# Generalizable Graph AI for Biomedicine: Data-Driven Self-Supervision and Principled Regularization

Yuning You

Ph.D. Final Defense; Chair of Committee & Advisor: Prof. Yang Shen
Committee Members: Prof. Zhangyang Wang, Prof. Ulisses Braga Neto, Prof. Srinivas Shakkottai

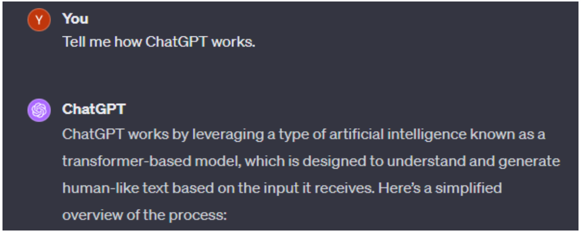
Department of Electrical and Computer Engineering
Texas A&M University

2024-06-14

# AI is Revolutionizing the World

Art

Language



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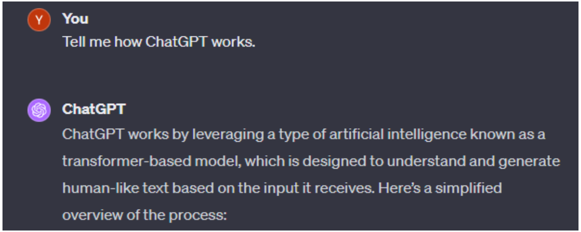


Game


Auto-Driving

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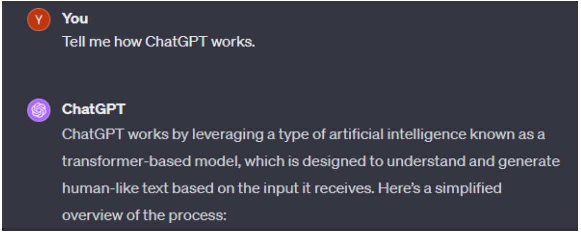


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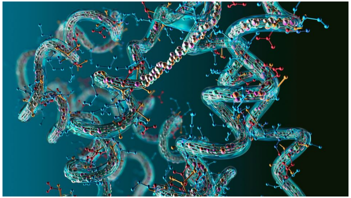
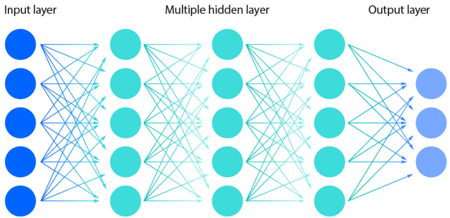


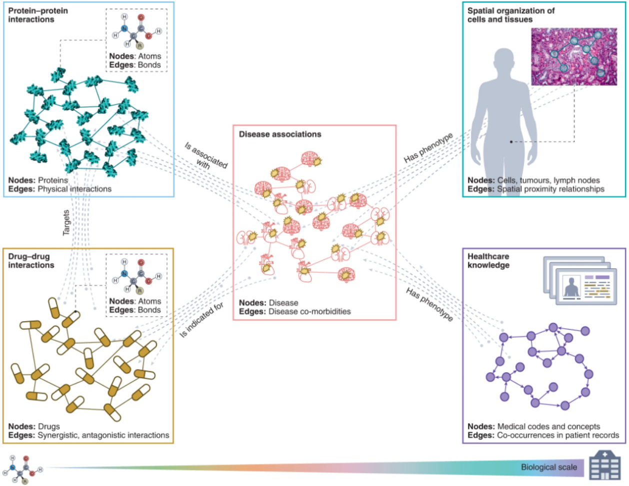
Medicine

# AI is Revolutionizing the Field of Medicine

AI




Biomedical Applications [LHZ'22]



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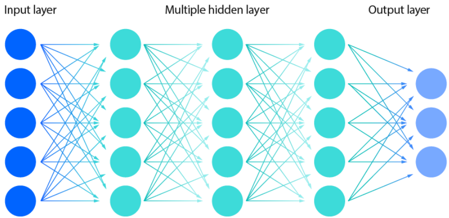
AI

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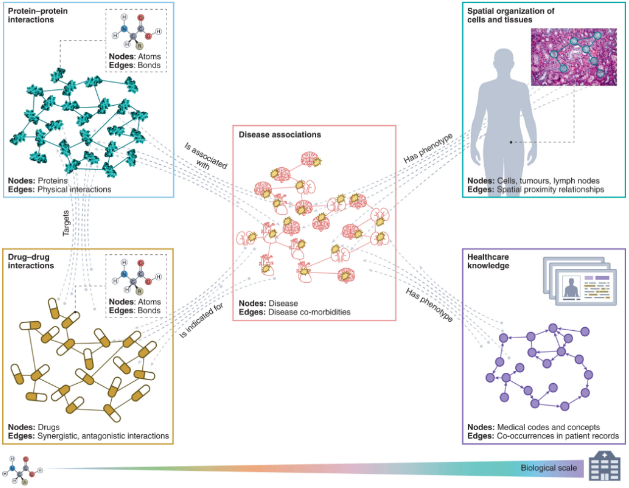

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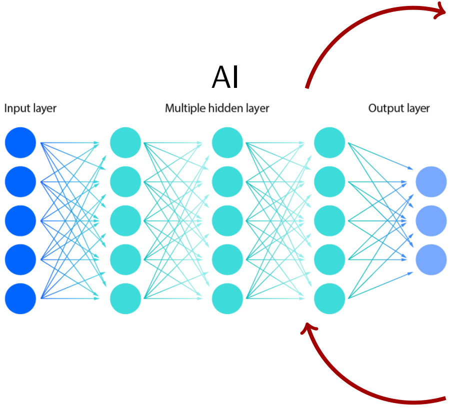


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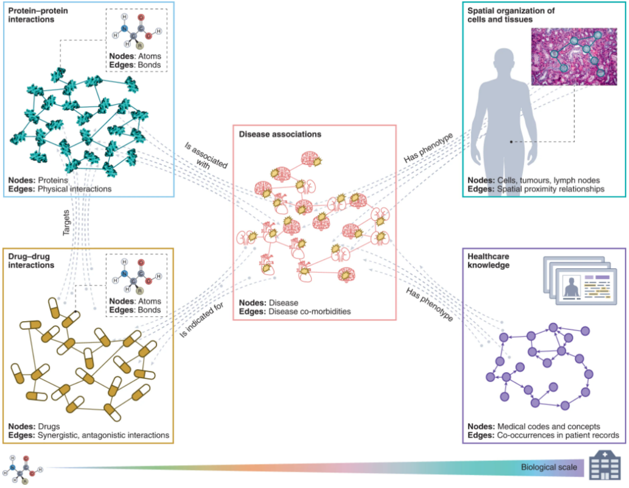
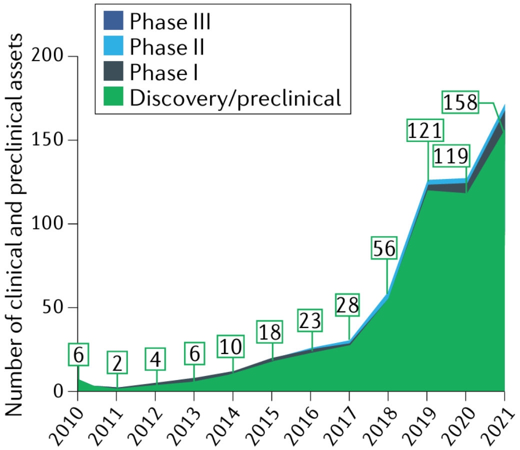


# AI's Potential has not been Fully Realized in Biomedicine

AI in Pharmas [JXRSM'22]



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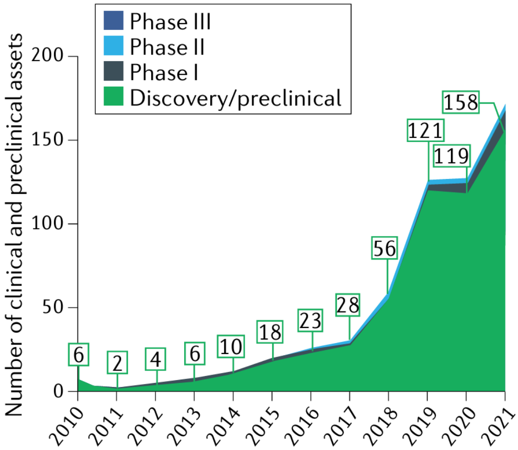



[D'23]

October 19, 2023 09:37 AM EDT
*Updated 11:05 AM*
AI, In Focus

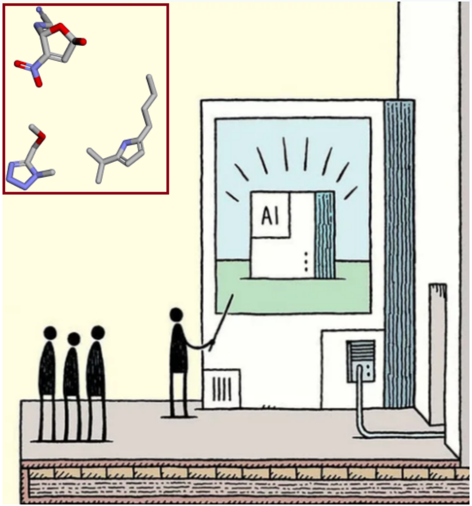
**ENDPOINTS** *in* **FOCUS**

**After years of hype, the first AI-designed drugs fall short in the clinic**

**Andrew Dunn**
Biopharma Correspondent

The first AI-designed drugs have ended with disappointment.

# AI4Biomed is Curbed in Generalization



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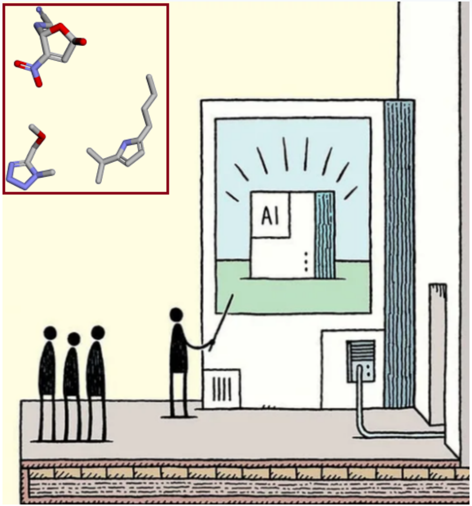


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Restricted in
Data Quantity & Quality

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#Data: >14M

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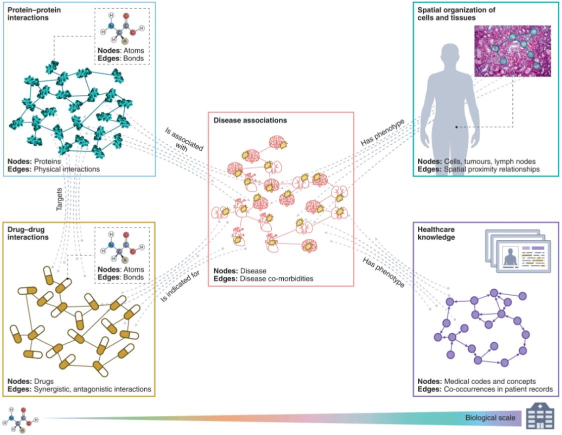
MoleculeNet

#Data: 1K – 40K (300 – 10,000 Times Smaller)

# AI4Biomed is Curbed in Generalization

## Complicated in Data Structure



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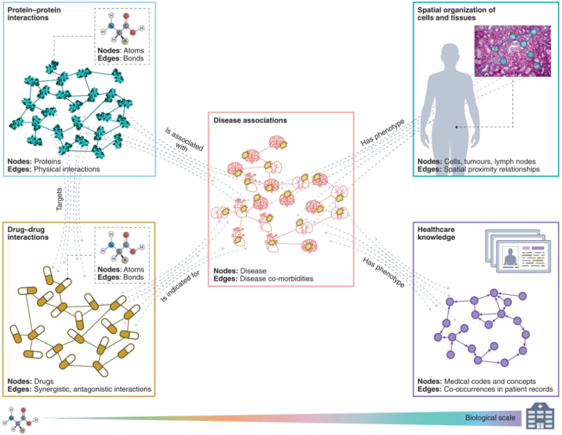
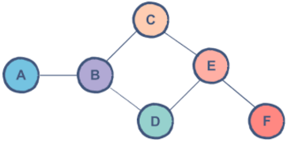



## Graph



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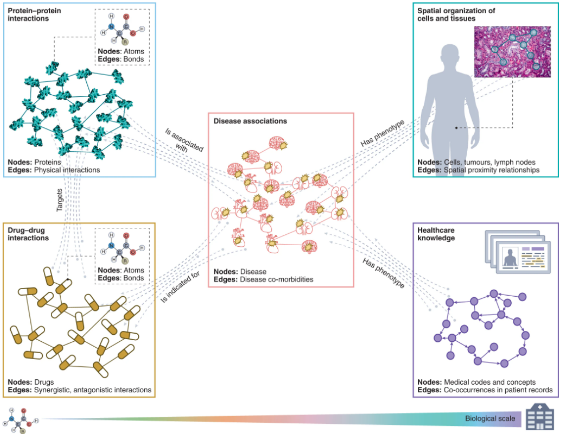
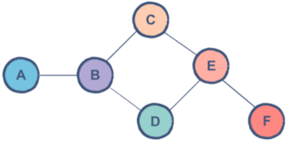
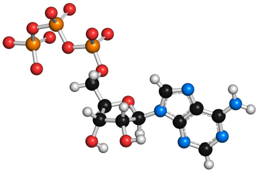
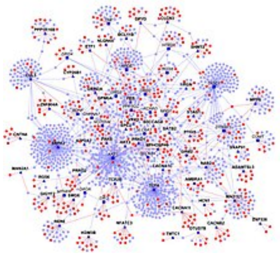



Graph



Molecule

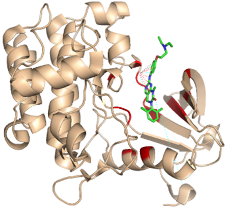


PPI Network

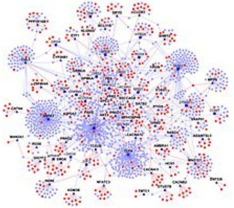
# Generalizable Graph AI is Demanded in Biomedical Modeling

**Real-World Biomed. Problems**

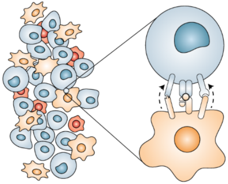
Molecules



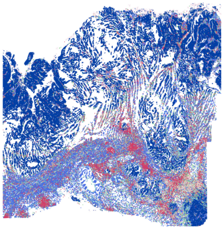
Interactions



Cells



Organ(oid)



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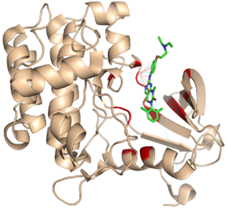
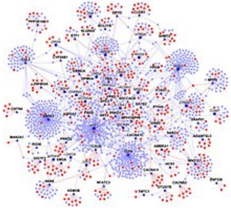


Interactions



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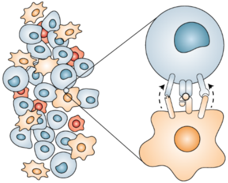

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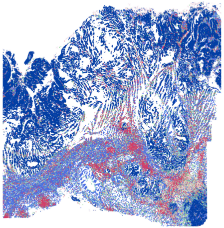
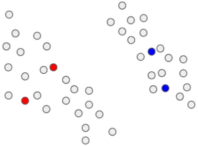
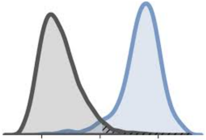
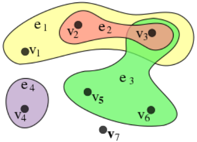




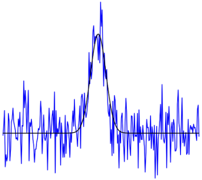
Few-Shot



OOD



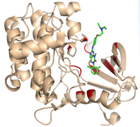

Heterogeneous

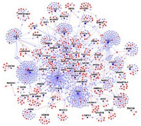


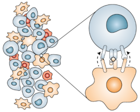
Noisy

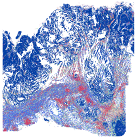
**Generalization Challenges**

# Generalizable Graph AI is Demanded in Biomedical Modeling



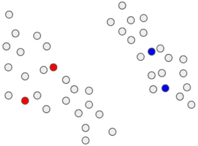




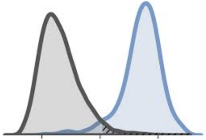


**Real-World Biomed. Generalization Challenges**

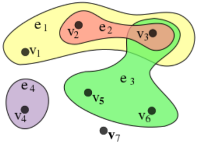
Few-Shot



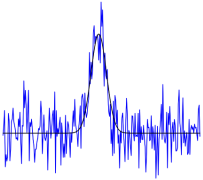
OOD



Heterogeneous




Noisy



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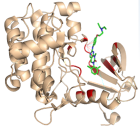

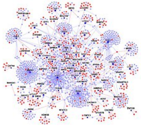

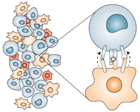

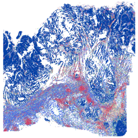

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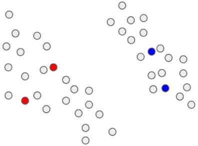

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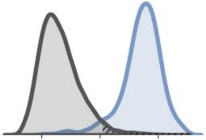

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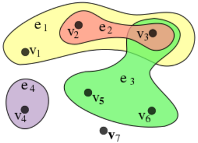


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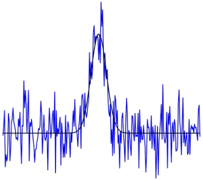
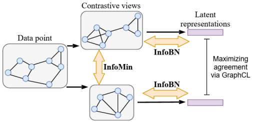
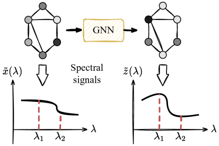
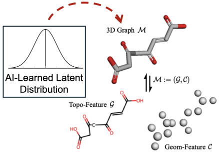





GraphCL




GNN SpecReg

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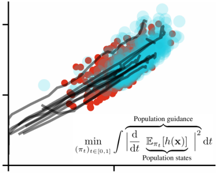


CLSB

**Foundational Graph AI Solutions**

# Overview of Ph.D. Research Accomplishments

- Overall goal: Improving AI model generalization on unseen (biomed.) graph data.

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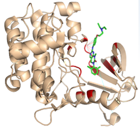
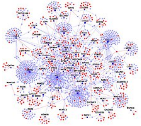
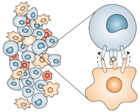
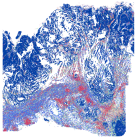


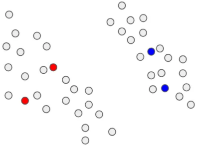




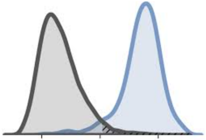


## Real-World Biomed. Generalization Challenges

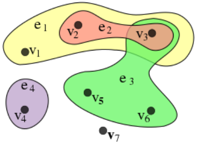
Few-Shot



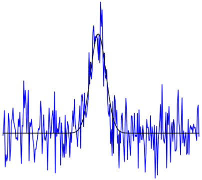
OOD

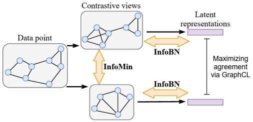


Heterogeneous

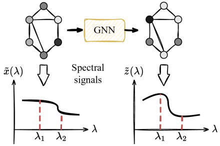



Noisy

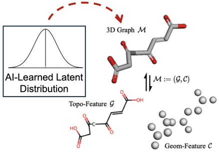




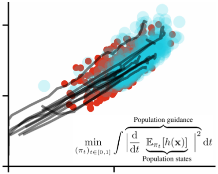

GraphCL




GNN SpecReg



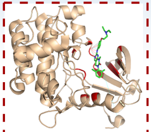

LDM-3DG

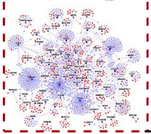


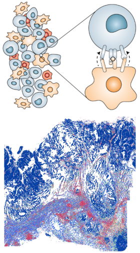

CLSB

## Foundational Graph AI Solutions

# Generalizable Graph AI is Demanded in Biomedical Modeling







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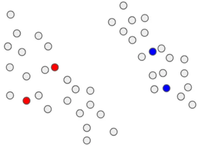
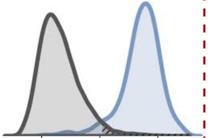
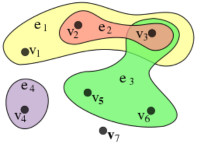


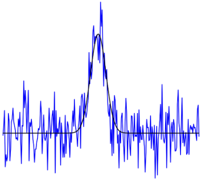
OOD

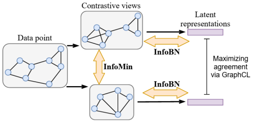


Heterogeneous




Noisy



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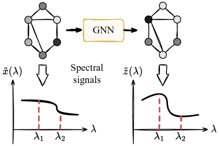


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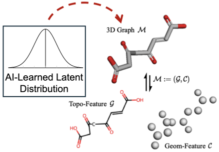


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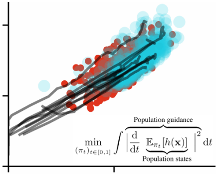
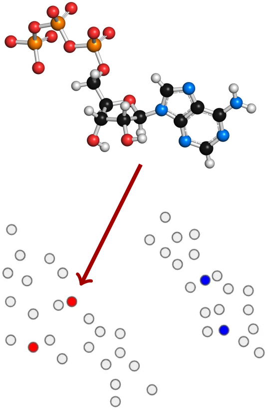



CLSB

## Foundational Graph AI Solutions

# **Mst 1:** Discrim. Model Generalization on Homogen. Graphs

Molecular Property Prediction



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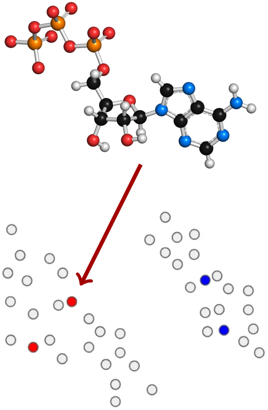
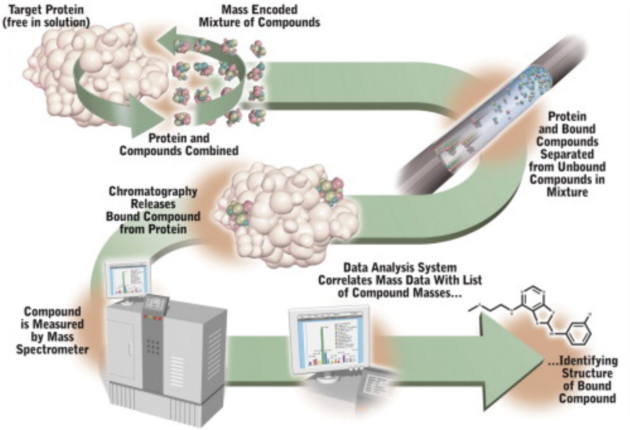
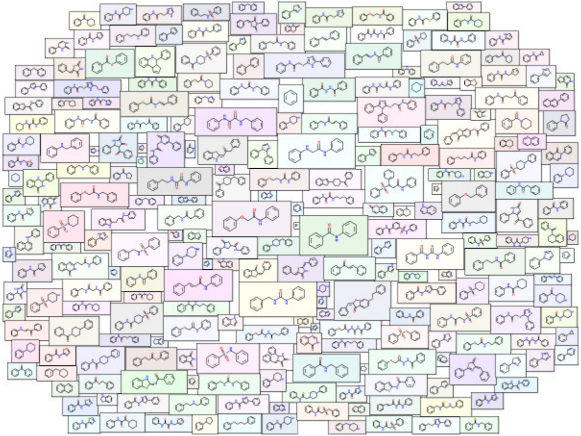


Annotation is Resource-Intensive



# GNN Generalizability Benefits from Unlabelled Data

Unlabelled Graphs



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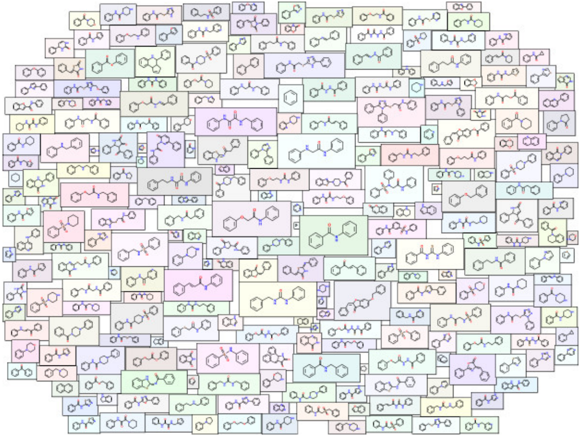


Self-Supervised Learning (SSL): Dark Matter of Intelligence

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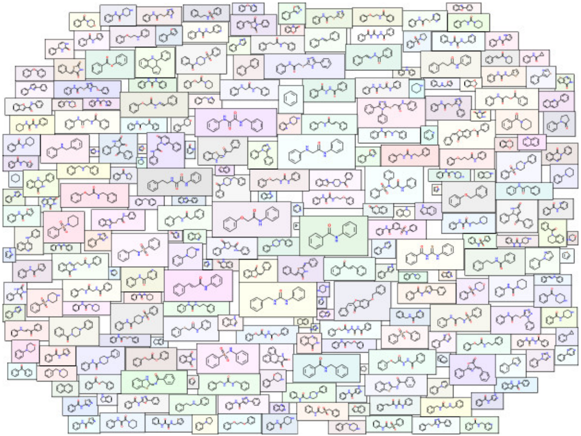
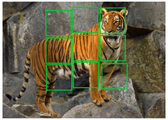


Self-Supervised Learning (SSL): Dark Matter of Intelligence

Vision SSL



Language SSL

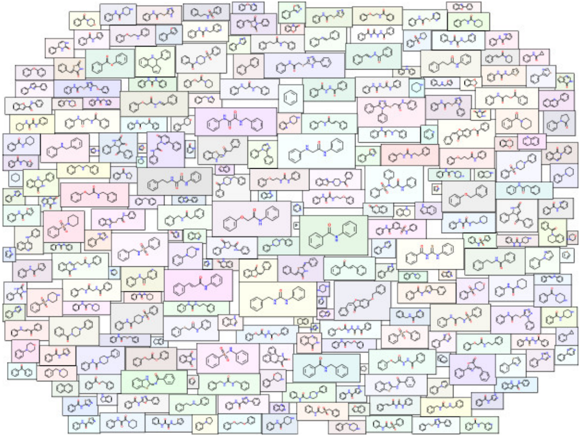
Randomly masked: A quick [MASK] fox jumps over the [MASK] dog

↓ ↓

Predict: A quick brown fox jumps over the lazy dog

# GNN Generalizability Benefits from Unlabelled Data

Unlabelled Graphs



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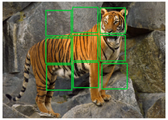

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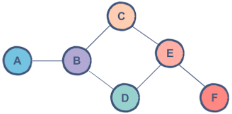


Graph SSL?
A Generic Framework?

# How to Leverage the more Accessible Unlabelled Graph Data?

Graph Contrastive Learning [YCSCWS NeurIPS'20]:

$\min_\theta \; L_{\mathsf{GCL}}(\theta, \phi, \{G^{(i)}\}_{i=1}^m)$

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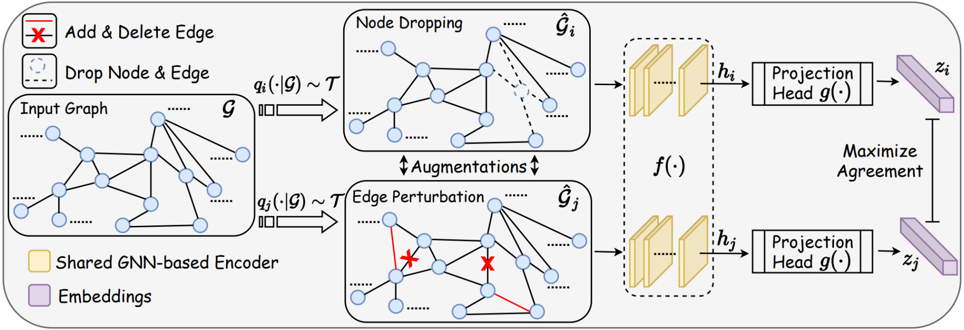

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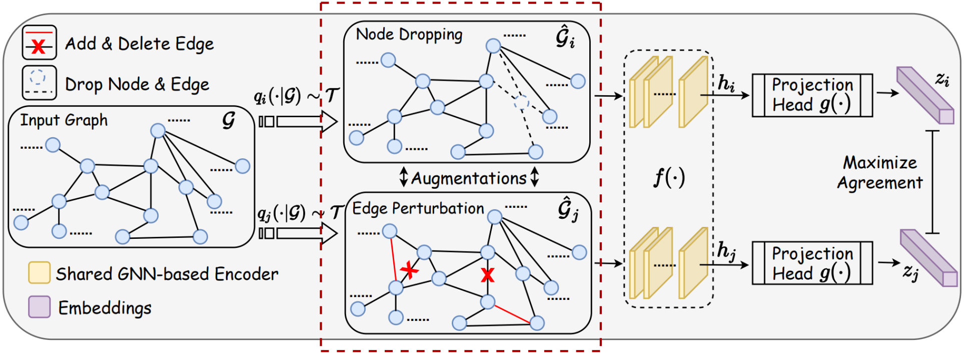


Graph Augmentation

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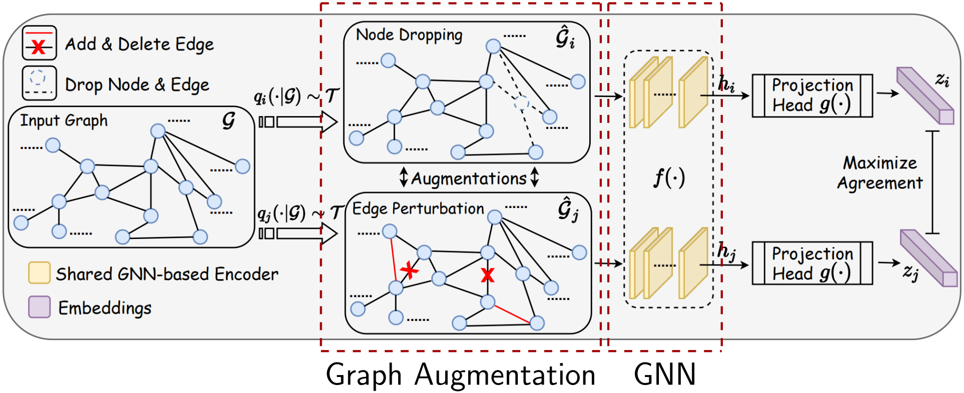

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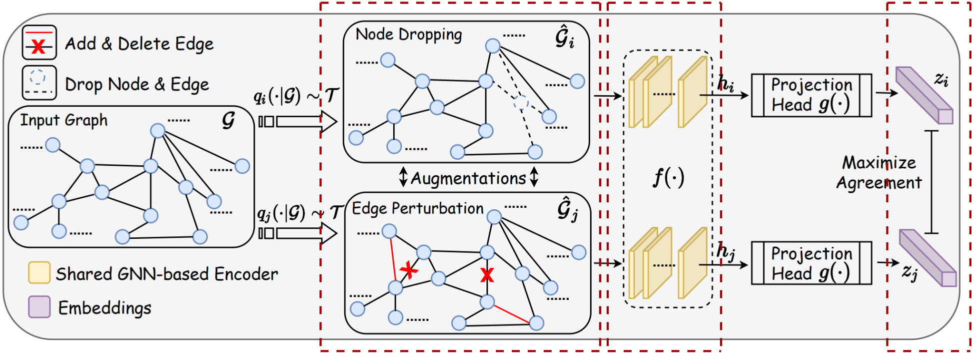
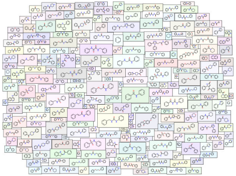



Graph Augmentation GNN Contrastive Loss

# Experiments on Molecular Property Prediction

ZINC [SI'15]



- MoleculeNet [WRFPLP'18]

| Category | Dataset | Data Type | Task Type | # Tasks | # Compounds | Rec - Split[a] | Rec - Metric[b] |
|---|---|---|---|---|---|---|---|
| Biophysics | MUV | SMILES | Classification | 17 | 93087 | Random | PRC-AUC |
| | HIV | SMILES | Classification | 1 | 41127 | Scaffold | ROC-AUC |
| | BACE | SMILES | Classification | 1 | 1513 | Scaffold | ROC-AUC |
| Physiology | BBBP | SMILES | Classification | 1 | 2039 | Scaffold | ROC-AUC |
| | Tox21 | SMILES | Classification | 12 | 7831 | Random | ROC-AUC |
| | ToxCast | SMILES | Classification | 617 | 8575 | Random | ROC-AUC |
| | SIDER | SMILES | Classification | 27 | 1427 | Random | ROC-AUC |
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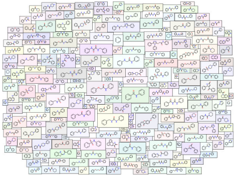

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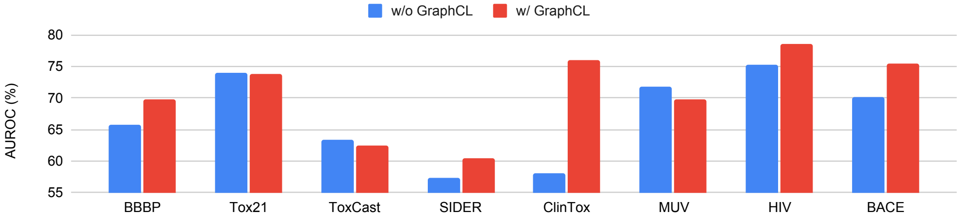

# GNN Generalizability Benefits from Principled Regularization

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$$+\,\mathcal{O}\Big(\sup_{\lambda_1,\lambda_2}\frac{|s(\lambda_1) - s(\lambda_2)|}{|\lambda_1 - \lambda_2|}\Big)\|\boldsymbol{A}_1 - \boldsymbol{P}^*\boldsymbol{A}_2\boldsymbol{P}^{*\top}\| + \mathcal{O}(\|\boldsymbol{A}_1 - \boldsymbol{P}^*\boldsymbol{A}_2\boldsymbol{P}^{*\top}\|^2)$$

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$$\|f_\theta(G_1) - f_\theta(G_2)\| \leq \underbrace{\boxed{\sup_\lambda\{|s(\lambda)|\}}}_{\text{Maximum Frequency Response (MFR)}} \|\boldsymbol{x}_1 - \boldsymbol{P}^*\boldsymbol{x}_2\| \quad \text{(GNN Stability)}$$

$$+ \underbrace{\boxed{\mathcal{O}(\sup_{\lambda_1,\lambda_2} \frac{|s(\lambda_1) - s(\lambda_2)|}{|\lambda_1 - \lambda_2|})}}_{\text{Spectral Smoothness (SS)}} \|\boldsymbol{A}_1 - \boldsymbol{P}^*\boldsymbol{A}_2\boldsymbol{P}^{*\top}\| + \mathcal{O}(\|\boldsymbol{A}_1 - \boldsymbol{P}^*\boldsymbol{A}_2\boldsymbol{P}^{*\top}\|^2)$$

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Spectral Smoothness (SS)

Denote $c_{f_\theta} = \max\left\{2\sup_\lambda\{|s(\lambda)|\}, \mathcal{O}(\sup_{\lambda_1,\lambda_2}\frac{|s(\lambda_1)-s(\lambda_2)|}{|\lambda_1-\lambda_2|})\right\}$

$$\begin{aligned} \epsilon_{\text{tgt}}(f_\theta) - \hat{\epsilon}_{\text{src}}(f_\theta) &\leq \mathcal{O}(1/\sqrt{m}) \qquad \text{(GNN Transferability)} \\ &+ c_{f_\theta}\mathrm{W}(p_{\text{src}}, p_{\text{tgt}}) + \min_{\theta', c_{f_{\theta'}} \leq c_{f_\theta}} \big(\epsilon_{\text{src}}(f_{\theta'}) + \epsilon_{\text{tgt}}(f_{\theta'})\big) \end{aligned}$$

# GNN Generalizability Benefits from Principled Regularization

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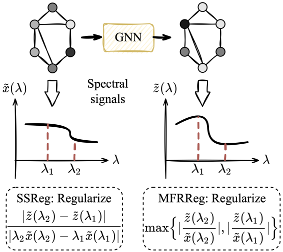
$$
\begin{aligned}
\epsilon_{\text{tgt}}(f_\theta) - \hat{\epsilon}_{\text{src}}(f_\theta) \quad &\leq \quad \mathcal{O}(1/\sqrt{m}) \qquad \text{(GNN Transferability [YCWS ICLR'23])} \\
&+ \quad \boxed{c_{f_\theta} \mathrm{W}(p_{\text{src}}, p_{\text{tgt}})} + \boxed{\min_{\theta', c_{f_{\theta'}} \leq c_{f_\theta}} \left(\epsilon_{\text{src}}(f_{\theta'}) + \epsilon_{\text{tgt}}(f_{\theta'})\right)}
\end{aligned}
$$

Adaptability$\propto$(SS/MFR) Discriminability$\bar{\propto}$(SS/MFR)

- Regularizing GNN stability $\Rightarrow$ Adaptability$\uparrow$, Discriminability$\downarrow$;




Stability Regularization

# GNN Generalizability Benefits from Principled Regularization

$$
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&+ \quad \underbrace{\boxed{c_{f_\theta} \mathrm{W}(p_{\mathsf{src}}, p_{\mathsf{tgt}})}}_{\text{Adaptability}\propto(\text{SS/MFR})} + \underbrace{\boxed{\min_{\theta', c_{f_{\theta'}} \le c_{f_\theta}} \left(\epsilon_{\mathsf{src}}(f_{\theta'}) + \epsilon_{\mathsf{tgt}}(f_{\theta'})\right)}}_{\text{Discriminability}\bar{\propto}(\text{SS/MFR})}
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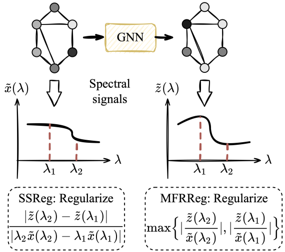
- Node-informative scenario: Regularizing SS;




Stability Regularization

# GNN Generalizability Benefits from Principled Regularization

$$\begin{aligned} \epsilon_{\mathsf{tgt}}(f_\theta) - \hat{\epsilon}_{\mathsf{src}}(f_\theta) \quad &\le \quad \mathcal{O}(1/\sqrt{m}) \qquad \text{(GNN Transferability [YCWS ICLR'23])} \\ &+ \quad \boxed{c_{f_\theta} \mathrm{W}(p_{\mathsf{src}}, p_{\mathsf{tgt}})} + \boxed{\min_{\theta', c_{f_{\theta'}} \le c_{f_\theta}} \left(\epsilon_{\mathsf{src}}(f_{\theta'}) + \epsilon_{\mathsf{tgt}}(f_{\theta'})\right)} \end{aligned}$$

Adaptability$\propto$(SS/MFR) Discriminability$\bar{\propto}$(SS/MFR)

- Regularizing GNN stability $\Rightarrow$ Adaptability$\uparrow$, Discriminability$\downarrow$;
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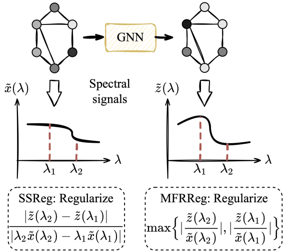
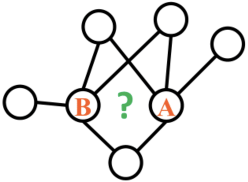


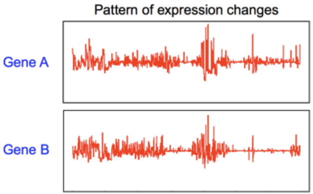

Stability Regularization

# Experiments on Co-Expression Interaction Prediction

[SKKBJM'23]




Co-Expression




- Nodes of genes, edges of gene relations;

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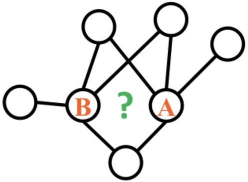


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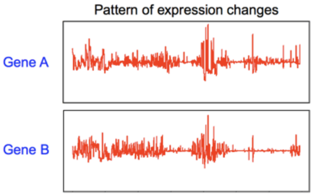


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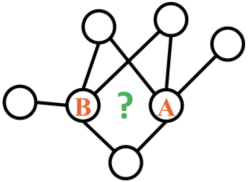


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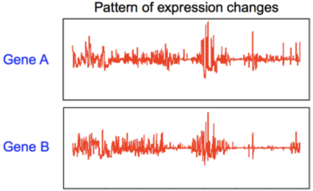


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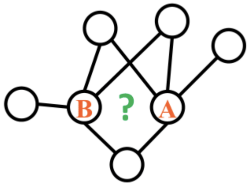


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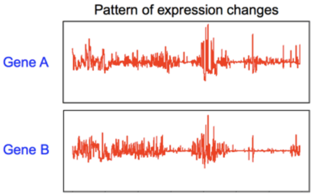


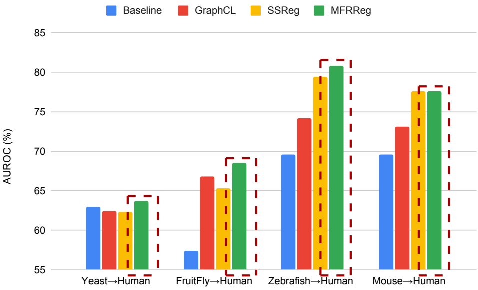


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# Experiments on Physical Interaction Prediction

[SKKBJM'23]

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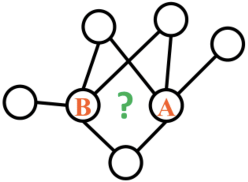
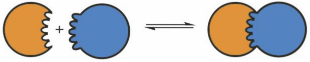



Physical Interaction

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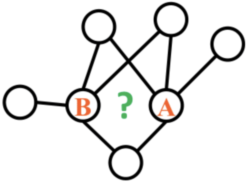


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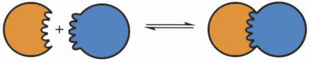


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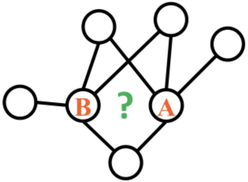


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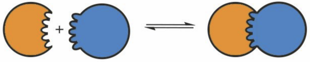


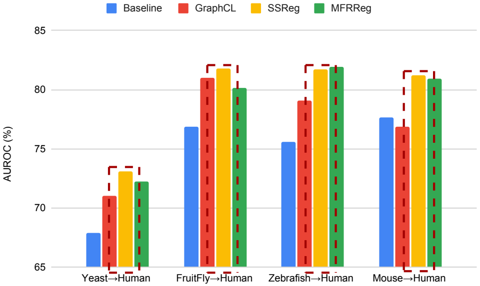


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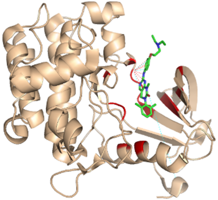
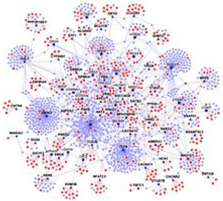
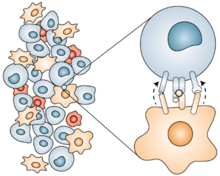
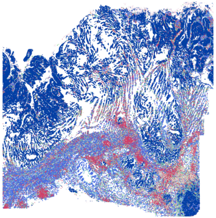
# **Mst 2:** Generalization cross Graph Datasets of Hete. Semant.

Heterogeneous Graph Data Semantics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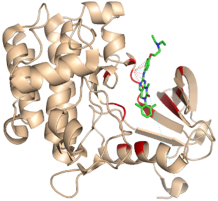
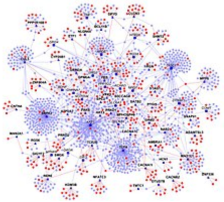
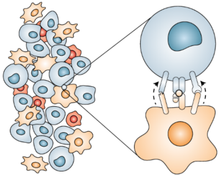
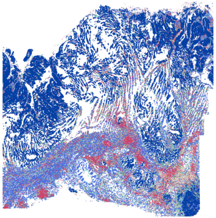
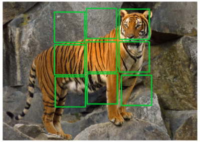








~~One SSL Task for All Scenarios~~



| | |
|---|---|
| Randomly masked | A quick [MASK] fox jumps over the [MASK] dog |
| | ↓ ↓ |
| Predict | A quick brown fox jumps over the lazy dog |

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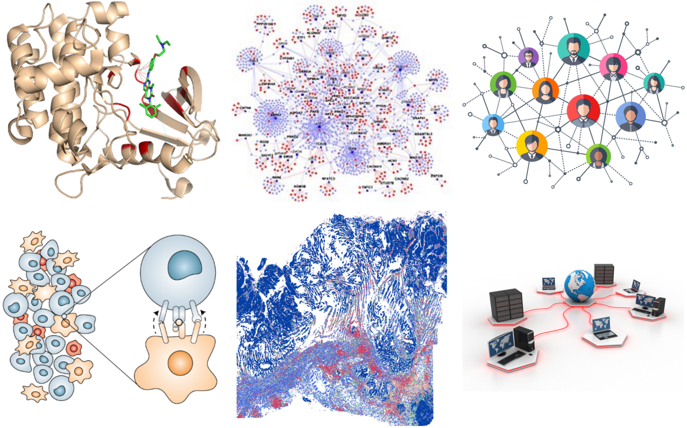

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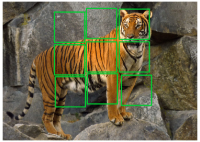

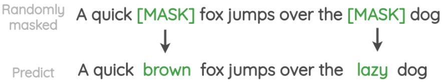


Searching for Graph SSL Tasks on Different Datasets

# How to Search for Graph SSL Tasks Automatically?

Graph SSL Search [YCSW ICML'21, YCWS WSDM'22]:

$$\min_\theta \; L_{\mathsf{GCL}}(\theta, \phi, \{G^{(i)}\}_{i=1}^m), \quad \text{s.t.} \quad \phi = \operatorname{argmin}_{\phi' \in \Phi} L_{\mathsf{srch}}(\theta, \phi', \{G^{(i)}\}_{i=1}^m)$$

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"Discrete" Parametrization

| Data augmentation | Underlying Prior |
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| Node dropping | Vertex missing does not alter semantics. |
| Edge perturbation | Semantic robustness against connectivity variations. |
| Attribute masking | Semantic robustness against losing partial attributes. |
| Subgraph | Local structure can hint the full semantics. |

$$\text{e.g. } \phi' = \left\{ \begin{array}{cccc} \mathsf{ND} & \mathsf{EP} & \mathsf{AM} & \mathsf{SG} \\ 0.4 & 0.3 & 0.2 & 0.1 \end{array} \right\}$$

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"Continuous" Param.

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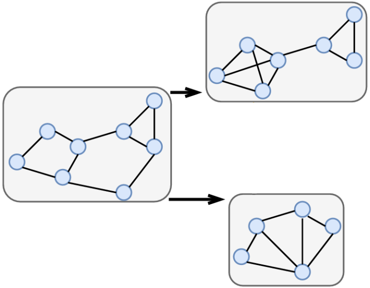

VGAE $q_{\phi'}(\tilde{\mathrm{G}}|\mathrm{G})$ [KW'16]

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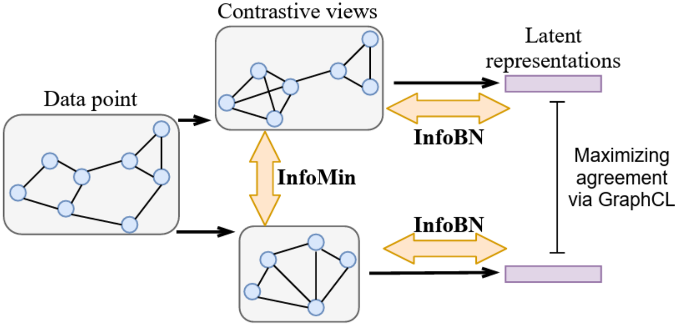

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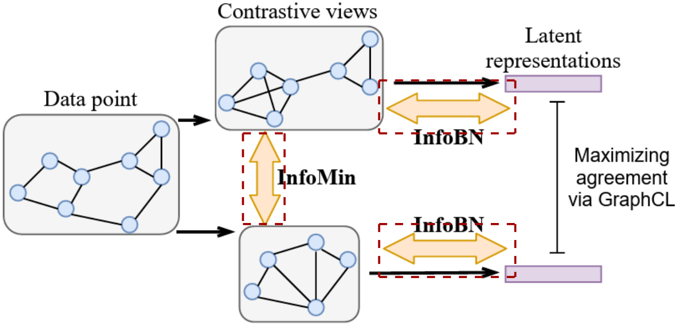
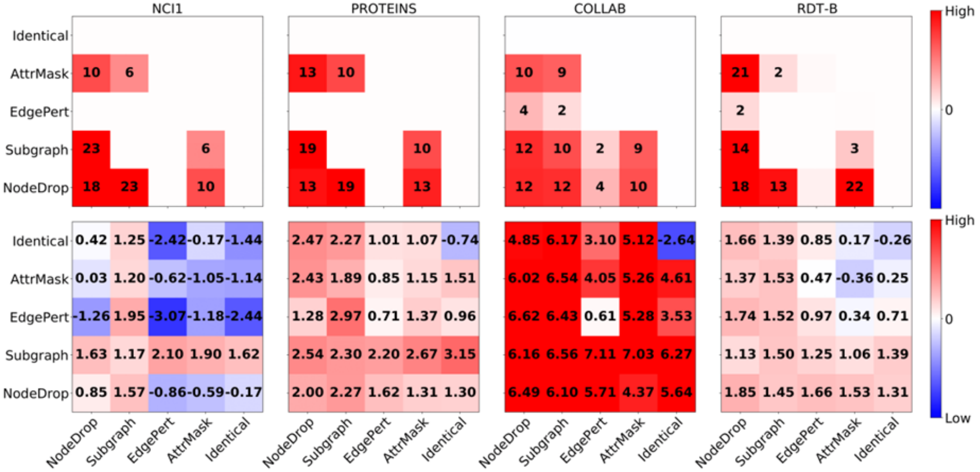


# Experiments on Various Graph Datasets

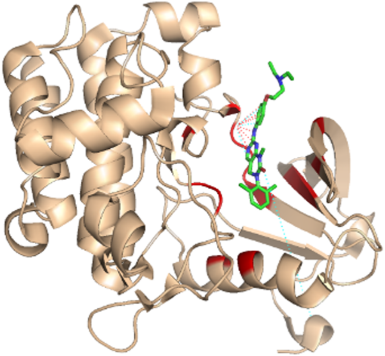
Learned Sampling Distribution




Downstream Performance

# Mst 3: Generalization more Complex Graph Data Structures

Graphs with Multi-Modal Features
[YS Bioinformatics'22]



Protein-Ligand Interaction Prediction

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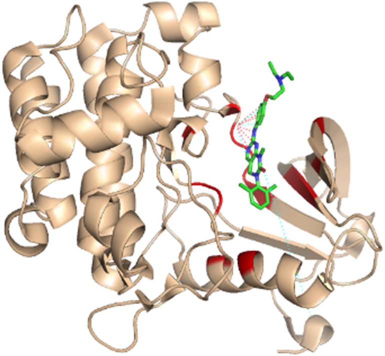

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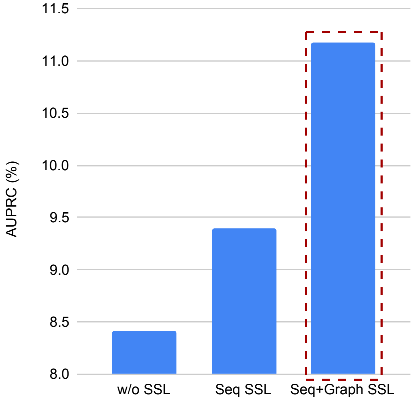
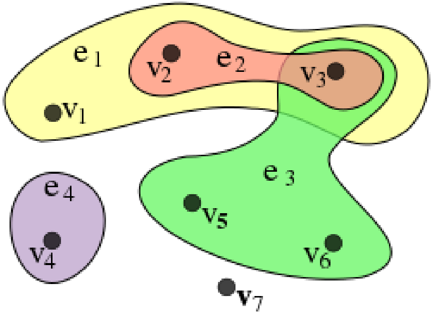



How to synergize sequence and structure representation learning?

# Mst 3: Generalization more Complex Graph Data Structures

Graphs with Many-Body Interactions
[WYCSHW NeurIPS'22]



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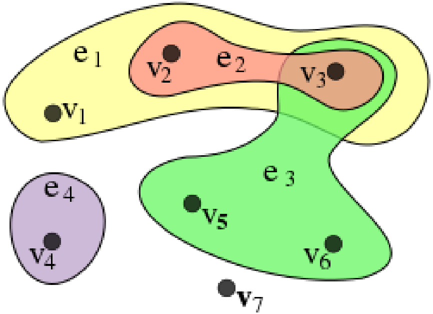


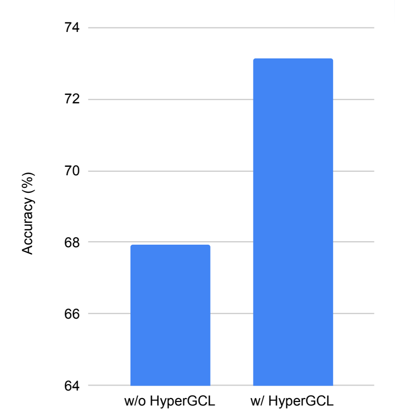


How to construct contrastive views for hypergraphs in representation learning?

# Conclusions for Msts 1-3

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- Our methods are applied to applications of molecular property prediction, gene interaction prediction, protein-ligand interaction prediction, and etc.

# Overview of Ph.D. Research Accomplishments

- Overall goal: Improving AI model generalization on unseen (biomed.) graph data.
- Milestone 1: Discriminative model generalization on few-shot/out-of-distributed homogeneous graphs (*ICML'20, NeurIPS'20, ICLR'23*);
- Milestone 2: Discriminative model generalization across graph datasets of heterogeneous semantics (*ICML'21 long presentation, WSDM'22*);
- Milestone 3: Discriminative model generalization on scarce labelled and more complex graph data structures of multi-model featured graphs & hypergraphs (*Bioinformatics'22, NeurIPS'22*);
- Milestone 4: Generative model generalization on spatial graphs of new conditions and time-series with graph features at unmeasured time stamps (*ICLR'24, preprint*);
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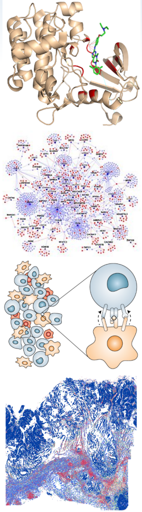
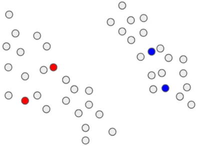
# Generalizable Graph AI is Demanded in Biomedical Modeling

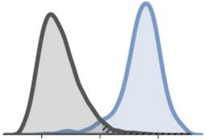


## Real-World Biomed. Generalization Challenges

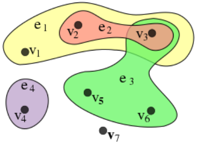
Few-Shot



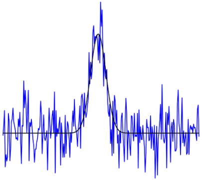
OOD

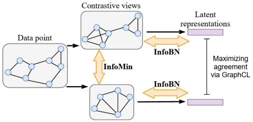


Heterogeneous

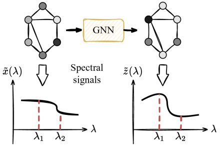



Noisy

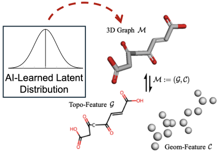




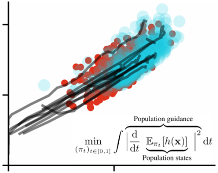

GraphCL




GNN SpecReg



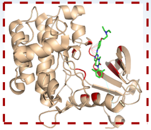

LDM-3DG

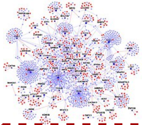


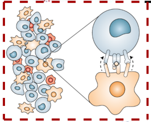

CLSB

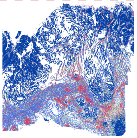
## Foundational Graph AI Solutions

# Generalizable Graph AI is Demanded in Biomedical Modeling



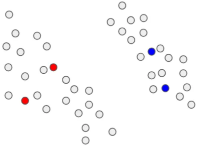




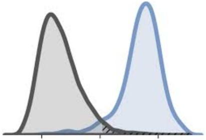


## Real-World Biomed. Generalization Challenges

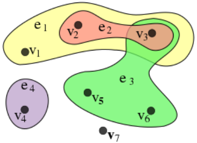
Few-Shot



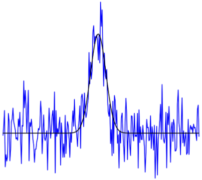
OOD

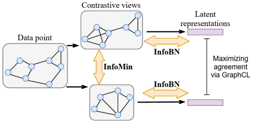


Heterogeneous

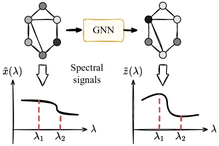



Noisy

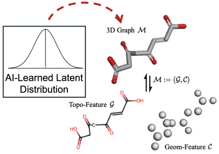




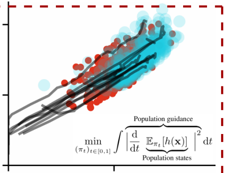

GraphCL




GNN SpecReg




LDM-3DG




CLSB

## Foundational Graph AI Solutions

# **Mst 4:** Generative Model Generalization on Graph Data

Example Task: Discovering Small-Molecule Drugs Binding Well to Protein Target

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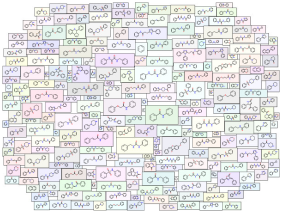
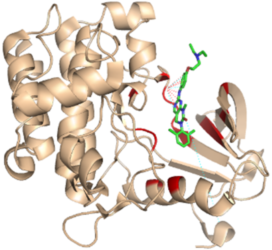
Discriminative Model:
Screening from Candidates



Candidates from
$> 10^{60}$ Molecules



Predicting Affinity

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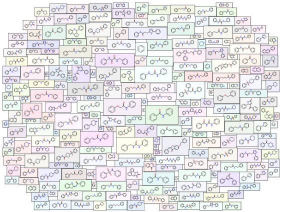

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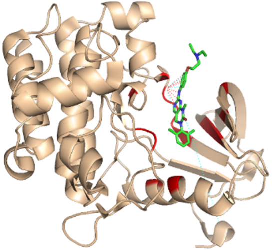
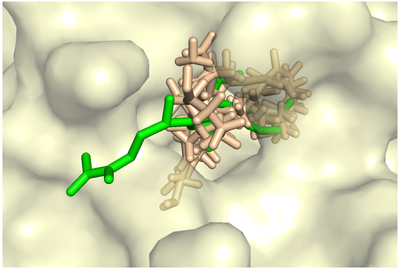


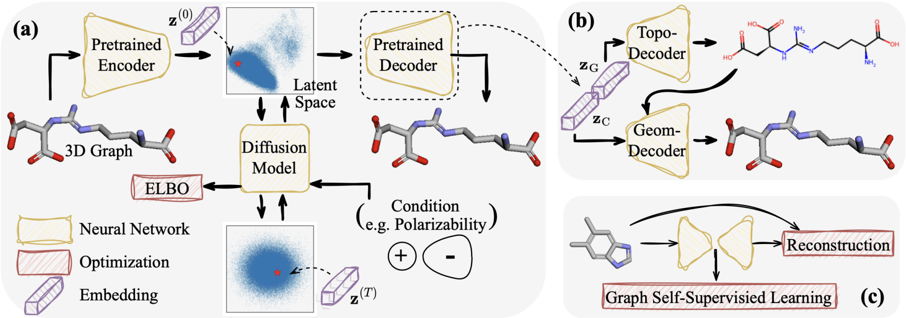
Predicting Affinity

Generative Model:
Exploring beyond Candidates



Conditional Generation

# Data-Driven Graph SSL Benefits Spatial Graph Generation



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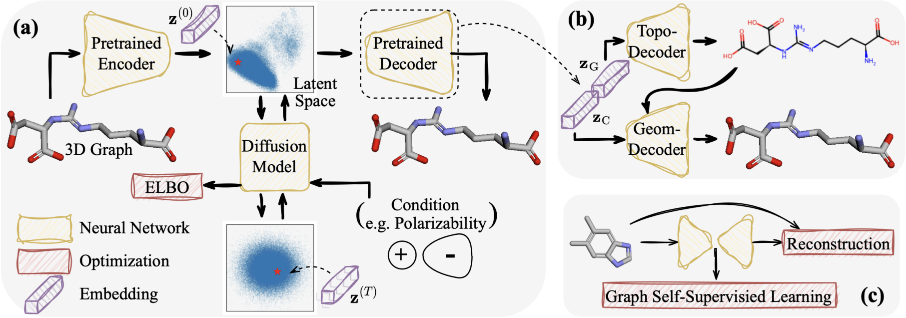
- Latent generative model for graphs ($\overrightarrow{f}_\theta, \overleftarrow{f}_\theta, q_\phi$):



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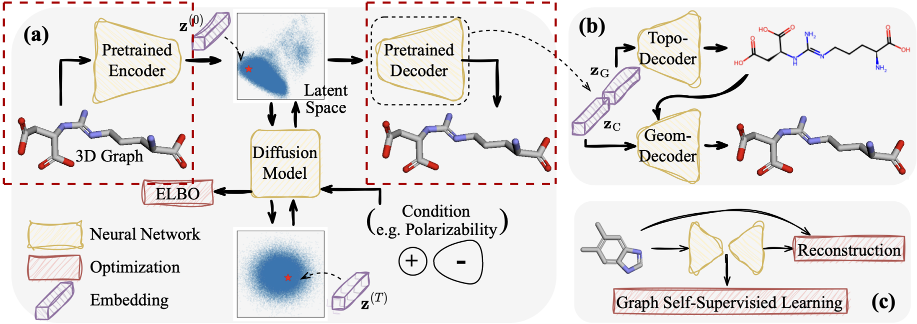
- Latent generative model for graphs $(\overrightarrow{f}_\theta, \overleftarrow{f}_\theta, q_\phi)$:
  - Auto-encoding for graphs: $\min_\theta \frac{1}{m}\sum_{i=1}^{m} L_{\text{rec}}\left(\overleftarrow{f}_\theta(\overrightarrow{f}_\theta(G_{\text{comp}}^{(i)})), G_{\text{comp}}^{(i)}\right)$;



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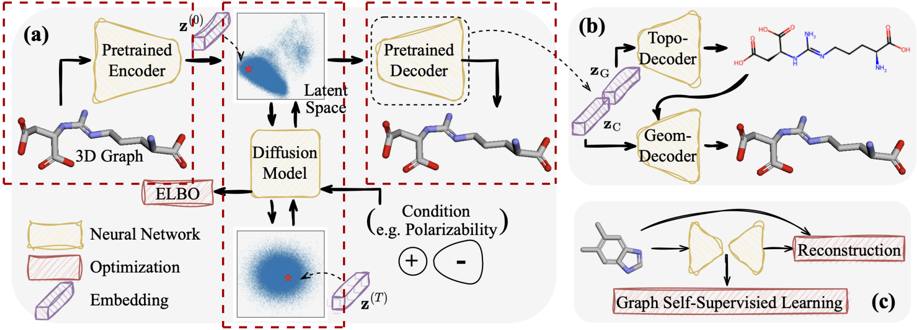
  - Diffusion generative modeling: $z_{\text{comp}} = \overrightarrow{f}_\theta(G_{\text{comp}})$, $\min_\phi -\frac{1}{m}\sum_{i=1}^{m} \log q_\phi(z^{(i)}_{\text{comp}} | G^{(i)}_{\text{prot}})$.



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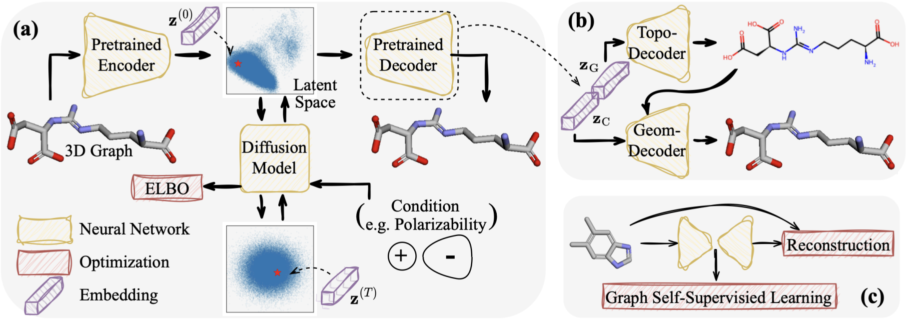

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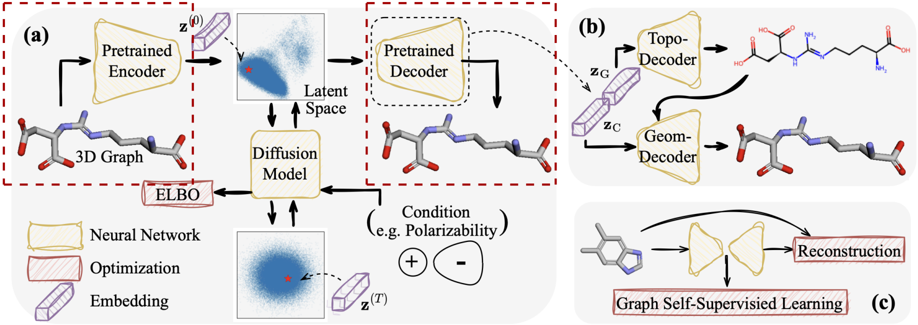

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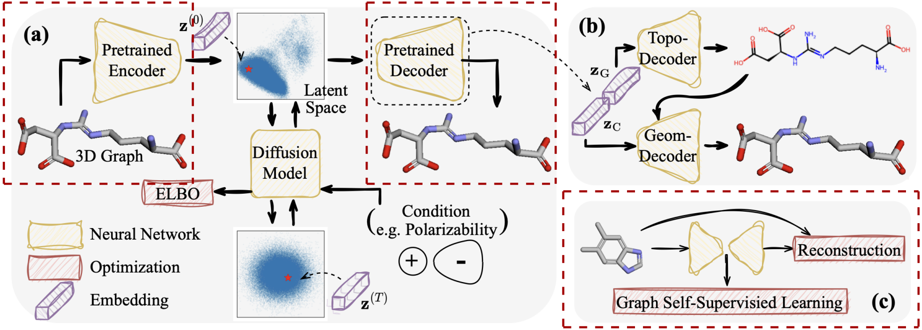
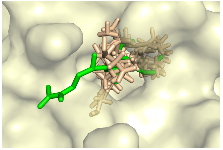
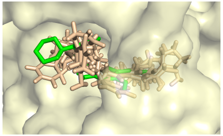
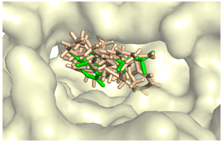


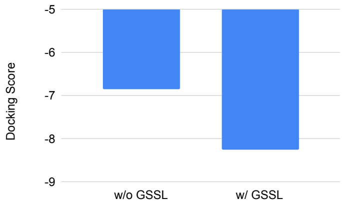
# Experiments on 3D Molecule Generation

Protein Target-Conditioned Gen. [FMSISK'20]









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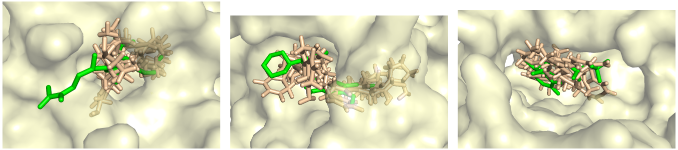
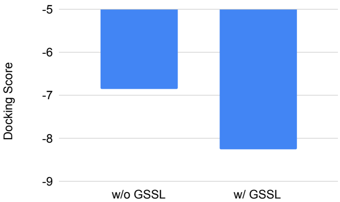
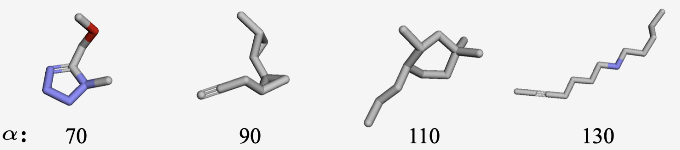
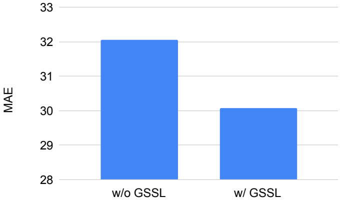


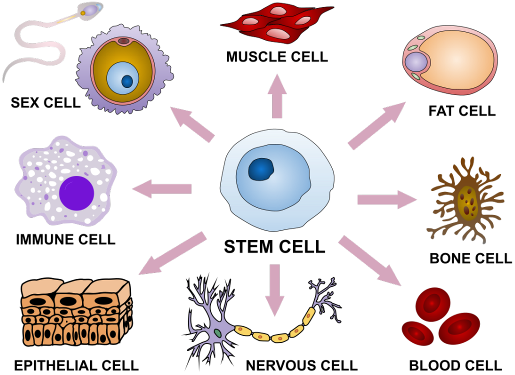



## Quantum Property-Conditioned Gen. [RDRL'14]



# Principled CorrReg Benefits Dynamics Simulation




Cell Development

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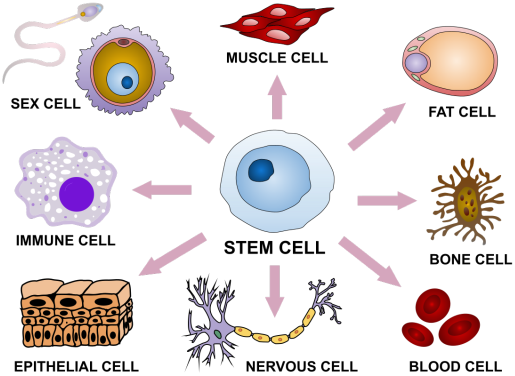


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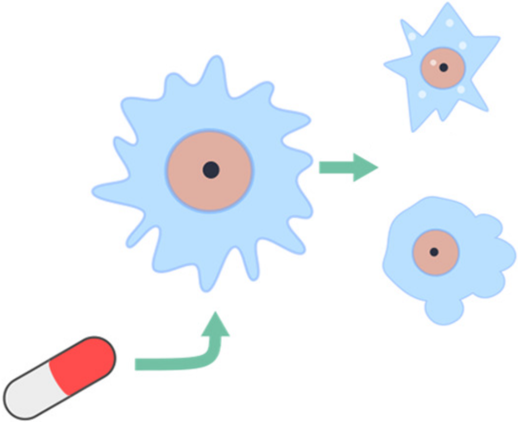
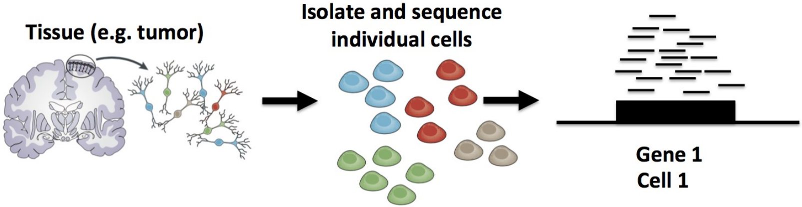


Cellular Responses to Drugs

# Advanced Biotech Enables AI Modeling of Cellular Dynamics

scRNA-seq



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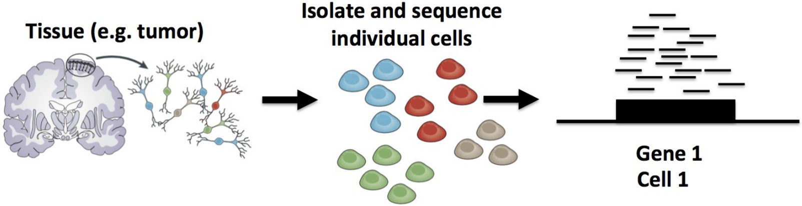


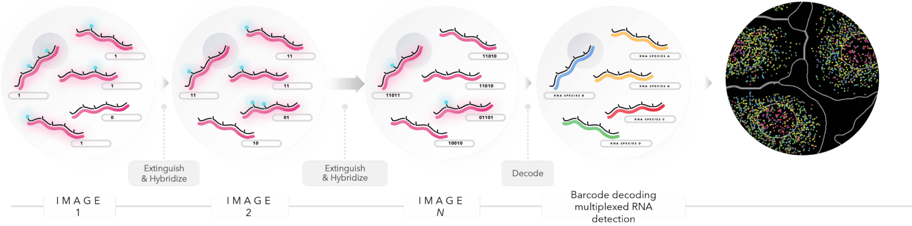


MERFISH

# Modeling Cellular Dynamics via Diffusion Generative Models

- $(\mathbf{x}_t)_{t\in[0,1]}$ obeys certain stochastic differential equation (SDE):

$$\mathrm{d}\mathbf{x}_t = \underbrace{\boldsymbol{f}_t(\mathbf{x}_t)}_{\text{Drift}}\,\mathrm{d}t + \underbrace{\boldsymbol{G}_t(\mathbf{x}_t)}_{\text{Diffusion}}\,\mathrm{d}\mathbf{w}_t;$$

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- Ind. 2. $(p_t)_{t\in[0,1]}$ satisfies the Fokker–Planck equation:

$$\frac{\partial}{\partial t}p_t(\boldsymbol{x}) = \underbrace{-\nabla\cdot\Big(p_t(\boldsymbol{x})\boldsymbol{f}_t(\boldsymbol{x})\Big)}_{\text{Evolution due to Drift}} + \underbrace{\frac{1}{2}\Big(\nabla\nabla^\top\Big)\bullet\Big(p_t(\boldsymbol{x})\boldsymbol{G}_t(\boldsymbol{x})\boldsymbol{G}_t^\top(\boldsymbol{x})\Big)}_{\text{Evolution due to Diffusion}}.$$

# Prior Work: Generative Modeling via Trajectory Alignment

- Parametrizing the dynamic with $\boldsymbol{v}_{t;\theta}(\cdot), \boldsymbol{\Sigma}_{t;\theta}(\cdot)$ for $\boldsymbol{f}_t(\cdot), \boldsymbol{G}_t(\cdot)$, respectively;

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$$\min_{\theta} \frac{1}{s-1} \sum_{i=1}^{s-1} \mathrm{KL}(\pi_{t_i,t_{i+1}} || p_{t_i,t_{i+1}}), \quad \text{s.t.} \quad \pi_{t_i} = p_{t_i}, i \in \{1, ..., s\};$$

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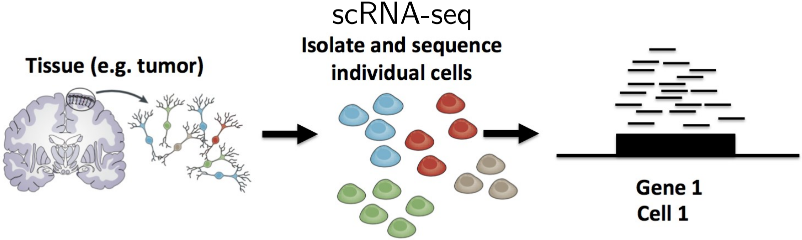
- BUT, $p_{t_i,t_{i+1}}$ could be not accessible for single-cell sequencing data;

# Single-Cell Sequencing Measure is Destructive

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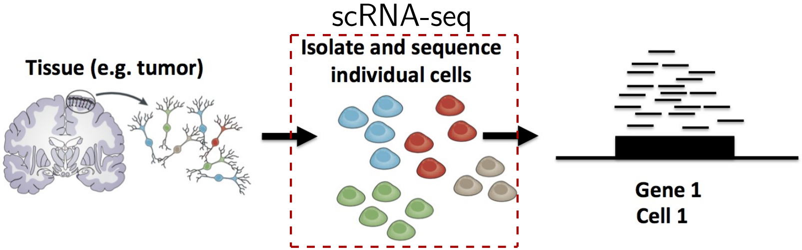


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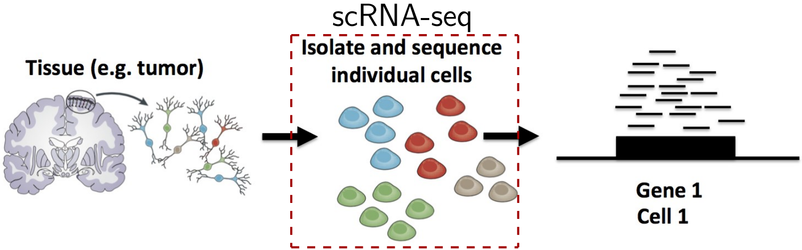


- BUT, $p_{t_i,t_{i+1}}$ could be not accessible for single-cell sequencing data;
- Sampling from the marginal distributions that $\boldsymbol{x}_{t_1} \sim p_{t_1}, \ldots, \boldsymbol{x}_{t_s} \sim p_{t_s}$.

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- Lagrangian Schrödinger bridge:

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where $\quad L_{\text{ind}}(\pi_t, h) = \overbrace{\mathbb{E}_{\pi_t}}^{\text{Application to all particles}} \Big[ \overbrace{\Big| \frac{\mathrm{d}}{\mathrm{d}t} \underbrace{h(\mathbf{x}_t)}_{\text{Individual state}} \Big|^2}^{\text{Regularization}} \Big], \quad h(\cdot)$ is domain-specific;

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- Principle of least action: $L_{\text{ind}}(\pi_t, h) = \mathbb{E}_{\pi_t}[|\boldsymbol{v}_{t;\theta}(\mathbf{x}_t)|^2]$;

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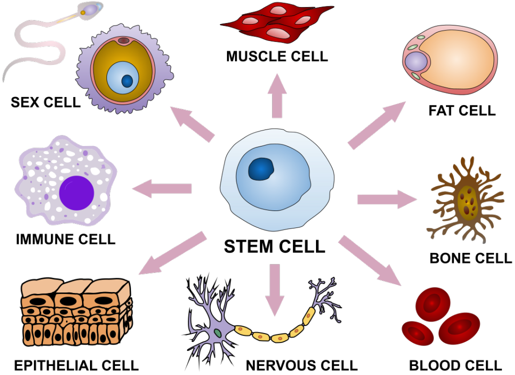


Intrinsic biodiversity exists in biosystems

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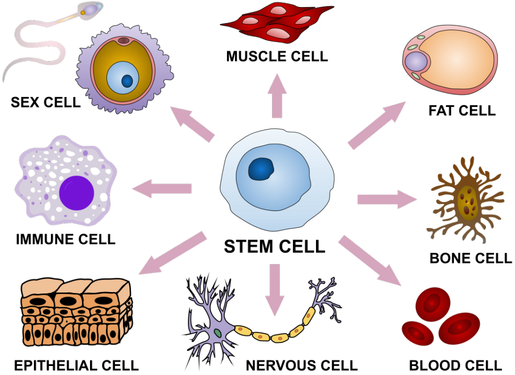


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- While requesting simulated individuals behave similarly by regularizing:

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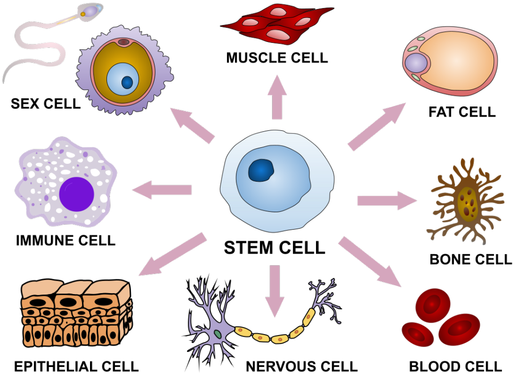


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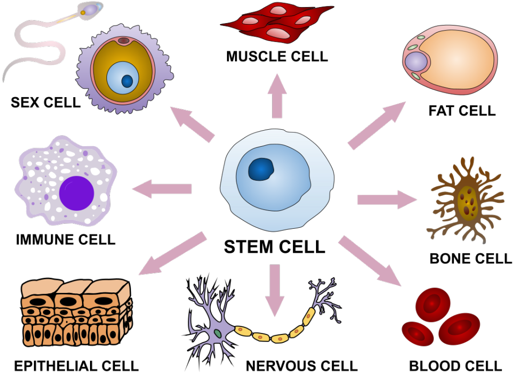


Intrinsic biodiversity exists in biosystems

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$$\overbrace{\mathbb{E}_{\pi_t}}^{\text{Application to all particles}} \overbrace{\left[\left|\frac{\mathrm{d}}{\mathrm{d}t} \underbrace{h(\mathbf{x}_t)}_{\text{Individual state}}\right|^2\right]}^{\text{Regularization}};$$

- Disregarding the heterogeneity in biological systems [THWDK'20].

# Generative Modeling with Population-Level Regularization

- Individual-level regularizer: $L_{\mathsf{ind}}(\pi_t, h) = \overbrace{\mathbb{E}_{\pi_t}}^{\text{Application to all particles}} \overbrace{\left[ \left| \frac{\mathrm{d}}{\mathrm{d}t} \underbrace{h(\mathbf{x}_t)}_{\text{Individual state}} \right|^2 \right]}^{\text{Regularization}}$;

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- Principle of least action at the population level.

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- Correlation in biosystems $\rightarrow$ Genetic co-expression, or regulation relations;
- Genetic regulatory mechanisms are robust in a lot of scenarios.

# Analytical Expression of Correlational Regularizer

- Correlational regularizer: $L_{\mathsf{corr}}(\pi_t, \widetilde{\mathcal{M}}, k) = \left| \frac{\mathrm{d}^k}{\mathrm{d}t^k} \mathbb{E}_{\pi_t} [\prod_{(j,m) \in \widetilde{\mathcal{M}}} (\mathrm{x}_{t,[j]})^m] \right|^2$;

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$$\frac{\partial}{\partial t}\pi_t(\boldsymbol{x}) = -\nabla \cdot \Big(\pi_t(\boldsymbol{x})\boldsymbol{v}_{t;\theta}(\boldsymbol{x})\Big) + \frac{1}{2}\Big(\nabla\nabla^\top\Big) \bullet \Big(\pi_t(\boldsymbol{x})\boldsymbol{\Sigma}_{t;\theta}(\boldsymbol{x})\boldsymbol{\Sigma}_{t;\theta}^\top(\boldsymbol{x})\Big),$$

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we derive (Proposition):

$$\begin{aligned} L_{\textsf{corr}}(\pi_t, \widetilde{\mathcal{M}}, 1) = \Big|&\mathbb{E}_{\pi_t}[\nabla\Big(\prod_{(j,m)\in\widetilde{\mathcal{M}}}(\mathrm{x}_{t,[j]})^m\Big)\cdot\boldsymbol{v}_t(\mathbf{x}_t)] \\ &+\frac{1}{2}\mathbb{E}_{\pi_t}[(\nabla\nabla^\top\Big(\prod_{(j,m)\in\widetilde{\mathcal{M}}}(\mathrm{x}_{t,[j]})^m\Big))\bullet(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))]\Big|^2. \end{aligned}$$

# Domain-Informed Instantiations of Correlational Regularizer

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- Instantiation 1. Regularizer on the "velocity" of covariance:

$$\sum_{\widetilde{\mathcal{M}}\in\mathcal{M}_{\mathsf{cov}}} L_{\mathsf{corr}}(\pi_t, \widetilde{\mathcal{M}}, 1) = \left\|\frac{\mathrm{d}}{\mathrm{d}t}\mathbb{E}_{\pi_t}[\mathbf{x}_t\mathbf{x}_t^\top]\right\|_{\mathsf{F}}^2$$

$$= \left\|\mathbb{E}_{\pi_t}[\mathbf{x}_t\boldsymbol{v}_t(\mathbf{x}_t)^\top + \boldsymbol{v}_t(\mathbf{x}_t)\mathbf{x}_t^\top + \frac{1}{2}\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t)]\right\|_{\mathsf{F}}^2.$$

# Domain-Informed Instantiations of Correlational Regularizer

- Instantiation 2. Regularizer on the "acceleration" of covariance:

# Domain-Informed Instantiations of Correlational Regularizer

$$
\begin{aligned}
&\sum_{\widetilde{\mathcal{M}}\in\mathcal{M}_{\mathsf{cov}}} L_{\mathsf{corr}}(\pi_t,\widetilde{\mathcal{M}},2) = \left\|\frac{\mathrm{d}^2}{\mathrm{d}t^2}\mathbb{E}_{\pi_t}[\mathbf{x}_t\mathbf{x}_t^\top]\right\|_{\mathsf{F}}^2 \\
&= \Bigg\|\mathbb{E}_{\pi_t}\Big[\mathbf{x}_t(\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{v}_t(\mathbf{x}_t))^\top + (\frac{\mathrm{d}}{\mathrm{d}t}\boldsymbol{v}_t(\mathbf{x}_t))\mathbf{x}_t^\top + \frac{1}{2}\frac{\mathrm{d}}{\mathrm{d}t}(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))\Big] \\
&\quad + \mathbb{E}_{\pi_t}\Big[\mathbf{x}_t(\nabla\boldsymbol{v}_t(\mathbf{x}_t)\boldsymbol{v}_t(\mathbf{x}_t))^\top + (\nabla\boldsymbol{v}_t(\mathbf{x}_t)\boldsymbol{v}_t(\mathbf{x}_t))\mathbf{x}_t^\top + 2\boldsymbol{v}_t(\mathbf{x}_t)\boldsymbol{v}_t(\mathbf{x}_t)^\top \\
&\quad + \frac{1}{2}\nabla(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))_{\underline{i_1i_2i_3}}\boldsymbol{v}_t^{\underline{i_3}}(\mathbf{x}_t)\Big] + \mathbb{E}_{\pi_t}\Big[\nabla\boldsymbol{v}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t) \\
&\quad + \boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t)\nabla^\top\boldsymbol{v}_t(\mathbf{x}_t) + \frac{1}{2}\mathbf{x}_t(\nabla\nabla^\top(\boldsymbol{v}_t(\mathbf{x}_t))_{\underline{i_1i_2i_3}}(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))^{\underline{i_2i_3}})^\top \\
&\quad + \frac{1}{2}(\nabla\nabla^\top(\boldsymbol{v}_t(\mathbf{x}_t))_{\underline{i_1i_2i_3}}(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))^{\underline{i_2i_3}})\mathbf{x}_t^\top \\
&\quad + \frac{1}{4}\nabla\nabla^\top(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))_{\underline{i_1i_2i_3i_4}}(\boldsymbol{\Sigma}_t(\mathbf{x}_t)\boldsymbol{\Sigma}_t^\top(\mathbf{x}_t))^{\underline{i_3i_4}}\Big]\Bigg\|_{\mathsf{F}}^2.
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- Denoting the observed co-expression as $\boldsymbol{Y} \in [0,1]^{d\times d}$ where $\boldsymbol{Y}_{[i,j]}$ is the confidence score of genes $i$ and $j$ being co-expressing;
- The regularizer is then instantiated as:

$$\sum\nolimits_{\widetilde{\mathcal{M}}\in\mathcal{M}_{\mathsf{cov}}} L_{\mathsf{corr}}(\pi_t, \widetilde{\mathcal{M}}, 0) = U\Big(\mathbb{E}_{\pi_t}[\mathbf{x}_t\mathbf{x}_t^\top], \boldsymbol{Y}\Big).$$

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$$\min_{\theta} \frac{1}{(s-1)} \sum_{i=1}^{s-1} \Big( L_{\mathsf{dist}}(\pi_{t_{i+1}}, \hat{p}_{t_{i+1}}) + \alpha_{\mathsf{ind}} \frac{1}{d} \sum_{j=1}^{d} \int_{t_i}^{t_{i+1}} L_{\mathsf{ind}}(\pi_t, j, 1)\mathrm{d}t$$

$$+ \sum_{k=0}^{2} \alpha_{\mathsf{corr},k} \frac{1}{|\mathcal{M}_{\mathsf{cov}}|} \sum_{\widetilde{\mathcal{M}} \in \mathcal{M}_{\mathsf{cov}}} \int_{t_i}^{t_{i+1}} L_{\mathsf{corr}}(\pi_t, \widetilde{\mathcal{M}}, k)\mathrm{d}t \Big);$$

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$$
\begin{aligned}
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& + \sum_{k=0}^{2} \alpha_{\mathsf{corr},k} \frac{1}{|\mathcal{M}_{\mathsf{cov}}|} \sum_{\widetilde{\mathcal{M}} \in \mathcal{M}_{\mathsf{cov}}} \int_{t_i}^{t_{i+1}} \underbrace{\boxed{L_{\mathsf{corr}}(\pi_t, \widetilde{\mathcal{M}}, k)}}_{\text{Population Regularizer}} \mathrm{d}t \Bigg);
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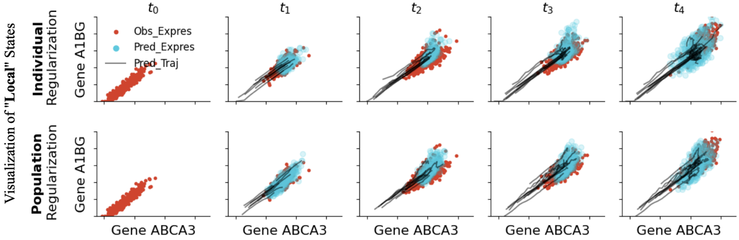
- Parametrizing drug treatments $\boldsymbol{c}$ with GNNs.

# Experiments on Stem Cell Dynamics Simulation

## Stem Cell Development Simulation [MDWIWK'19]



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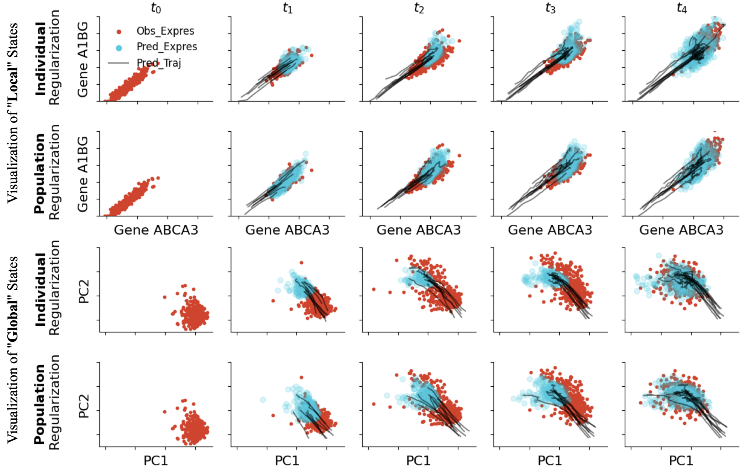

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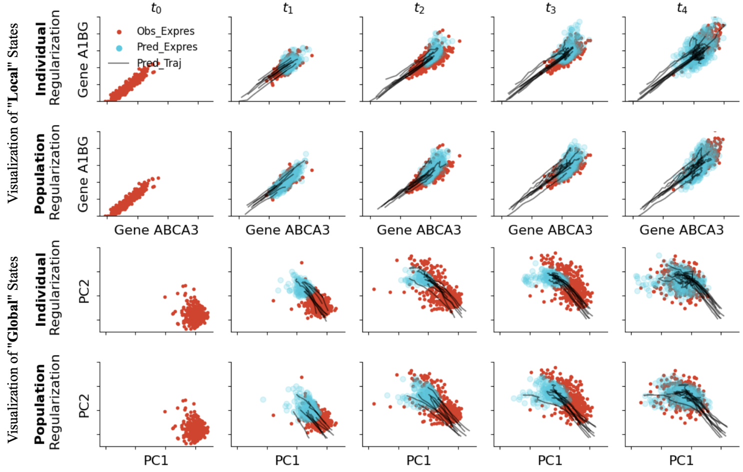


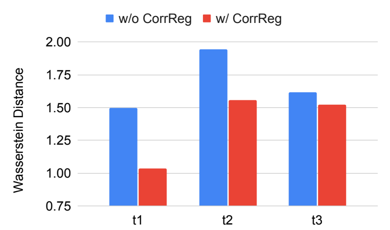

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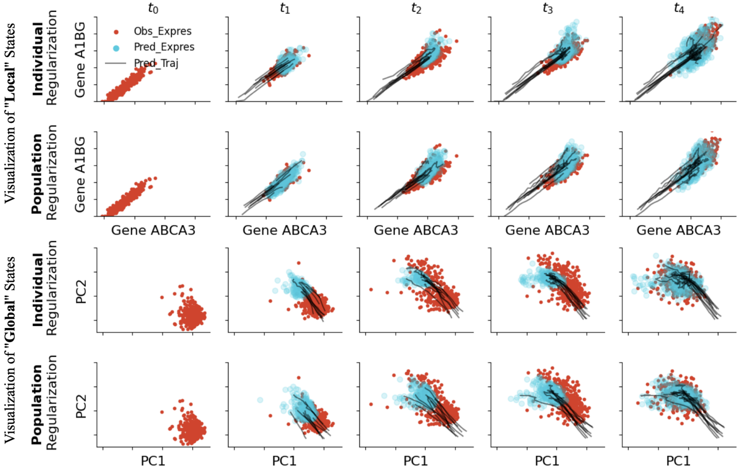
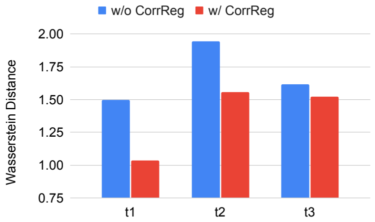
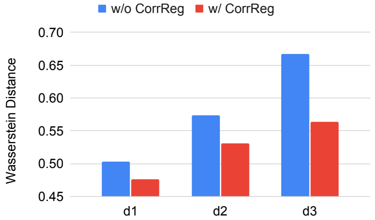
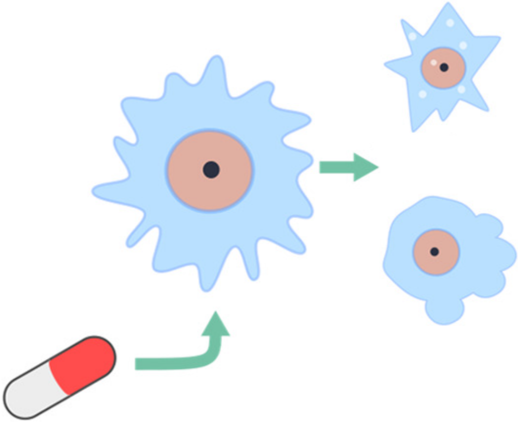



## Conditional Generation



# Mst 5: Interpretable Gen. Model Generalization on Graph Data



Cellular Responses to Drugs

- Problem setup extent from [YZS'24]:

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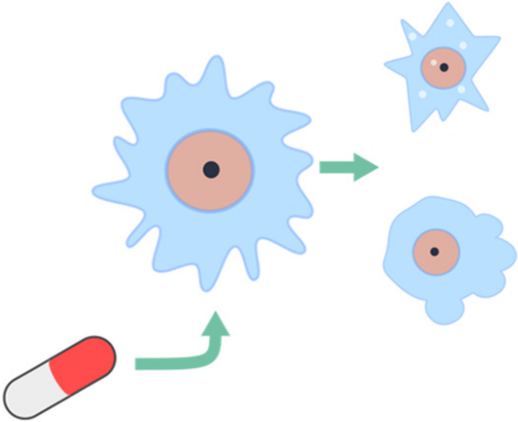

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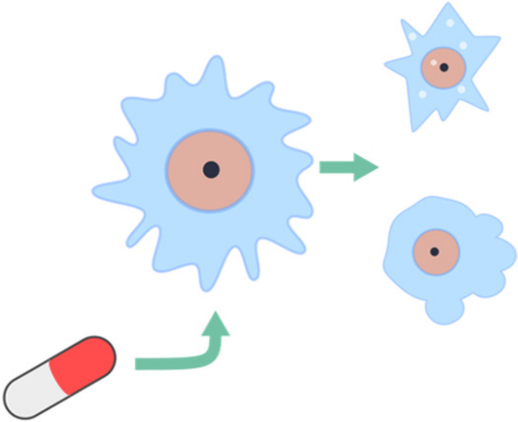

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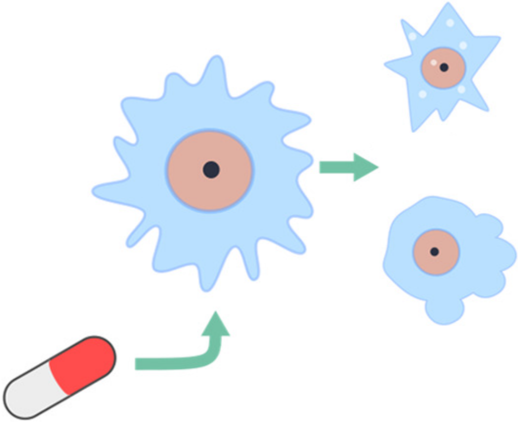

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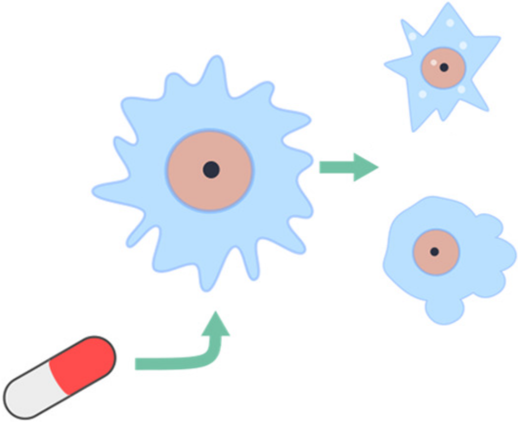

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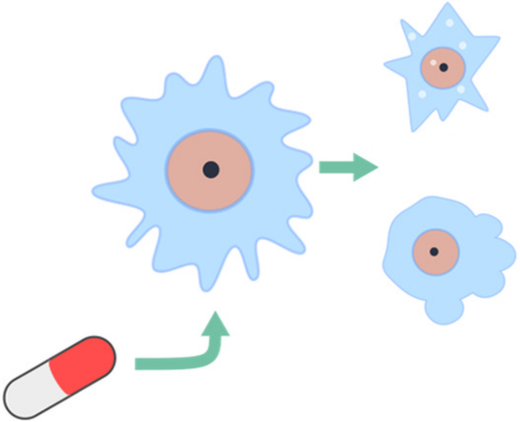

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- Very useful for drug discovery.

# New Task: Generative and Interpretable Dynamics Modeling

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  - Unperturbed expressions $\{\mathbf{x}_0^{(1)}, ..., \mathbf{x}_0^{(n)}\}$, $\mathbf{x}_0 \in \mathbb{R}^d_{\geq}$;
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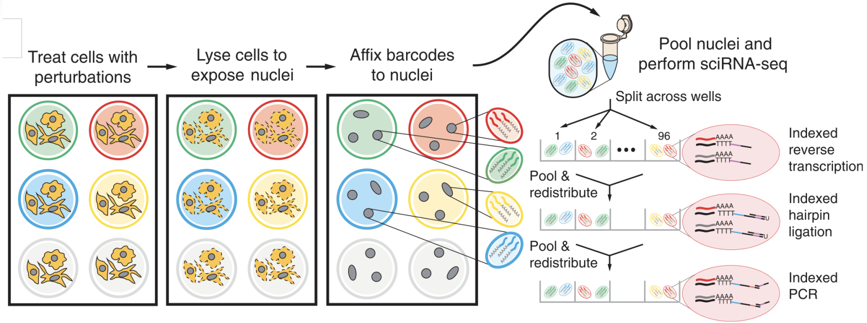
# New Task: Generative and Interpretable Dynamics Modeling

- Model inputs:
  - Unperturbed expressions $\{\mathbf{x}_0^{(1)}, ..., \mathbf{x}_0^{(n)}\}$, $\mathbf{x}_0 \in \mathbb{R}^d_{\geq}$;
  - Drug condition $\mathbf{c}$;
- Ground-truth:
  - Perturbed expressions $\{\mathbf{x}_1^{(1)}, ..., \mathbf{x}_1^{(\hat{n})}\}$;
  - Drug targets $\mathbf{m}_0 \in \{0, 1\}^d$;
- Model outputs $(\hat{\mathbf{x}}_1, \hat{\mathbf{m}}_0) = \mathrm{Model}(\mathbf{x}_0, \mathbf{c})$ that
  - Predicts the accurate perturbed expression that minimizes $\mathrm{WD}(\hat{\mathbf{x}}_1, \mathbf{x}_1)$ (Wasserstein);
  - Predicts the target genes that minimizes $\mathrm{BCE}(\hat{\mathbf{m}}_0, \mathbf{m}_0)$ (binary cross entropy).

# Dataset: sci-Plex Single-Cell Perturb-Seq × ChEMBL MOA

sci-Plex: High-throughput Perturb-Seq dataset at single-cell scale



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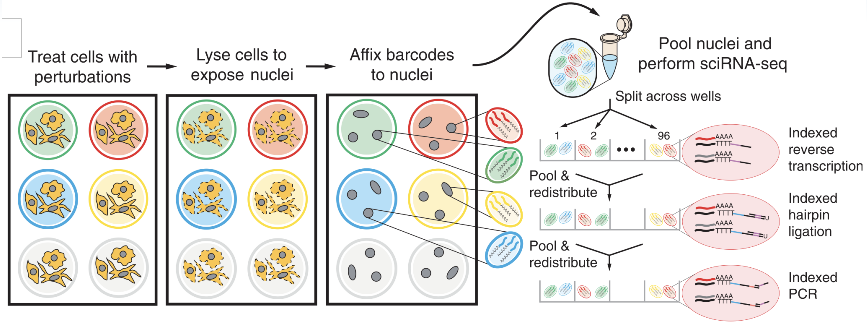


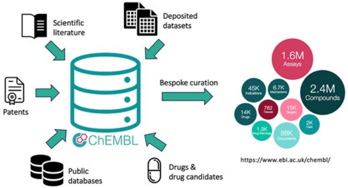


ChEMBL: Drug target gene cross-reference

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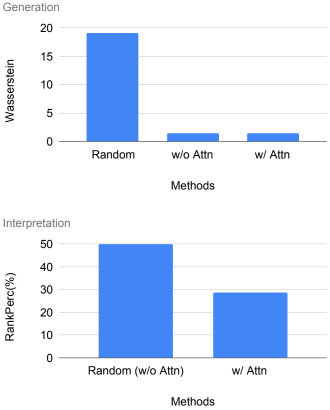


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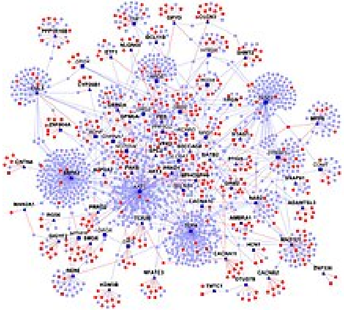

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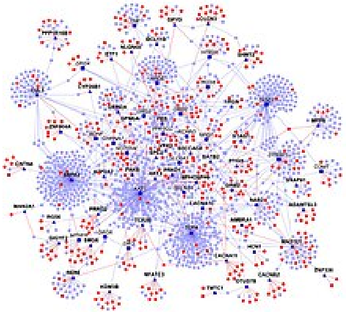

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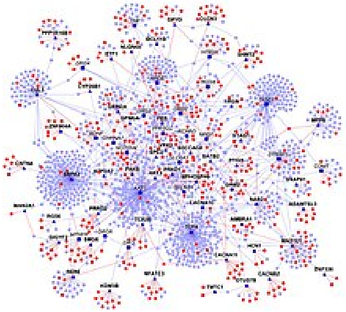

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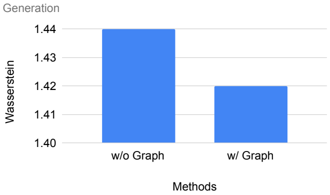


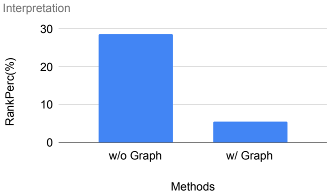


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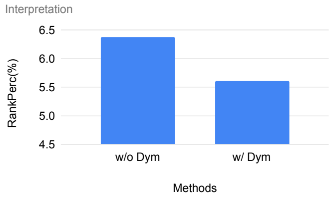


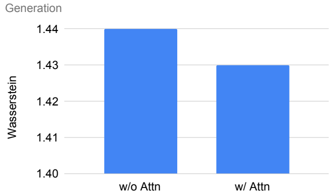

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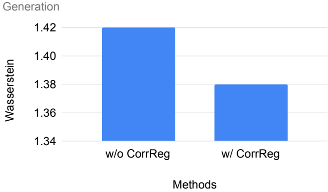


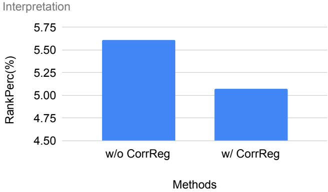

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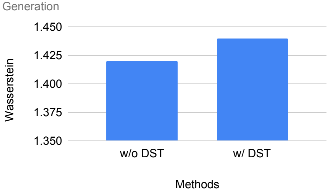


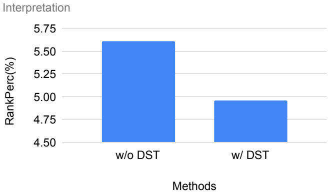

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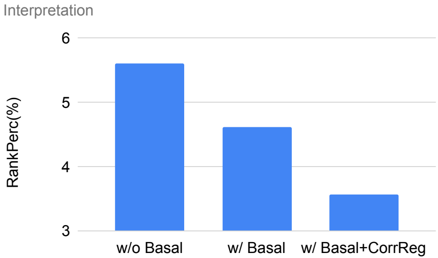


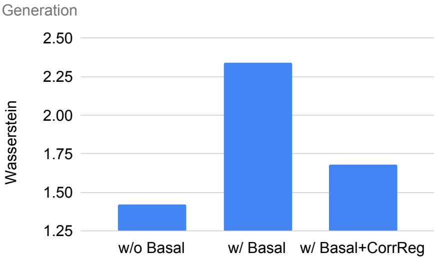

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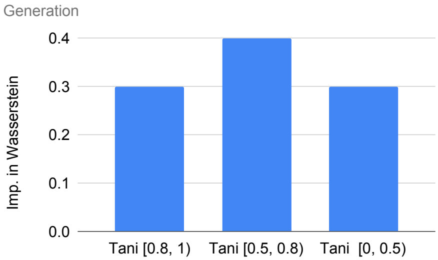
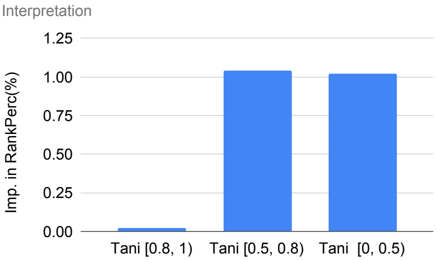
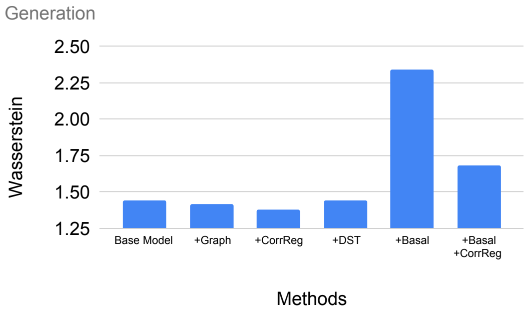
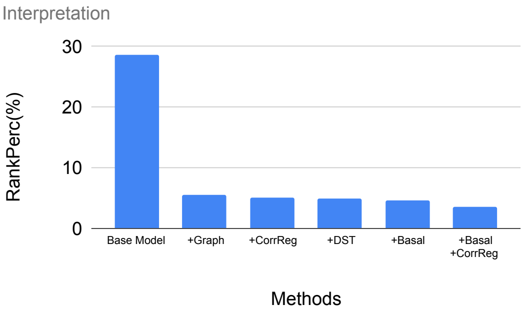


# Summary of Results



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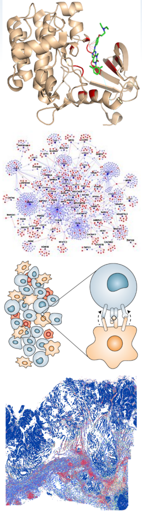
- Our methods are applied to applications of 3D molecule design, stem-cell differentiation simulation, drug perturbation effect prediction, and etc.

# Overview of Ph.D. Research Accomplishments

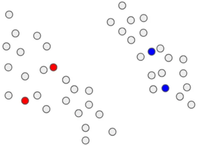
- Overall goal: Improving AI model generalization on unseen (biomed.) graph data.
- Milestone 1: Discriminative model generalization on few-shot/out-of-distributed homogeneous graphs (*ICML'20, NeurIPS'20, ICLR'23*);
- Milestone 2: Discriminative model generalization across graph datasets of heterogeneous semantics (*ICML'21 long presentation, WSDM'22*);
- Milestone 3: Discriminative model generalization on scarce labelled and more complex graph data structures of multi-model featured graphs & hypergraphs (*Bioinformatics'22, NeurIPS'22*);
- Milestone 4: Generative model generalization on spatial graphs of new conditions and time-series with graph features at unmeasured time stamps (*ICLR'24, preprint*);
- Milestone 5: Interpretable generative model generalization on time-series with graph features of new conditions (*draft*).

# Generalizable Graph AI is Demanded in Biomedical Modeling

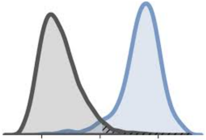


## Real-World Biomed. Generalization Challenges

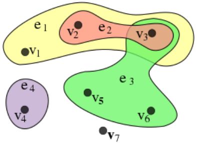
Few-Shot



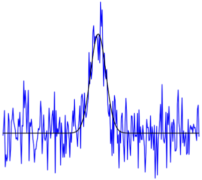
OOD

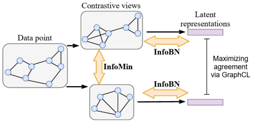


Heterogeneous

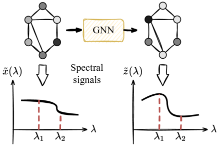



Noisy

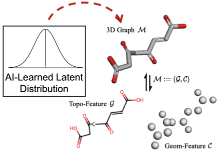




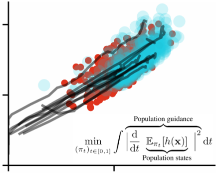

GraphCL




GNN SpecReg




LDM-3DG




CLSB

## Foundational Graph AI Solutions

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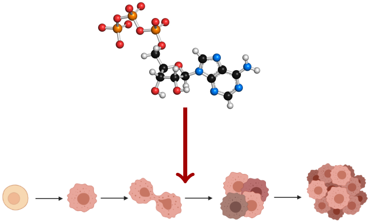

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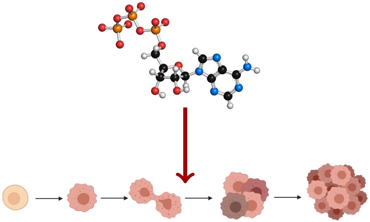
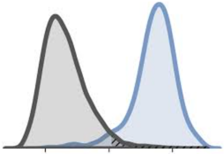
Learning on Multi-Modal &
Heter. (MMH) Graphs

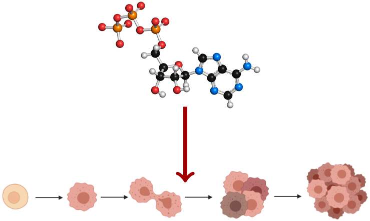


NN Generalization on
MMH Graphs:
Representation, Generation,
Interpretation

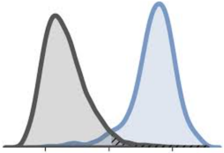


# Uprising Field of Interdisciplinary Research, and Way to Go!

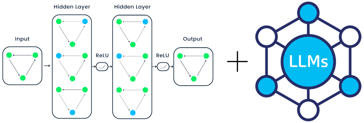
Molecular Modeling $\rightarrow$ System Modeling: Learning on Multi-Modal & Heter. (MMH) Graphs



NN Generalization on MMH Graphs: Representation, Generation, Interpretation

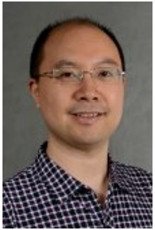


Human-in-the-Loop: Incorporation of LLMs with GNNs



# Acknowledgement

Yang Shen



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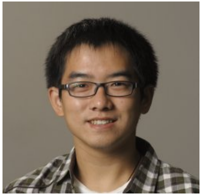

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Ruida Zhou

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# Acknowledgement


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Thank You! Q&A