Blood-Brain Barrier Permeability Prediction using Graph Neural Networks

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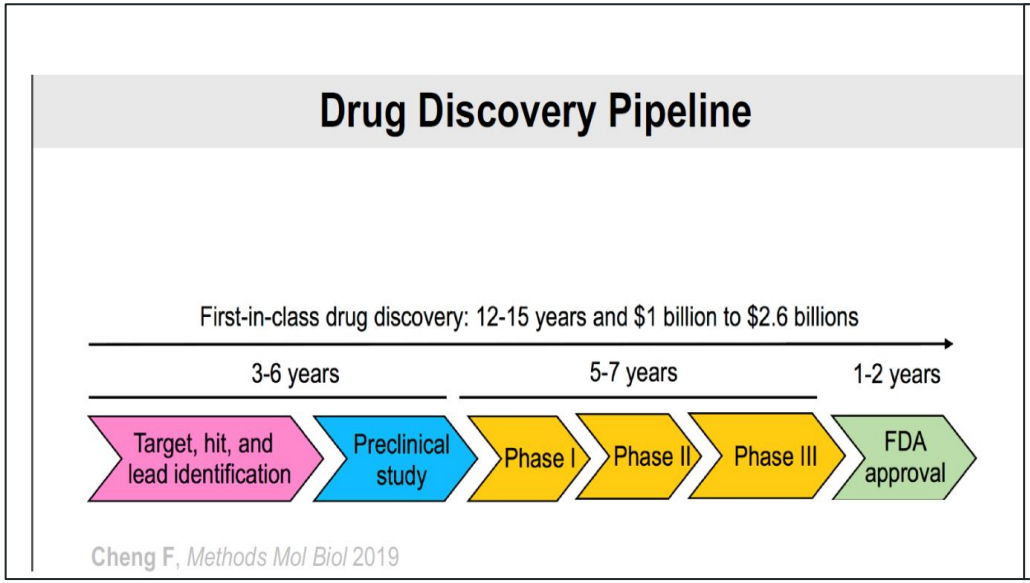
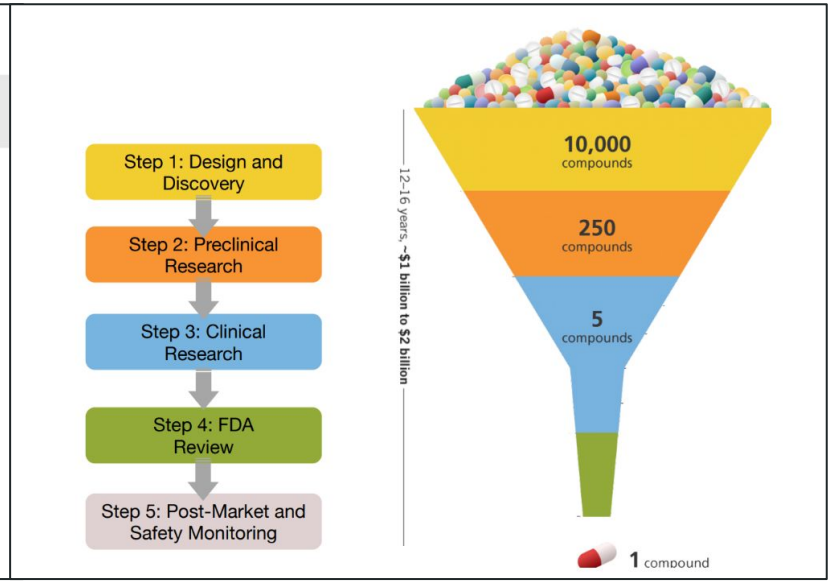
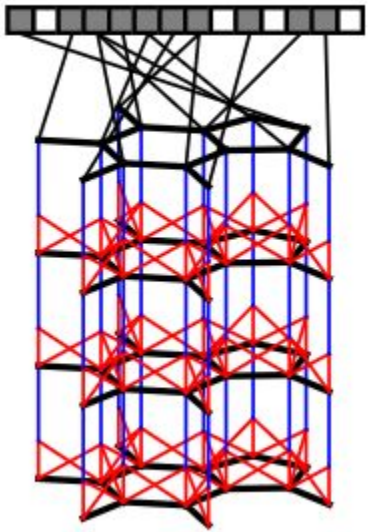

Drug Discovery Pipeline
First-in-class drug discovery: 12-15 years and $1 billion to $2.6 billions
3-6 years
5-7 years
1-2 years
Target, hit, and lead identification
Preclinical study
Phase I
Phase II
Phase III
FDA approval
Cheng F, Methods Mol Biol 2019


Step 1: Design and Discovery
Step 2: Preclinical Research
Step 3: Clinical Research
Step 4: FDA Review
Step 5: Post-Market and Safety Monitoring
12–16 years, ~$1 billion to $2 billion
10,000 compounds
250 compounds
5 compounds
1 compound

Motivation

Convolutional Networks on Graphs for Learning Molecular Fingerprints by Duvenaud *et al.*

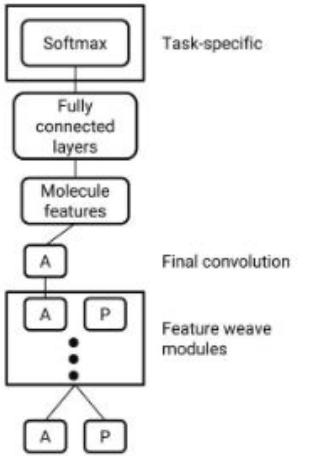


Input: molecule, radius R, hidden weights $H_1^1 \dots H_R^5$, output weights $W_1 \dots W_R$
Initialize: fingerprint vector $\mathbf{f} \leftarrow \mathbf{0}_S$
for each atom a in molecule
  $\mathbf{r}_a \leftarrow g(a)$ ▷ lookup atom features
for $L = 1$ to R ▷ for each layer
  for each atom a in molecule
    $\mathbf{r}_1 \dots \mathbf{r}_N = \text{neighbors}(a)$
    $\mathbf{v} \leftarrow \mathbf{r}_a + \sum_{i=1}^{N} \mathbf{r}_i$ ▷ sum
    $\mathbf{r}_a \leftarrow \sigma(\mathbf{v} H_L^N)$ ▷ smooth function
    $\mathbf{i} \leftarrow \text{softmax}(\mathbf{r}_a W_L)$ ▷ sparsify
    $\mathbf{f} \leftarrow \mathbf{f} + \mathbf{i}$ ▷ add to fingerprint
Return: real-valued vector $\mathbf{f}$

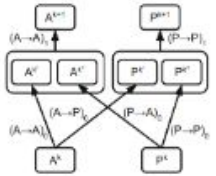
Neural fingerprints could not distinguish stereoisomers.

Related Works

Molecular graph convolutions: moving beyond fingerprints by Kearnes *et al.*



(a) Graph Convolutional module



(b) Weave module

The proposed representation of atom layer, pair layer achieves the desired properties of order invariance, atom and pair permutation invariance, and pair order invariance.

Related Works

Neural Message Passing for Quantum Chemistry by Gilmer *et al.*

They improved Gated Graph Neural Networks (GG-NN) by trying different input representations (chemical graph, distance bins, and raw distance vector), different message functions(edge network, pair message, and virtual graph elements) and different readout functions. The developed multi-tower structure improves training time and also showed some evidence of improving generalization.

Analyzing Learned Molecular Representations for Property Prediction by Yang *et al.*

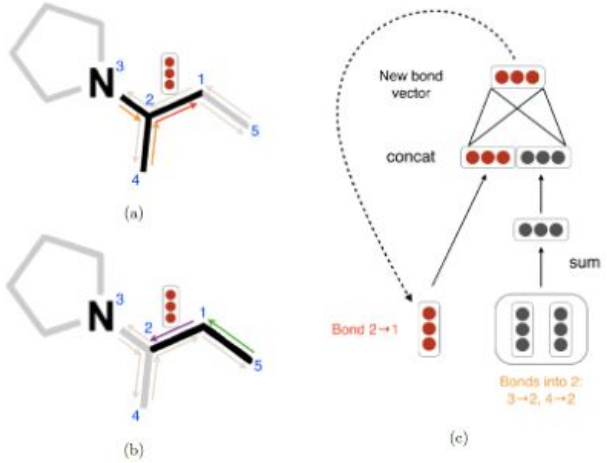
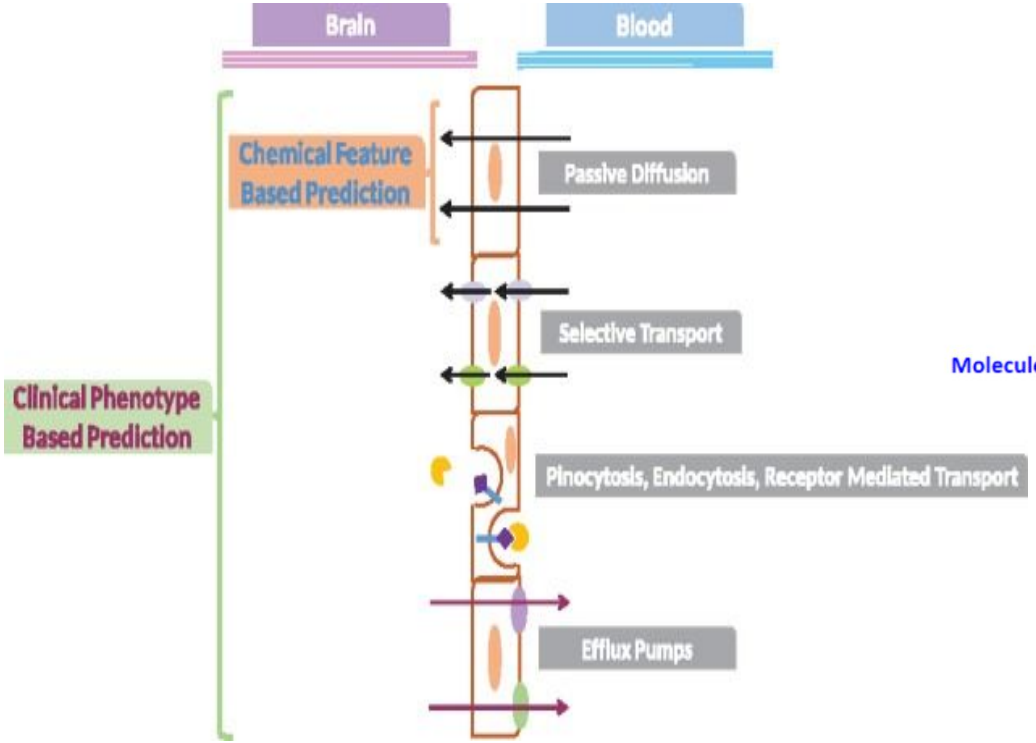


Figure 3.1: Bond-level message passing D-MPNN. (a): Messages from the orange directed bonds are used to update the hidden state of the red directed bond. By contrast, in a traditional MPNN, messages are passed from atoms 1, 3, and 4 to atom 2. (b): Messages from the green directed bonds are used to update the hidden state of the purple directed bond. (c): Update function for the hidden representation of the red directed bond.

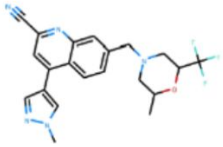
Directed Message Passing Neural Network (D-MPNN) utilizes a hybrid representation that combines molecular convolutions and computed molecule-
level features. D-MPNN builds off the Message Passing Neural Network (MPNN)
framework proposed by Gilmer *et al.*

D-MPNN adopts directed bond-level message passing rather than propagating information along atoms. By doing
so, D-MPNN has greater control over the information flow.

Related Works



Molecule Property Prediction



Property

Research Problem

We modelled blood-brain barrier permeability as **graph regression and graph classification** following the **empirical risk minimization in supervised learning**.

For a dataset of *n* molecule graph and property pairs $\{(G_1, y_1) , \ldots , (G_n , y_n)\}$, the objective to optimize is:

$$\min_\theta \sum_i \ell (GNN_\theta (G_i) , y_i)$$

where $GNN_\theta (\cdot)$ is a GNN model parameterized by θ to predict blood-brain barrier permeability from an input molecule graph G_i and $\ell(\cdot , \cdot)$ measures the difference between the prediction and the experimental data label.

Problem Formulation

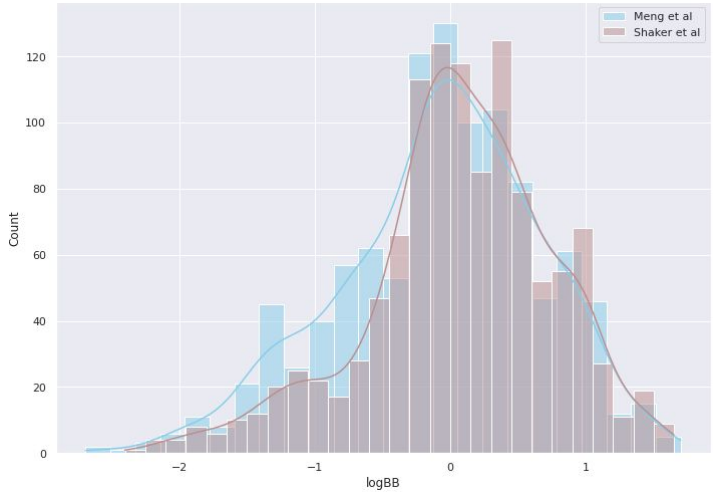
1. The quantitative modeling of BBB permeability as a regression problem is seldom possible because of the limited availability of numerical experimental data (such as logBB) of compounds
    a. Qualitative modeling of BBB permeability as a binary classification problem is the simpler problem among the two.

2. Computational predictive models trained on smaller datasets like MoleculeNet are unable to make reliable predictions for novel compounds due to the lower chemical diversity in the training datasets.

Identified Research Gaps

1. Finding representative and public blood-brain barrier data from literature.
2. Generate atom and bond descriptors.
3. Train hyperparameter tuned graph regression and classification models.
4. Report meaningful performance metrics.

	Meng *et al.* [54]	Shaker *et al.* [47]
No. of compounds	7807	7162
No. of BBB permeable compounds	4956	5453
No. of BBB non permeable compounds	2851	1709
No. of compounds with log BB values	1058	7162



Methodology Cont. - Datasets

Descriptor	Values
Atom degree	1, 2, 3, 4, 6
Atom type	Ar, B, Br, C, Ca, Cl, F, H, I, Kr, Li, N, Na, Ne, O, P, Rn, S, Se, Si, Xe
Atom chiral tag	CW, CCW, unspecified
Atom formal charge	-1, 0, 1, 2
Atom hybridization	S, SP, SP2, SP3, SP3D, SP3D2
Atom explicit valence	0,1,2,3,4,5,6
Atom implicit valence	0,1,2,3,4
Aromatic atom	True, False
Bond type	aromatic, single, double, triple
Conjugated bond	True, False
Bond stereo configuration	OE, OZ, NONE
Bond direction	ENDDOWNRIGHT, ENDUPRIGHT, NONE

Methodology Cont. - Feature Descriptors

Hyperparameter	Value
Message passing steps	6
set2set steps	6
set2set layers	3
Hidden edge embedding size	128
Output node embedding size	64
Batch size	128
Learning rate	3e-4

(a) MPNN

Hyperparameter	Value
GCN layers	2
Hidden node embedding size	256
Readout layer embedding size	128
Dropout	0.05
Batch size	128
Learning rate	2e-2

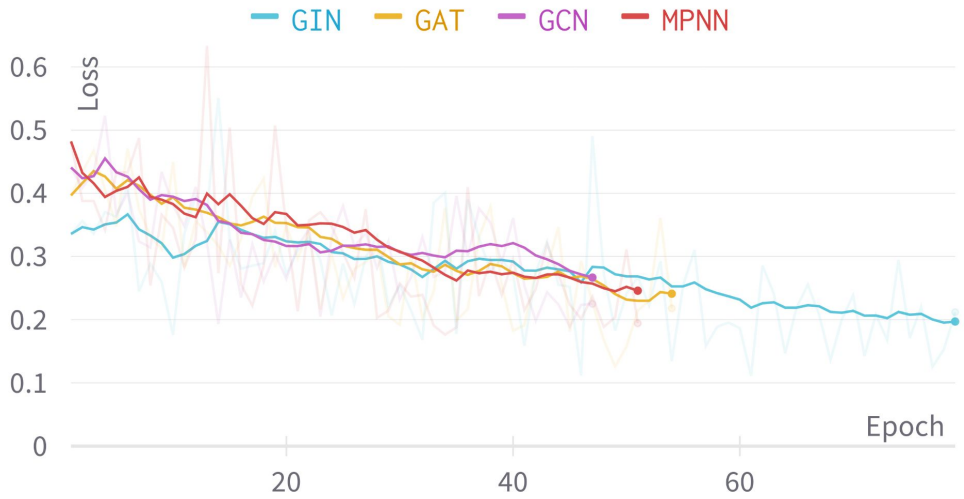
(b) GCN

Hyperparameter	Value
GAT layers	5
Attention heads	8
Hidden node embedding size	64
Readout layer embedding size	128
Dropout	0.05
Batch size	128
Learning rate	3e-4

(c) GAT

Hyperparameter	Value
GIN layers	5
Node embedding size	300
Dropout	0.05
Batch size	128
Learning rate	2e-2

(d) GIN



DEEP GRAPH LIBRARY

PyTorch

RDKit
Open-Source Cheminformatics and Machine Learning

Weights & Biases

Methodology Cont. - Models

Model	Dataset	RMSE ↓	Average RMSE ↓
MPNN	Meng *et al.*	0.91 ± 0.07	0.77
	Shaker *et al.*	0.63 ± 0.04	
GCN	Meng *et al.*	0.93 ± 0.15	0.78
	Shaker *et al.*	0.63 ± 0.04	
GAT	Meng *et al.*	0.89 ± 0.08	**0.76**
	Shaker *et al.*	0.62 ± 0.03	
GIN	Meng *et al.*	0.89 ± 0.05	0.93
	Shaker *et al.*	0.96 ± 0.58	

Table 3: Test performance of the regression models. We report mean and standard deviation of the results of 10 random runs with scaffold-splitting. The rightmost column averages the mean of the test RMSE across the 2 datasets for each model.

					Average		
Model	Dataset	AUROC ↑	Sensitivity ↑	Specificity ↑	AUROC ↑	Sensitivity ↑	Specificity ↑
MPNN	Meng *et al.*	0.87 ± 0.01	0.79 ± 0.04	0.77 ± 0.05	0.85	**0.85**	0.66
	Shaker *et al.*	0.82 ± 0.01	0.92 ± 0.02	0.55 ± 0.03			
GCN	Meng *et al.*	0.86 ± 0.01	0.75 ±0 .07	0.82 ± 0.05	0.86	0.82	**0.75**
	Shaker *et al.*	0.86 ± 0.01	0.89 ± 0.04	0.67 ± 0.06			
GAT	Meng *et al.*	0.89 ± 0.01	0.82 ± 0.04	0.77 ± 0.05	**0.87**	**0.85**	0.71
	Shaker *et al.*	0.85 ± 0.01	0.87 ± 0.06	0.65 ± 0.07			
GIN	Meng *et al.*	0.88 ± 0.01	0.84 ± 0.07	0.77 ± 0.06	**0.87**	**0.85**	**0.75**
	Shaker *et al.*	0.86 ± 0.01	0.86 ± 0.05	0.72 ± 0.05			

TABLE IV: Test performance of the classification models. We report mean and standard deviation of the results of 10 random runs with scaffold-splitting. The 3 rightmost columns average the mean of the corresponding test performance metric across the 2 datasets for each model.

Results

1. Given the rapid rate of progress in GNNs and lack of previous works with GNNs on BBB datasets representative of the real world, an evaluation of the applicability of the 4 most popular GNN variants for blood-brain barrier permeability prediction was warranted. To the best of our knowledge, this is the most exhaustive benchmarking study done that evaluates the capability of the popular GNN models to perform blood-brain barrier permeability prediction.
    a. In this study, we explored and evaluated the performance and generalizability of 8 graph representation learning based BBB predictive models - 4 regression and 4 classification models
2. Generalizability of the models were given utmost importance. This was achieved by:
(i) training the models on the largest public BBB permeability dataset instead of the small, private, and non representative datasets,
(ii) making the models performant for both the positive and the negative class, and
(iii) reporting the out-of-distribution generalization performance

3. In order to maximize the effectiveness of this work for early CNS drug screening, future scope entails exploring the avenue of multi-task learning and incorporating statistical tests of significance.

Conclusion

References

[1] J. M. Luco, “Prediction of the brain- blood distribution of a large set of drugs from structurally derived descriptors using partial least-squares (pls) modeling,” Journal of chemical information and computer sciences, vol. 39, no. 2, pp. 396–404, 1999.

[2] M. Adenot and R. Lahana, “Blood-brain barrier permeation models: discriminating between potential cns and non-cns drugs including p-glycoprotein substrates,” Journal of chemical information and computer sciences, vol. 44, no. 1, pp. 239–248, 2004.

[3] R. C. Young, R. C. Mitchell, T. H. Brown, C. R. Ganellin, R. Griffiths, M. Jones, K. K. Rana, D. Saunders, and I. R. Smith, “Development of a new physicochemical model for brain penetration and its application to the design of centrally acting h2 receptor histamine antagonists,” Journal of medicinal chemistry, vol. 31, no. 3, pp. 656–671, 1988.

[4] K. Lanevskij, P. Japertas, R. Didziapetris, and A. Petrauskas, “Ionization- specific prediction of blood–brain permeability,” Journal of pharmaceutical sciences, vol. 98, no. 1, pp. 122–134, 2009.

[5] L. Zhang, H. Zhu, T. I. Oprea, A. Golbraikh, and A. Tropsha, “Qsar modeling of the blood–brain barrier permeability for diverse organic compounds,” Pharmaceutical research, vol. 25, no. 8, pp. 1902–1914, 2008.

[6] Z. Gao, Y. Chen, X. Cai, and R. Xu, “Predict drug permeability to blood–brain-barrier from clinical phenotypes: drug side effects and drug indications,” Bioinformatics, vol. 33, no. 6, pp. 901–908, 2017.

[7] S. J. Barigye, “A simple method to predict blood–brain barrier permeability of drug-like compounds using classification trees,” Med. Chem, vol. 13, pp. 1–6, 2017.

[8] I. F. Martins, A. L. Teixeira, L. Pinheiro, and A. O. Falcao, “A bayesian approach to in silico blood-brain barrier penetration modeling,” Journal of chemical information and modeling, vol. 52, no. 6, pp. 1686–1697, 2012.

[9] A. Guerra, J. A. P´aez, and N. E. Campillo, “Artificial neural networks in admet modeling: prediction of blood–brain barrier permeation,” QSAR & Combinatorial Science, vol. 27, no. 5, pp. 586–594, 2008.

[10] B. Shaker, M.-S. Yu, J. S. Song, S. Ahn, J. Y. Ryu, K.-S. Oh, and D. Na, “Lightbbb: computational prediction model of blood–brain-barrier penetration based on lightgbm,” Bioinformatics, vol. 37, no. 8,pp. 1135–1139, 2021.

[11] Q. Tang, F. Nie, Q. Zhao, and W. Chen, “A merged molecular representation deep learning method for blood–brain barrier permeability prediction,” Briefings in Bioinformatics, vol. 23, no. 5, 2022.

[12] F. Meng, Y. Xi, J. Huang, and P. W. Ayers, “A curated diverse molecular database of blood-brain barrier permeability with chemical descriptors,” Scientific Data, vol. 8, no. 1, pp. 1–11, 2021.