ChemicalX: A Deep Learning Library for Drug Pair Scoring

Turing Workshop on Open-Source AI Software for Healthcare

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The presentation covers ideas and results from:

A Unified View of Relational Deep Learning for Drug Pair Scoring. Rozemberczki et al. IJCAI 2022.

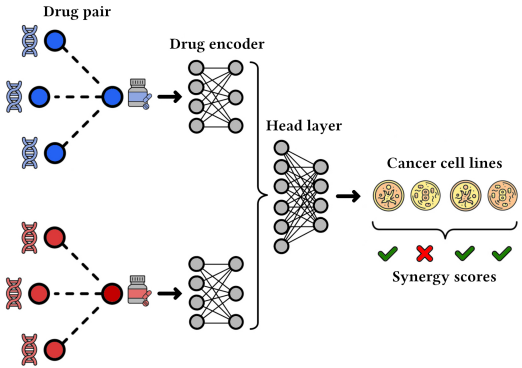
ChemicalX: A Deep Learning Library for Drug Pair Scoring. Rozemberczki et al. KDD 2022.

MOOMIN: Deep Molecular Omics Network for Anti-Cancer Drug Combination Therapy. Rozemberczki et al. CIKM 2022.

1. Drug Pair Scoring
2. A System for Repurposing
3. Experimental Results
4. Conclusions

Drug Pair Scoring

What is drug pair scoring?



- The drug pair scoring task
- Motivation
  - Timelines
  - Material costs (assays)
  - Labour costs
  - Tractability
- Application domains - tasks
  - Interaction
  - Polypharmacy side effect
  - Synergy
- Multi-objective optimization

How do we represent drugs in drug pair scoring?

Let $G = (\mathcal{V}, \mathcal{R}, \mathcal{E})$ be a heterogeneous biological graph with drug entities $\mathcal{D} \subset \mathcal{V}$.

1. **Molecular - low level encoders:**

$$\mathbf{h}^d = f_{\Theta_D}(\mathcal{M}^d)$$

2. **Systems biology based - high level encoders:**

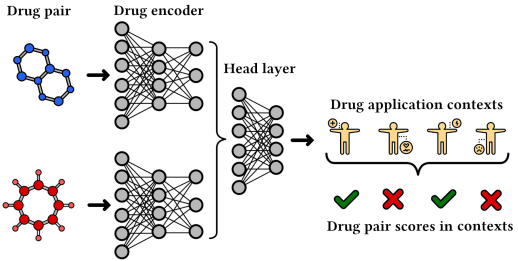
$$\mathbf{h}^d = \text{AGGREGATE}(\{\Theta^u, \forall u \in \mathcal{N}(d)\})$$

3. **Hierarchical encoders (structure and systems view):**

$$\mathbf{h}^d = \text{AGGREGATE}(\{f_{\Theta_D}(\mathcal{M}^u), \forall u \in \mathcal{N}(d)\})$$

				Entity Types			Drug Features			
Task	Method	Model view	Induction	Drug	Protein	Disease	SMILES	Graph	Geometry	Generic
Polypharmacy	DECAGON	Higher		•	•					
	KBLRN	Higher		•	•					
	SDHINE	Higher		•	•	•				
	ESP	Higher		•	•					
	MHCADDI	Lower	•					•		
	TIP	Higher		•	•					
Interaction	DeepCCI	Lower	•				•			•
	MVGAE	Hierarchical	•	•	•	•	•			
	DeepDDI	Lower	•				•			
	D^3I	Hierarchical		•						•
	MR-GNN	Lower	•					•		
	SkipGNN	Higher		•	•	•				
	CASTER	Lower	•				•			
	DeepDrug	Lower	•				•	•	•	
	GoGNN	Hierarchical		•				•		
	DPDDI	Lower	•							•
	KGNN	Higher		•	•	•				
	BiGNN	Hierarchical	•	•	•			•		
	MIRACLE	Hierarchical	•	•				•		
	EPGCN-DS	Lower	•							
	SumGNN	Higher		•	•	•				
	DANN-DDI	Higher		•	•					
	SSI-DDI	Lower						•		
	MTDDI	Hierarchical		•	•	•				•
	MUFFIN	Hierarchical		•	•	•	•			
	DDIAAE	Higher		•	•	•				
	RWGCN	Higher		•	•	•				
	SmileGNN	Hierarchical		•	•		•			
	GCN-BMP	Lower	•	•			•			

Why molecule level models?



- Induction
- Attribution (explanation)
- Pre-training
- Transfer learning
- Structural ablation

How do we represent biological contexts and score pairs?

Given $\mathcal{C}$ a set of biological contexts the representation of $c \in \mathcal{C}$ is:

$$\mathbf{h}_c = f_{\Theta_C}(\mathbf{x}_c).$$

We score the pair $d, d' \in \mathcal{D}$ in the context $c \in \mathcal{C}$ with:

$$\widehat{\mathbf{y}}^{d,d',c} = f_{\Theta_H}(\mathbf{h}^d, \mathbf{h}^{d'}, \mathbf{h}^c).$$

The loss for the pair in the context is defined as:

$$\ell_{d,d',c} = \ell(\widehat{\mathbf{y}}^{d,d',c}, \mathbf{y}^{d,d',c}).$$

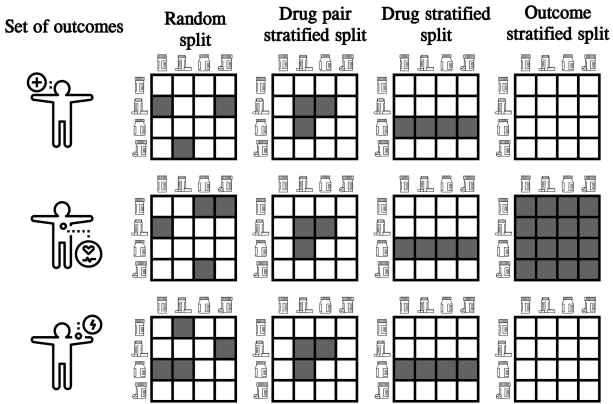
The parametric functions $f_{\Theta_D}(\cdot)$, $f_{\Theta_C}(\cdot)$, and $f_{\Theta_H}(\cdot)$ can be trained jointly by minimizing the cost accumulated from data point level losses.

How do we conceptualize these models?

Data: $\mathcal{X}_{\mathcal{D}}$ - Drug feature set.
$\mathcal{X}_{\mathcal{C}}$ - Context feature set.
$\mathcal{B}$ - Labeled drug pair - context batch.
Result: $\mathcal{L}$ - The cost for the batch.

$\mathcal{L} \leftarrow 0$
for $(d, d', c, y^{d,d',c}) \in \mathcal{B}$ **do**
  $\mathbf{h}^{d} \leftarrow f_{\Theta_D}(\mathbf{x}^{d}, \mathcal{G}^{d}, \mathbf{X}_N^{d}, \mathbf{X}_E^{d})$ // Compute drug representation for $d \in \mathcal{D}$.
  $\mathbf{h}^{d'} \leftarrow f_{\Theta_D}(\mathbf{x}^{d'}, \mathcal{G}^{d'}, \mathbf{X}_N^{d'}, \mathbf{X}_E^{d'})$ // Compute drug representation for $d' \in \mathcal{D}$.
  $\mathbf{h}^{c} \leftarrow f_{\Theta_C}(\mathbf{x}^{c})$ // Compute context representation for $c \in \mathcal{C}$.
  $\widehat{y}^{d,d',c} \leftarrow f_{\Theta_H}(\mathbf{h}^{d}, \mathbf{h}^{d'}, \mathbf{h}^{c})$ // Score based on the representations.
  $\mathcal{L} \leftarrow \mathcal{L} + \ell(y^{d,d',c}, \widehat{y}^{d,d',c})$ // Add loss to the accumulated cost.
end

How do we design evaluation regimes?



	Evaluation metric					
Model	AUPRC	AUROC	Precision	Recall	Accuracy	F_1
DECAGON	•	•	•			
KBLRN	•	•	•			
SDHINE		•	•			
ESP	•	•	•			
MHCADDI		•				
TIP	•	•	•			
DeepCCI		•			•	•
MVGAE	•	•				
DeepDDI			•	•	•	•
D^3I			•	•	•	•
MR-GNN		•		•		•
SkipGNN	•					•
CASTER	•	•				•
DeepDrug	•	•				
GoGNN		•	•			
DPDDI	•	•	•	•	•	•
KGNN	•	•			•	•
BiGNN		•	•			•
MIRACLE	•	•				•
EPGCN-DS		•				•
SumGNN	•	•	•			•
DANN-DDI	•	•	•	•	•	•
SSI-DDI	•	•			•	
MTDDI	•	•	•	•	•	•
MUFFIN		•	•	•	•	•
DDIAAE	•	•	•			
RWGCN	•	•				
SmileGNN		•			•	•

A System for Repurposing

What is ChemicalX?

README.md

pypi package 0.1.0 | docs passing | codecov 95% | CI passing | ArXiv 2202.05240

Documentation | External Resources | Datasets | Examples

ChemicalX is a deep learning library for drug-drug interaction, polypharmacy side effect, and synergy prediction. The library consists of data loaders and integrated benchmark datasets. It also includes state-of-the-art deep neural network architectures that solve the drug pair scoring task. Implemented methods cover traditional SMILES string based techniques and neural message passing based models.

https://github.com/AstraZeneca/chemicalx/

How did you engineer it?

- Documentation
- Unit and integration tests with coverage reports
- Tutorials
- Example datasets
- Continuous integration
- Linting, type hinting and docstrings

What are the competitors of ChemicalX?

Library	Year	Backend	Drug Domain	Pair Scoring
PyG [7]	2018	PT	✘	✘
DGL [24]	2019	PT/TF/MX	✘	✘
StellarGraph [5]	2019	TF	✘	✘
DeepChem [19]	2019	TF	✔	✘
CHChem [16]	2019	CH	✔	✘
Jraph [8]	2020	JAX	✘	✘
Spektral [9]	2020	TF	✘	✘
DIG [15]	2021	PT	✘	✘
TorchDrug [28]	2021	PT	✔	✘
CogDL [3]	2021	PT	✘	✘
TFG [10]	2021	TF	✘	✘
DGL-LS [13]	2021	PT	✔	✘
Our Work	2022	PT	✔	✔

What is included in ChemicalX?

Model	Year	Domain	Encoder
DeepDDI [20]	2018	Interaction	Feedforward
DeepSynergy [18]	2018	Synergy	Feedforward
MHCADDI [6]	2019	Polypharmacy	GAT
MR-GNN [25]	2019	Interaction	GCN
CASTER [12]	2019	Interaction	Feedforward
SSI-DDI [17]	2020	Interaction	GAT
EPGCN-DS [21]	2020	Interaction	GCN
DeepDrug [2]	2020	Interaction	GCN
GCN-BMP [4]	2020	Interaction	GCN
DeepDDS [23]	2021	Synergy	GCN or GAT
MatchMaker [1]	2021	Synergy	Feedforward

How do we load the dataset?

```python
from chemicalx.data import DrugCombDB, BatchGenerator

loader = DrugCombDB()

context_set = loader.get_context_features()
drug_set = loader.get_drug_features()
triples = loader.get_labeled_triples()

generator = BatchGenerator(batch_size=1024,
                           context_features=True,
                           drug_features=True,
                           drug_molecules=False,
                           context_feature_set=context_set,
                           drug_feature_set=drug_set,
                           labeled_triples=triples)
```

How do we train a model?

```
import torch
from chemicalx.models import DeepSynergy

model = DeepSynergy(context_channels=112,
                    drug_channels=256)

optimizer = torch.optim.Adam(model.parameters())
model.train()
loss = torch.nn.BCELoss()

for epoch in range(200):
    for batch in generator:
        optimizer.zero_grad()
        prediction = model(batch.context_features,
                           batch.drug_features_left,
                           batch.drug_features_right)
        loss_value = loss(prediction, batch.labels)
        loss_value.backward()
        optimizer.step()
```

How do we score a dataset with the model?

```python
import pandas as pd
from chemicalx.data import HAEM

model.eval()

loader = HAEM()

generator.labeled_triples = loader.get_labeled_triples()

predictions = []
for batch in generator:
    prediction = model(batch.context_features,
                       batch.drug_features_left,
                       batch.drug_features_right)
    prediction = prediction.detach().cpu().numpy()
    identifiers = batch.identifiers
    identifiers["prediction"] = prediction
    predictions.append(identifiers)
predictions = pd.concat(predictions)
```

How can you BYOD (Bring Your Own Data)?

Training and scoring for specific pairs would only need these things:

- Drug pairs with biological/chemical contexts and labels.
- Context set with context identifier keys and context feature vector values.
- Drug set with SMILES strings and molecule level features.

Checkout the following link for an example:

`https://github.com/AstraZeneca/chemicalx/tree/main/dataset/drugbankddi`

Experimental Results

What are the datasets integrated?

Table 1: Datasets available in ChemicalX in the domain of the pair scoring task and the number of drugs ($|\mathcal{D}|$), administration contexts ($|\mathcal{C}|$), and labeled triples ($|\mathcal{Y}|$).

Dataset	Task	$\lvert\mathcal{D}\rvert$	$\lvert\mathcal{C}\rvert$	$\lvert\mathcal{Y}\rvert$
TWOSIDES [22]	Polypharmacy	644	10	499,582
Drugbank DDI [20]	Interaction	1,706	86	383,496
DrugComb [26, 27]	Synergy	4,146	288	659,333
DrugCombDB [14]	Synergy	2,956	112	191,391
OncolyPharm [11]	Synergy	38	39	23,052

How about predictive performance?

Table 2: The predictive performance of (some) models in *ChemicalX* on TWOSIDES [22]. Feed-forward encoder based architectures are noted with a ■.

		AUROC	AUPR	F_1
DeepDDI [20]	■	$.929 \pm .001$	$.907 \pm .001$	$.848 \pm .009$
DeepSynergy [18]	■	$.940 \pm .001$	$.919 \pm .001$	$.887 \pm .001$
MR-GNN [25]		$.937 \pm .002$	$.917 \pm .001$	$.875 \pm .002$
SSI-DDI [17]		$.823 \pm .002$	$.800 \pm .003$	$.756 \pm .001$
EPGCN-DS [21]		$.855 \pm .003$	$.834 \pm .002$	$.785 \pm .004$
DeepDrug [2]	■	$.923 \pm .004$	$.904 \pm .002$	$.857 \pm .002$
GCN-BMP [4]		$.709 \pm .003$	$.694 \pm .002$	$.592 \pm .003$
DeepDDS [23]		$.915 \pm .002$	$.898 \pm .002$	$.839 \pm .003$
MatchMaker [1]	■	$.912 \pm .002$	$.892 \pm .001$	$.849 \pm .001$

How about training time?

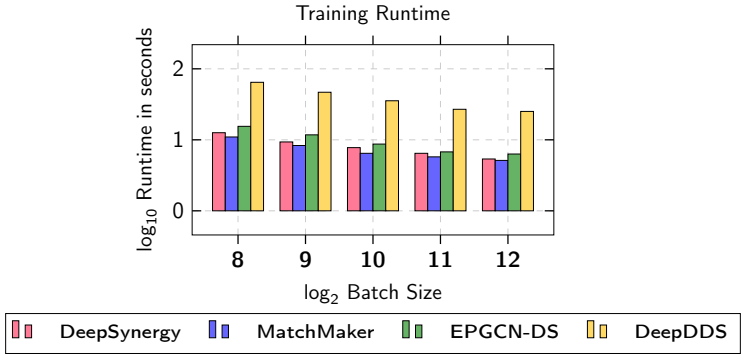


Figure 1: The average runtime of doing an epoch on DrugBankDDI [11].

How about inference time?

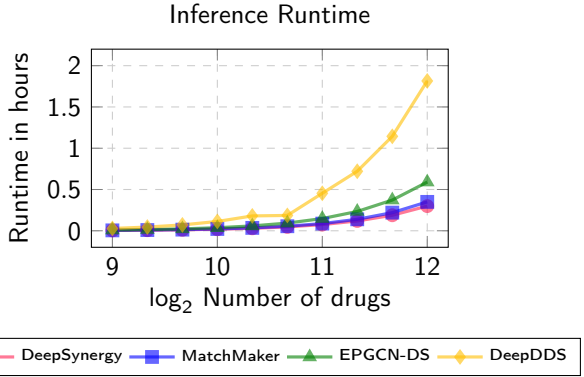


Figure 2: The average runtime of doing a scoring pass for all combinations in DrugBankDDI [11].

Conclusions

What are the main takeaways?

Having impact!

- ChemicalX is used for targeting haematological malignancies.
- Early oncology scientists in AstraZeneca are using ChemicalX self-service.

Having fun!

- Internal and external collaborations.
- Skills elevated for people in AZ who are not core machine learning.

What could be improved?

- Splits that take scaffolds into account.
- Geometric graph encoders.
- Scaling with locality sensitive hashing.

Thank you for the kind attention!

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