Towards Precision Medicine with Graph Representation Learning

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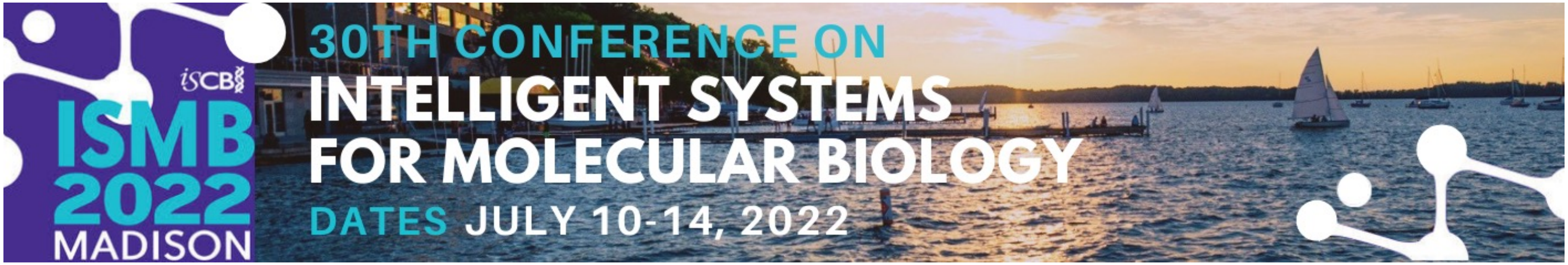


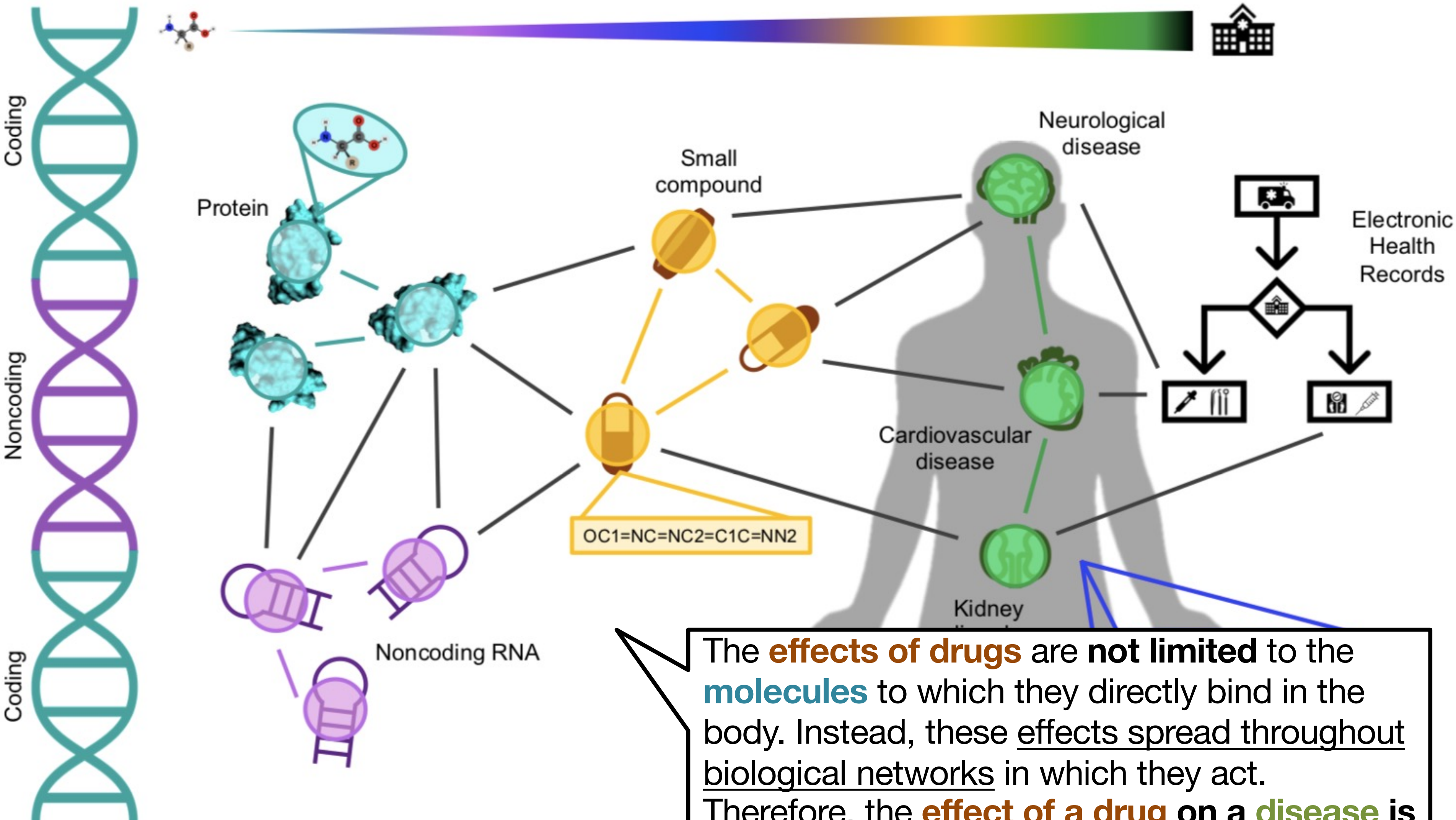
Tutorial VT4

July 7, 2022 at 9am – 1pm CDT

All tutorial materials are available at

zitniklab.hms.harvard.edu/biomedgraphml

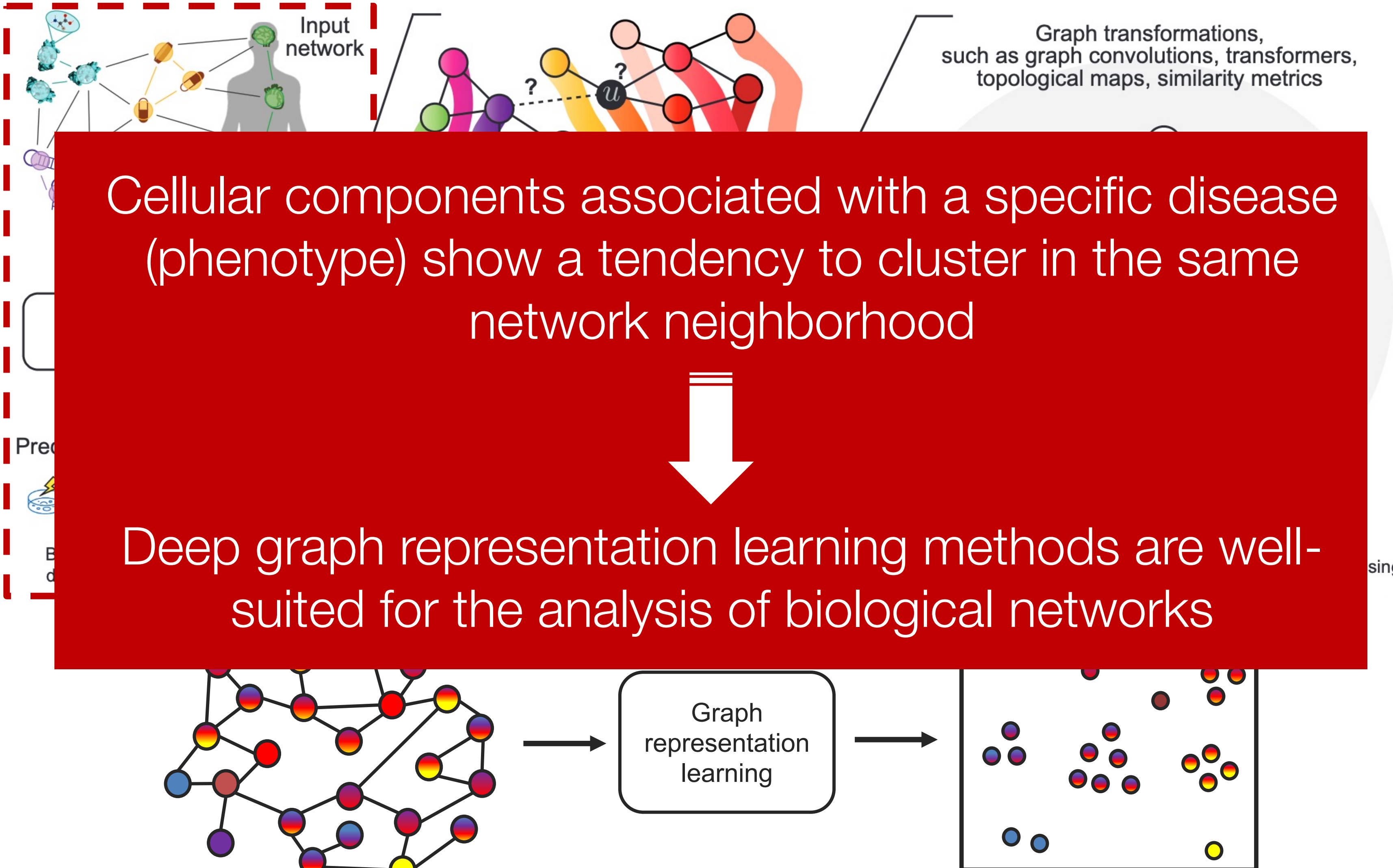
Biology is interconnected



The **effects of drugs** are **not limited** to the **molecules** to which they directly bind in the body. Instead, these effects spread throughout biological networks in which they act. Therefore, the **effect of a drug on a disease is inherently a network phenomenon**

Graph Representation Learning for Biomedicine, *Nature Biomedical Engineering* (in press), 2022, arXiv:2104.04883

Graph representation learning realizes key network principles for data-rich biomedicine



Cellular components associated with a specific disease (phenotype) show a tendency to cluster in the same network neighborhood

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Deep graph representation learning methods are well-suited for the analysis of biological networks

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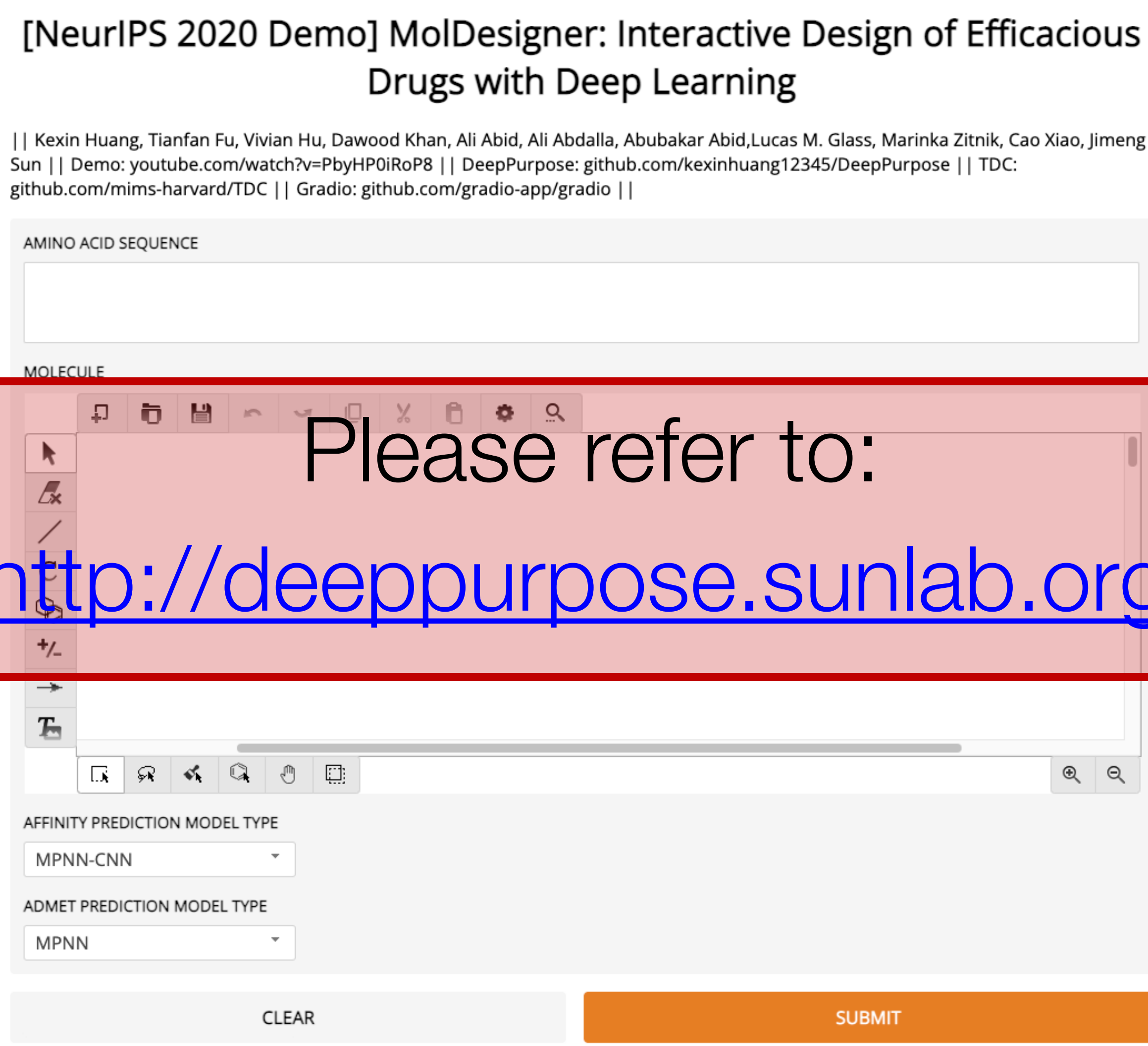
This Tutorial

✓ 1. Methods: Network diffusion, shallow network embeddings, graph neural networks, equivariant neural networks

✓ 2. Applications: Fundamental biological discoveries and precision medicine

3. Hands-on exercises: Demos, implementation details, tools, and tips

Hands-on Exercise



Please refer to:

http://deeppurpose.sunlab.org/

Practical Advice & Tips

Network & machine learning packages

- Data science & machine learning basics: Numpy, pytorch, pandas, scipy, scikit-learn
- Visualization basics: Matplotlib, plotly, UMAP, seaborn
- Network construction & analysis: NetworkX, iGraph, Stanford Network Analysis Platform (SNAP)
- Graph machine learning: Pytorch Geometric (+ tutorials), Deep Graph Library (+ public slack channel), Pytorch Lightning

Developer tools for graphs & machine learning

- Network visualization: Gephi, Cytospace, GraphVis, Neo4j
- Model visualization: Weights & Biases, Neptune, TensorBoard, Comet, HiPlot
- Code profilers: cProfile/profile for Python3
- Making paper-ready figures: draw.io, Adobe color wheel

Quick tip: New packages and software are released all the time, but there's no need to be overwhelmed! Stick with a few that you like and be proficient in them!

Practical Advice & Tips

Helpful tools for programming

- Notebooks: Google Colab (free GPUs), Jupyter Notebook
- Version control: GitHub
- Environment management system: Conda
- Integrated Development Environment (IDE): Visual Studio Code, PyCharm, Spyder
- Terminal multiplexers: Screen, tmux
- Runtime: tqdm
- Use debuggers and breakpoints (e.g., pdb package, built-in debuggers in IDEs)

Implementation tips

- Normalize by degree (e.g., node features, node weights)
- Apply batch and/or layer normalization
- Use minibatching (especially on large graphs)
- Experiment with the number of layers (deeper GNNs do not necessarily yield better performance)

Practical Advice & Tips

Training tips: Data & metrics

- Split dataset into train, validation, and test sets (avoid data leakage!)
- For self-supervised learning, carefully define negative samples
- Define metrics carefully (e.g., Is the data is balanced or imbalanced?)
  - Balanced: Receiver operating characteristic (ROC) curve
  - Imbalanced: Average precision (AP) score
- Start small (e.g., toy dataset) and then scale up
- Log everything (e.g., print statements, progress bars, model visualization software)

Training tips: Model evaluation

- Ensure that the model can overfit on training data (e.g., >90% ROC)
- Avoid over- or under-training the model (e.g., specify number of epochs, define early-stopping criteria)
- Evaluate hyperparameters on left-out validation set (e.g., grid search, random search) – *Don't be overwhelmed by all the possible parameters; start with learning rate! Consider using a learning rate scheduler.*
- Establish strong baseline models (e.g., consider domain-specific as well as classic machine learning models)
- Set a seed for code to ensure reproducibility
- Save models at critical points (e.g., new minimum loss, new maximum ROC)
- Make sure code *actually* works before requesting tons of resources (e.g., cluster)

Practical Advice & Tips

Common bugs in implementation

- Performance is random / opposite to what is expected
  - Edges are unintentionally shuffled during training
  - An imported function is re-indexing, and it is unaccounted for in our code
- Out-of-memory error on GPU
  - Implement minibatching or decrease batch size
  - Decrease model size (e.g., number of layers, number of attention heads)

Common model training issues

- Model has near-perfect performance on the validation/test set
  - Data leakage between train and validation/test set
- Model takes forever to start running
  - Minimize preprocessing steps done at launch
  - Consider loading only the necessary data (e.g., columns/rows in dataframe)
- Model takes a long time to converge
  - Increase learning rate
  - Apply normalization (e.g., batch norm, which allows us to increase learning rate too!)
- Model is overfitting
  - Apply dropout layer
  - Simplify model (e.g., remove layers)
  - Use early stopping

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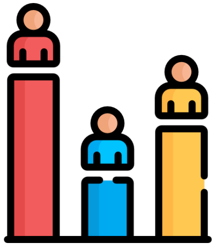
- ✓ 3. Hands-on exercises: Demos, implementation details, tools, and tips



Time for a poll question about…

OUR TUTORIAL

1. What is the most memorable thing about graph representation learning that you learned today? *Fill in the blank*
2. What topic would you like us to cover in future iterations of this tutorial? *Fill in the blank*

ISMB 2022 Tutorial Feedback

Which tutorial did you attend? (If you attended more than one tutorial, you will have the opportunity to submit a second survey) *

- ○ Tutorial IP1: Gene regulatory network inference from single-cell transcriptomics data
- ○ Tutorial IP2: A practical introduction to the design, quantification, and analysis of

Please refer to:

docs.google.com/forms/d/e/1FAIpQLSftVbI5O-P6EidL-PBgmqjdVE9QX3SfsgGKqkX6DDxJzGvrfQ/viewform

- ○ Tutorial VT1: Introduction to Python programming for bioscientists
- ○ Tutorial VT2: Building Interactive Visualizations of Genomics Data with Gosling
- ○ Tutorial VT3: Federated Learning in Biomedicine
- ◉ Tutorial VT4: Towards Precision Medicine with Graph Representation Learning
- ○ Tutorial VT5: Computational analysis of antibody repertoires, with applications for therapeutic discovery
- ○ Tutorial VT6: Online tools for visualizing RNA structure

Resources

- Books & survey papers
  - William Hamilton, *Graph Representation Learning* (morganclaypool.com/doi/abs/10.2200/S01045ED1V01Y202009AIM046)
  - Li et al., Graph Representation Learning for Biomedicine (arxiv.org/abs/2104.04883)

- Keynotes & seminars
  - Michael Bronstein, “Geometric Deep Learning: The Erlangen Programme of ML” (ICLR 2021 keynote) (youtube.com/watch?v=w6Pw4MOzMuo)
  - Broad Institute Models, Inference & Algorithms: Actionable machine learning for drug discovery; Primer on graph representation learning (youtube.com/watch?v=9YpTYdru0Rg)
  - Stanford University (CS224W Lecture): Graph neural networks in computational biology (youtube.com/watch?v=_hy9AgZXhbQ)
  - AI Cures Drug Discovery Conference (youtube.com/watch?v=wNXSkISMTw8)

- Conferences & summer schools
  - London Geometry and Machine Learning Summer School (logml.ai)
  - Learning on Graphs Conference (logconference.github.io)

Resources

- Software & packages
  - PyTorch Geometric
  - NetworkX
  - Stanford Network Analysis Platform (SNAP)

- Tutorials & code bases
  - Pytorch Geometric Colab Notebooks (pytorch-geometric.readthedocs.io/en/latest/notes/colabs.html)
  - Zitnik Lab Graph ML Tutorials (github.com/mims-harvard/graphml-tutorials)
  - Stanford University's CS224 (web.stanford.edu/class/cs224w)

- Datasets
  - Precision Medicine Oriented Knowledge Graph (PrimeKG) (zitniklab.hms.harvard.edu/projects/PrimeKG)
  - Therapeutic Data Commons (TDC) (tdcommons.ai)
  - BioSNAP (snap.stanford.edu/biodata/)
  - Open Graph Benchmark (OGB) (ogb.stanford.edu)