Notes/Questions (To Be Deleted) I

- Touch on geometric DL in general? Or just focus on GNN's and not worry about placing within the DL landscape?
- Touch on AlphaFold? GNN's used I believe but unconfirmed, and architecture is complicated/seems infeasible (at least for my time right now)
- Still unsure how to tie in PrimeKG paper
- Methods for edge selection/identification? Some instances we only want to preserve structure, but sometimes we want to predict/fit edges, how does that fit into message-passing/GCN methods or other extensions?
- Example of graph-level classification?

Notes/Questions (To Be Deleted) II

- Diffpool article as extension of general GNN, hierarchical pooling over global readout functions? https://papers.nips.cc/paper_files/paper/2018/file/e77dbaf6759253c7c6d0efc5690369c7-Paper.pdf

Graphical Neural Networks

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November 28, 2023

Outline

1. Set-Up and Motivation 5ish minutes
2. General Construction 10-20ish minutes
3. Applications and Extensions 20-25ish minutes
   - Multimodal Graph Learning (MGL)
   - Knowledge-Graph Data
   - Structure-Based Drug Design (SBDD)

Goals

- Provide a useful overview of Graphical Neural Networks (GNN)
  - Motivation for necessity of GNN's
  - Provide a general framework of fitting
- Describe applications and extensions of the general GNN model
  - Multimodal Physiological/Biomedical Data
  - Integration of Knowledge-Graph and EHR Data

KG Application

Image here. Or maybe drop, 4 might be overkill

Multi-modal Biomedical Data

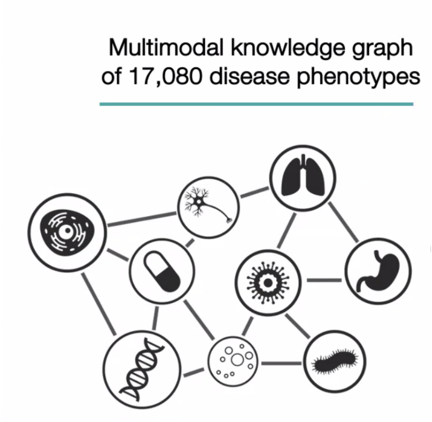
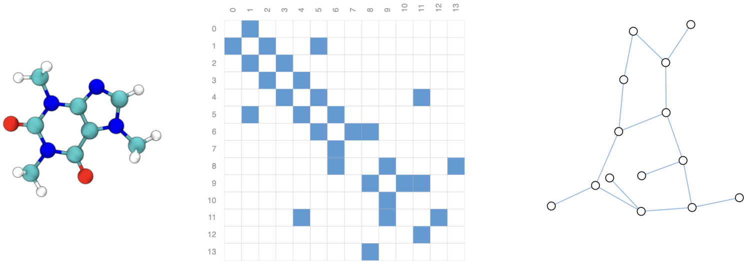


Image courtesy of partial figure from McDermott et al. *Structure-inducing pre-training* [8]

Molecular/Biochemical



(Left) 3d representation of the Caffeine molecule (Center) Adjacency matrix of the bonds in the molecule (Right) Graph representation of the molecule.

Image courtesy of https://distill.pub/2021/gnn-intro/ [9]

Protein Representation

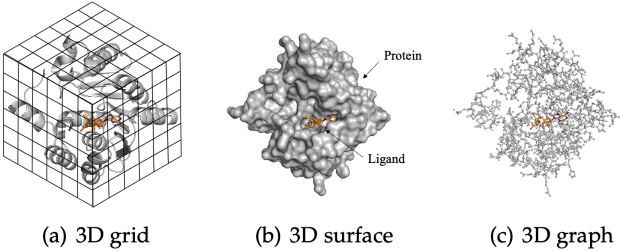


Fig. 2. 3D representations of proteins used for geometric deep learning: (a) 3D grid, (b) 3D surface, and (c) 3D graph, illustrated for PDB ID 2avd.

Fig 2. of Zhang (2023) *Geometric Deep Learning for Structure-Based Drug Design: A Survey* [13]

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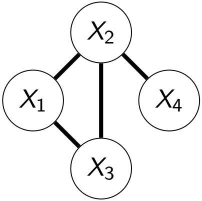
Motivation

- Want to utilize the input structure of the graph
  - Respect/Maintain
  - Update/Estimate
- "Flattening" graphical data for DNN, CNN, etc. omits useful topology from our data
- Early methods attempting to retain topological info included recursive neural networks and random walk models, which GNN methodology extended [10]

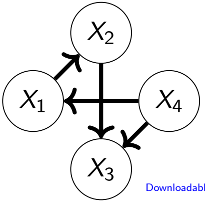
Notation/Set-Up

- Consider the graph $\mathcal{G} = (V, E), E \subseteq V \times V$, where any node v has a related "feature vector" $x_v \in \mathbb{R}^d$
  - Let $N = N$
- Let $\mathcal{N}_s(v)$ represent the s-hop neighborhood of any node v (and implicitly $\mathcal{N}(v) \equiv \mathcal{N}_1(v)$)
- Can construct adjacency matrix $\mathbf{A} \in \mathbb{R}^{N \times N}$ to capture structure of edge set E
  - $\mathbf{A}_{ij} = w_{ij} \mathbb{1}\{(i,j) \in E\}$ for scalar weight $w_{ij} \in \mathbb{R}$

Undirected Graph



Directed Graph



Topology Representations

- Simplest/Naïve method is to use $\mathbf{A}$
- Consider also the Laplacian matrix $\mathbf{L} = \mathbf{D} - \mathbf{A}$
  - $\mathbf{D} = \text{diag}(\mathbf{A1_N})$
- Can use an eigenvalue-normalized Laplacian $\widetilde{\mathbf{L}} = \mathbf{I} - \mathbf{D}^{-1/2}\mathbf{A}\mathbf{D}^{-1/2} = \mathbf{D}^{-1/2}\mathbf{L}\mathbf{D}^{-1/2}$
- Define graph convolution here?
- Note on necessity of permutation invariant functions (permutations of adjacency matrix represent same graph but consistent behavior of NN/GNN is not assured by permutd A matrices)

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What do we estimate about graph structure?

See supp note 1 on Multimodal learning with graphs

$$\text{GNN learning can be} \begin{cases} \text{Node-wise } \Phi(\mathcal{G}, v) : (v \in V) \to \mathbb{R}^m \\ \\ \text{Edge-wise } \Phi(\mathcal{G}, e) : (e \in E) \to \mathbb{R}^m \\ \\ \text{Graph-level characteristics } \Phi(\mathcal{G}) \end{cases}$$

What do we estimate about graph structure?

Planning (very tentatively) to note that I focus of node-wise estimation as primary interest. My understanding (with still much to read/learn) is that edge/graph-level characteristics are then essentially secondary outputs of node-characteristics. i.e. we fit the GNN, predict node labels/values/embeddings, then fit separate models to predict edge-/graph-level information

$$\text{GNN learning can be } \begin{cases} \text{Node-wise } \Phi(\mathcal{G}, x) : (x \in V) \to \mathbb{R}^m \\ \\ \text{Graph-level characteristics } \Phi(\mathcal{G}, e) : (e \in E) \to \mathbb{R}^m \\ \\ \text{Graph-level characteristics } \Phi(\mathcal{G}) \end{cases}$$

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General Framework[1]

We begin with the general Message Passing Neural Networks (MPNN) structure of a GNN:

1: Initialize $h^{(0)} \leftarrow x_v, \forall v \in V$
2: **for** $\kappa = 0, ..., K$ **do**:
3: **for** $v \in \mathcal{G}$ **do**:
4: $h_{agg}^{\kappa+1} \leftarrow$ Aggregate$(\{h_u^{(\kappa)} \mid u \in \mathcal{N}_v\})$ or Message$(\cdot)$
5: $h^{(\kappa+1)} \leftarrow$ Update$(h^{(\kappa)}, h_{agg}^{(\kappa)})$
6: $\hat{y} \leftarrow$ Transform$(\{h_v^K | v \in \mathcal{G}\})$ or Readout$(\cdot)$

[1]See [2, 4, 11]

General Framework

Can succinctly represent the κth layer as:

$$\mathbf{h}_v^{(\kappa+1)} = \text{Update}\left(x_v^{(\kappa)}, \text{Aggregate}(h_v^{(\kappa)}, x_u^{(\kappa)}, e_{u,v}^{(\kappa)})\right)$$

Choices of (differentiable) functions for Aggregate, Update, and Readout determine the architecture of your GNN

Trained end-to-end via backpropagation

Aggregate & Update

- **Aggregate**$(\cdot)$ produces a representation of information from a node's neighborhood
  - Also **Message**$(\cdot)$ in the context of MPNN's [4]
- Differentiable, *permutation invariant* functions
- Can include weights (edge-wise or learned)
- Over later iterations, this includes information from further and further distant nodes to any one target node
- We then **Update**$(\cdot)$ our current state using this aggregated neighborhood-level information

Transform/Readout

- **Transform**$(\cdot)$ translates our learned node representations to some desired outcome
  - Regression
  - Binary/Multi-class classification
  - MLP/DNN's
  - **Readout**$(\cdot)$ is common term for translating node-level output to graph-level
  - *Global Pooling* - Methods applied over entire graph (e.g. averaging, fitting "regular" deep neural network, etc.)

Graph Convolutional Network

- Proposed in 2017 by Thomas Kipf, Max Welling [7], can consider one example of "Laplacian-based methods" [4]

$$\mathbf{H}^{(\kappa+1)} = \mathrm{ReLu}\left(\widetilde{\mathbf{D}}^{-1/2}\widetilde{\mathbf{A}}\widetilde{\mathbf{D}}^{-1/2}\mathbf{H}^{(\kappa)}\boldsymbol{\Theta}\right)$$

- Motivated by considering the graph convolution[2] $x \star g = UgU^T x$ as the message passing function
- Learned weight/parameter matrix $\boldsymbol{\Theta}$

Review paper, comment on applications briefly (KG setting), also motivate through graph convolutions?

[2] U the matrix of eigenvectors of $\mathbf{L}$

Graph Convolutional Network

- Proposed in 2017 by Thomas Kipf, Max Welling [7], can consider one example of "Laplacian-based methods" [4]

$$\mathbf{H}^{(\kappa+1)} = \underbrace{\text{ReLu}}_{\text{Update}} \underbrace{\left(\widetilde{\mathbf{D}}^{-1/2}\widetilde{\mathbf{A}}\widetilde{\mathbf{D}}^{-1/2}\mathbf{H}^{(\kappa)}\boldsymbol{\Theta}\right)}_{\text{Aggregate/Message}}$$

- Motivated by considering the graph convolution[3] $x \star g = UgU^T x$ as the message passing function
- Learned weight/parameter matrix $\boldsymbol{\Theta}$

Review paper, comment on applications briefly (KG setting), also motivate through graph convolutions?

[3] U the matrix of eigenvectors of $\mathbf{L}$

Graph Convolutional Network

Intuitive "derivation":

$$\mathbf{H}^{(\kappa+1)} = \sigma\left(\mathbf{A}\mathbf{H}^{(\kappa)}\Theta\right)$$

$$\mathbf{H}^{(\kappa+1)} = \sigma\left(\mathbf{D}^{-1}\mathbf{A}\mathbf{H}^{(\kappa)}\Theta\right) \qquad \text{Normalizing by degree}$$

$$\mathbf{H}^{(\kappa+1)} = \sigma\left(\mathbf{D}^{-1/2}\mathbf{A}\mathbf{D}^{-1/2}\mathbf{H}^{(\kappa)}\Theta\right) \qquad \text{Symmetric normalization}$$

$$\mathbf{H}^{(\kappa+1)} = \sigma\left(\widetilde{\mathbf{D}}^{-1/2}\widetilde{\mathbf{A}}\widetilde{\mathbf{D}}^{-1/2}\mathbf{H}^{(\kappa)}\Theta\right) \qquad \text{Adding self-loop}$$

where $\widetilde{\mathbf{A}} = \mathbf{A} + \mathbf{I}$, $\widetilde{\mathbf{D}}_{ii} = \sum_j \widetilde{\mathbf{A}}_{ij}$, σ is any activation function, $\mathbf{H}$ is simply the matrix of $\mathbf{h}_v$ for all nodes

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General Framework (Re-emphasized)

Initialize $h^{(0)} \leftarrow x_v, \forall v \in V$

for $\kappa = 0, ..., K$ **do**:

  for $v \in \mathcal{G}$ **do**:

    $h^{\kappa+1}_{agg} \leftarrow$ Aggregate$(\{h^{(\kappa)}_u \mid u \in \mathcal{N}_v\})$ or Message$(\cdot)$

    $h^{(\kappa+1)} \leftarrow$ Update$(h^{(\kappa)}, h^{(\kappa)}_{agg})$

$h_{\mathcal{G}} \leftarrow$ Transform$(\{h^K_v | v \in \mathcal{G}\})$ or Readout$(\cdot)$

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Multimodal Graph Learning (MGL)

Multimodal Graph Learning (MGL)

- Ektefaie (2023) *Multimodal learning with graphs* [2]
- Cite 14-16 in multimodal paper for multi improvement over uni VAE
- Topology is complicated by multimodality of input data
  - Modal collapse [6]
  - Differential data availability
  - Can mention Kipf algorithm does well in semi-supervised setting (even with limited labels available within a given "cluster"), so if we have some gold standard data (biomarker/strong proxy, etc.) that is difficult to obtain, can be VERY useful to include for MGL and lead to good performance, no bullet point here just mention

Mutimodal

Clinical Data

- Clinical text
- -omics data
- Laboratory measurements
- Clinical imaging

Protein Structures

- 1° AA Sequence
- 2° Helix interactions
- 3° Folding, bridges

Framework

Authors propose a four component "blueprint"

1. Identifying entitites (i.e. modalities)
2. Uncovering topology
    - *A priori*
    - Adaptively learned
3. Propagating information
4. Mixing representation

Framework

Authors propose a four component "blueprint"

$$\left.\begin{array}{l}\text{1. Identifying entitites (i.e. modalities)}\\ \text{2. Uncovering topology}\end{array}\right\}\text{Structure Learning}$$

$$\left.\begin{array}{l}\textbf{3. Propagating information}\\ \textbf{4. Mixing representation}\end{array}\right\}\text{Learning On-Structure Phase}$$

Structure Learning

- Consider patients as *nodes*
- Consider modalities as *entities* (colored nodes)
  - Clinical text/narrative data
  - Laboratory/Physiological measurements
  - Image/Video data
  - Patient reported measurements/symptoms
  - etc.

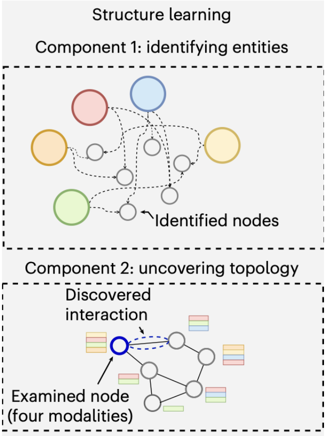

Figure: Subset of Fig 2c [2]

Learning on Structure

Proteins and Structure-Based Drug Design (SBDD)

AlphaFold

Image and very brief acknowledgement/link for AlphaFold, ESMFold here (30s)

Structure-Based Drug Design (SBDD)

- Zhang (2023) *Geometric Deep Learning for Structure-Based Drug Design: A Survey* [13]
- SBDD aims to improve drug-discovery by understanding 3D protein structures and predicting drug efficacy/behavior

Conclusion

References I

- Some diagrams generated in conjunction with ChatGPT 3.5

[1] David Duvenaud et al. *Convolutional Networks on Graphs for Learning Molecular Fingerprints*. arXiv:1509.09292 [cs, stat]. Nov. 2015.

[2] Yasha Ektefaie et al. "Multimodal learning with graphs". en. In: *Nature Machine Intelligence* 5.4 (Apr. 2023). Number: 4 Publisher: Nature Publishing Group, pp. 340–350.

[3] Oleksandr Ferludin et al. *TF-GNN: Graph Neural Networks in TensorFlow*. arXiv:2207.03522 [physics, stat]. July 2023.

[4] Justin Gilmer et al. *Neural Message Passing for Quantum Chemistry*. arXiv:1704.01212 [cs]. June 2017.

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[5] M. Gori, G. Monfardini, and F. Scarselli. "A new model for learning in graph domains". In: *Proceedings. 2005 IEEE International Joint Conference on Neural Networks, 2005.* Vol. 2. ISSN: 2161-4407. July 2005, 729–734 vol. 2.

[6] Adrián Javaloy, Maryam Meghdadi, and Isabel Valera. *Mitigating Modality Collapse in Multimodal VAEs via Impartial Optimization*. en. arXiv:2206.04496 [cs]. June 2022.

[7] Thomas N. Kipf and Max Welling. *Semi-Supervised Classification with Graph Convolutional Networks*. arXiv:1609.02907 [cs, stat]. Feb. 2017.

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[9] Benjamin Sanchez-Lengeling et al. "A Gentle Introduction to Graph Neural Networks". en. In: *Distill* 6.9 (Sept. 2021), e33.

[10] F. Scarselli et al. "The Graph Neural Network Model". en. In: *IEEE Transactions on Neural Networks* 20.1 (Jan. 2009), pp. 61–80.

[11] Keyulu Xu et al. *How Powerful are Graph Neural Networks?* arXiv:1810.00826 [cs, stat]. Feb. 2019.

[12] Zhitao Ying et al. "Hierarchical Graph Representation Learning with Differentiable Pooling". In: *Advances in Neural Information Processing Systems*. Vol. 31. Curran Associates, Inc., 2018.

[13] Zaixi Zhang et al. *A Systematic Survey in Geometric Deep Learning for Structure-based Drug Design*. arXiv:2306.11768 [cs, q-bio]. Oct. 2023.

Appendix Slides

Implementations

- PyTorch Geometric with directed extension PyTorch Geometric Signed Directed
- TensorFlow GNN [3]
- GraphNeuralNetworks.jl
- Spektral, Keras-based Pythhon package
- Limited but some implementation in R
    - scapGNN, package GNN implementation but specific/narrow for single-cell -omics data

Abbreviated History

- Graph Neural Network first(?) coined in Gori (2005) [5] and subqeuently in Scarselli (2009) *The Graph Neural Network Model* [10]
- Graph Convolutional Network by Kipf (2017) [7] but with similar convolutional message-passing algorithms (within GNN's) proposed in at least 2015 [1]
- Message passing GNN proposed in Gilmer (2017), applications in molecular chemistry [4]

Additional Applications, Interesting Papers I

- Applications in travel time prediction, 2021 (https://arxiv.org/pdf/2108.11482.pdf)
- Someone has compiled graph-/GNN-relevant talks for NeurIPS 2023 at https://github.com/XiaoxinHe/neurips2023_learning_on_graphs

DiffPool

Figure 1 from Ying (2018) *Hierarchical Graph Representation Learning with Differentiable Pooling* [12]

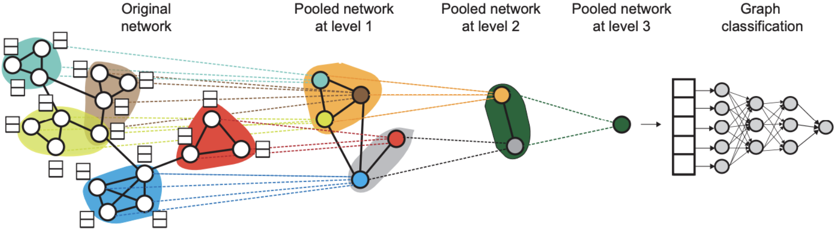

Figure 1: High-level illustration of our proposed method DiffPool. At each hierarchical layer, we run a GNN model to obtain embeddings of nodes. We then use these learned embeddings to cluster nodes together and run another GNN layer on this coarsened graph. This whole process is repeated for L layers and we use the final output representation to classify the graph.

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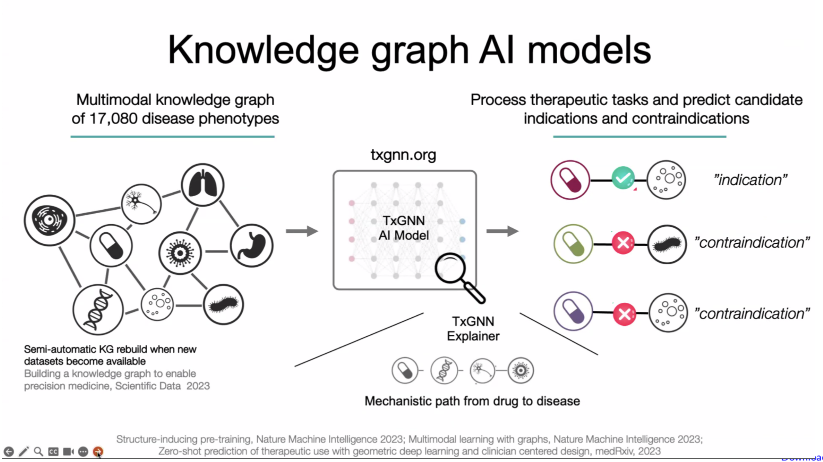
KG AI Models

Full figure from McDermott et al. [8], cropped and presented in Introduction:



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