Machine Learning in Bioinformatics

Graph Neural Networks

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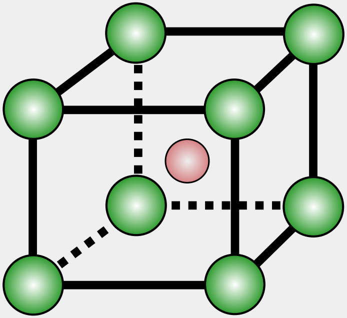
Graph data



Outline

- Graph Convolutional Neural Networks (GCNN)
- General graph neural networks (GNN)
- Graph isomorphisms and discriminative power of GNNs
- Advanced models and applications

Graph Convolutional Neural Networks (GCNNs)

Graph convolutions

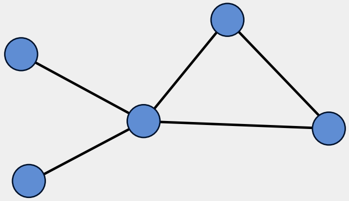
- Convolutions are not only restricted to image and time-series data
- Graph convolutions are used to model the interaction between nodes
- Let $G = (N, E)$ denote a graph with nodes N and edges E
- How could we implement a convolution of G with a weight matrix W?
- The result of a convolution is again a graph[1], i.e.

$$G' = G * W$$

[1]Remember that convolution on images also returns an image

Graph convolutions

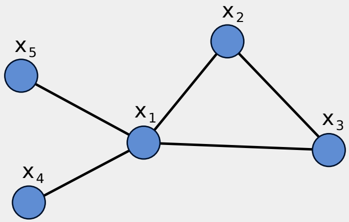
- Graph G with 5 nodes and 5 edges:



- We assign a feature vector $x_i \in \mathbb{R}^p$ to the i-th node
- The feature vector can depend on the type of the node
- Nodes of the same type might share the same feature vector

Graph convolutions

- Graph G with 5 nodes and 5 edges:



- We assign a feature vector $x_i \in \mathbb{R}^p$ to the i-th node
- The feature vector can depend on the type of the node
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Graph convolutions

- Let $A = (a_{ij})_{ij} \in \mathbb{R}^{k \times k}$ denote the adjacency matrix of a graph with k nodes
- The strength of the connection between node i and j is given by a_{ij}
- Self-connections $a_{ii} \neq 0$ allow to incorporate the features of the nodes itself
- The convolution operation updates the feature vector of node i by summing over all neighbor nodes, i.e.

$$x_i' = \sigma\left(\sum_j a_{ij} W x_j\right) = \sigma\left(\sum_{j \to i} W x_j\right)$$

where $W \in \mathbb{R}^{p \times p}$ and σ is the activation function[2]

[2]Graph convolutions are *permutation equivariant*

Graph convolutions

- For the full graph we obtain

$$\underbrace{X'}_{k\times p} = \sigma(\underbrace{A}_{k\times k}\underbrace{X}_{k\times p}\underbrace{W^\top}_{p\times p})$$

  where $X \in \mathbb{R}^{k\times p}$ is the matrix of k feature vectors
- Note that the weight matrix W does not depend on the size and connectivity of the graph
- W can be applied to multiple graphs and optimized during training of the graph convolutional neural network (GCNN)
- GCNNs typically apply multiple convolutions and afterwards compute summary statistics of the feature vectors, the result can then be used in a conventional neural network

[2] Many extensions and generalizations exist [Battaglia et al., 2018, Dwivedi et al., 2020]

GCNN
Generalizated Update Rules

Graph convolutions - Self-connections

- Graph convolutional networks as introduced so far, can be efficiently computed, but are limited in their expressive power
- The same weight matrix W is used for all nodes
- A simple extension is to introduce a separate weight matrix V for self-connections

$$x_i' = \sigma\left(Vx_i + \sum_{j \to i} Wx_j\right)$$

- Note that now the sum over $\{j \to i\}$ should not include any self-connections

Graph convolutions - Edge gates

- Another important generalization are edge gates [Marcheggiani and Titov, 2017]
- Edge gates allow the network to learn what edges are important for the graph learning task
- The update function is given by

$$x_i' = \sigma\left(\sum_{j \to i} \eta_{ij} \odot W x_j\right)$$

  where $\odot$ denotes the element-wise multiplication (Hadamard product)
- The $\eta_{ij} \in \mathbb{R}^p$ act as edge gates and are computed as

$$\eta_{ij} = \sigma\left(A x_i + B x_j\right)$$

Graph convolutions - Edge features

- Even more general are networks that contain separate features on edges [Joshi et al., 2019]
- Node features and edge features e_{ij} between nodes i and j are updated as follows

$$x'_i = \sigma\left(\sum_{j \to i} \eta_{ij} \odot W x_j\right)$$

$$e'_{ij} = \sigma\left(A x_i + B x_j + C e_{ij}\right)$$

$$\eta_{ij} = \frac{\sigma(e_{ij})}{\sum_k \sigma(e_{ik}) + \epsilon}$$

- Note that η_{ij} is a normalized version of $\sigma(e_{ij})$

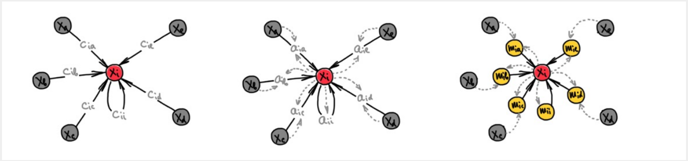
Graph Neural Networks (GNNs)

Permutation equivariance on graphs

- Let $X \in \mathbb{R}^{k \times p}$ be the feature matrix of a graph G with k nodes
- Let $\varphi_G(X)$ denote the result of applying a graph neural network φ_G to X
- $\tau(G, X)$ denotes a row-permutation of X with corresponding relabeling of nodes in G
- We require that φ_G is *equivariant* with respect to τ (permutation equivariant), i.e.

$$\begin{tikzcd}
(G, X) \arrow[r, "\varphi_G"] \arrow[d, "\tau"'] & (G, Y) \arrow[d, "\tau"] \\
(G', X') \arrow[r, "\varphi_{G'}"] & (G', Y')
\end{tikzcd}$$

Graph neural networks (GNNs)



- Three types of GNNs:

  Convolution, Attention, Message passing

Update rule of GNNs [Bronstein et al., 2021]

$$x_i' = \phi\left(x_i, \bigoplus_{j \to i} \psi(x_i, x_j)\right)$$

where $\bigoplus$ is a permutation invariant aggregation function, ϕ and ψ are learnable functions

Graph neural networks - GCNNs

- General update formula of GNNs [Bronstein et al., 2021]:

$$x_i' = \phi\left(x_i, \bigoplus_{j \to i} \psi(x_i, x_j)\right)$$

  where $\bigoplus$ is a permutation invariant aggregation function

- GCNNs are an instance of GNNs, because

$$x_i' = \phi\left(x_i, \bigoplus_{j \to i} \psi(x_i, x_j)\right) = \sigma\left(Vx_i + \sum_{j \to i} Wx_j\right)$$

  where $\phi(x_i, z) = \sigma(Vx_i + z)$, $\bigoplus = \sum$, and $\psi(x_i, x_j) = Wx_j$

Graph neural networks - Self-attention

- General update formula of GNNs [Bronstein et al., 2021]:

$$x_i' = \phi\left(x_i, \bigoplus_{j \to i} \psi(x_i, x_j)\right)$$

  where $\bigoplus$ is a permutation invariant aggregation function

- Self-attention layers are characterized by

$$\psi(x_i, x_j) = a(x_i, x_j)\psi'(x_j)$$

  where a denotes the attention mechanism. The computation of the attention value differs from the attention used in transformers [Veličković et al., 2017]

- The message $\psi'(x_j)$ from node j is weighted by the attention value $a(x_i^\top, x_j)$

Graph neural networks - Message passing

- General update formula of GNNs [Bronstein et al., 2021]:

$$x_i' = \phi\left(x_i, \bigoplus_{j\rightarrow i} \psi(x_i, x_j)\right)$$

  where $\bigoplus$ is a permutation invariant aggregation function

- The most general version of GNNs are *message passing* networks, where ψ is a neural network itself. The message received by node *i* is computed from both the feature vectors of node *i* and *j* [Gilmer et al., 2017]

Disciminative Power of GNNs

Graph isomorphism

Graph isomorphism

Let G and H be two graphs with vertex sets $V(G)$ and $V(H)$. A graph isomorphism f between G and H is defined as a function $f : V(G) \mapsto V(H)$ such that for all vertices u, v adjacent in G it follows that $f(u)$ and $f(v)$ are adjacent in H.

- Two graphs are called isomorphic if there exists a graph isomorphism
- Finding graph isomorphisms is difficult, i.e. for a graph with n nodes we have to test $n!$ node permutations
- *Weisfeiler-Lehman Isomorphism Test* can be used as a computationally fast heuristic

Weisfeiler-Lehman Isomorphism Test (1-WL) [Weisfeiler and Leman, 1968]

For both graphs G and H, assign each node i an initial node color $x_i = 1$. Within each iteration, the node color is updated using a given hash function according to the update rule

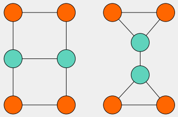
$$x_i \leftarrow \mathrm{hash}\left(x_i, \{\{\, x_j \mid j \to i \,\}\}\right) ,$$

where $\{\{\, \cdot \,\}\}$ denotes a multiset. The hash function maps the current node color and the multiset of neighboring node colors to a new node color from a *discrete* set.

Nodes are partitioned according to their colors. The algorithm terminates if node partitions are stable. G and H pass the test if $n_x(G) = n_x(H)$ for all x, where $n_x(G) = \sum_{i \in G} \mathbb{1}_{x = x_i}$ is the number of occurrences of color x [Huang and Villar, 2021].

Graph isomorphism

- Note that the feature vectors x_i might never become stable, however, the node partitions will
- The Weisfeiler-Lehman Isomorphism Test has limited power
  - { Test fails } $\rightarrow$ graphs are not isomorphic
  - Some graphs that pass the test are not isomorphic
- Example of non-isomorphic graphs that pass the test:



Graph isomorphism - k-WL test

- The k-WL test improves on this difficulty by coloring node sets of size k [Maron et al., 2019]
- The sub-graph structure of nodes in the k-tuples determine the initial k-tuple colors
- Colors are updated based on the colors of the neighborhood of k-tuples, which is all tuples where one node has been replaced by another node
- 1-WL and 2-WL test are equivalent in discriminative power
- Otherwise $k+1$-WL is more powerful than k-WL

Expressive power of graph networks

- Recall the update rule of graph neural networks

$$x_i' = \phi\left(x_i, \bigoplus_{j \to i} \psi(x_i, x_j)\right)$$

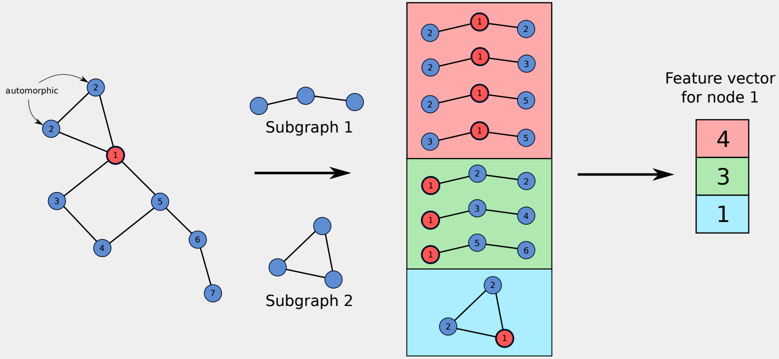
- The rule is identical to the hash function of the 1-WL test
- GNNs are therefore only as powerful as the 1-WL test in discriminating graphs [Xu et al., 2018]
- Although we seem to need permutation equivariance for graph neural networks, we then loose essential information on the graph structure and cannot distinguish between all graphs

Beyond 1-WL

- There exist several strategies to increase the power of GNNs beyond 1-WL:
  - Design models equivalent to the k-WL test with $k > 1$ [Maron et al., 2018, Maron et al., 2019, Keriven and Peyré, 2019, Azizian and Lelarge, 2020]
  - Specific pre-coloring of nodes to encode positional information[3]
    - Pre-coloring based on graph substructures [Bouritsas et al., 2022]
    - Using simplicial- or cell-complexes [Bodnar et al., 2021b, Bodnar et al., 2021a]
    - Graph Laplacian eigenvectors [Dwivedi et al., 2020]
  - Work with sub-graphs and local equivariance, e.g. natural graph networks [de Haan et al., 2020]

[3]Remember that the WL test uses the same initial color for all nodes

Subgraph isomorphic counting



- Features encode local environment through subgraph counting [Bouritsas et al., 2022]

Natural Graph Networks (NGNs)

- Recall the update function of CGNNs

$$x_i' = \sigma\left(\sum_{j\to i} W x_j\right)$$

- NGNs [de Haan et al., 2020] generalize this update formula as follows

$$x_i' = \sigma\left(\sum_{j\to i} W_{ij}^{G} x_j\right)$$

  i.e. the weight matrix depends on the graph G and the edge (i, j).

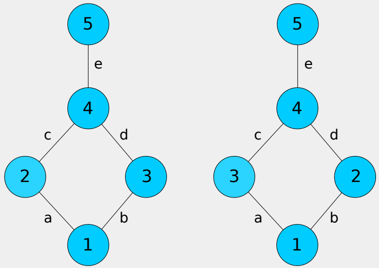
- Isomorphic graphs share the same weights

- Automorphic graphs constrain the weight matrices

Natural Graph Networks (NGNs)

- Automorphic graphs constrain weight matrices
- Given the following graph *G* and assume for simplicity that $W^G_{ij} = W^G_{ji}$

	1	2	3	4	5
1		a	b		
2	a			c	
3	b			d	
4		c	d		e
5				e	



	1	2	3	4	5
1		b	a		
2	b			d	
3	a			c	
4		d	c		e
5				e	

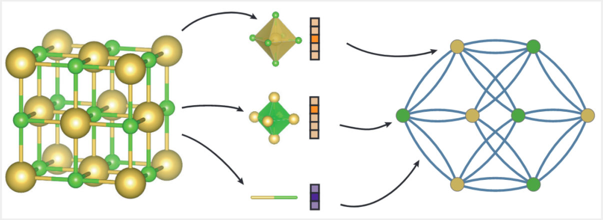
- Edges a, b and c, d must have the same weights, i.e. $W^G_{12} = W^G_{13}$ and $W^G_{24} = W^G_{34}$

Natural Graph Networks (NGNs)

- Natural graphs in this form are too general, i.e. each set of isomorphic graphs receives its own weights
- With this minimal weight sharing no learning across graphs is possible
- *Local natural graphs (LNGs)* solve this issue by looking at small sub-graphs

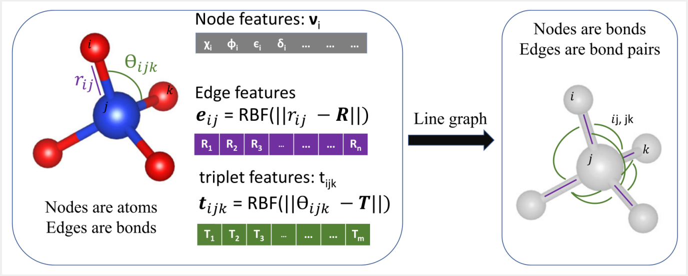
GNNs in Practice

CGCNN



- Crystal Graph Convolutional Neural Network (CGCNN) [Xie and Grossman, 2018], one of the first and simplest crystal graph networks
- Initial node features: Group number, periodic number, electronegativity, covalent radius, valence electrons, first ionization energy, electron affinity, block, atomic volume
- Initial edge features: Atom distance

ALIGNN



Node features: $\mathbf{v}_i$
χ_i ϕ_i ϵ_i δ_i … … …
Edge features
$\boldsymbol{e}_{ij}$ = RBF($||r_{ij} - \boldsymbol{R}||$)
R_1 R_2 R_3 … … … R_n
triplet features: t_{ijk}
$\boldsymbol{t}_{ijk}$ = RBF($||\Theta_{ijk} - \boldsymbol{T}||$)
T_1 T_2 T_3 … … … T_m
r_{ij}
Θ_{ijk}
i
j
k
Nodes are atoms
Edges are bonds
Line graph
Nodes are bonds
Edges are bond pairs
ij, jk

[Choudhary and DeCost, 2021]

ALIGNN

- ALIGNN [Choudhary and DeCost, 2021] performs edge-gated graph convolution simultaneously on both the atomistic bond graph and the line graph
- Atomistic bond graph: Atoms are nodes, bonds are edges
  - Initial node features: Electronegativity, group number, covalent radius, valence electrons, first ionization energy, electron affinity, block, and atomic volume
  - Initial edge features: RBF expanded interatomic bond distances
- Line graph: Bonds are nodes, bond pairs with one common atom (or atom triplets) are edges. Nodes correspond to bonds in the atomistic bond graph
  - Node features: Edge features of the bond graph
  - Initial edge features: RBF expanded bond angles

Furhter reading

- Review of graph neural networks [Zhou et al., 2020]
- Geometric deep learning [Bronstein et al., 2021]

Software

GNNs are implemented in PyTorch Geometric:

- Website:
  `https://pyg.org/`
- Documentation:
  `https://pytorch-geometric.readthedocs.io`

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