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 Drugs are the major analysis subjects in computational bioinformatics to produce conclusions in treatment of diseases. While scientific methods are progressing with experiments and medical principles, they are still expensive means to discover the cure of new diseases. In principle, the high computing systems can be used to reduce the costs related to discovery. With the evolving nature of disease for instance, due to mutation, there has been extensive research work on exploring the fundamental properties of proteins and drugs to find the correct match in treatment. Finding the interaction between drugs and proteins based on their molecular fingerprints and protein sequences has been explored using statistical methods and rule-based methods. The representation of drugs in fingerprints and proteins in sequence are used to map them to different domains, which are then trained in a deep neural net to produce a regression solution. Instead of relying on binary classification, the more superior KIBA scores are used to quantify the interaction score between the drugs and proteins. The feature vectors, PSSMDT, Embedding and RPT, are combined to aid the deep learning state-of-art solution with convolution and dense layers, and aid to prediction score of 89%.

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Chapter 1: Introduction

1.1 Background

Treatment of diseases are mostly associated with applying foreign medicinal components into human body. The rudimentary means of curing diseases has been growing with applied ayurbedas since the past. The chemical perspective of curing diseases slowly evolved into modern chemistry as drug facilities developed around the globe. The extensive research and documentation changed the world where people have come to trust fully in chemist's drugs to mitigate the ailments in the body. With the growing chemical intereset in the community, the need to develop better drugs and quick solutions increased even higher. With the identification of new diseases and dire need of understanding the mechanism to cure such diseases, the drug research started gaining its speed.

Computer-aided drug discovery (CADD) mechanism have been developing bioinformatics ever since the "Next Industrial Revolution" possibilities started grow [1, 2]. The interest started as Fortune magazine published the article "Designing Drugs by Computer at Merk". Experimenting with computational power and technical human resources in biomedicine, the concepts started to form scopes like High Throughput Screening (HTS) – A technique to screen desired drugs from other drugs. HTS was evolving eventually to find precedence over finding novel therapeutics. The desire to increase high hit rate did grow as the traditional HTS led to few probable leads. As research developed on computational drug design, CADD study broadened based on the computational resources required. CADD can be classified into two general categories: Structure-based CADD and Ligand-based CADD.

Structure based CADD relies on knowledge of structural analysis of protein structures in particular to identify the drug leads. It associates to phenomenons like Binding Site Analyses, Docking Simulations, and Scoring Algorithms. In brief, all the struc-

tural properties of proteins are exploited to identify the possible drug candidates – the molecules which fit in the protein structure description. This work borrows the representational feature sets of proteins and drugs from this discipline.

Ligand-based CADD exploits similarities of known active and inactive molecules. It further exploits the chemical, electrical and functional properties from drugs and proteins. This work borrows the feature representations of chemical-electrical properties in the form of Residue Residue Statistical Residual Vector (R2RSRV).

This work relates mostly to the Structure based CADD and partly to Ligand-based CADD. Target Structure and Ligand Structures are the major parameters of the research. The de-novo design has not been explored yet but the research method in this work can be used to test the drug designs for Structure Generator[1]. The other aspects of target identification – Molecular Dynamics, Pharmacophore modeling, Ligand Docking, Quantitative Structure Activity Relation (QSAR) etc. are beyond the scope of this work. So, the predictions from the model may not be sufficient to conclude the predicted interaction results. The pharmacophore models could take the results from this work and make decisive conclusions.

The Dataset contains scores of the interaction of proteins and drugs based on KIBA scores. We use 52498 drugs from CHEMBL and 254 proteins from UniProt to get their structural information. The interaction of 180244 is obtained from the research work produced by [3], and by removing the unrecognized interactions. The interactions is based on KIBA score – an integrated approach by combining the power of thermodynamic constants and activity percentage of drug-target interaction profile.

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

[1]Structure Generator: The molecules which are highly active, readily synthesizable and devoid of undesirable properties are used to construct new possible drugs and can be tested with multiple targets.

drugs encoding information can be used to make drug related predictions, the protein encodings require additional feature vector input to properly form their representational vectors. For instance, the docking of drugs to protein structure doesn't only depend on surface area –a condition that structural representation can learn with proper algorithm –, but also with electric field and H-bond properties [4]. Therefore, modeling a machine learning algorithm sometimes overfit the situation or poorly classify the problem. In this work, we explore various features integration like R2RSRV and PSSM matrix along with sequence feature set 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, KIBA scores are used for the prediction of drug and protein interaction problem. The main reasons as found in [3, Tang et al.] being: STITCH scores don't fully explore the primary thermodynamic dissociation constants used for drug-target interaction profile and other scores are used by KIBA. Again, KIBA scores database consists of experimental data and secondary 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 for prediction of interaction.

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 [3, 5]. We concentrate on proteins dataset, specifically because their interaction is quite tricky when considered among chemical, atomic, structural and electrical nature of protein residues [6]. Our basis for forming the matrices and vectors related to protein sequence comes from the fact that these features 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 effective feature matrices related to protein.
- To determine the right machine learning algorithm for predicting 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, Coevolutionary features, Sequence Representation.

1.4.2 Deep Learning Network Selection

Convnets, as they still are quite helpful in solving an image recognition problem, we used the stack of CNN with other keras layers to understand the performance of prediction of interaction with protein drug set. The image problem is in analogy as the different canonical dimension of drugs being mapped with canonical dimension of proteins. The value of pixel can be thought of as an interaction value of drug substituent with protein substituent.

1.4.3 Training and Testing

A basic PC was used to create initial models. Google Colabs was used to train the deep convolutionary stack due to requirement of GPU. The models were saved on the runtime so that the next training could be resumed immediately after the cease of Colab's VM Session.

Chapter 2: Theorical Background

2.1 No Free Lunch Algorithm (NFL)

The no free lunch theorem for search and optimization applies to finite spaces and algorithms that do not resample points. It states "All algorithms that search for an extrema of a cost function perform exactly the same when averaged over all possible cost functions." To increase the scope of NFL-like analyses, we need to make two slight extensions: first, we must broaden the definition of performance measures to allow for dependence on f-the list of multiple functions, and second, we need to generalize fitness functions to allow for nondeterminism. [7]

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 for a given problem. Generalized Optimization follows that when these different algorithms that are optimized in different sample spaces are included in one algorithm, then the method provides us the best predictions.

2.2 Literature Review

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.

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 folding 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.[8] 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 [9].Thus it will solve issues of wrong medication hazards, which are the general scenario for the developing and under-developed countries.

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 field of bioinformatics, the long-standing problem of computationally predicting the structure of a protein remains unsolved[10]. 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 [11].

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 [12]. 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.

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. [13]

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 facilites around the globe. The Critical Assessment of Structure Prediction (CASP) experiments is such community which holds competition to determine and advance the state of art in modeling the protein sequence from amino acids.[14] 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.[4]

No Free Lunch Theorem [7] 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 Overview

3.1.1 Data Collection

The dataset is collected from open-internet database. There are basically three types of data required in this work: protein, drug and interaction sets. The UniProt Library has been used for extracting proteins features, PubChem for drug features, and NCBI for interaction scores. Additionally, PSI-BLAST is used to generate PSSM matrices for the protein features downloaded.

UniProt contains database of 173,281 proteins of human (Homo sapiens) (until 2019). The protein document consists of the taxonomic classification, identifiers to other databases for cross-linking, molecular properties, related specific bioactivity, functional property, canonical and isoforms of protein sequence. The protein fasta sequence in particular is of interest to the work produced. An api can be used to download the available information. `https://www.uniprot.org/help/programmatic_access`

>O00311

MEASLGIQMDEPMAFSPQRDRFQAEGSLKKNEQNFKLAGVKKDIEKLY
EAVPQLSNVFKIEDKIGEGTFSSVYLATAQLQVGPEEKIALKHLIPTSHPIRIAAEL
QCLTVAGGQDNVMGVKYCFRKNDHVVIAMPYLEHESFLDILNSLSFQEVREYM
LNLFKALKRIHQFGIVHRDVKPSNFLYNRRLKKYALVDFGLAQGTHDTKIELLK
FVQSEAQQERCSQNKSHIITGNKIPLSGPVPKELDQQSTTKASVKRPYTNAQIQIK
QGKDGKEGSVGLSVQRSVFGERNFNIHSSISHESPAVKLMKQSKTVDVLSRKLA
TKKKAISTKVMNSAVMRKTASSCPASLTCDCYATDKVCSICLSRRQQVAPRAG
TPGFRAPEVLTKCPNQTTAIDMWSAGVIFLSLLSGRYPFYKASDDLTALAQIMTI
RGSRETIQAAKTFGKSILCSKEVPAQDLRKLCERLRGMDSSTPKLTSDIQGHASH

QPAISEKTDHKASCLVQTPPGQYSGNSFKKGDSNSCEHCFDEYNTNLEGWNEVP
DEAYDLLDKLLDLNPASRITAEEALLHPFFKDMSL

PubCHEM and CHEMBL are drug databases used for feature extraction of drug molecules. PubCHEM is a database containing 96,881,514 drug compounds and associates to each using CID identifier. It allows programmatic access and downloads of database text files. The SMILES structure provided by the PubChem library is used to generate features corresponding to each drug molecule. The properties associated with the molecule is explored using CHEMBL database using a programmatic api request provided.

`https://pubchemdocs.ncbi.nlm.nih.gov/programmatic-access`, `https://chembl.gitbook.io/chembl-interface-documentation/web-services`.

CHEMBL379218

PubCHEM CID 11314340

CC1=C2C=C(C=CC2=NN1)C3=CC(=CN=C3)OCC(CC4=CC=CC=C4)N

For the drug-target interaction (i.e. drug-protein interaction), we use KIBA scores [3] instead of binary classification. Thus, we try to solve the problem into a regression problem to predict the drug and protein interaction. The KIBA score regression has two major advantages over binary classification: interaction strength of similarly interacting ligands-target (drugs-protein) can be compared and the bias problem of unknown interactions is refrained [3, 15]. Higher score means that there is more strength of interaction between the two. We use 52498 ligands as drugs and 254 human proteins as target for the prediction problem.

Table 3.1: KIBA Score Table

	O00238	O00311	O00329	O00418
CHEMBL10	3.518514	3.100002	4.0	3.6
CHEMBL102000	NaN	NaN	NaN	NaN

3.2 System Block

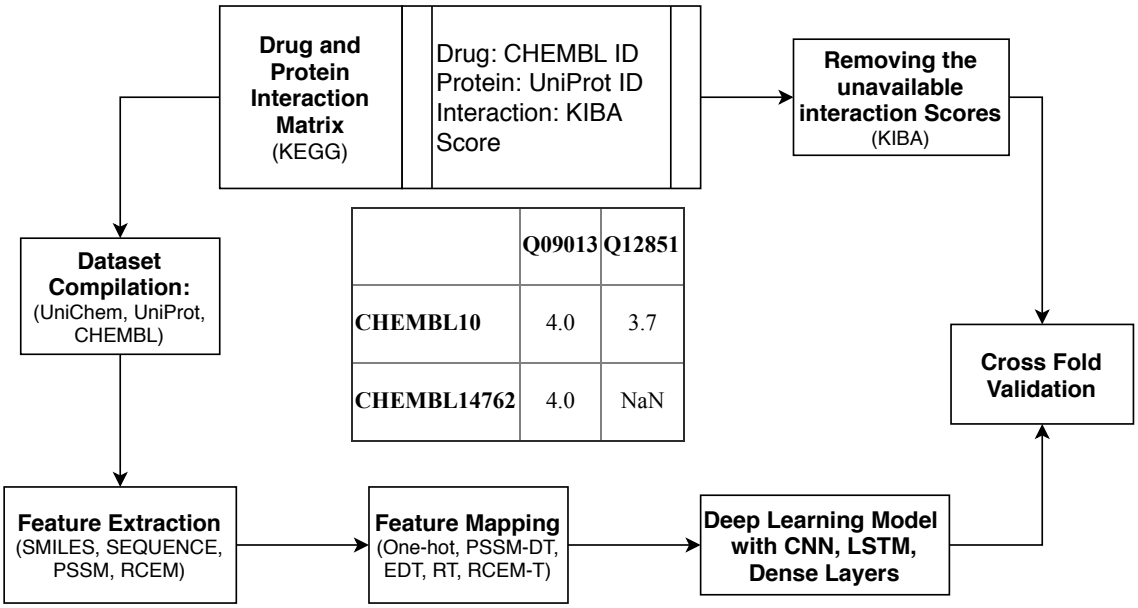


Figure 3.1: Schematic Block Diagram for Protein-Drug Prediction

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 primary canonical structure of protein-drug set are fed into interaction block. The interaction parameter is filtered accordingly to the filter type. Similarly, the drug feature set are created to be trained with the machine learning algorithm. Finally, after training the training dataset, we cross validate the model with test dataset.

3.3 Dataset Description

3.3.1 Kinase Inhibitor Bioactivity (KIBA)

The Kinase Inhibitor Bioactivity (KIBA) Scores are collected from the publicly made available dataset [3, *Tang. et al.*]. The scores are actually based on thermodynamic

constants K_i and K_d and, remaining enzyme activity(Activity % – IC_{50}) .

$$KIBA = \begin{cases} K_i.adj & if\ IC_{50}\ and\ K_i\ are\ present \\ K_b.adj & if IC_{50}\ and\ K_d\ are\ present \\ \frac{K_i.adj\ K_b.adj}{2} & if\ IC_{50}\ ,K_i\ and\ K_d\ are\ present \end{cases} \tag{3.1}$$

where,

$$K_i.adj = \frac{IC_{50}}{1 + L_i(IC_{50}/K_i)} \tag{3.2}$$

$$K_d.adj = \frac{IC_{50}}{1 + L_d(IC_{50}/K_d)} \tag{3.3}$$

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} [3] is the concentration at which the inhibitor causes a 50% inhibition of enzymatic activity and K_i is defined by

$$Ki = \frac{IC_{50}}{1 + [S]K_m} \tag{3.4}$$

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

All the bioactivity types are available from CHEMBL[16]. 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, it represents a total of 254 proteins and 52498 drugs.

3.3.2 Position Specific Score Matrix

Position Specific Scoring Matrix (PSSM) is a very useful protein feature. The protein feature represented by PSSM depends on the sequence of all the proteins in consid-

Table 3.2: PSSM Analysis Design

(a)

protein fasta sequence

1	GAGGTAAAC
2	TCCGTAAGT
3	CAGGTTGGA
4	ACAGTCAGT
5	TAGGTCATT
6	TAGGTACTG
7	ATGGTAACT
8	CAGGTATAC
9	TGTGTGAGT
10	AAGGTAAGT

(b)

Frequency Table

	1	2	3	4	5	6	7	8	9
A	3	6	1	0	0	6	7	2	1
C	2	2	1	0	0	2	1	1	2
G	1	1	7	10	0	1	1	5	1
T	4	1	1	0	10	1	1	2	6

(c)

Log-Likelihood Matrix

	1	2	3	4	5	6	7	8	9
A	0.3	0.6	0.1	0.00	0.00	0.6	0.7	0.2	0.1
C	0.2	0.2	0.1	0.00	0.00	0.2	0.1	0.1	0.2
G	0.1	0.1	0.7	1.00	0.00	0.1	0.1	0.5	0.1
T	0.4	0.1	0.1	0.00	1.00	0.1	0.1	0.2	0.6

(d)

Log-Likelihood Matrix for the motif

	1	2	3	4	5	6	7	8	9
A	0.3						0.7		
C			0.1	0.00	0.00	0.20			0.2
G		0.1						0.5	
T									

Table 3.3: Sliding Window Score Calculation

eration. The HUMAN genome protein (a database of more than 100,000) is downloaded from UniProt Library and we construct the PSSM matrix for each of the kinase proteins based on this HUMAN Genome Protein Database. Doing so, we try to characterize the PSSM matrix according to human proteins in a motivation to anticipate the prediction of new identified kinase proteins.

The Table 3.2 shows a rudimentary process of calculating PSSM score values. The sequence following shows the process of calculating the scores once the PSSM distribution of the whole family is calculated. Table 3.3 shows the score distribution of lowercase amino acid sequence (starting after 4th position) determined by the size of the sliding

window.

ACTCagccccagcGGAGGTGAAGGACGTCCTTCCCCAGGAGCCGGTGAGA
AGCGCAGTCGGGGGCACGGGGATGAGCTCAGGGGCCTCTAGAAAGATGTAG
CTGGGACCTCGGGAAGCCCTGGCCTCCAGGTAGTCTCAGGAGAGCTACTCA
GGGTCGGGCTTGGGGAGAGGAGGAGCGGGGGTGAGGCCAGCAGCA

.3, .1, .1, 0, 0, .2, .7, .5, .2 == Sum(2.1) - posix(4) – See Table 3.4

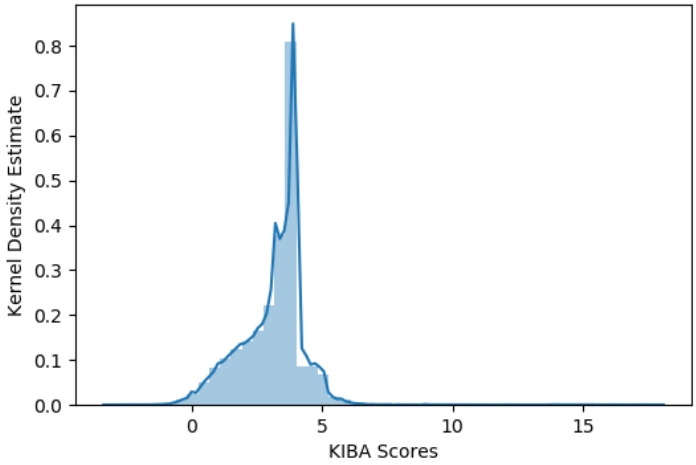
Table 3.4: Score of sliding window motifs

0	1.099
1	1
2	2.2
3	2.1
4	2.1
5	1.300
6	1.3
7	1.4
8	2
9	2.9

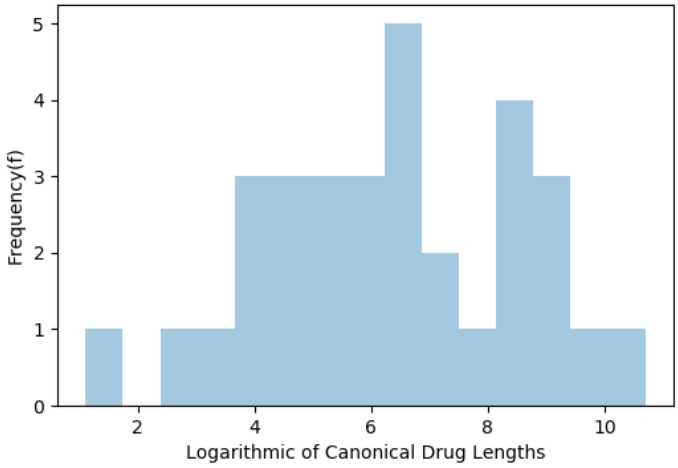
3.3.3 PSI-BLAST

PSI-Blast tools relates with multiple sequence alignments from a family of protein sequences[17]. 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 [17, KEGG] protein. PSSM profile is a matrix of L*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.[17, PSSM]

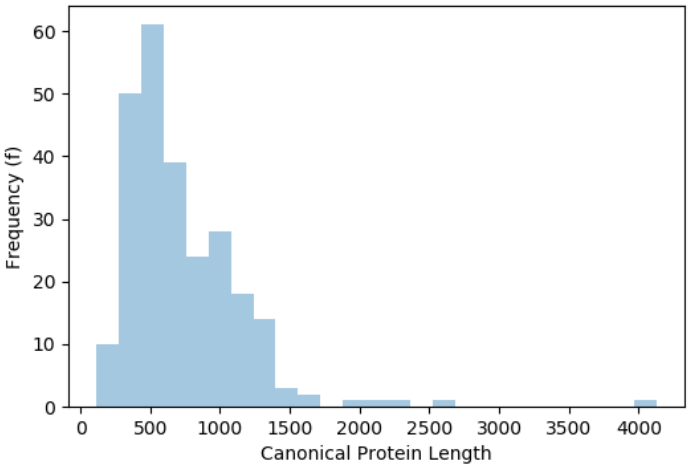
$$PSSM = \begin{bmatrix} P_{1,1} & P_{1,2} & \dots & P_{1,20} \\ P_{2,1} & P_{2,2} & \dots & P_{2,20} \\ \vdots & \vdots & \ddots & \vdots \\ P_{2,1} & P_{2,2} & \dots & P_{2,20} \end{bmatrix} \tag{3.5}$$



(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

PSSM-DT

Two forms of PSSM distance transformation techniques are used to transform the PSSM information into fixed dimensional vectors [18]. 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:

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

lg = distance of separation between same amino acid sequence

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

i_1 and i_2 refer to tow different types of amino acids

Thus we have [380 (3.7)+20 (3.6) = 400] x 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[19]. 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):

$$P = [\partial_1, \partial_2, \ldots, \partial_\Omega] \tag{3.8}$$

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:

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

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 the 20 different amino acids in the protein sequence. Finally we spread the $f(A_x, A_y)$ in equation 3.8 as: $\partial_1 = f(A_1, A_2)$, $\partial_{400} = f(A_{20}, A_{20})$

3.3.4 Residue feature

The Statistical Residue Vector Space R2RSRV [4] 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 1 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 Jeong et al.[20], and implemented by Pujan et al.[21], emphasize domains with similar conservation rates by grouping domain families based on their conservation score in the PSSM profile.

$$RPT = \begin{bmatrix} S_{1,1} & S_{1,2} & \dots & S_{1,20} \\ S_{2,1} & S_{2,2} & \dots & S_{2,20} \\ \vdots & \vdots & \ddots & \vdots \\ S_{2,1} & S_{2,2} & \dots & S_{2,20} \end{bmatrix} \tag{3.10}$$

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

$$V = [f_{s_{1,1}}, f_{s_{1,2}}, \ldots, f_{s_{i,j}}, \ldots, f_{s_{20,20}}] \tag{3.11}$$

where,

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

3.3.5 Labelled Encodings

The labeled encoding techniques is used to represent the canonical structure of drugs and proteins. The structural canonical information is preserved while sending the feature set to deep learning method. An array of integers is formed from particular sequence while representing the structural information.

The Labelled Encodings of protein and drugs can be defined by Table 3.5 :

Protein Labeled Encoding Technique	A –> 1	C –> 2	B –> 3	E –> 4
	D –> 5	G –> 6	F –> 7	I –> 8
Drugs Labeled Encoding Technique	# –> 1	% –> 2	: –> 3	+ –> 5
	4 –> 13	7 –> 14	F –> 25	I –> 26

Table 3.5: Labeled Encoding of Proteins and Drugs

3.4 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 3.6.

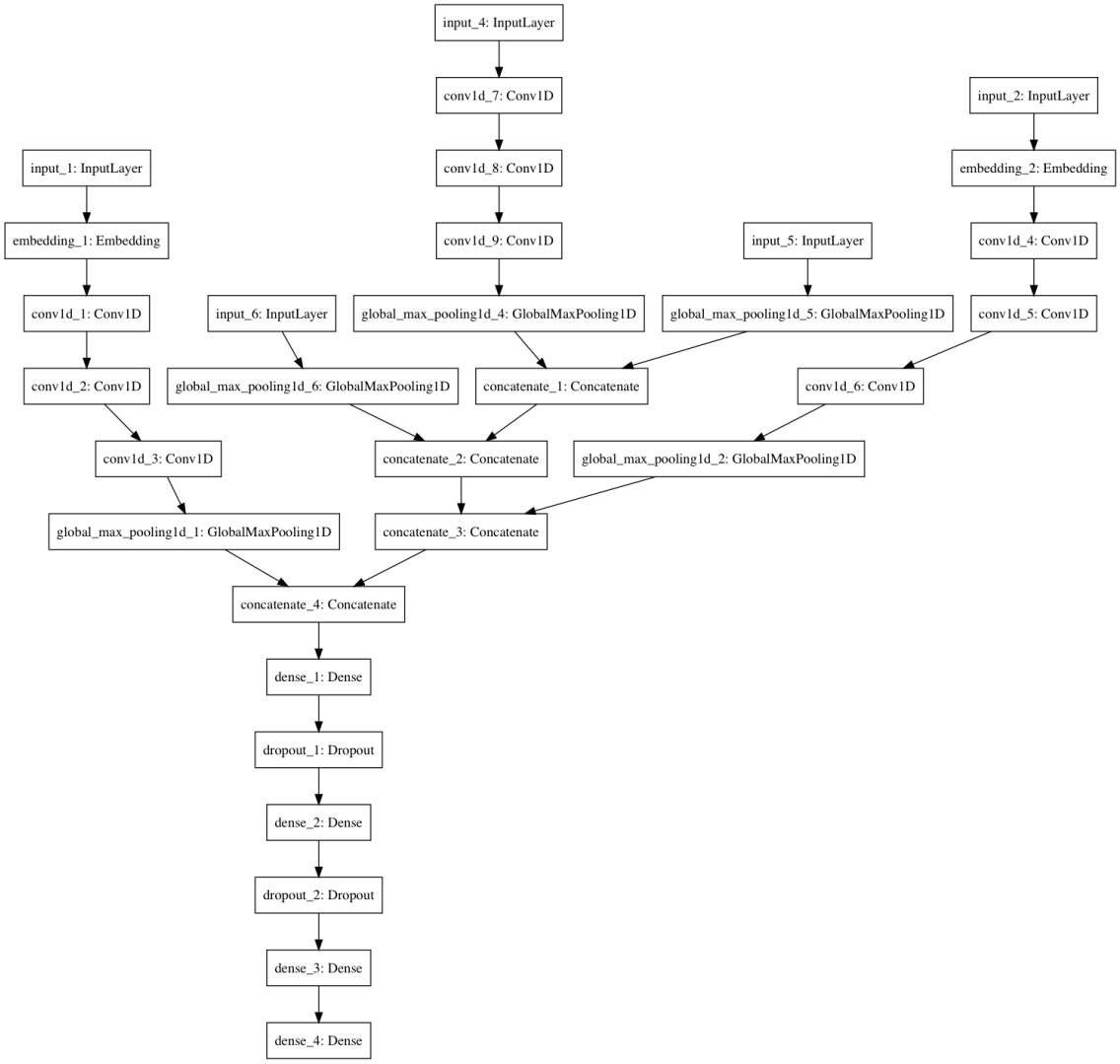


Figure 3.3: Deep Learning Model to predict Protein-Drug Interaction

3.4.1 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]] -> [[0.25, 0.1], [0.6, -0.2]].

Table 3.6: Inputs Used in the Deep Learning Network

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

Dense Layer

Dense Layer is a neural layer which fully connects the input layer to output layer. It can be used to learn the global pattern of the feature data. The representation can be seen from Figure 3.4.

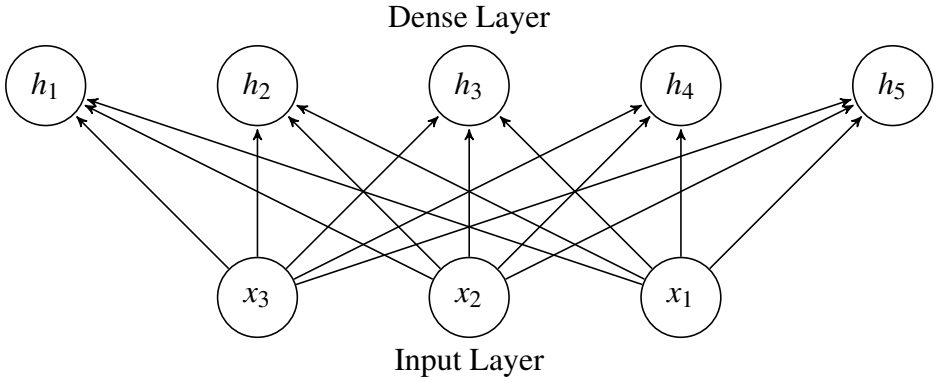


Figure 3.4: Dense Layer

Dropout Layer

Our model becomes 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 diagrammatically in the Figure 3.5.

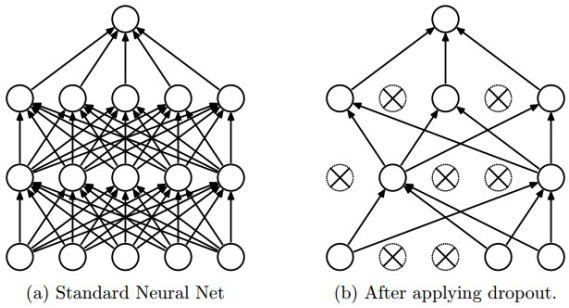


Figure 3.5: a) Standard neural network whose all the nodes have weights connected to higher nodes and lower nodes. b) Certain nodes belonging to same levels are disconnected. Some weights are also disconnected from other nodes depending on the percentage of dropout applied.

Pooling Layer

The Pooling layer is used to downsample 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).

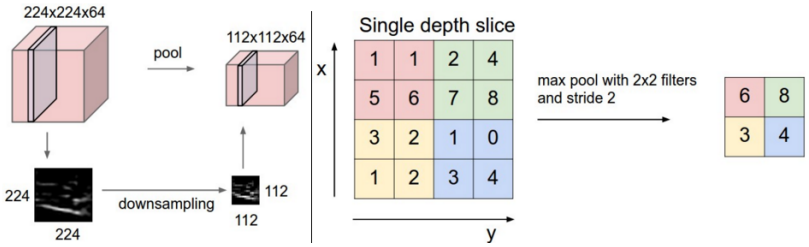


Figure 3.6: Pooling Layer

Concatenation Layer

Concatenation Layer as the name implies 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.

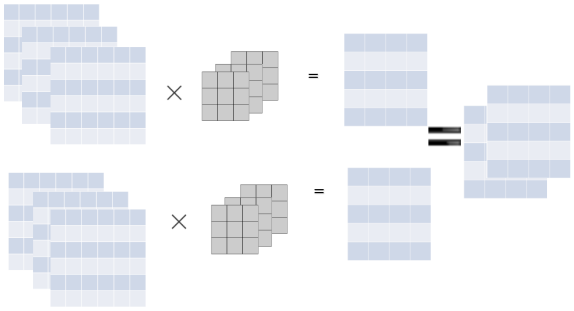


Figure 3.7: Convolutional Neural Network

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

The sequence information of drugs and proteins live in their canonical form. Exploring to 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 Poisson-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[17]. 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 quad-core processor. 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)[18] as defined by equation 4.1:

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

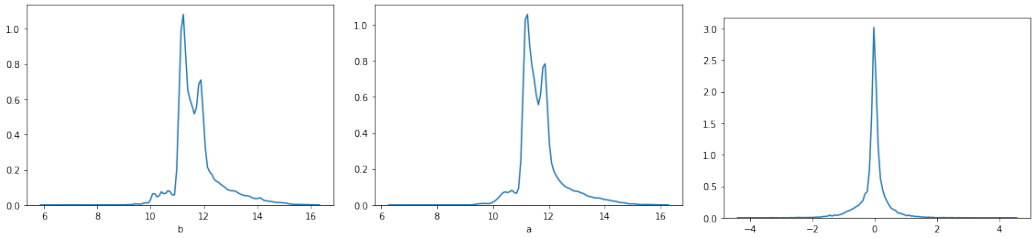
where b_i is the prediction value for higher affinity δ_i and b_j is the prediction value for smallery affinity δ_j, Z is the normalization constant and $h(m)$ is the unit step function:

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

4.2 Results

The training of the model proved a better choice as we placed a LSTM layer to get a generalization of all the feature sets extracted from the drug and protein sequence. In a primordial network, the c-index rised from 70% to 75% simply between the choice of Dense Layer and LSTM Layer.

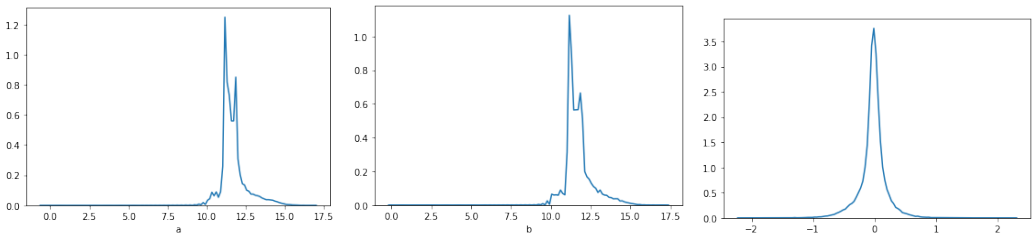
The validation loss and the cindex scores(equation 4.1) were 16% and 89% respectively when we used our full model. The plot of KIBA prediction scores and the actual scores for training sets is shown in Figure 4.1



(a) Training Actual Scores (b) Training Predicted Scores (c) Training Scores Difference

Figure 4.1: Training Results based on KIBA Score Prediction

Similarly, the prediction scores and actual scores for validation sets is shown in Figure 4.2



(a) Testing Actual Scores (b) Testing Predicted Scores (c) Testing Scores Difference

Figure 4.2: Testing Results on KIBA score Prediction

Chapter 5: Conclusion

5.1 Limitations

This work only relates with the molecular properties of drugs and proteins to determine the best targets. The limitations to the deep learning method of protein-drug prediction in this manner are:

- Pharmacophore model of drugs and proteins have not been addressed. This is due to inavailability of proper datasets and highly complex nature of protein mechanism that the work become out of scope.
- The protein folds haven't been analyzed because the processer requirements of such algorithms rise exponentially with every components cascaded one over the another.

5.2 Remaining Works

We have only approached the sample space of No Free Lunch Algorithm (NFL) by forming the different feature-sets. However, the generalized optimization has not been achieved yet. The grid-search CV and Stacking Generalization will be used to create a better optimized machine learning method to solve the problem of protein-drug interaction from sequence information.

R2RSRV

Table 1: R2RSRV Matrix

	I	V	L	F	C	M	A	G	T	S	W	Y	P	H	E	Q	D	N	K	R
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	-2.23	-2.14
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	0.66	-1.42
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	-2.10	0.19
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	-1.71	-1.33
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	-1.80	-0.84
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	-0.72	-1.51
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	-1.11	-2.74
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	1.72	1.22
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	0.29	-0.74
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	0.11	-0.38
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	-0.27	4.08
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	0.87	-0.33
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	0.14	-0.40
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	-1.90	-0.06
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	3.52	3.45
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	-0.67	0.24
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	0.86	2.73
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	-0.63	-0.43
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	2.61	-3.54
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	-3.54	0.73

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