Protein families classification using Machine/Deep Learning

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Motivation/Objective:

- Proteins are the complex biomolecules that plays an important role in living organism.
- Proteins are made up of amino acids; a long chain of chemical units represented by alphabets
- There are 20 most common amino acids that are arranged randomly in a sequence which generates millions of unique proteins
- Traditional experimental methods uses chemical and physical properties to classify protein families, which is complex and time consuming
- This project aims to classify protein families using several Machine/Deep Learning approaches.

Data wrangling

- Protein sequence data is downloaded from Kaggle. (https://www.kaggle.com/shahir/protein-data-set)
- There are two data files, one contains protein sequence whereas other is physical and chemical properties of protein.
- More than 85000 instances are present in the datasets
- Each features are carefully examine for missing values and the missing instances are removed from the data set.
- After cleaning, approximately 75000 instances are available for the further steps.

Understanding data

Dataset 1

```
Data columns (total 14 columns):
 #   Column                    Non-Null Count   Dtype
---  ------                    --------------   -----
 0   structureId               141401 non-null  object
 1   classification            141399 non-null  object
 2   experimentalTechnique     141401 non-null  object
 3   macromoleculeType         137636 non-null  object
 4   residueCount              141401 non-null  int64
 5   resolution                128589 non-null  float64
 6   structureMolecularWeight  141401 non-null  float64
 7   crystallizationMethod     96242 non-null   object
 8   crystallizationTempK      97039 non-null   float64
 9   densityMatthews           124724 non-null  float64
 10  densityPercentSol         124749 non-null  float64
 11  pdbxDetails               118534 non-null  object
 12  phValue                   105110 non-null  float64
 13  publicationYear           117602 non-null  float64
```

Dataset 2

```
 #   Column             Non-Null Count   Dtype
---  ------             --------------   -----
 0   structureId        104813 non-null  object
 1   chainId            104812 non-null  object
 2   sequence           104812 non-null  object
 3   residueCount       104813 non-null  int64
 4   macromoleculeType  101336 non-null  object
```

Amino acids are represented by alphabets

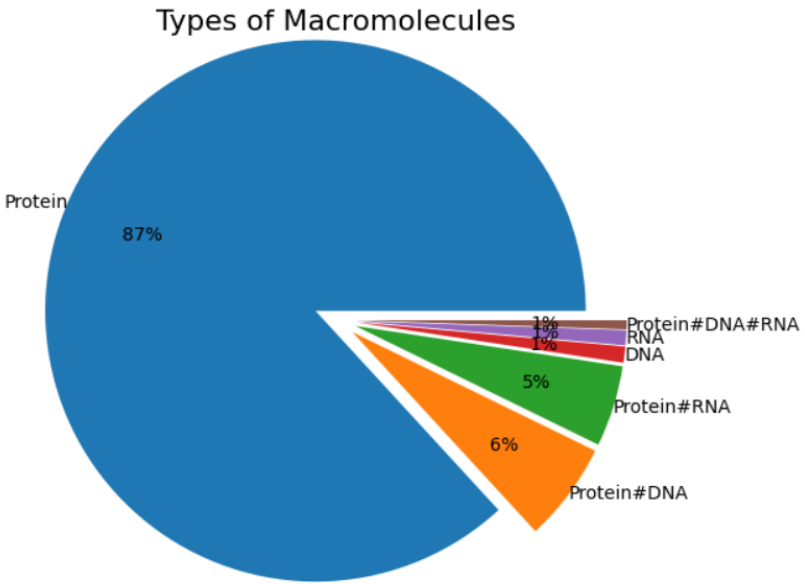
Amino Acid	3-Letter Code	1-Letter Code
Alanine	Ala	A
Cysteine	Cys	C
Aspartic acid or aspartate	Asp	D
Glutamic acid or glutamate	Glu	E
Phenylalanine	Phe	F
Glycine	Gly	G
Histidine	His	H
Isoleucine	Ile	I
Lysine	Lys	K
Leucine	Leu	L
Methionine	Met	M
Asparagine	Asn	N
Proline	Pro	P
Glutamine	Gln	Q
Arginine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

“Hydrolase” family with 286 amino acid units

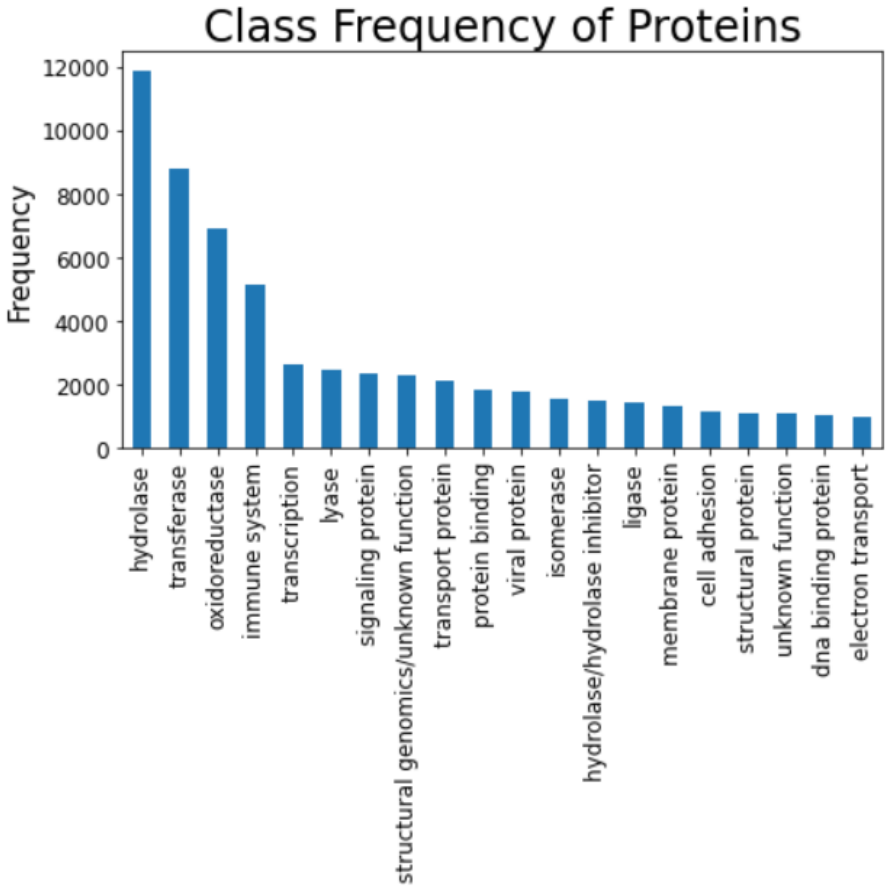
```
'TYTTRQIGAKNTLEYKV
YIEKDGKPVSAFHDIPLY
ADKENNIFNMVVEIPRWT
NAKLEITKEETLNPIIQD
TKKGKLRFVRNCFPHHGY
IHNYGAFPQTWEDPNVSH
PETKAVGDNEPIDVLEIG
ETIAYTGQVKQVKALGIM
ALLDEGETDWKVIAIDIN
DPLAPKLNDIEDVEKYFP
GLLRATNEWFRIYKIPDG
KPENQFAFSGEAKNKKYA
LDIIKETHDSWKQLIAGK
SSDSKGIDLTNVTLPDTP
TYSKAASDAIPPASLKAD
APIDKSIDKWFFISGSV'
```

Protein families	Numerical Labels:
'hydrolase'	: 1
'hydrolase/hydrolase inhibitor'	: 13
'immune system'	: 4
'isomerase'	: 12
'ligase'	: 14
'lyase'	: 6

Exploratory Data Analysis



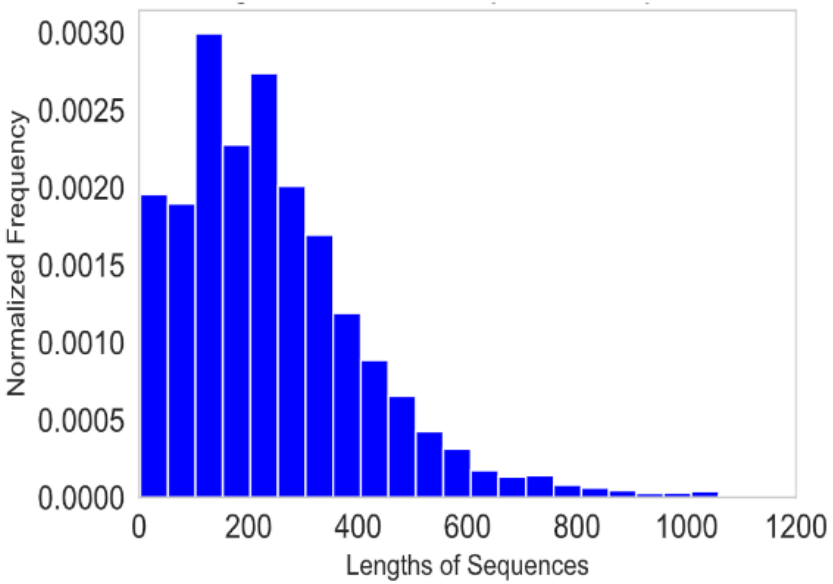
87% of Macromolecules belong to Protein



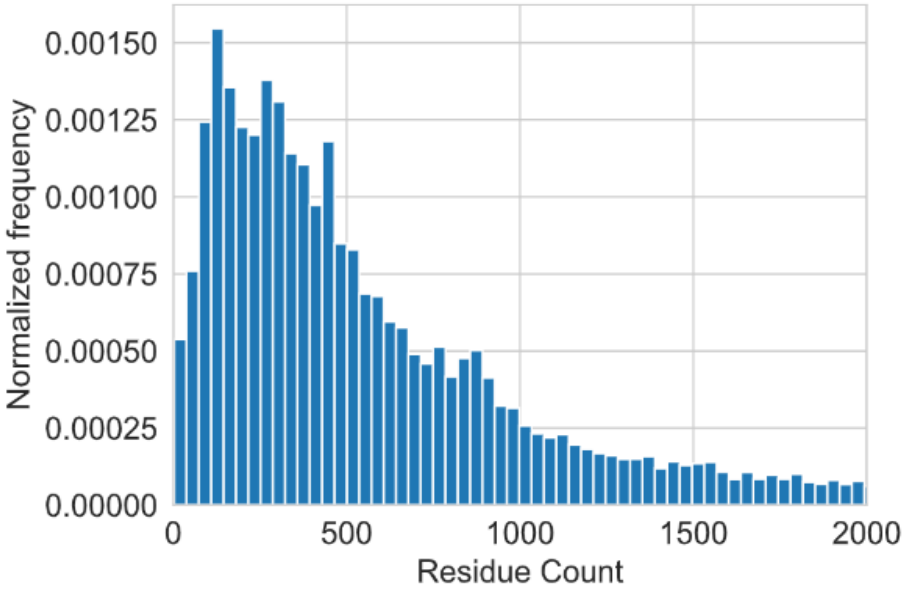
Protein family class (label)

Exploratory Data Analysis

Normalized frequency distribution:



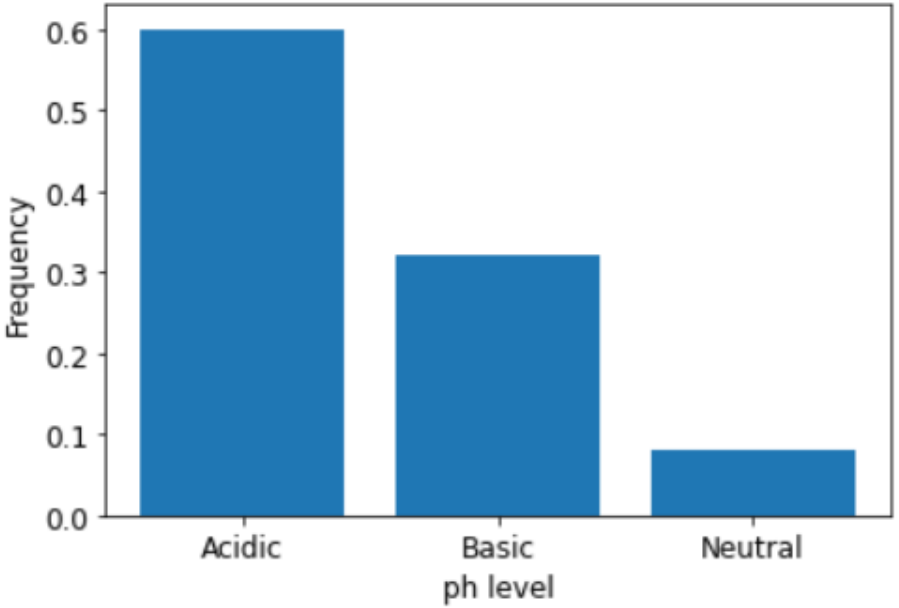
Majority of sequences have lengths less than 500 units



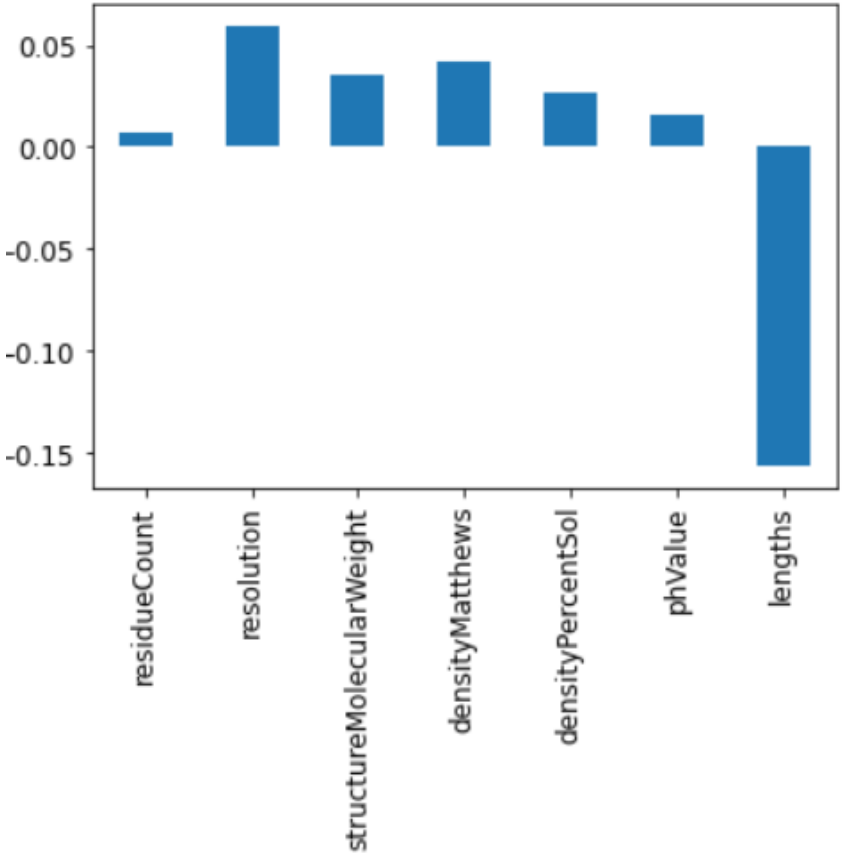
number of residues in macromolecules

a residue refers to a single unit that makes up an amino acid in a protein

Exploratory Data Analysis



Features correlation with the classes label



Acidic: PhValue < 7
Basic: PhValue > 7
Neutral: PhValue = 7

Part I: Machine Learning Models

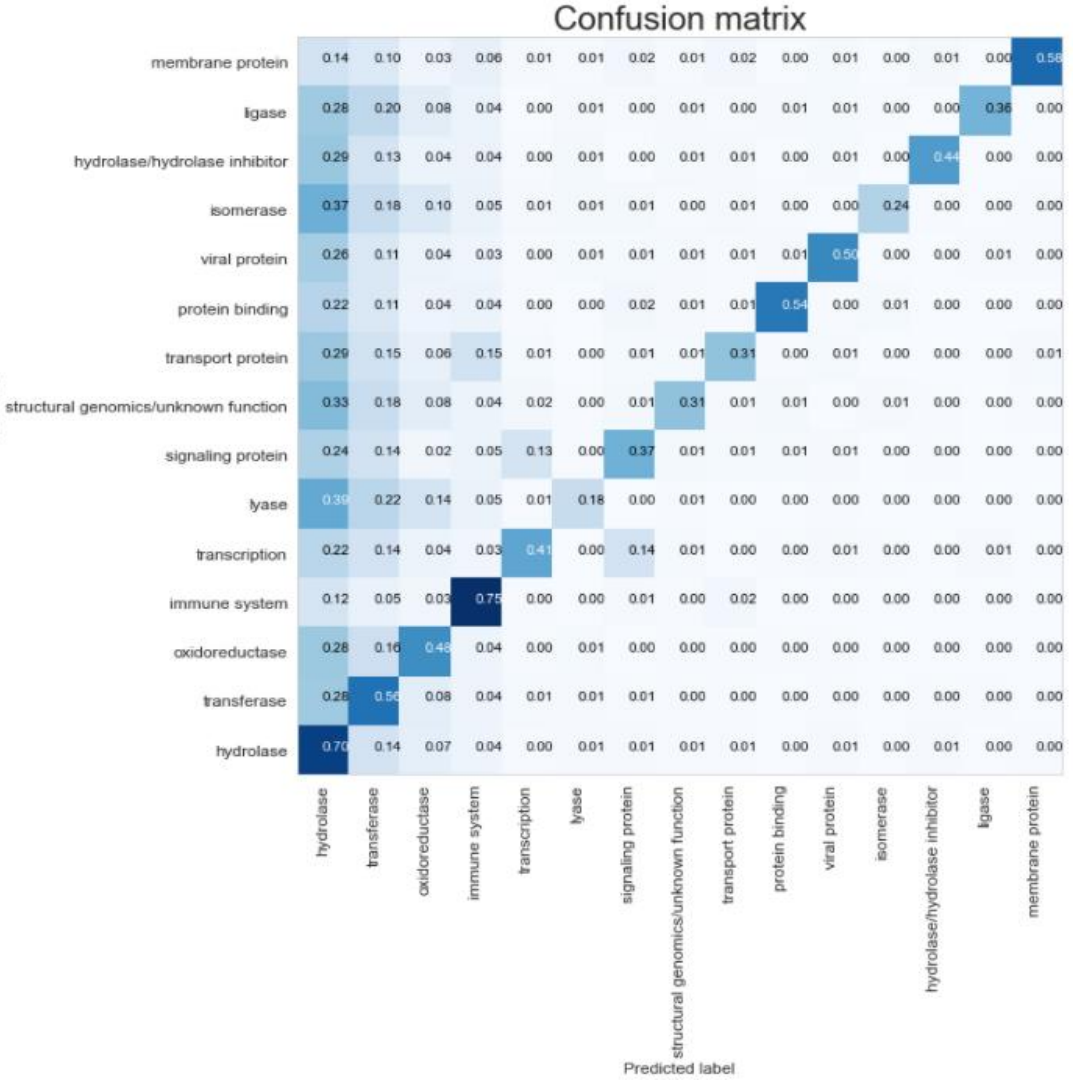
Three ML algorithms (Random Forest, Decision Tree, and KNN) are trained and tested.

75% data are used to train the model and the remaining 25% are tested

Hyperparameters are tuned in each model

Models	Accuracy	Recall	precision
Decision Tree	0.43	0.43	0.49
Random Forest	**0.52**	**0.52**	**0.57**
KNN	0.28	0.28	0.27

Random Forest



Part II: Deep Learning Models

“Hydrolase” family with 286 amino acid units

```
'TYTTRQIGAKNTLEYKV
YIEKDGKPVSAFHDIPLY
ADKENNIFNMVVEIPRWT
NAKLEITKEETLNPIIQD
TKKGKLRFVRNCFPHHGY
IHNYGAFPQTWEDPNVSH
PETKAVGDNEPIDVLEIG
ETIAYTGQVKQVKALGIM
ALLDEGETDWKVIAIDIN
DPLAPKLNDIEDVEKYFP
GLLRATNEWFRIYKIPDG
KPENQFAFSGEAKNKKYA
LDIIKETHDSWKQLIAGK
SSDSKGIDLTNVTLPDTP
TYSKAASDAIPPASLKAD
APIDKSIDKWFFISGSV'
```

Character to numerical vectors:

Tf-idf is used to convert to the numerical vectors

ngram = 3. (it collects all the possible combinations of 3 adjacent letters from the whole datasets)

Tf-idf provides value between 0 to 1. Most important word has value closer to 1.

Protein families	Numerical Labels:
'hydrolase'	: 1
'hydrolase/hydrolase inhibitor'	: 13
'immune system'	: 4
'isomerase'	: 12
'ligase'	: 14
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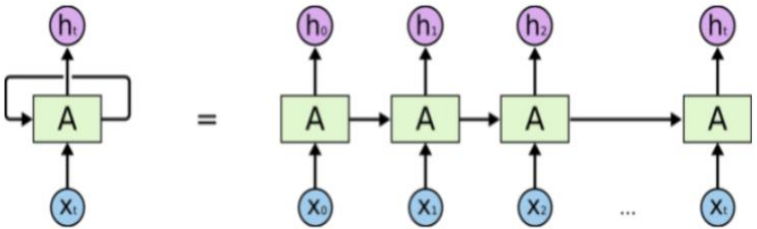
Levels are converted to the numerical vectors by one hot encoding method

Brief intro of Sequential model

- RNN are the "time series version" of ANNs. They are meant to process *sequences* of data.
- A looping constraint on the hidden layer of ANN turns to RNN.
- An RNN can be thought of as multiple copies of the same network, each passing a message to a successor.



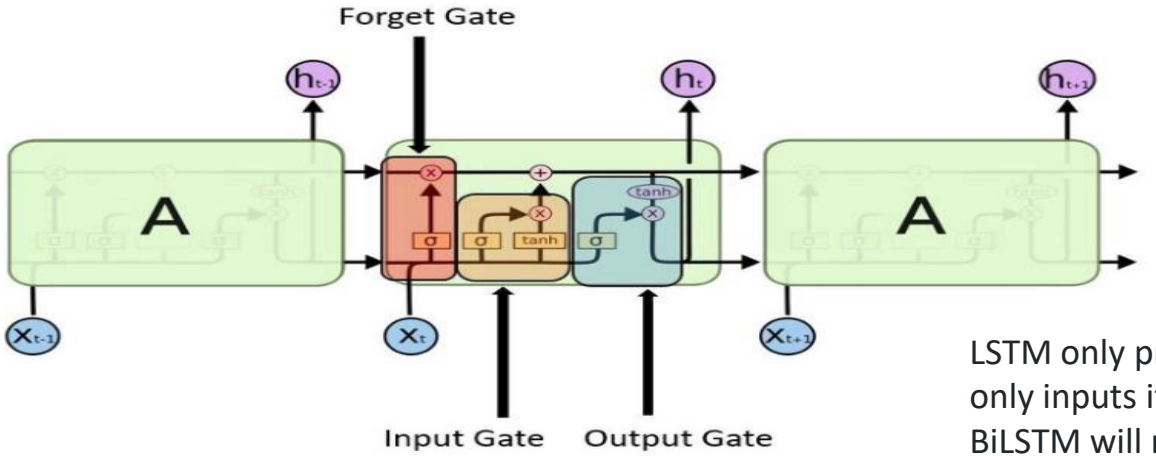
An unrolled recurrent neural network.

- RNNs can learn to use the past information but as that gap grows, RNNs become unable to learn to connect the information.
- Also, vanishing and exploding gradient issues come with a simple RNN.

Reference: https://colah.github.io/posts/2015-08-Understanding-LSTMs/

LSTM & BiLSTM

- “LSTMs” – are a special kind of RNN, capable of learning long-term dependencies
- The key to LSTMs is the cell state
- The LSTM does have the ability to **remove or add information to the cell state**, carefully regulated by structures called gates.



Forget gate: what is relevant to keep from the prior steps?

Input gate: what information is relevant to add from the current state

Output gate: determines next hidden states

LSTM only preserves information of the **past** because the only inputs it has seen are from the past.
BiLSTM will run your inputs in two ways, one from past to future and one from future to past so it preserve information from **both past and future**.

Deep Learning Models (Model architecture):

LSTM

Layer (type)	Output Shape	Param #
lstm (LSTM)	(None, 1, 256)	5383168
dropout (Dropout)	(None, 1, 256)	0
lstm_1 (LSTM)	(None, 1, 256)	525312
dropout_1 (Dropout)	(None, 1, 256)	0
lstm_2 (LSTM)	(None, 256)	525312
dense (Dense)	(None, 15)	3855

Total params: 6,437,647
Trainable params: 6,437,647
Non-trainable params: 0

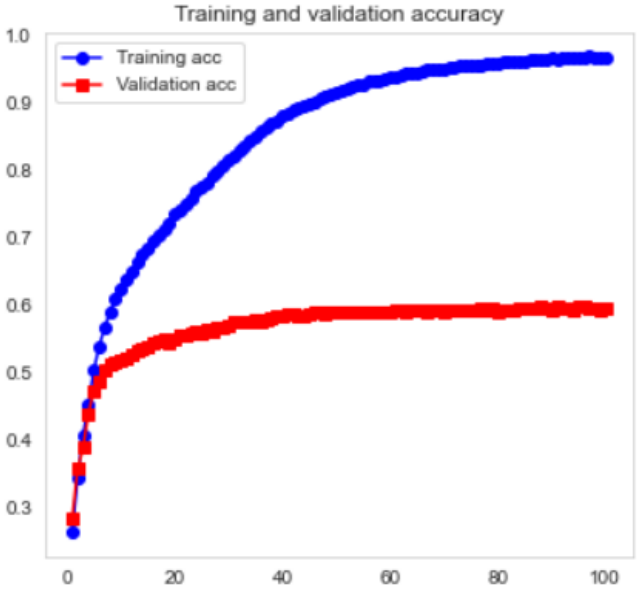
BiDirectional LSTM

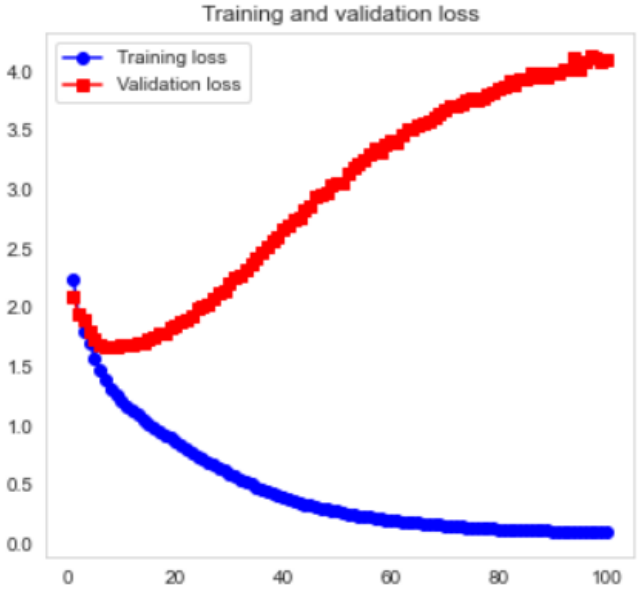
Layer (type)	Output Shape	Param #
bidirectional (Bidirectional	(None, 1, 512)	10766336
dropout_2 (Dropout)	(None, 1, 512)	0
bidirectional_1 (Bidirection	(None, 1, 512)	1574912
dropout_3 (Dropout)	(None, 1, 512)	0
bidirectional_2 (Bidirection	(None, 512)	1574912
dense_1 (Dense)	(None, 15)	7695

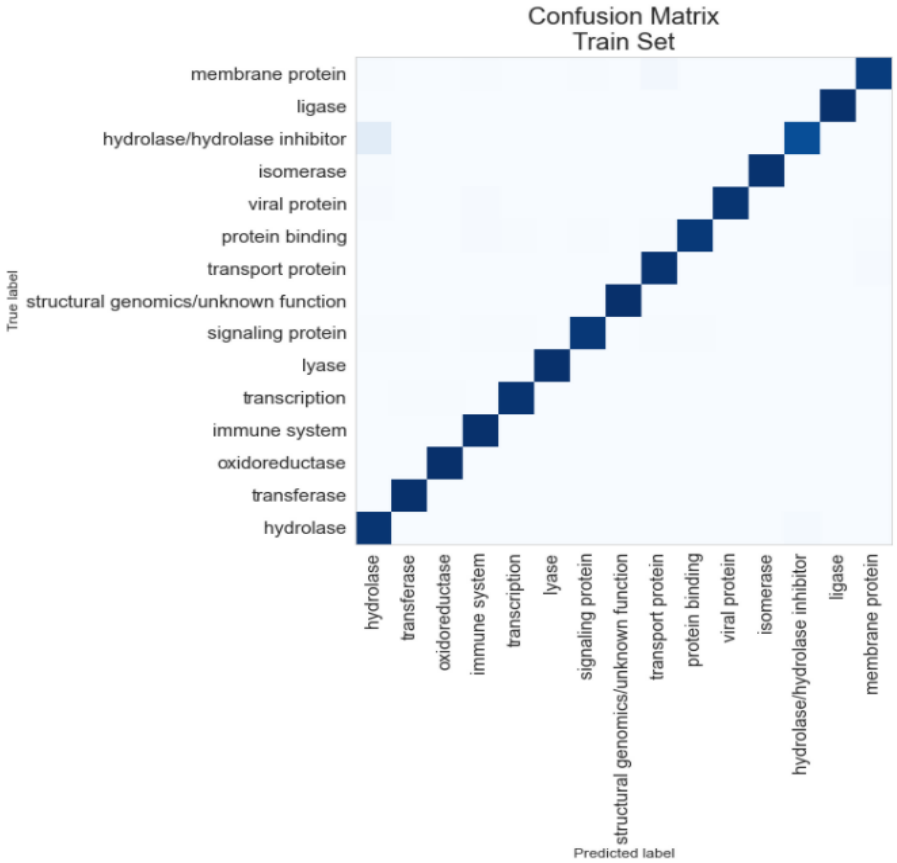
Total params: 13,923,855
Trainable params: 13,923,855
Non-trainable params: 0

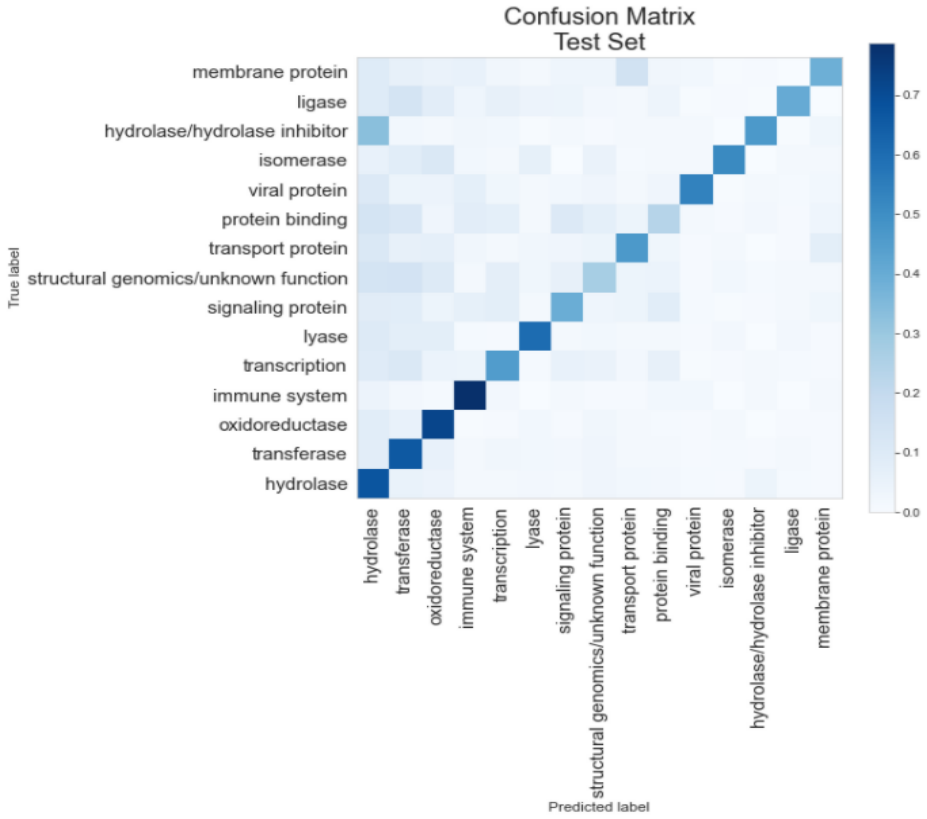
Model evaluation

Models	Accuracy	Recall	precision	AUC
LSTM	0.59	0.59	0.61	0.83
BiLSTM	0.59	0.59	0.60	0.84






Confusion Matrix
Train Set
membrane protein
ligase
hydrolase/hydrolase inhibitor
isomerase
viral protein
protein binding
transport protein
structural genomics/unknown function
signaling protein
lyase
transcription
immune system
oxidoreductase
transferase
hydrolase
True label
hydrolase
transferase
oxidoreductase
immune system
transcription
lyase
signaling protein
structural genomics/unknown function
transport protein
protein binding
viral protein
isomerase
hydrolase/hydrolase inhibitor
ligase
membrane protein
Predicted label


Confusion Matrix
Test Set
membrane protein
ligase
hydrolase/hydrolase inhibitor
isomerase
viral protein
protein binding
transport protein
structural genomics/unknown function
signaling protein
lyase
transcription
immune system
oxidoreductase
transferase
hydrolase
True label
hydrolase
transferase
oxidoreductase
immune system
transcription
lyase
signaling protein
structural genomics/unknown function
transport protein
protein binding
viral protein
isomerase
hydrolase/hydrolase inhibitor
ligase
membrane protein
Predicted label
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0

Summary and recommendation:

- This projects aims to classify 15 most common protein families using two separate approaches (Machine Learning and Deep Learning).
- Machine learning algorithm uses physical and chemical properties of protein whereas deep learning uses amino acid sequence to predict the protein families.
- Machine learning algorithms are not much useful to classify protein families because of the limited features.
- Both LSTM and BiLSTM are some how useful to classify protein families.

Recommendation:

- More features are need to ML model to improve its predictability.
- More data is needed for LSTM to improve its predictability.

Thank you.