



PROTEIN DRUG INTERACTION FROM THEIR SEQUENCE

Using the SMILES and SEQUENCE information

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This Thesis is carried out as a part of the education at the Tribhuwan University and is therefore approved as a part of this education. However, this does not imply that the University answers for the methods that are used or the conclusions that are drawn.

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Abstract

Protein and Drug interactions are long debated terms in the field of computational bioinformatics. Finding them based on molecular fingerprints and protein sequences alone is itself challenging as the process involving the true interaction depends on pathways, molecular properties, chaperones and more. Moreover the structural properties in the case of protein has different dimensions among which the efficient representation exists in the form of primary and secondary information. In this work the representation of drugs in fingerprints and proteins in sequence are used to generate features. The major components of feature vectors used in this work that bring the better prediction are PSSM-DT, Embedding and RPT vectors. These features are transformed to create suitable feature sets for training a deep learning algorithm using state of art technique. We use KIBA score to quantify the interaction to discriminate the similarly interacting proteins and drugs.

Acknowledgement

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Chapter 1: Introduction

1.1 Background

Computer-aided drug discovery methods are the developing paradigms in bio-informatics ever since the "Next Industrial Revolution" possibilities started growing with computational power and technical human resources in biomedicine [1].

The Dataset we used scores the interaction of proteins and drugs based on K_b scores. We use 52498 drugs from ChEMBL and 254 proteins from UniProt to get an interaction of 180244, by removing the unrecognized interactions. The interactions are based on KIBA score, collected from KEGG(Kyoto Encyclopedia of Genes and Genomes) dataset [2].

1.2 Statement of Problem

The simple technique of encoding the sequence information of drugs and proteins to identify if a drug will interact with the protein or not has a major issue in that while drugs encoding information can be used to make drug related predictions, the protein encodings don't properly form their representational vectors. Therefore, modeling a machine learning algorithm sometimes overfit the situation or poorly classify the problem. In this work, we explore various techniques and reproduce a regression problem for solving the prediction problem.

1.2.1 Selection of Prediction Score

Out of the many score functions; STITCH, Davis, Metz_Anastassiadis and KIBA scores, we found that the prediction of drug and protein interaction problem is convenient with KIBA scores. Again, KIBA scores database consists of experimental data and sec-

ondary data (from literature) of drug-target interaction. Choosing the KIBA as the output score for two protein and drug sequences, we model our machine learning algorithm by following a proper feature encoding technique.

1.2.2 Selection of Features

For the protein family, the focus here is with the kinase target family because of its essential roles in cellular signaling transduction for many cancers and inflammatory diseases. We concentrate on proteins dataset, specifically because their interaction is quite tricky when considered among chemical, atomic, structural and electrical nature of protein residues. Our basis for forming the matrices and vectors related to protein sequence comes from the fact that these feature sets represent specific properties related to the protein and its residues. Also, the literatures describing the feature sets characteristics and results motivates us towards the selection of these parameters: PSSM-DT, EDT, RPT and embedding vectors.

1.3 Objectives

The objectives of the research are:

- To determine the efficient different transformation matrices related to protein.
- To determine the right machine learning algorithm for modeling the protein-drug interactions.

1.4 Organization of Report

1.4.1 Choosing Method of Interaction

Out of the two methods of contact prediction: Global Methods and Local Methods, where Global Method tries to predict the label of one residue pair considering the

label of others while Local Method tries to predict the label of one residue pair without considering the label of others; we use Global Methods as a means of contact prediction. We try to run different variations in Residual Methods: Using Distance Prediction, Folding, Coevolutionary features engineering.

1.4.2 Creating Analogy with Image

For any protein sequence, instead of regarding them as segments, we try to run the whole protein sequence as an image: the residual contacts representing the pixels of the image.

1.4.3 Deep Learning Network Selection

Convnets, as they still are quite helpful in solving an image recognition problem, we used their variations to understand the performance with protein drug set. As a higher level of optimization problem, we use LSTM to create different components of Model Selection.

1.4.4 Training and Testing

A basic PC was used to create initial models. A server with 4 CPUs was then used thence after the models were selected for training. The testing was done in normal PC for validation and respective Confusion Matrices and results were evaluated.

Chapter 2: Theoretical Background

2.1 No Free Lunch Algorithm (NFL)

The no free lunch theorem for search and optimization [3] applies to finite spaces and algorithms that do not resample points. All algorithms that search for an extrema of a cost function perform exactly the same when averaged over all possible cost functions.

The search problem in case of proteins can be thought to comprise of different sample spaces: Primary Structures, Secondary Structures, Evolutionary Structures, Chemical Parameters, Atomic Parameters etc. This work only tries to explore the primary, secondary and evolutionary nature of protein-residues.

Generalized Optimization

The major implication of NFL is useful when the sample spaces are operated by different algorithms. The theorem being that all algorithms in different sample spaces produce the highest optimum results. Generalized Optimization follows hence when these different algorithms are optimized to work on different sample spaces of the problem at hand.

2.2 Literature Review

Protein molecules are the workhorses of our body. For example: the blood protein hemoglobin is functional for O_2 / CO_2 transportation, antibodies defend against viruses and hormonal protein insulin regulates our blood sugar level. The protein has differences in structure, according to the desirable functional characteristics of our body. This structure is so important for our health, that understanding them can aid to cure diseases. For example, diseases like Parkinson's is unrelated to bacteria/virus but due to incorrect fold-

ing of proteins.

Our bodily functions are dependent on protein structure and their interdependent interactions play a vital role. Some of these proteins are of critical interest to biochemistry and biomedicine researchers.[4] For example, a protein known as amyloid beta, which forms plaques in the human brain, is a key to understanding Alzheimer's disease. Improving our understanding of correct protein structures can lead to the design of drug treatments that can target deactivation of proteins of interest. Also, the personalized treatment of any sick person by taking sample of protein structure may help design cure for specific cases (eg. due to mutation changes of protein structure), which otherwise is referred in for general case of differently related protein. Thus it will solve issues of wrong medication hazards, which are the general scenario for the developing and under-developed countries.

In the field of bioinformatics, the long-standing problem of computationally predicting the structure of a protein remains unsolved[5]. The key to solving this problem is to accurately predict 'contacts', which requires measuring the physical distances between the amino acids of a folded protein. The current state-of-the-art methods like ProC_S3 and SVMcon are about 50% accurate [6].

Deep learning, which is a subfield of machine learning, has recently enabled accurate face recognition in Facebook, Google Photos etc. Google's self driving car already uses automatic driving [7]. It has also helped to accurately detect skin cancer. These demonstrated successes of deep learning algorithms clearly highlight its potential to greatly accelerate scientific problems such as protein contact prediction.

Finding the interaction between drugs and proteins based simply on their primary structure information is one of the many challenges faced in drug-synthesis process. The experimental methods are quite expensive in terms of time, money and resources. Still the mutation in cells are growing higher due to extensive use of chemical and electromagnetic radiations in our environment. In one hand, diseases are getting powerful and in the other hand, the experimental method can take months when finding a right cure is considered. One of the solutions to this is use of high computing ends that can automate some of its

repetitive works. Therefore, computational methods help to lessen the amount of works required to find right drug partner for the evolving diseases.

The rise of new machine learning methods and deep-learning techniques are closing the gaps to create better predictions. The cure of evolving diseases can be computationally researched by use of knowledge-based community. The community contributed databases in drugs and protein sectors are growing at the same pace. Clearly, both the data resources and algorithmic techniques can help human community to counter-act against such circumstances.

In the other hand chemical properties of drugs and the targets complicate the situation as they react differently with slight change in protein sequence. While computational techniques have helped to simulate the different conditions, the fundamental dataset is still long way to go. The reason being that the identification of proteins structure can take months. Again the isomeric states of proteins' structures can have different functional aspects to the body physiology. Moreover, the complexes tend to behave similarly even when the protein sequences are distantly related, one of the results of tertiary structures that the proteins are form of.

The deep learning methods are quite good at predicting the molecular behaviour of the drug. However they present no good means when predicting the behaviour of proteins. This can be thought as protein-folding problem which when solved will help escalate the development of treatment facilities around the globe. The CASP experiments is such community which holds competition to determine and advance the state of art in modeling the protein sequence from amino acids. To find the computational measure to predict the drug for a given protein, the major fallback is that the simple encoding techniques don't incorporate the proteins behaviour related to hydrophobicity, acidity, secondary and tertiary structures information.

No Free Lunch Theorem [3] can be used for on the other hand works by basing the prediction guesses based on a number of prediction functions. Here, we use the sequence information of proteins to calculate the predictions on different feature transformation

techniques and generalize those predictions using a stack of dense layers.

Chapter 3: Methodology

3.1 System Block Diagram

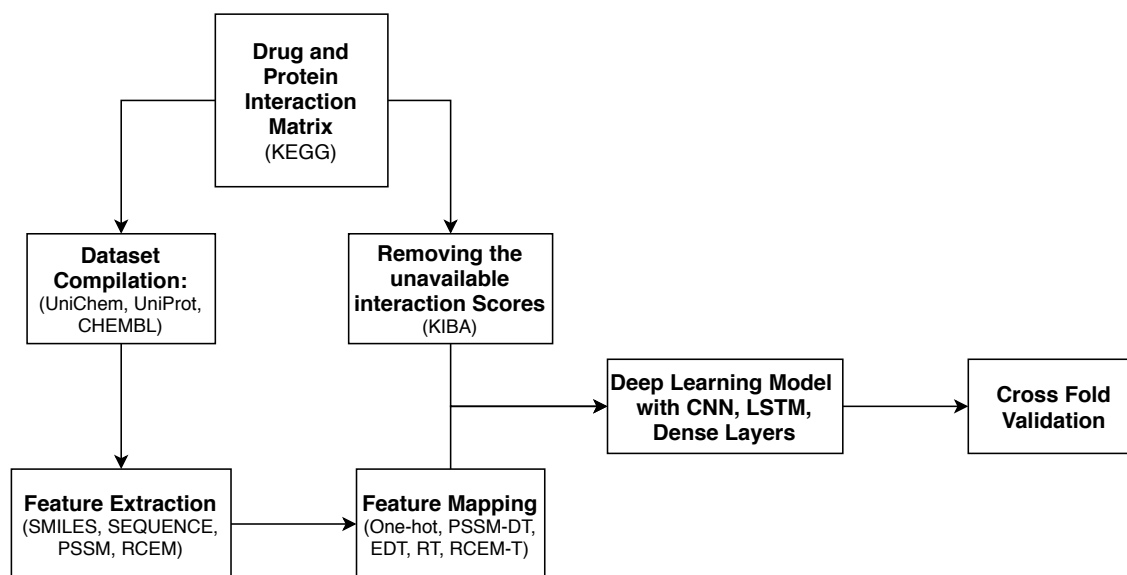


Figure 3.1: System Block Diagram

The Figure 3.1 shows the various components used to form the prediction system. The idea is basic in that protein interaction depends on the structural and chemical properties. The structural components are fulfilled and

3.2 Dataset

3.2.1 KEGG

It is a community-driven database which holds large-scale molecular datasets generated by genome sequencing and high-throughput experimental technique.[2] We use KEGG DRUG dataset for finding the interaction set between DRUG and PROTEIN. The

interaction score is based on Equation 3.1:

$$[ht]KIBA = \begin{cases} K_i.adj & \text{if } IC_{50} \text{ and } K_i \text{ are present} \\ K_b.adj & \text{if } IC_{50} \text{ and } K_d \text{ are present} \\ \frac{K_i.adj + K_b.adj}{2} & \text{if } IC_{50}, K_i \text{ and } K_d \text{ are present} \end{cases} \quad (3.1)$$

where L_d and L_i are parameters defining weights of IC_{50} in model adjustments for K_i and K_b

For a kinase inhibitor drug–target interaction, we consider the medians of three major bioactivity types IC_{50} , K_i , K_d where IC_{50} [8] is the concentration at which the inhibitor causes a 50% inhibition of enzymatic activity and K_i is defined by

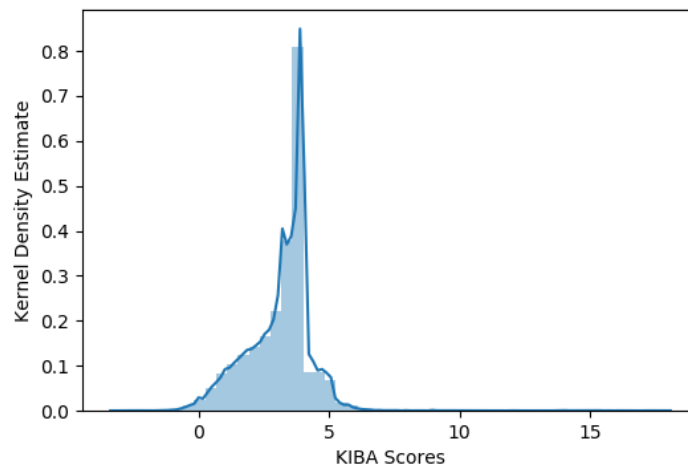
$$Ki = \frac{IC_{50}}{1 + [S]K_m} \quad (3.2)$$

where, $[S]$ is the experimental substrate concentration and K_m is the concentration of the substrate.

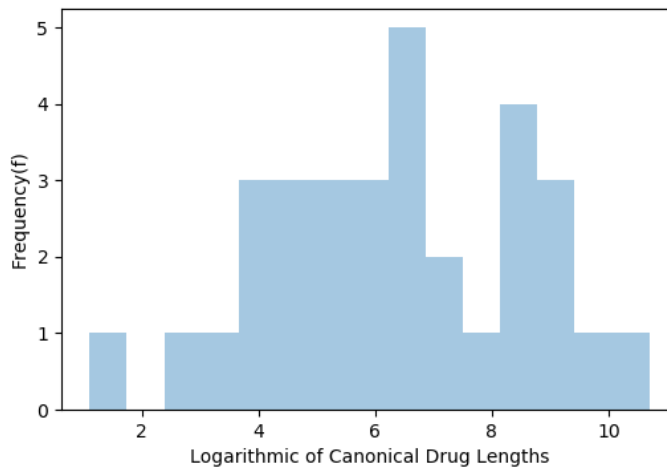
$$K_i.adj = \frac{IC_{50}}{1 + L_i(IC_{50}/K_i)} \quad (3.3)$$

$$K_d.adj = \frac{IC_{50}}{1 + L_d(IC_{50}/K_d)} \quad (3.4)$$

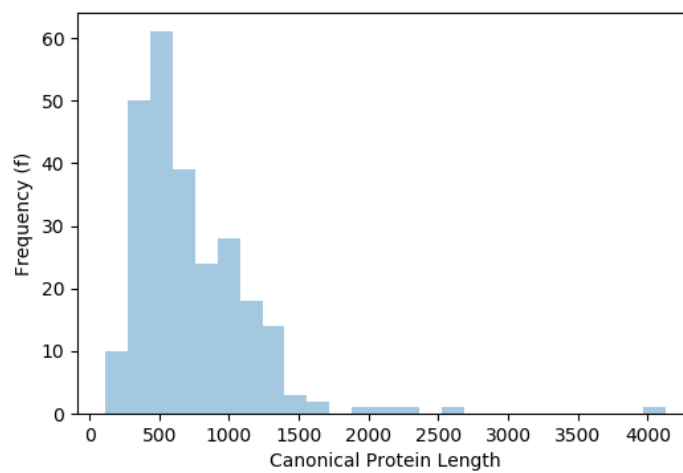
All the bioactivity types are available from ChEMBL.[9] We thus have 254 proteins and 52498 drugs. Based on interaction data available, we remove the unknown values and get a total of 180244 interaction KIBA score values in the range of -3.09 to 17.8. With the standard deviation of 1.22, we try to predict the best KIBA score of drug and protein based on the sequence information alone.



(a) KIBA Scores



(b) Logarithmic One Hot Encodings of Drug Sequence



(c) One Hot Encodings of Protein Sequence

Figure 3.2: Data Distribution of KIBA-interaction scores, Drug Sequences and Protein Sequences

3.2.2 UniProt and ChEMBL

UniProt

The sequence related information of protein is referenced using UniProt Identifier and protein sequence (FASTA) is called using the api from UniProt. [10]

ChEMBL

The molecular fingerprints related to drugs are referenced using ChEMBL Identifier and the drug sequence is called from ChEMBL database. [9]

3.2.3 PSI-BLAST

It relates with multiple sequence alignments from a family of protein sequences[11]. This helps us to create a PSSM - Equation (3.5) - matrix referred to as secondary protein structure. The improvement in drug-contact prediction can be thought for amino acid composition being tuned with the scoring system. For this study, the PSSM profile of every protein sequence is obtained by executing iteration of PSI-BLAST against [11, KEGG] protein. PSSM profile is a matrix of $L \times 20$ dimensions where, 20 referring to standard type of amino acids and L being the length of the protein. The larger positive scores represent conserved positions, which in turn implies critical functional residues that are required to perform various intermolecular interactions.[11, PSSM]

$$PSSM = \begin{bmatrix} P_{1,1} & P_{1,2} & \dots & P_{1,20} \\ P_{2,1} & P_{2,2} & \dots & P_{2,20} \\ \vdots & \vdots & \ddots & \vdots \\ P_{L,1} & P_{L,2} & \dots & P_{L,20} \end{bmatrix} \quad (3.5)$$

PSSM-DT

Two forms of PSSM distance transformation techniques are used to transform the PSSM information into fixed dimensional vectors [12]. The PSSM-DT (PSSM-Distance Transformation) can transform the PSSM information into uniform numeric representation by approximately measuring the occurrence probabilities of any pairs of amino acid. It results in two types of feature matrices: PSSM-SDT and PSSM-DDT defined by:

$$PSSM - SDT(i, lg) = \sum_{j=1}^{L-lg} S_{i,j} \times \frac{S_{i,j+lg}}{L-lg} \quad (3.6)$$

lg = distance of separation between same amino acid sequence

$$PSSM - DDT(i_1, i_2, lg) = \sum_{j=1}^{L-lg} S_{i_1,j} \times \frac{S_{i_2,j+lg}}{L-lg} \quad (3.7)$$

i_1 and i_2 refer to tow different types of amino acids

Thus we have $[380 \text{ (3.7)} + 20 \text{ (3.6)} = 400] \times lg$ matrix which will be used as protein-specific vector in this work.

Evolutionary Distance Transformation Matrix

The mutational information of protein can be more informative than the sequence information itself[13]. Evolutionary difference formula(EDF) is used to represent mutation difference between adjacent residues. Secondly, the PSSM is converted into 20 x 20 matrix (ED-PSSM). This extracts the non co-occurrence probability for two amino acids separated by a certain distance d in the protein from the PSSM profile. For example, $d=1$ implies that the two amino acids are consecutive; $d=2$ implies that there is one amino acid between the two. Then the EDT feature vector computed from ED-PSSM can be represented as (3.8):

$$P = [\partial_1, \partial_2, \dots, \partial_\Omega] \quad (3.8)$$

where Ω is an integer that represents the dimension of the vector whose value is 400.. The non-co-occurrence probability of two amino acids separated by distance d can be computed as:

$$f(A_x, A_y) = \sum_{d=1}^D \frac{1}{L-d} \sum_{i=1}^{L-d} (P_{i,x} - P_{i+d,y})^2 \quad (3.9)$$

where $P_{i,x}$ and $P_{i+d,y}$ are the elements in the PSSM profile; A_x and A_y represent any of the 20 different amino acids in the protein sequence. Finally we spread the $f(A_x, A_y)$ in equation 3.8 as: $\partial_1 = f(A_1, A_2)$, $\partial_{400} = f(A_{20}, A_{20})$

3.2.4 Residue feature

The Statistical Residue Vector Space R2RSRV [14] plays an important role in Residue Residue Interaction and thus creates a basis for structural stability of the protein sequence itself. Though related more to the tertiary structure of protein sequence itself, we regard it to create a correlated sequence information where two proteins are related distantly by sequence but highly related with functional characteristic of protein. Table ?? shows the table used in this work. It is a 20 x 20 matrix whose rows and columns represent 20 standard amino acids.

Residue Probing Transformation(RPT) feature

RPT as proposed by [15, Jeong et al.], and implemented by [16, Pujan et al.], emphasizes domains with similar conservation rates by grouping domain families based on their conservation score in the PSSM profile.

$$RPT = \begin{bmatrix} H_{1,1} & H_{1,2} & \dots & H_{1,20} \\ H_{2,1} & H_{2,2} & \dots & H_{2,20} \\ \vdots & \vdots & \ddots & \vdots \\ H_{20,1} & H_{20,2} & \dots & H_{20,20} \end{bmatrix} \quad (3.10)$$

The RPT matrix (Equation 3.10) is then transformed into feature vector of 400 dimensions, as shown in Equation 3.11.

$$V = [f_{s_{1,1}}, f_{s_{1,2}}, \dots, f_{s_{i,j}}, \dots, f_{s_{20,20}}] \quad (3.11)$$

where,

$$f_{s_{i,j}} = \frac{s_{i,j}}{L} (i, j = 1, 2, \dots, 20) \quad (3.12)$$

3.3 Deep Learning Model

The Features thus formed are then subjected to deep learning model using keras library in python. We use the Embedding feature provided by keras as other features for both drug fingerprint and protein sequence. The implemented model is represented by Figure 3.3. The input layers are described in Table ??.

S.No.	Input Layer Name	Used Feature Vector	Type
1	input_1	One Hot Encoding	Drug
2	input_2	One Hot Encoding	Protein
3	input_3	Evolutionary Distance Transformation Vector	Protein
4	input_4	PSSM-DT Vector	Protein
5	input_5	Residue Probing Transformation Vector	Protein

Table 3.1: Inputs Used in the Deep Learning Network

3.3.1 Components description used from Tensorflow (Keras)

Embedding Layer

The one-hot encodings of the drugs and protein sequences are inputs to this layer. It turns positive integers (indexes) into dense vectors of fixed size. eg. $[[4], [20]] \rightarrow [[0.25, 0.1], [0.6, -0.2]]$.

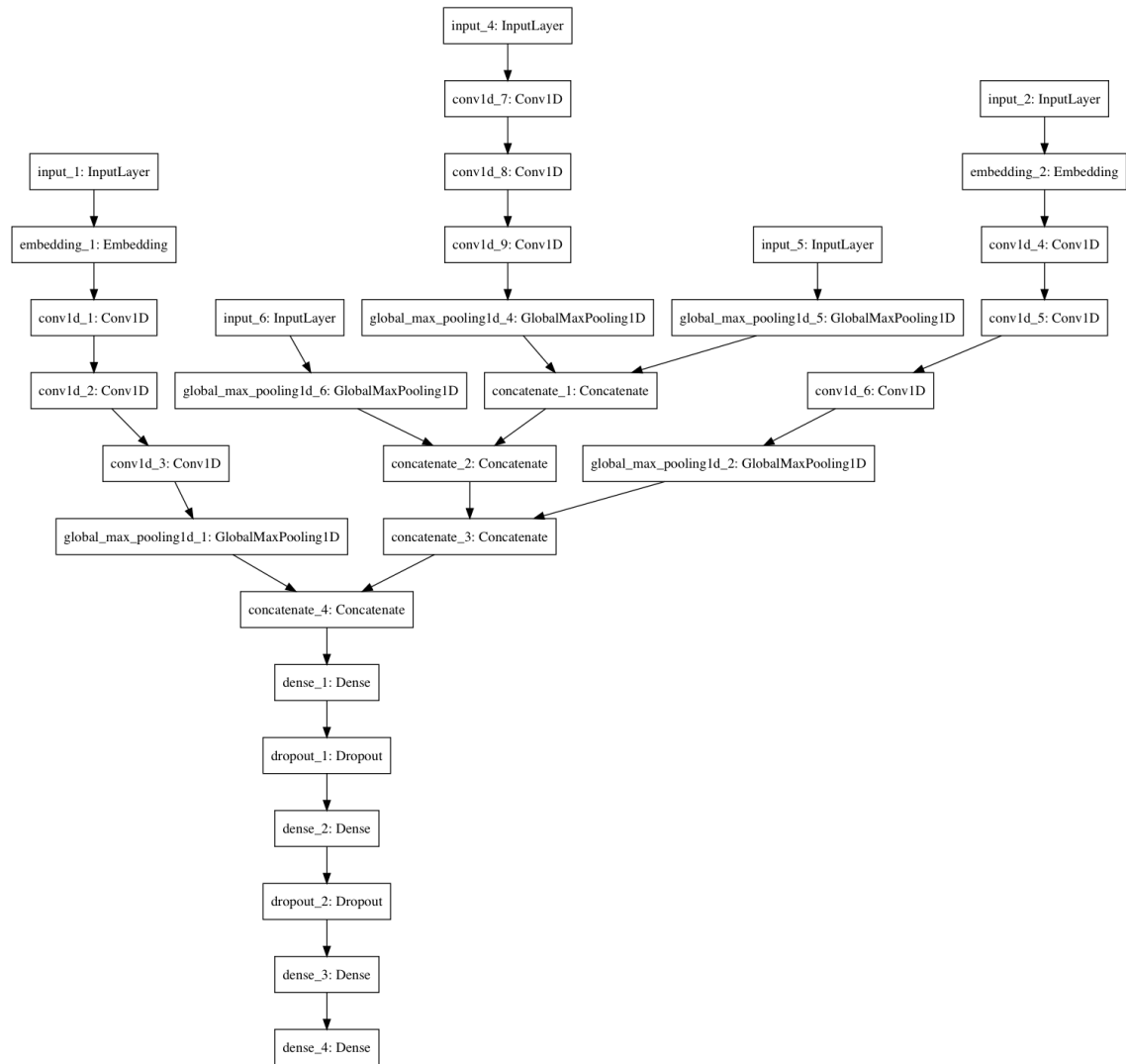


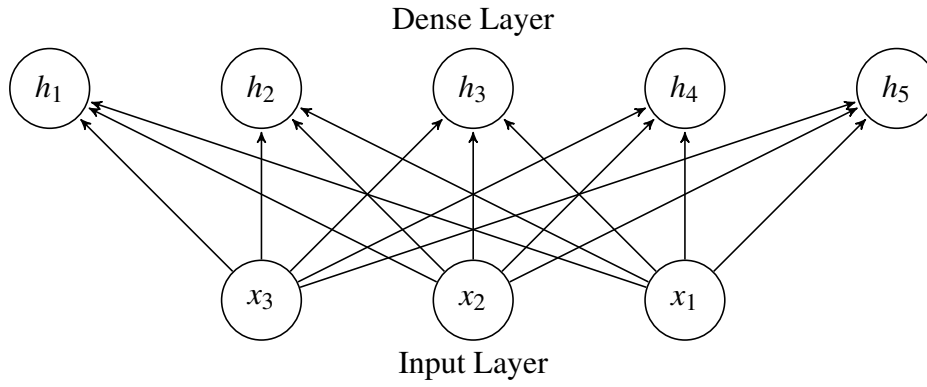
Figure 3.3: Deep Learning Model

Dense Layer

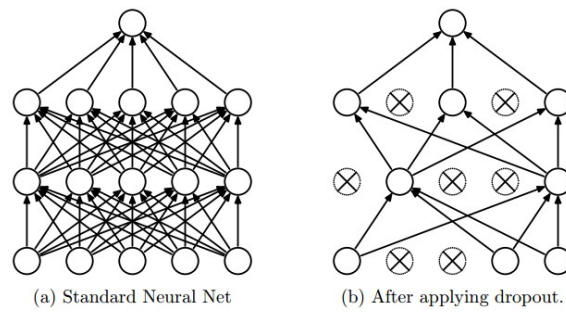
It is a neural layer which fully connects the input layer to output layer. It can be seen from Figure 3.4.

Dropout Layer

It is undesirable when every component of the input layer makes a significant changes to the output layer. To reduce the effect of unimportant features we use dropout layer. Thus the backpropagation network tries to ignore the noise features and minimizes the unrealizable prediction of the learning problem. This can be expressed diagrammati-

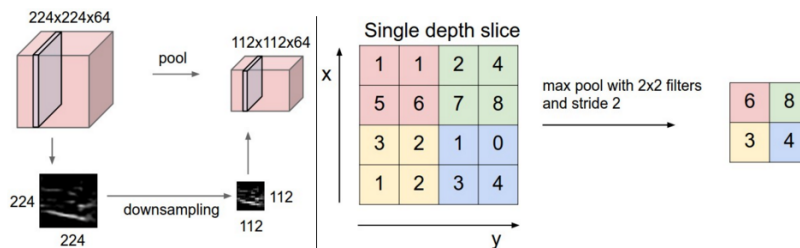
**Figure 3.4:** Dense Layer

cally in the Figure 3.5.

**Figure 3.5:** Dropout Layer

Global Max Pooling Layer

We use this to sample the learned parameters from the grid of 3 dimensions returned by Convolution Layer. It gets reduced to 1 dimension by taking the highest values from the window size (corresponding to shape of 1st dimensional element).

**Figure 3.6:** Pooling Layer

Concatenation Layer

It is used to simply join two vectors so that we create a feature set comprising of multiple features whose positional index indicates the feature set being manipulated.

Convolution Neural Network

To learn the local patterns in the input vector, we use CNN. While Dense Layers and LSTM learn the global patterns, CNN is used to understand the local patterns. It does so by increasing the depth layer, which in turn is designed to learn different patterns as shown in Figure 3.7.

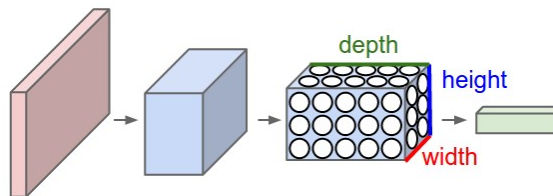


Figure 3.7: Convolutional Neural Network

LSTM

As the RNN often suffers from vanishing gradient problem, we use a LSTM Layer to learn the global pattern of the feature sets resulting after concatenation of different stacked layers outputs. The LSTM architecture can be seen in figure below:

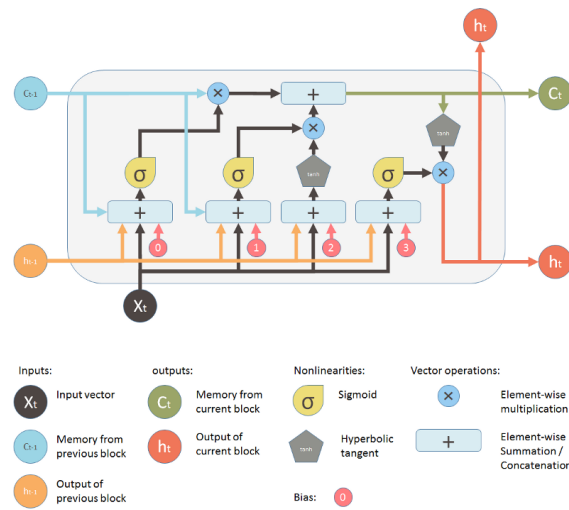


Figure 3.8: Long Short Term Memory

Chapter 4: Experiments and Results

4.1 Experiments

The focus of the experiments are concentrated on the properties of protein as they have complex structures. The binding of protein and drug depend on various attributes of protein like acidity, hydrophobicity, binding pockets etc and the structure of drug. The attributes are quite closely related to primary and secondary structure of protein themselves. Therefore, our model aims to relate all these multiple components with matrix representation and confirming to the Figure. 3.2 prediction.

4.1.1 Features Selection

Primary Feature Selection

We explored the other embedding technique used in language theory. The modified N-Grams Skip-Grams (m-NGSG) was supposed to undertake the mutational agreements when the proteins and drug interaction was brought in question. However, it fared quite badly than the Neural Net Sequence Embeddings. Mostly the issue can be related to that if the algorithm misses the tight relationship among the amino-acid neighborhood, then the protein with different structure may seem to act similarly: a strong disagreement on principle that certain proteins with slight modification on the sequence have different functional and chemical properties. It could still be used for Poission-Hidden Markov Model for some other properties, but primary encodings can't be relied on m-NGSG.

Therefore we relied on Neural Net Sequence Embedding technique to form the primary representation. Both protein and drug were converted to Embedding vectors after creating their one-hot encoding.

Secondary Features Selection

These are the structural components of protein especially related to alpha and beta strands of Protein segments. All the protein Sequences are subjected to Equation (3.5) from the one-hot encodings. The PSSM matrix is calculated using PSI-BLAST[11]. Then all the testing protein sets are evaluated with the resultant PSSM to form a new PSSM matrix specific to the testing protein. Thus, we expect to explore how proteins relate with the interaction experiments with the protein domain. From the PSSM, we evaluate the other evolutionary and distance vectors using equations 3.10, 3.7, 3.6 and 3.9.

4.1.2 Implementation

Stacked Features, LSTM Network

Basically, we implement the 3.3 for our model design. It is implemented in Python using the TensorFlow framework consisting of keras. The training contained of 100 epochs and required full 4 complete days to complete the training in a high GPU processors. The training and testing was done in a 5-fold cross-validation set prepared manually. To evaluate the performance of the model, we used concordance index(CI)[12] as defined by equation 4.1:

$$CI = \frac{1}{Z} \sum_{\delta_i > \delta_j} h(b_i - b_j) \quad (4.1)$$

where b_i is the prediction value for higher affinity δ_i and b_j is the prediction value for smallery affinity δ_j , Z is the normalization constant and $h(m)$ is the unit step function:

$$h(x) = \begin{cases} 1, & if x > 0 \\ 0.5, & if x = 0 \\ 0, & if x < 0 \end{cases} \quad (4.2)$$

4.2 Results

The validation loss and the cindex scores were 16% and 90% respectively when we used our full model.

Chapter 5: Conclusion

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Appendix A: R2RSRV

	I	V	L	F	C	M	A	G	T	S	W	Y	P	H	E	Q	D	N
I	5.21	2.42	0.88	1.71	-1.59	1.13	0.95	0.48	-1.05	-3.20	0.65	1.44	-0.82	-1.54	-0.94	-0.62	-1.66	-3.14
V	2.42	9.46	1.33	0.49	-0.32	0.54	1.55	-2.12	-0.91	-1.80	-2.88	-1.05	-0.81	-1.32	-0.29	-0.58	-2.39	-3.69
L	0.88	1.33	9.90	1.08	-0.42	2.17	2.41	-2.29	-3.40	-2.32	0.48	-0.77	-2.28	1.67	-0.77	-0.08	-3.49	-2.16
F	1.71	0.49	1.05	6.11	0.55	0.89	0.52	-2.00	-1.10	-2.09	-0.11	1.14	0.83	-1.33	-1.79	0.42	-3.62	-0.96
C	-1.59	-32	-0.42	0.55	15.35	-1.35	-0.21	0.59	-1.52	1.53	-1.07	-1.16	0.28	0.95	-0.52	-1.47	-1.95	-2.23
M	1.13	0.54	2.17	0.89	-1.35	5.40	-0.28	0.44	-2.15	-1.50	-0.71	-0.33	-0.31	0.19	0.01	0.27	-3.38	-1.74
A	0.95	1.55	2.41	0.52	-0.21	-0.28	7.08	-2.04	-1.04	-0.61	-1.15	-1.22	-1.58	0.11	-0.53	-0.82	-1.06	0.17
G	0.48	-2.12	-2.29	-2.00	0.59	0.44	-2.04	5.65	1.67	-1.32	-0.82	0.27	-0.60	0.75	-2.24	1.68	0.70	-1.01
T	-1.05	-0.91	-3.40	-1.10	-1.52	-2.15	-1.04	1.67	4.42	1.23	0.59	-1.36	-0.04	-1.48	-0.06	-2.61	4.66	0.02
S	-3.20	-1.80	-2.32	-2.09	1.53	-1.50	-0.61	-1.32	1.23	6.22	-1.10	-1.40	-0.79	-2.66	2.14	-0.08	4.57	0.95
W	0.65	-2.88	0.48	-0.11	-1.07	-0.71	-1.15	-0.82	0.59	-1.10	1.08	-0.45	5.88	0.15	-2.84	-2.84	-1.98	-1.35
Y	1.44	-1.05	-0.77	1.14	-1.16	-0.33	-1.22	0.27	-1.36	-1.40	-0.45	6.40	0.21	1.11	0.75	-2.73	-3.07	-0.45
P	-0.82	-0.81	-2.28	0.83	0.28	-0.31	-1.58	-0.60	-0.04	-0.79	5.88	0.21	1.73	-1.13	0.66	0.82	-2.51	1.37
H	-1.54	-1.32	1.67	-1.33	0.95	0.19	0.11	0.75	-1.48	-2.66	0.15	1.11	-1.13	5.03	-2.22	0.32	3.11	-1.46
E	-0.94	-0.29	-0.77	-1.79	-0.52	0.01	-0.53	-2.24	-0.06	2.14	-2.84	0.75	0.66	-2.22	2.59	-1.98	-4.29	0.07
Q	-0.62	-0.58	-0.08	0.42	-1.47	0.27	-0.82	1.68	-2.61	-0.08	-2.84	-2.73	0.82	0.32	-1.98	3.44	0.79	0.92
D	-1.66	-2.39	-3.49	-3.62	-1.95	-3.38	-1.06	0.70	4.66	4.57	-1.98	-3.07	-2.51	3.11	-4.29	0.79	1.69	3.85
N	-3.14	-3.69	-2.16	-0.96	-2.23	-1.74	0.17	-1.01	0.02	0.95	-1.35	-0.45	1.37	-1.46	0.07	0.92	3.85	7.91
K	-2.23	0.66	-2.10	-1.71	-1.80	-0.72	-1.11	1.72	0.29	0.11	-0.27	0.87	0.14	-1.90	3.52	-0.67	0.86	-0.63
R	-2.14	-1.42	0.19	-1.33	-0.84	-1.51	-2.74	1.22	-0.74	-0.38	4.08	-0.33	-0.40	-0.06	3.45	0.24	2.73	-0.43

Table A.1: R2RSRV Matrix

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