



# 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 Tribhuvan 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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Institute of Engineering  
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*Dedicated to my parents, brother in law and sister.*

# 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

I would like to express the deepest appreciation to my supervisor and Head of Department of Electronics and Computer Engineering, Pulchowk Campus Dr. Surendra Shrestha for his guidance throughout the period of this work. His invaluable support, understanding and expertise have been very important in completing this work. It was a great honor for me to pursue my thesis under his supervision.

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I would like to express my heartily gratitude towards the Institute of Engineering, Pulchowk Campus along with all my respected teachers, my friends, my family for giving me continuous support for their invaluable help.

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# Chapter 1

## Introduction

### 1.1 Background

Finding the interaction of drugs and proteins based simply on primary structure information of drugs and proteins is one of the many challenges faced in drug-synthesis process.

With the advent of new machine learning techniques and along with the rise of deep-learning techniques, we are closer to create a good prediction of analogy. However, the chemical properties of drugs and the targets complicate the situation as they react differently with slight change in protein sequence. 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. The major fallback being that the simple encoding techniques don't incorporate the proteins behaviour related to hydrophobicity, acidity, secondary and tertiary structures information.

The Stacked Generalized Prediction 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. The Dataset we used scores the interaction of proteins and drugs based on Kb 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 [1].

## **1.2 Statement of Problem**

## **1.3 Objectives**

## **1.4 Scope of Work**

## **1.5 Organization of Report**

## **Chapter 2**

# **Theoretical Background**

### **2.1 No Free Lunch Algorithm**

### **2.2 Stacking Generalization**

### **2.3 Literature Review**

## Chapter 3

# Methodology

### 3.1 System Block Diagram

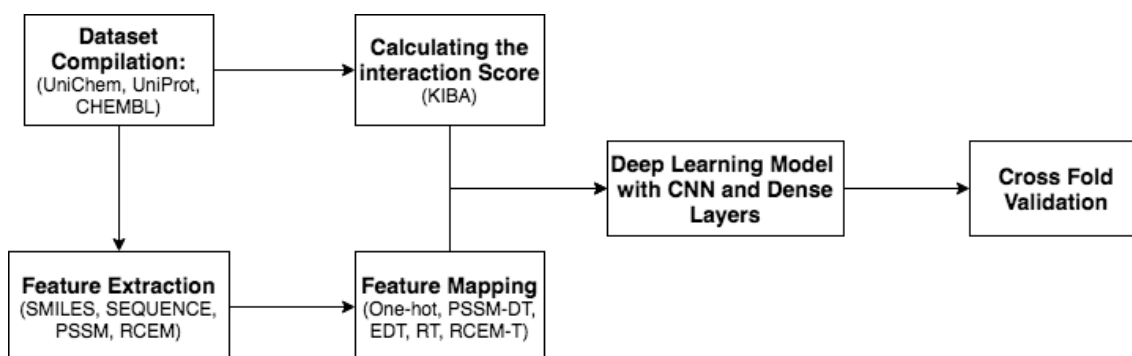


Figure 3.1: System Block Diagram

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.[1] We use KEGG DRUG dataset for finding the interaction set between DRUG and PROTEIN. The interaction score is based on:

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

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  $IC_{50}$  [2] 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.[3] 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 0 to 17.2. With the standard deviation of 0.84, we try to predict the best KIBA score of drug and protein based on the sequence information alone.

### 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. [4]

#### ChEMBL

The molecular fingerprints related to drugs are referenced using ChEMBL Identifier and the drug sequence is called from ChEMBL database. [3]

### 3.2.3 PSI-BLAST

It relates with multiple sequence alignments from a family of protein sequences[5]. This helps us to create a PSSM 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 [5, 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.[5, PSSM]

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

### PSSM-DT

Two forms of PSSM distance transformation techniques are used to transform the PSSM information into fixed dimensional vectors [6]. 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 Eqn: 3.7+20 Eqn: 3.6 = 400) x  $lg$  matrix which will be used as protein-specific vector in this work.

### 3.2.4 Residue Residue feature

The Statistical Residue Vector Space R2RSRV [7] 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 A 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 [8, Jeong et al.], and implemented by [9, Pujan et al.], emphasizes domains with similar conservation rates by grouping domain families based on their conservation score in the PSSM profile.

$$RPT = \begin{bmatrix} H_{1,1} & H_{1,2} & \dots & H_{1,20} \\ H_{2,1} & H_{2,2} & \dots & H_{2,20} \\ \vdots & \vdots & \ddots & \vdots \\ H_{20,1} & H_{20,2} & \dots & H_{20,20} \end{bmatrix} \quad (3.8)$$

The RPT matrix (Equation 3.8) is then tranformed into feature vector of 400 dimensions, as shown in Equation 3.9.

$$V = [f_{s_{1,1}}, f_{s_{1,2}}, \dots, f_{s_{i,j}}, \dots, f_{s_{20,20}}] \quad (3.9)$$

where,

$$f_{s_{i,j}} = \frac{S_{i,j}}{L} (i, j = 1, 2, \dots, 20) \quad (3.10)$$

### 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 Fig. 3.2.

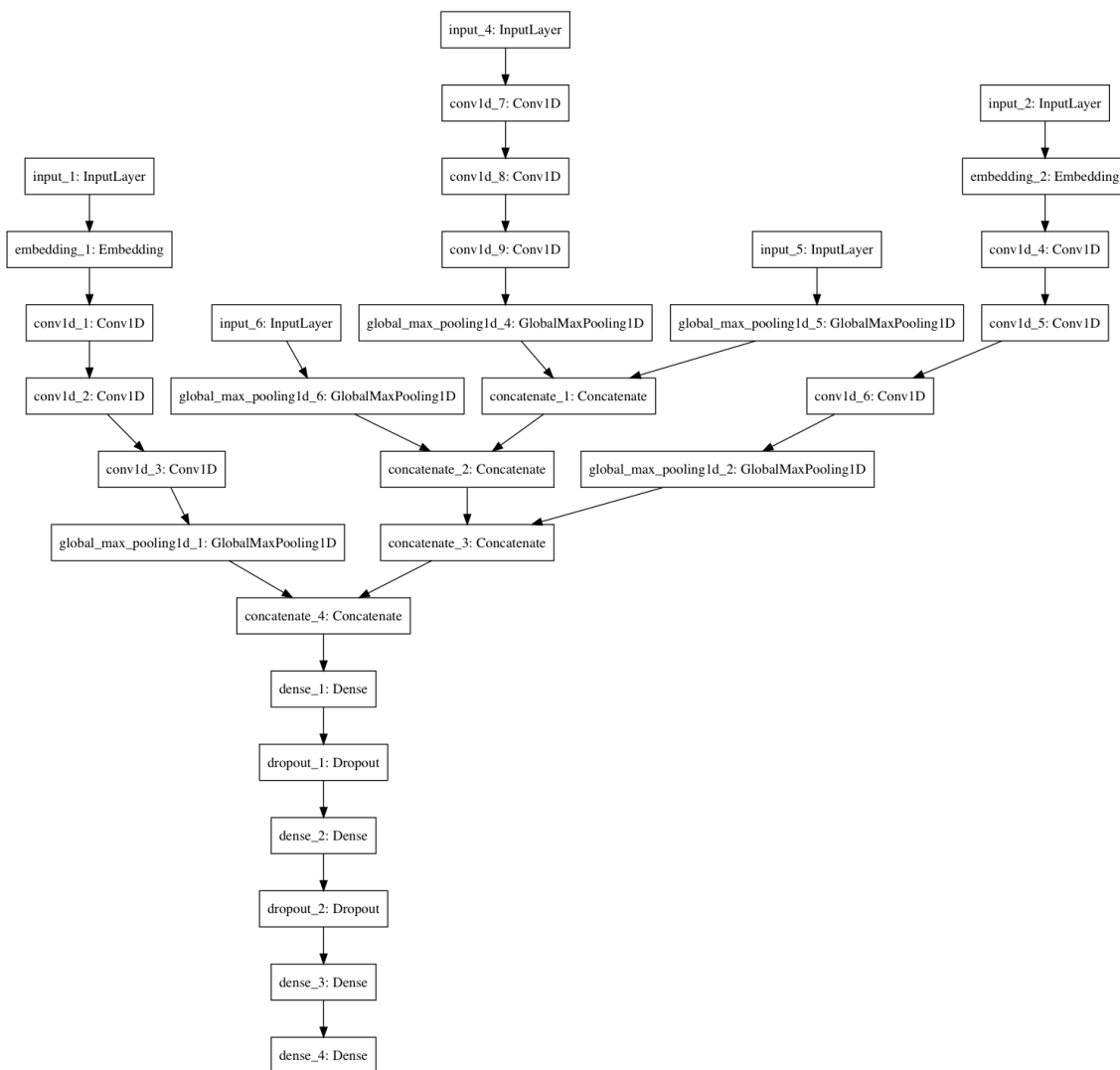


Figure 3.2: Deep Learning Model

#### 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.  $[[4], [20]] \rightarrow [[0.25, 0.1], [0.6, -0.2]]$ .

### Dense Layer

It is a neural layer which fully connects the input layer to output layer. It can be seen from Figure 3.3.

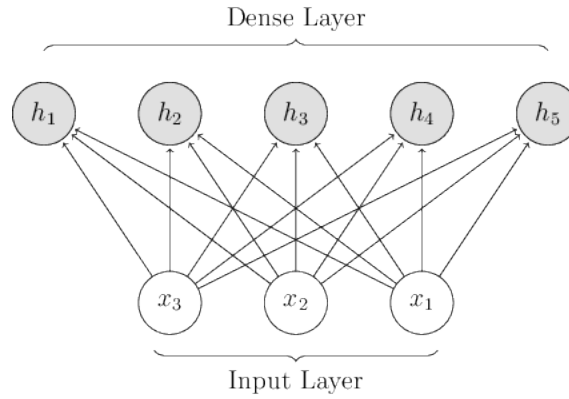


Figure 3.3: Dense Layer

### 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 diagrammatically in the figure 3.4 below:

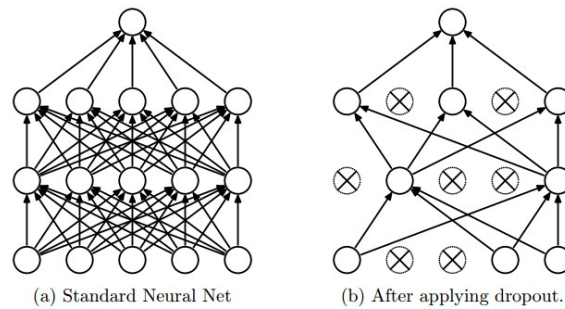


Figure 3.4: Dropout Layer

### 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 1<sup>st</sup> dimensional element).

### 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.



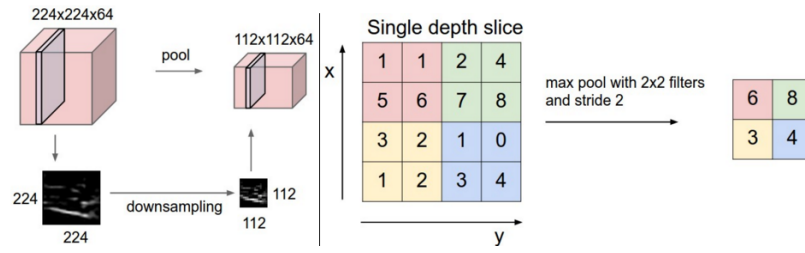


Figure 3.5: Pooling Layer

### 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 3.6.

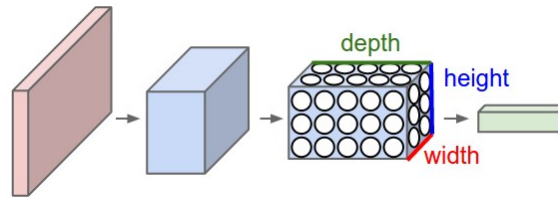


Figure 3.6: Convolutional Neural Network

### LSTM

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

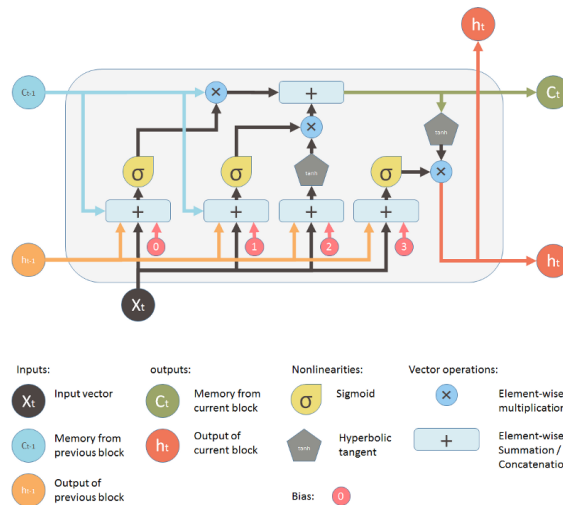


Figure 3.7: Long Short Term Memory

## Chapter 4

# Results

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### 4.1 First Section

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## 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	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

Table A.1: R2RSRV Matrix

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