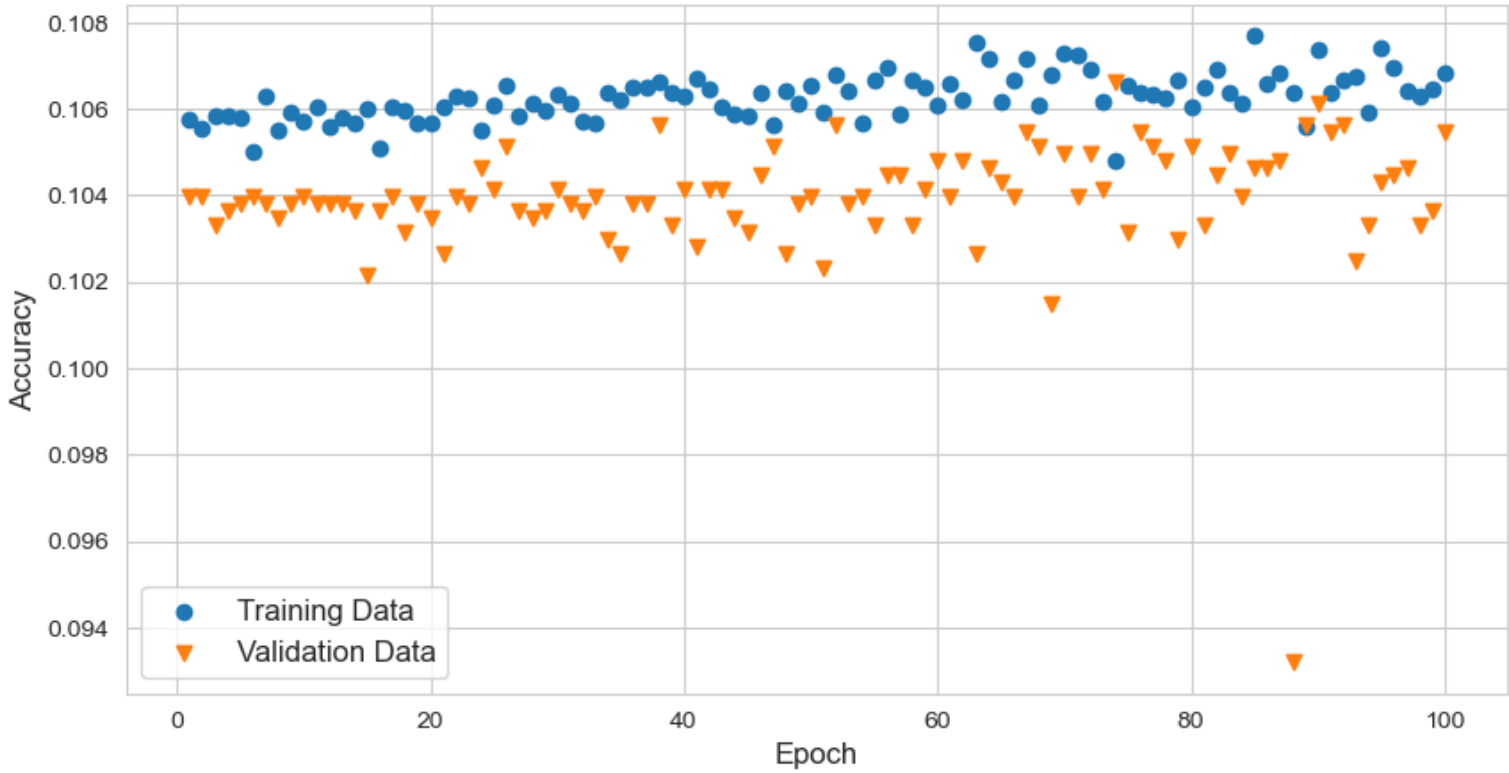
- Filter for kinases
- Vectorize with TfidfVectorizer()
- Accuracy = 8.9%

https://www.analyticsvidhya.com/blog/2021/10/support-vector-machinessvm-a-complete-guide-for-beginners/

Keras

- **Limitations:**
  - Computational resources
  - Time
  - For ex)
    - Epochs = 100
    - Subsample_size = 10,000
    - Batch_size = 32

    --> 6.3 years to run



- **Solution:**
  - K-mer numeric representation
  - Filter for kinases
  - Accuracy = 10-11%
  - Choose less expensive layers

    ex) GlobalAveragePooling1D over LSTM

Conclusion

- Keras neural network performed best at 10-11%
- Optimization would require greater memory capacity
- Future prospective:
  - Optimize:
    - Layer choice
    - Batch size
    - Encoding strategy
  - Identify signature sequences on predicted kinases
  - Differentiate prokaryotic and eukaryotic kinases
  - Comparative proteomics studies