An Introduction to Graph Neural Networks (GNNs) for Molecules

MPS6 Course

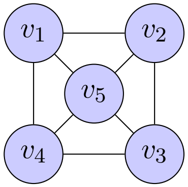
10.04.2025

Course Outline

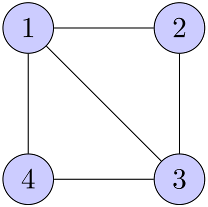
- What is a graph?
- Representing molecules as graphs
- Different tasks with GNNs
- Message passing on molecular graphs
- Introduction to PyTorch Geometric
- Developing a GCN from scratch
- Hands-on implementation

What is a Graph?

- A graph $G = (V, E)$ consists of:
    - Nodes/vertices V
    - Edges E connecting nodes
- Graphs represent relational data
- Natural representation for molecules



Adjacency Matrix



Adjacency matrix $A \in \{0,1\}^{n \times n}$:

$$A = \begin{pmatrix} 0 & 1 & 1 & 1 \\ 1 & 0 & 1 & 0 \\ 1 & 1 & 0 & 1 \\ 1 & 0 & 1 & 0 \end{pmatrix}$$

- $A_{ij} = 1$ if nodes i and j are connected
- $A_{ij} = 0$ otherwise
- Can also have weighted edges where $A_{ij} \in \mathbb{R}$

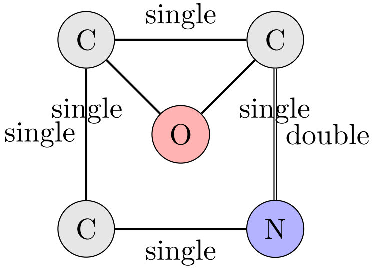
Node and Edge Features

Node Features:

- Each node v_i has features $\mathbf{x}_i$
- Can be categorical or continuous
- For molecules: atom type, charge, hybridization, etc.

Edge Features:

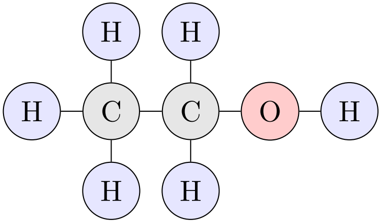
- Each edge (v_i, v_j) has features $\mathbf{e}_{ij}$
- For molecules: bond type, distance, etc.



Representing a Molecule as a Graph

- Nodes = Atoms
- Edges = Bonds
- Node features = Atom properties
- Edge features = Bond properties

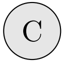
CH_3 —— CH_2 —— OH



Node Features for Molecules

Common atom (node) features:

- Atomic number (one-hot or embedding)
- Atom type (C, H, O, N, etc.)
- Formal charge
- Hybridization state (sp, sp^2, sp^3)
- Number of hydrogens attached
- Is in aromatic ring?
- Chirality
- Partial charge

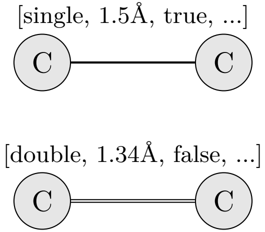


Feature vector: [6, 0, sp^3, 3, false, ...]

Edge Features for Molecules

Common bond (edge) features:

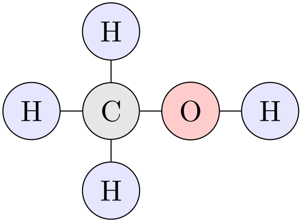
- Bond type (single, double, triple, aromatic)
- Bond distance
- Is in ring?
- Conjugation
- Stereochemistry (cis/trans)



Methanol Example

Methanol (CH_3OH)

$$CH_3 — OH$$



Graph Representation:

Nodes:

- C: [6, 0, sp^3, 3, 0]
- O: [8, 0, sp^3, 1, 0]
- H_1-H_4: [1, 0, s, 0, 0]

Adjacency Matrix:

$$A = \begin{pmatrix} 0 & 1 & 1 & 1 & 1 & 0 \\ 1 & 0 & 0 & 0 & 0 & 1 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 1 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 \end{pmatrix}$$

Node ordering: C, O, H_1, H_2, H_3, H_4

Hands-On Session

Let's put theory into practice!

- Open your Python notebook
- We'll learn how to represent graph in Python
- We'll learn graph representation in PyTorch Geometric
- Resources: `https://github.com/HFooladi/GNNs-For-Chemists/blob/main/notebooks/01_GNN_representation.ipynb`

Different Tasks with Graph Neural Networks

Node-level tasks:

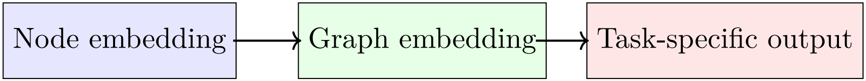
- Atom property prediction
- Reaction site prediction
- Partial charge prediction

Edge-level tasks:

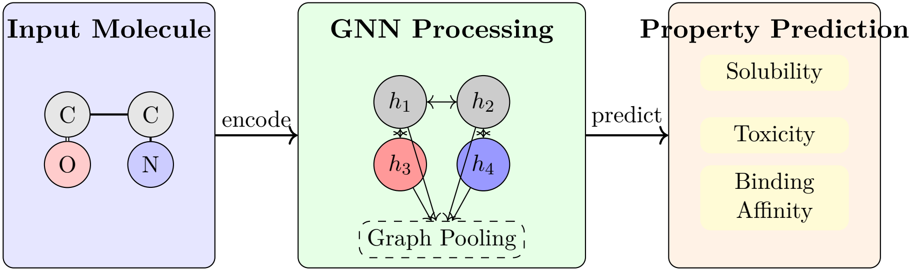
- Bond property prediction
- Link prediction (e.g., potential bonds)

Graph-level tasks:

- Molecular property prediction
  - Solubility
  - Toxicity
  - Drug efficacy
  - Binding affinity
- Molecule generation
- Molecule classification



Graph-Level Property Prediction



Process:

- Encode molecular structure
- Message passing between atoms
- Pool features → molecule representation
- Predict properties

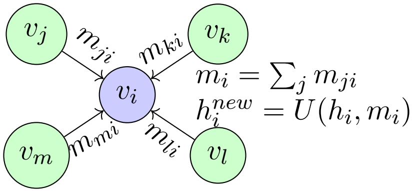
Applications:

- Binding affinity prediction
- Virtual screening
- Toxicity screening
- Reaction yield prediction

Message Passing Neural Networks

Message Passing Framework:

1. Each node sends messages to its neighbors
2. Each node aggregates incoming messages
3. Each node updates its features based on aggregated messages



Mathematical formulation:

$$m_i^{(l+1)} = \sum_{j \in \mathcal{N}(i)} M(h_i^{(l)}, h_j^{(l)}, e_{ij}) \tag{1}$$

$$h_i^{(l+1)} = U(h_i^{(l)}, m_i^{(l+1)}) \tag{2}$$

where M is the message function and U is the update function.

Message passing allows the model to:

- Capture local chemical environment
- Learn hierarchical representations
- Handle molecules of different sizes

What is Equivariance?

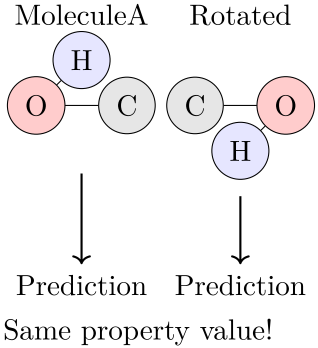
Equivariance means that transformations of input lead to predictable transformations of output.

For molecules:

- Rotation/translation of a molecule shouldn't change its properties
- Permutation equivariance

Why it matters:

- Ensures consistent predictions regardless of orientation
- Reduces required training data
- More physically meaningful representations



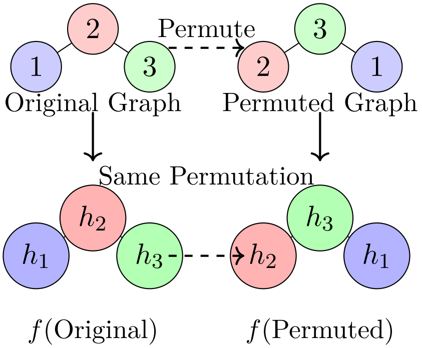
Permutation Equivariance in GNNs

Permutation Equivariance:

- Reordering nodes before applying a GNN should give the same result as applying the GNN first and then reordering nodes
- Critical for molecules where node ordering is arbitrary

Mathematically: for a GNN function f and permutation P:

$$f(PX, PAP^T) = Pf(X, A)$$



Same representation, different order

Hands-On Session

Let's put theory into practice!

- Open your Python notebook
- We'll learn how to implement message passing
- Resources: `https://github.com/HFooladi/GNNs-For-Chemists/blob/main/notebooks/02_GNN_message_passing.ipynb`

Introduction to PyTorch Geometric (PyG)

- PyTorch Geometric (PyG) is a library for deep learning on irregular structures (graphs, point-clouds, etc.)
- Built on top of PyTorch
- Provides tools for working with graphs
- Efficient implementations of many GNN architectures

```
# Installing PyTorch Geometric
pip install torch-geometric

# Basic imports
import torch
from torch_geometric.data import Data
from torch_geometric.nn import GCNConv
```

Downloading and Loading Datasets

```python
from torch_geometric.datasets import MoleculeNet

# Download BACE dataset (biological activity prediction)
dataset = MoleculeNet(root='data/molecule_datasets', name='BACE')

print(f'Dataset size: {len(dataset)}')
print(f'Number of features: {dataset.num_features}')
print(f'Number of classes: {dataset.num_classes}')

# Look at the first graph
data = dataset[0]
print(data)

# Splitting into train, validation, test
from torch_geometric.loader import DataLoader
from sklearn.model_selection import train_test_split

train_idx, test_idx = train_test_split(
    range(len(dataset)), test_size=0.2, random_state=42)
train_idx, val_idx = train_test_split(
    train_idx, test_size=0.25, random_state=42)

train_dataset = dataset[train_idx]
val_dataset = dataset[val_idx]
test_dataset = dataset[test_idx]
```

Exploring the Dataset Features

```
# Explore a single molecule
data = dataset[0]

print("Node features shape:", data.x.shape)
print("Edge indices shape:", data.edge_index.shape)
print("Edge attributes shape:", data.edge_attr.shape)
print("Target:", data.y)

# Visualize the molecule
import matplotlib.pyplot as plt
from rdkit import Chem
from rdkit.Chem import Draw

smiles = data.smiles  # Get SMILES string
mol = Chem.MolFromSmiles(smiles)
img = Draw.MolToImage(mol, size=(300, 300))
plt.imshow(img)
plt.axis('off')
plt.show()

# Analyzing feature distributions
node_features = []
for data in dataset[:100]:  # First 100 molecules
    node_features.append(data.x.mean(dim=0))
average_features = torch.stack(node_features).mean(dim=0)
plt.bar(range(len(average_features)), average_features.numpy())
plt.title("Average node feature values")
plt.show()
```

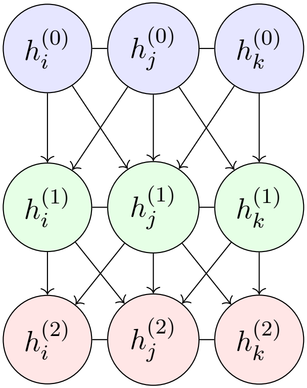
Graph Convolutional Network (GCN) Layer

GCN update rule:

$$H^{(l+1)} = \sigma(\tilde{D}^{-\frac{1}{2}}\tilde{A}\tilde{D}^{-\frac{1}{2}}H^{(l)}W^{(l)}) \qquad (3)$$

where:

- $\tilde{A} = A + I$ (adjacency matrix with self-loops)
- $\tilde{D}$ is the degree matrix of $\tilde{A}$
- $H^{(l)}$ is the node feature matrix at layer l
- $W^{(l)}$ is the learnable weight matrix
- σ is a non-linear activation function



Implementing a GCN Layer

```python
import torch
import torch.nn as nn
import torch.nn.functional as F
from torch_geometric.nn import MessagePassing
from torch_geometric.utils import add_self_loops, degree

class GCNConv(MessagePassing):
    def __init__(self, in_channels, out_channels):
        super().__init__(aggr='add')  # Aggregation method: "add"
        self.lin = nn.Linear(in_channels, out_channels)

    def forward(self, x, edge_index):
        # Add self-loops to the adjacency matrix
        edge_index, _ = add_self_loops(edge_index, num_nodes=x.size(0))

        # Linear transformation
        x = self.lin(x)

        # Compute normalization
        row, col = edge_index
        deg = degree(row, x.size(0), dtype=x.dtype)
        deg_inv_sqrt = deg.pow(-0.5)
        norm = deg_inv_sqrt[row] * deg_inv_sqrt[col]

        # Start propagating messages
        return self.propagate(edge_index, x=x, norm=norm)

    def message(self, x_j, norm):
        # x_j has shape [E, out_channels]
        # Normalize messages
        return norm.view(-1, 1) * x_j
```

Building a Complete GNN Model

```python
class GCN(torch.nn.Module):
    def __init__(self, num_node_features, num_classes):
        super(GCN, self).__init__()
        self.conv1 = GCNConv(num_node_features, 64)
        self.conv2 = GCNConv(64, 64)
        self.conv3 = GCNConv(64, 64)
        self.lin = nn.Linear(64, num_classes)

    def forward(self, data):
        x, edge_index = data.x, data.edge_index

        # First Graph Conv layer with ReLU
        x = self.conv1(x, edge_index)
        x = F.relu(x)
        x = F.dropout(x, p=0.1, training=self.training)

        # Second Graph Conv layer with ReLU
        x = self.conv2(x, edge_index)
        x = F.relu(x)
        x = F.dropout(x, p=0.1, training=self.training)

        # Third Graph Conv layer with ReLU
        x = self.conv3(x, edge_index)
        x = F.relu(x)

        # Global pooling: average all node features for graph-level prediction
        x = global_mean_pool(x, data.batch)

        # Final classifier
        x = self.lin(x)

        return x
```

Loss Function and Optimization

Common Loss Functions:

- Binary classification: Binary Cross Entropy
- Multi-class: Cross Entropy
- Regression: Mean Squared Error

Optimization:

- Adam optimizer is commonly used
- Learning rate scheduling can help
- Early stopping based on validation

```
# Binary classification
criterion = nn.BCEWithLogitsLoss()

# Regression
criterion = nn.MSELoss()

# Optimizer
optimizer = torch.optim.Adam(
    model.parameters(),
    lr=0.01,
    weight_decay=5e-4
)

# Learning rate scheduler
scheduler = torch.optim.
     lr_scheduler.ReduceLROnPlateau
     (
    optimizer,
    mode='min',
    factor=0.5,
    patience=5
)
```

Training Loop

```python
def train(model, loader, optimizer, criterion):
    model.train()
    total_loss = 0

    for data in loader:
        optimizer.zero_grad()
        out = model(data)
        loss = criterion(out, data.y)
        loss.backward()
        optimizer.step()
        total_loss += loss.item() * data.num_graphs

    return total_loss / len(loader.dataset)

def evaluate(model, loader, criterion):
    model.eval()
    total_loss = 0

    with torch.no_grad():
        for data in loader:
            out = model(data)
            loss = criterion(out, data.y)
            total_loss += loss.item() * data.num_graphs

    return total_loss / len(loader.dataset)

# Training process
for epoch in range(1, 101):
    train_loss = train(model, train_loader, optimizer, criterion)
    val_loss = evaluate(model, val_loader, criterion)
    scheduler.step(val_loss)

    print(f'Epoch: {epoch}, Train Loss: {train_loss:.4f}, Val Loss: {val_loss:.4f}')
```

Evaluation on Test Data

Evaluation Metrics:

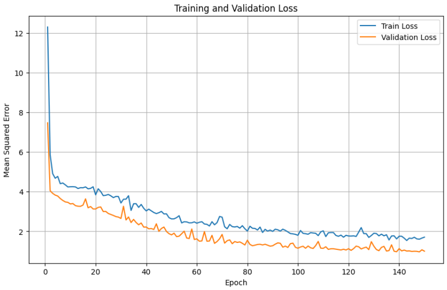
- Classification: Accuracy, F1-score, AUC-ROC
- Regression: RMSE, MAE, R^2

Evaluation Process:

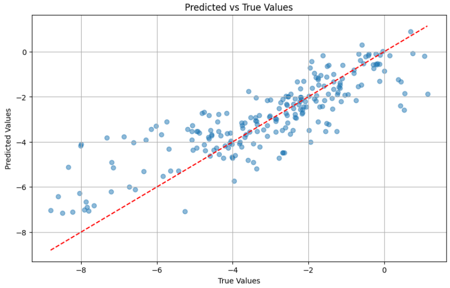
1. Load the best model (lowest validation loss)
2. Run predictions on test set
3. Calculate metrics
4. Analyze errors or failure cases

```python
from sklearn.metrics import roc_auc_score

# Load best model
model.load_state_dict(torch.load('best_model
    .pt'))

# Evaluate on test set
model.eval()
preds = []
targets = []

with torch.no_grad():
    for data in test_loader:
        pred = torch.sigmoid(model(data))
        preds.append(pred)
        targets.append(data.y)

preds = torch.cat(preds, dim=0).numpy()
targets = torch.cat(targets, dim=0).numpy()

# Calculate AUC-ROC
auc = roc_auc_score(targets, preds)
print(f'Test AUC-ROC: {auc:.4f}')
```

Visualizing Results



Loss Curves



Prediction vs Actual

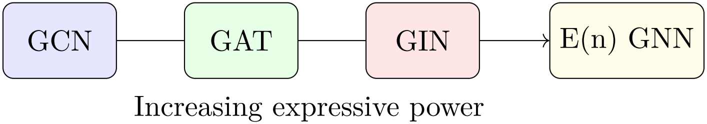
GNN Advanced Concepts

Advanced Architectures:

- GraphSAGE: Scalable inductive representation learning
- Graph Attention Networks (GAT): Attention-based message passing
- Graph Isomorphism Network (GIN): More powerful than GCN
- E(n) Equivariant GNNs: 3D-aware models

Advanced Techniques:

- Virtual nodes: Connect all nodes to improve long-range information flow
- Edge features: Include bond information
- Residual connections: Skip connections in message passing
- Graph normalization: Batch norm for graphs
- Pre-training: Self-supervised learning on molecules



Resources and Further Reading

GitHub Repository:

- `https://github.com/HFooladi/GNNs-For-Chemists`

Tutorials:

- "A Gentle Introduction to Graph Neural Networks"
- "Understanding Convolutions on Graphs"
- PyTorch Geometric Documentation

Research Papers:

- Kipf & Welling, "Semi-Supervised Classification with Graph Convolutional Networks"
- Gilmer et al., "Neural Message Passing for Quantum Chemistry"
- Veličković et al., "Graph Attention Networks"
- Xu et al., "How Powerful are Graph Neural Networks?"

Questions? Let's discuss!