Predicting Small Molecule Binding Affinity to Serotonin Receptors

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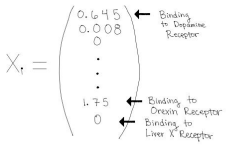
Overview

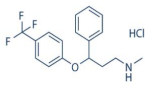
- We construct a deep neural network to predict the binding affinity to serotonin receptors.
- Understanding the binding behavior of these receptors is important for a diverse range of future mental health drug research.
- We show representing small molecules as vectors with binding constants for other targets can provide predictive information.
- Our neural network approach outperforms a simple linear regression model as well as a more complex matrix completion method. The metric used is the F_1 score.

Data Representation

- To represent the small molecule we construct a vector in which the i^{th} entry gives the binding constant, K_B, of the small molecule to the i^{th} chosen target (939 other targets aside from serotonin).
- A large K_B value indicates that the small molecule binds well to the target.

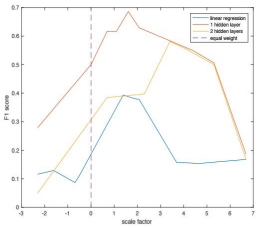


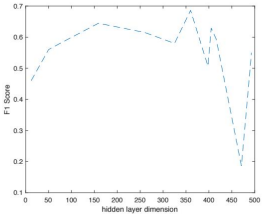
Experimental Results



Comparison Methods: Sparse Matrix Completion, Linear Regression
Metric of performance: F_1 score

$$F_1 = \frac{2 * \text{true positive}}{2 * \text{true positive} + \text{false negative} + \text{false positive}}$$





Method	F_1 Score	Positive Example Accuracy	Negative Example Accuracy
Linear Regression	0.423	0.46/0.84	0.98/0.38
Matrix Completion	0.571	**0.80**	0.88
Neural Network	**0.686**	0.66/0.77	0.98/**0.89**

References

Han Altae-Tran, Bharath Ramsundar, Aneesh S Pappu, and Vijay Pande. Low data drug discover with one-shot learning. *ACS central science*, 3(4):283-293, 2017.
David E Nichols and Charles D Nichols. Serotonin receptors. *Chemical reviews*, 108(5):1614-1641,2008.
The binding database.

Model

Loss function:

$$L(p) = -\frac{1}{N}\sum_{i=1}^{N} s(y_i \log p_i) + (1 - y_i)\log(1 - p_i).$$

- s allows us to give greater weight to correctly identifying positive examples. We include this to deal with the sparsity of positive examples in the dataset.
- We explore the effect of s as well as the number of layers of our neural network on the performance (as measured by F1 score). For a *k*-layer net we have,

$$A_0 = X,$$
$$A_j = f(W_j A_{j-1} + b_j),$$
$$p = \sigma(W_k A_{k-1} + b_k).$$

Where $f()$ is a ReLU or a sigmoid.

- Prediction is done by:

$$\hat{y}_i = p > 0.5$$

Discussion

- A shallow neural network architecture shows promising performance in predicting the binding affinity to serotonin receptors.
- Future research must implement more comparison methods to get a better sense of the kind of F_1 score that would be helpful.
- Unlike matrix completion methods, constructing a loss function with scaling factor *s* allows freedom in tuning the specificity/sensitivity ratio
- To increase speed of training, dimensionality reduction methods should be explored in the vector representation of the small molecule.

Thank you!!