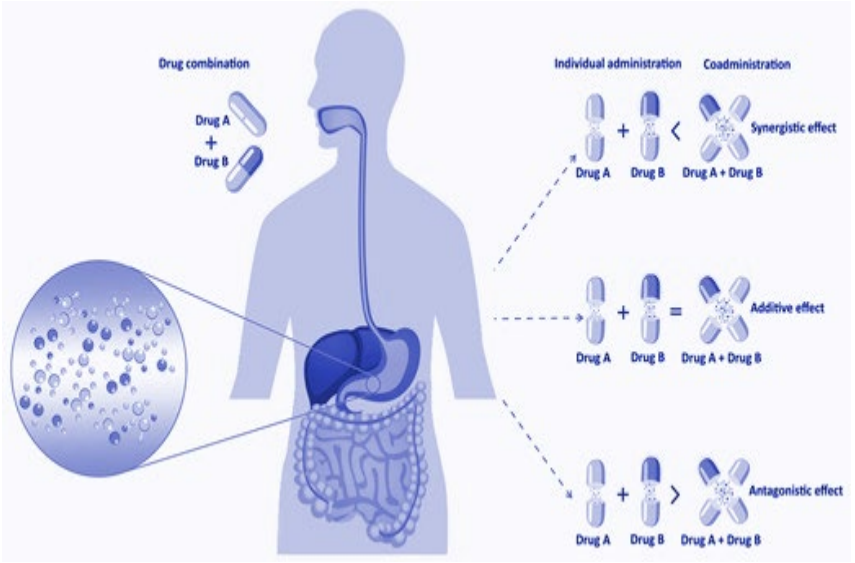
Cancer Drug Synergy Prediction using Graph Convolutional Neural Networks



Group 2

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Introduction

Drug A → Specific response for A on cell line

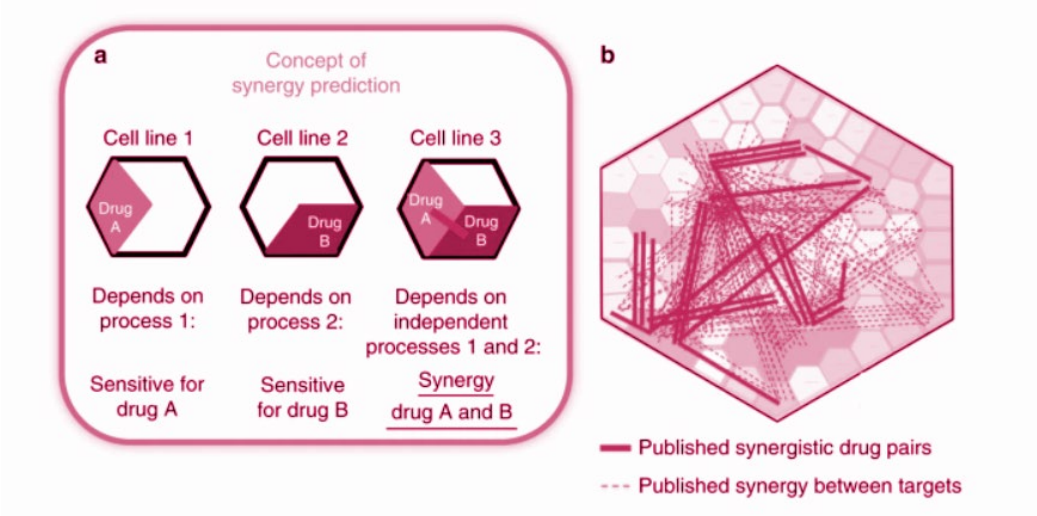
Drug B → Specific response for B on cell line

Synergy of A and B →

Combined response of

A and B on cell line.

Synergy could be additive or inhibitive.



Methods to predict synergy-scores

- Naive method: based on clinical experiences - trial and error method

- High-throughput Screening (HTS)

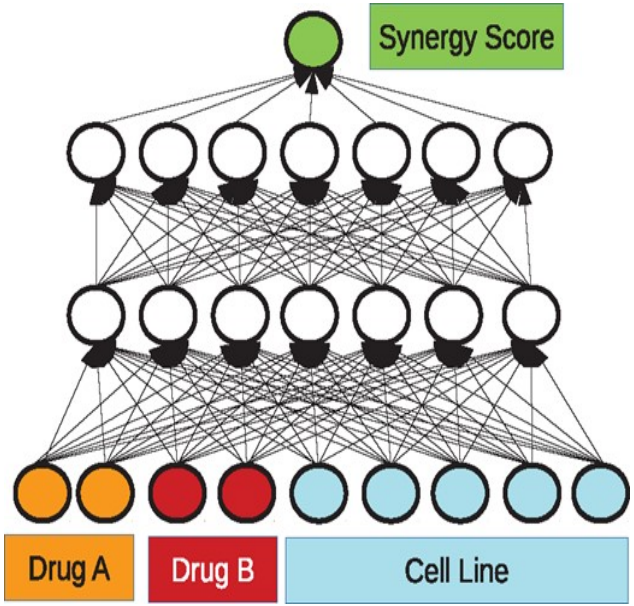
- Machine learning approach

Primary Research Paper

Finding synergistic drug pairs for a particular cancer type is important for improving efficacy of anticancer treatment.

Each sample:

two compounds + a cell line



[Kristina Preuer, Richard P I Lewis, Sepp Hochreiter, Andreas Bender, Krishna C Bulusu, Günter Klambauer, DeepSynergy: predicting anti-cancer drug synergy with Deep Learning, *Bioinformatics*, Volume 34, Issue 9, 01 May 2018, Pages 1538–1546, https://doi.org/10.1093/bioinformatics/btx806]

Data: Main Drug Data with Synergy Scores

Drug details: http://www.bioinf.jku.at/software/DeepSynergy/

	Unnamed: 0	drug_a_name	drug_b_name	cell_line	synergy	fold	drug_a_structure	drug_b_structure
0	5-FU_ABT-888_A2058	5-FU	ABT-888	A2058	7.693530	2	O=c1[nH]cc(F)c(=O)[nH]1	CC1(c2nc3c(C(N)=O)cccc3[nH]2)CCCN1
1	5-FU_ABT-888_A2780	5-FU	ABT-888	A2780	7.778053	2	O=c1[nH]cc(F)c(=O)[nH]1	CC1(c2nc3c(C(N)=O)cccc3[nH]2)CCCN1
2	5-FU_ABT-888_A375	5-FU	ABT-888	A375	-1.198505	2	O=c1[nH]cc(F)c(=O)[nH]1	CC1(c2nc3c(C(N)=O)cccc3[nH]2)CCCN1
3	5-FU_ABT-888_A427	5-FU	ABT-888	A427	2.595684	2	O=c1[nH]cc(F)c(=O)[nH]1	CC1(c2nc3c(C(N)=O)cccc3[nH]2)CCCN1
4	5-FU_ABT-888_CAOV3	5-FU	ABT-888	CAOV3	-5.139971	2	O=c1[nH]cc(F)c(=O)[nH]1	CC1(c2nc3c(C(N)=O)cccc3[nH]2)CCCN1

	drug_a_structure	drug_b_structure	cell_line	synergy
0	Cc1nc(Nc2ncc(C(=O)Nc3c(C)cccc3Cl)s2)cc(N2CCN(C...	Cn1c(=O)n(-c2ccc(C(C)(C)C#N)cc2)c2c3cc(-c4cnc5...	ZR751	21.548383
1	CS(=O)(=O)CCNCc1ccc(-c2ccc3ncnc(Nc4ccc(OCc5ccc...	COC1CC2CCC(C)C(O)(O2)C(=O)C(=O)N2CCCCC2C(=O)OC...	VCAP	14.617611
2	COc1cccc2c1C(=O)c1c(O)c3c(c(O)c1C2=O)CC(O)(C(=...	NC(=O)c1cccc2cn(-c3ccc(C4CCCNC4)cc3)nc12	PA1	-13.653373
3	COC12C(COC(N)=O)C3=C(C(=O)C(C)=C(N)C3=O)N1CC1NC12	CCN(CC)CCNC(=O)c1c(C)[nH]c(C=C2C(=O)Nc3ccc(F)c...	RPMI7951	-5.641747
4	CS(=O)(=O)CCNCc1ccc(-c2ccc3ncnc(Nc4ccc(OCc5ccc...	O=C(O)C1(Cc2cccc(Nc3nccs3)n2)CCC(Oc2cccc(Cl)c2...	LOVO	28.431355

Data: Cancer Cell Line

Cell line: https://sites.broadinstitute.org/ccle/

	#	#.1	CellLine	CHL1	HMCB	HS852T	HS695T	A101D	HS294T	SNU466	...	HEL9217	HEL	UT7	SET2
0	#	#	Tissue	skin	skin	skin	skin	skin	skin	central nervous system	...	haematopoietic and lymphoid tissue	haematopoietic and lymphoid tissue	haematopoietic and lymphoid tissue	haematopoietic and lymphoid tissue
1	GeneSym	NaN	GeneID/NA	na	na	na	na	na	na	na	...	na	na	na	na
2	LBH	na	81606	-0.0	-0.0	0.0	-0.0	-0.0	0.0	0.0	...	0.0	0.0	0.0	0.0
3	GLI2	na	2736	0.0	1.0	0.0	0.0	0.0	0.0	0.0	...	-0.0	0.0	-0.0	-0.0
4	PAPPA	na	5069	0.0	-0.0	0.0	-0.0	0.0	0.0	0.0	...	0.0	0.0	0.0	0.0

5 rows × 1040 columns

Data: Protein-Protein Interactions

PPI: https://snap.stanford.edu/biodata/datasets/10000/10000-PP-Pathways.html

	Protein1	Protein2
0	1394	2778
1	122704	54460
2	2597	2911
3	4790	79155
4	109	27115
5	324	10982
6	26268	6500
7	3609	3954
8	152485	57504
9	1537	55967
10	8452	7278

Performance Metrics

Mean Squared Error (MSE):

$$\mathrm{MSE} = \frac{1}{n}\sum_{i=1}^{n}(Y_i - \hat{Y}_i)^2$$

MSE = mean squared error

n = number of data points

Y_i = observed values

$\hat{Y}_i$ = predicted values

R2 Score:

$$R^2 = 1 - \frac{\sum_i (y_i - \hat{y}_i)^2}{\sum_i (y_i - \mu)^2}.$$

$$R = sign\left(R^2\right)\sqrt{|R^2|},$$

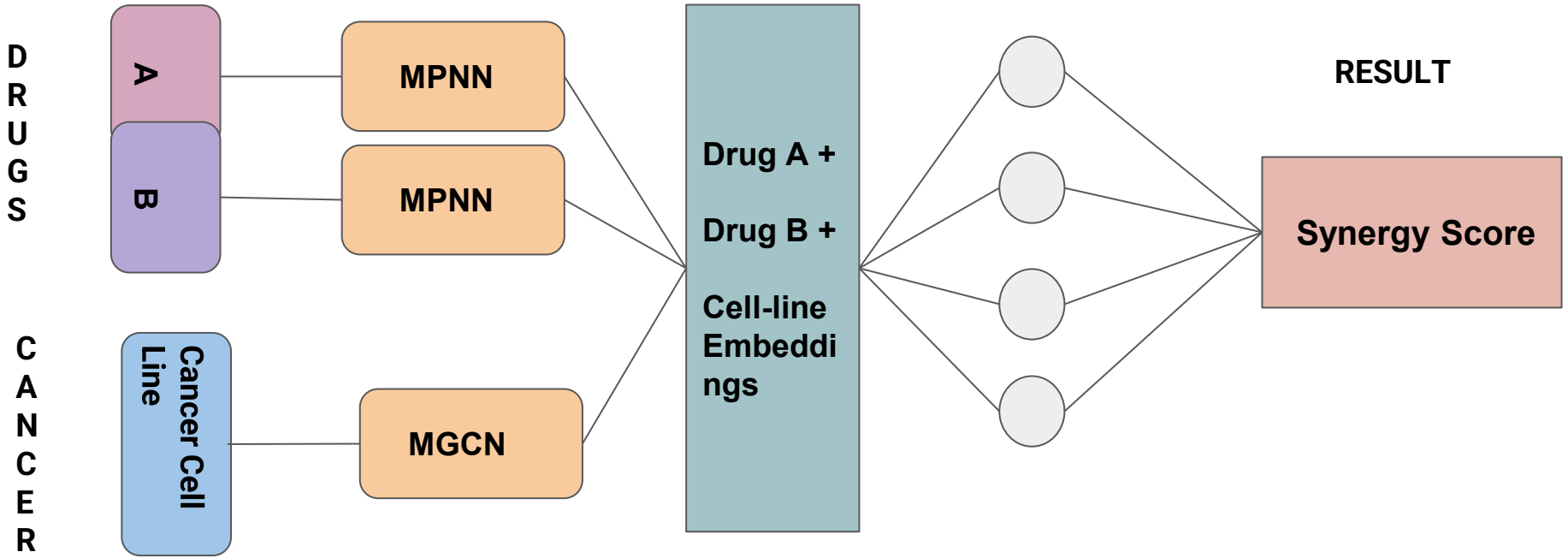
(Image Source: https://emilia-orellana44.medium.com/not-nice-square-error-2d18c248391c)

Model Architecture

1) Graph Neural Network - Message Passing Neural Network
2) Molecular Graph Convolutional Neural Network

And a feed forward neural network that takes input from these two embeddings and predicts a synergy score.

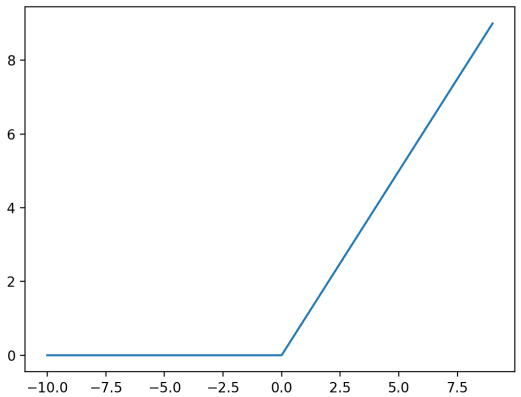
Flow of Modelling



Model: Activation Functions

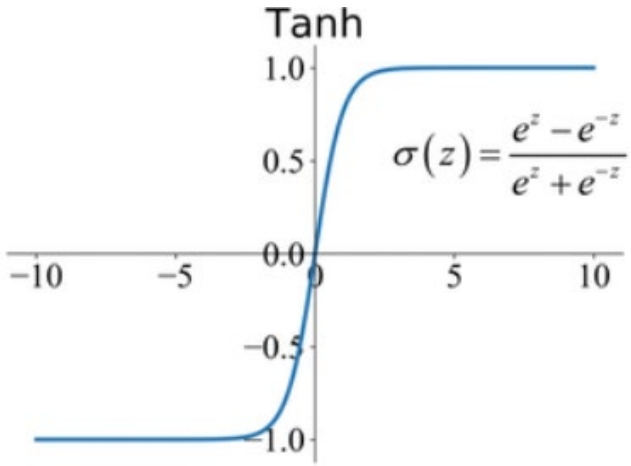
ReLU: (rectified linear activation unit)

f(x) = max(0, x)



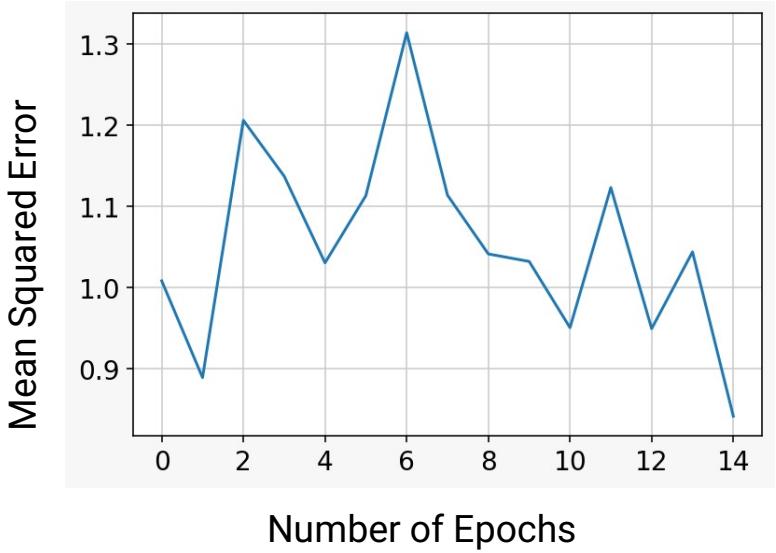
https://machinelearningmastery.com/wp-content/uploads/2018/10/Line-Plot-of-Rectified-Linear-Activation-for-Negative-and-Positive-Inputs.png

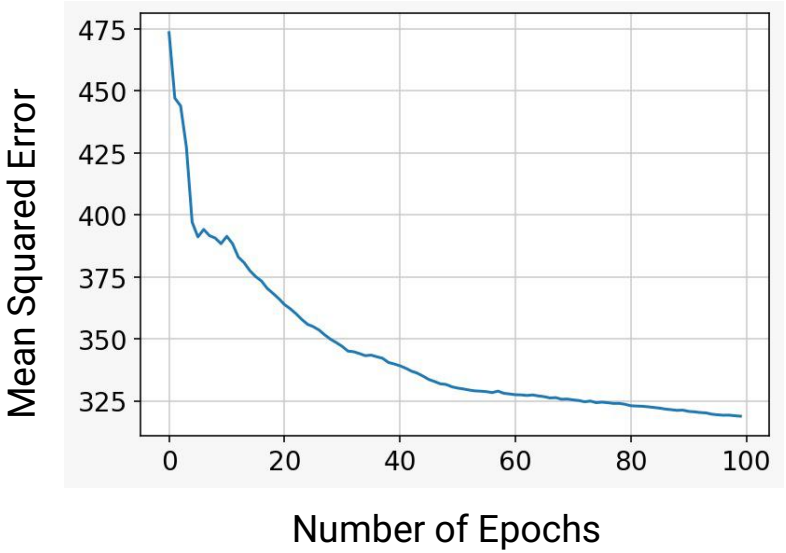
TanH



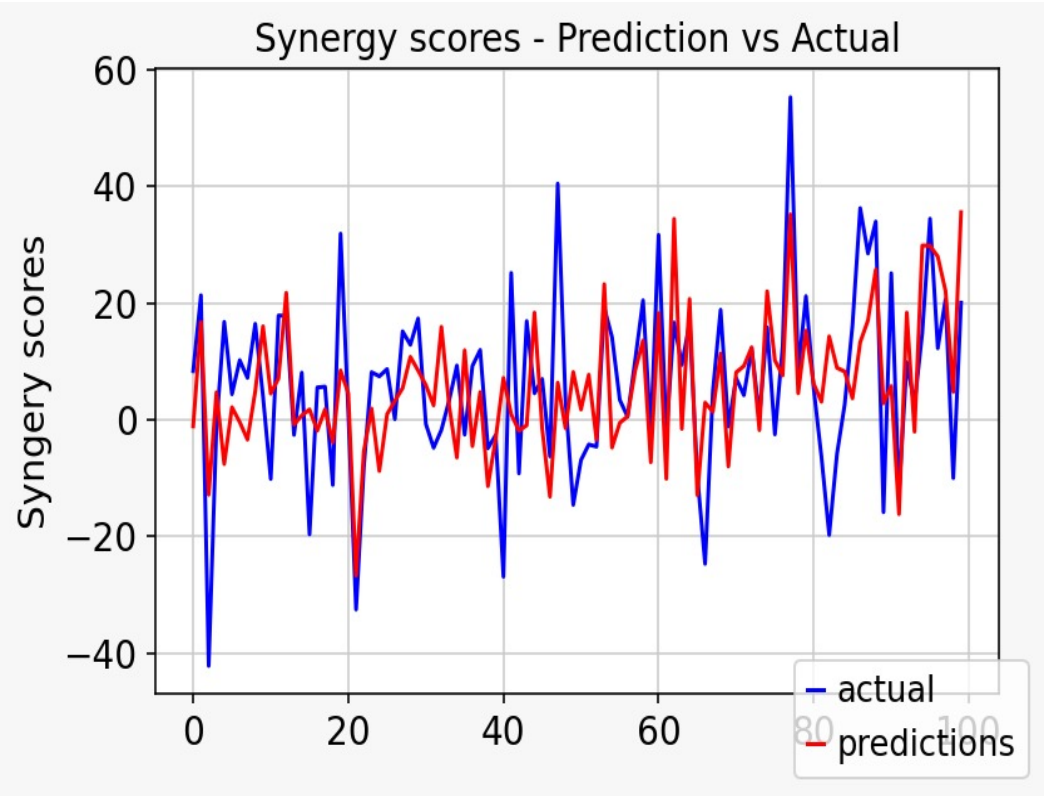
https://www.researchgate.net/figure/Commonly-used-activation-functions-a-Sigmoid-b-Tanh-c-ReLU-and-d-LReLU_fig3_335845675

Results: Training Curve





Results: Predictions



Training (MSE) = 318.786

Testing (MSE) = 160.579

Testing R-Squared Value = 0.354

Conclusion:

1. We have developed a novel graph based deep learning method to predict synergy scores.

1. Since it requires more number of epochs, this method showed difficulty in generalizing on novel drugs-cell line combination when trained on lower parameters. Also, need to look at other activation functions and also decay weights in some epochs.

1. We've demonstrated that this method can also perform decent enough on external unseen test dataset

1. Overall, with more improvement, this could be a valuable tool for selecting drug-combinations for cancer cell-lines.

Limitations

- Need large number of epochs (at-least 500) to get a good convergence.
- Due to the complexity of the model, it requires too much computational time for training.
- Since the dataset has only a limited number of different drugs and cell lines all methods show difficulties to generalize well across novel drugs and cell lines.
- Evaluating performance of ML models on individual cancer-cell types.
- Since the models are extremely complex, their interpretability is difficult.

References:

- https://doi.org/10.1093/bib/bbac075
- https://doi.org/10.1158/1535-7163.MCT-15-0843
- https://doi.org/10.3389/fchem.2019.00509
- https://doi.org/10.1093/bioinformatics/btx806
- https://www.nature.com/articles/s41598-021-90923-y
- https://github.com/KristinaPreuer/DeepSynergy
- https://keras.io/examples/graph/mpnn-molecular-graphs/
- https://github.com/tkipf/pygcn
- http://snap.stanford.edu/deepnetbio-ismb/ipynb/Graph+Convolutional+Prediction+of+Protein+Interactions+in+Yeast.html
- https://jhoonline.biomedcentral.com/articles/10.1186/s13045-020-00850-0

Q&A