Supplemenatry Material of AACDR

Training Results of 100 Random Initializations of AACDR

We randomly initialized the AACDR model with the best hyperparameters 100 times, trained it, and then tested it on the **Expr Dataset**. The final results were divided into two parts, "Seen" and "Unseen", based on whether the drugs in the test entries appeared in the training set. The final results can be found on AACDR.

Results of 28 Different Hyperparameters of AACDR and PANCDR

We trained and tested 28 reasonable hyperparameters combinations of AACDR and PANCDR on the expr dataset. For each hyperparameters combination, to mitigate the impact of randomness, we performed 10 random initializations and recorded the mean AUC on the test set. The detailed results can be found on AACDR.

To Improve the OOD Problem

Through dual validation with the Kolmogorov-Smirnov test and the Mann-Whitney U test, we found that the gene expression profiles from PDX, cell lines, and cancer patients represent different distributions, as shown in Table 1

Table 1: The Result of OOD test.

$Domain_1$ - $Domain_2$	**Kolmogorov-Smirnov test**	**Mann-Whitney U test**
PDX - Cell Lines	701	646
PDX - Patients	702	657
PDX - Patients_Unlabeled	701	666
Cell Lines - Patients	699	665
Cell Lines - Patients_Unlabeled	701	684
Patients - Patients_Unlabeled	498	417

We conducted the analysis using data standardized by z-score. The numbers in the table

represent how many of the 702 selected genes are considered to have different distributions according to the corresponding detection methods.

How we make the PDX dataset for training and test

- Download the original data from Gao et al.[1].
- Convert FPKM value to TPM value and apply log2 transformation.
- Apply z-score normalized for each sample.
- Select 702 genes from the COSMIC Cancer Gene Census https://cancer.sanger.ac.uk/census)[2].
- Delete all recoreds which do not use single small molecule drugs.
- Treat "CR" and "PR" in the ResponseCategory as sensitive to the drug(labeled as 1), and "SD" and "PD" as resistant(labeled as 0).
- Use RDKit and DeepChem[3] to convert Isomeric SMILES into atom-level feature matrices and adjacency matrices. Then pad virtual node.
- All positive samples (labeled as 1) were placed into the test set as (PDX_gene expr, drug, label) entries.
- For negative samples, if the corresponding PDX appeared in the positive samples, the entry was also included in the test set, resulting in a test set consisting of 331 instances made up of 24 PDX models and 42 drugs (68 positive samples and 263 negative samples).
- Due to the limited size of the dataset, all PDX gene expression data were included in the training set as an unlabeled target domain dataset for transfer learning, totaling 399 gene expression values.

Here are all durgs and its Isomeric SMILES we found in Gao's data:

- **paclitaxel**:

  `CC1=C2[C@H](C(=O)[C@@]3([C@H](C[C@@H]4[C@]([C@H]3[C@@H]([C@@](C2(C)C)(C[C@@H]1OC(=O)[C@@H]([C@H](C5=CC=CC=C5)NC(=O)C6=CC=CC=C6)O)O)OC(=O)C7=CC=CC=C7)(CO4)OC(=O)C)O)C)OC(=O)C`

- **INC280**:

  `CNC(=O)C1=C(F)C=C(C=C1)C1=NN2C(CC3=CC4=C(C=C3)N=CC=C4)=CN=C2N=C1`

- **BGJ398**:

  `CCN1CCN(CC1)C2=CC=C(C=C2)NC3=CC(=NC=N3)N(C)C(=O)NC4=C(C(=CC(=C4Cl)OC)OC)Cl`

- **LEE011**:

  `CN(C)C(=O)C1=CC2=CN=C(N=C2N1C3CCCC3)NC4=NC=C(C=C4)N5CCNCC5`

- **CGM097**:

  `CC(C)OC1=C(C=C2CC(=O)N([C@H](C2=C1)C3=CC=C(C=C3)Cl)C4=CC=C(C=C4)N(C)CC5CCC(CC5)N6CCN(C(=O)C6)C)OC`

- **LGH447**:

  C[C@H]1C[C@H](C[C@H](C1)N)C2=C(C=NC=C2)NC(=O)C3=NC(=C(C=C3)F)C4=C(C=CC=C4F)F

- **LDE225**:

  C[C@@H]1CN(C[C@@H](O1)C)C2=NC=C(C=C2)NC(=O)C3=CC=CC(=C3C)C4=CC=C(C=C4)OC(F)(F)F

- **dacarbazine**:

  CN(C)/N=N/C1=C(NC=N1)C(=O)N

- **abraxane**:

  CC1=C2[C@H](C(=O)[C@@]3([C@H](C[C@@H]4[C@]([C@H]3[C@@H]([C@@](C2(C)C)(C[C@@H]1OC(=O)[C@@H]([C@H](C5=CC=CC=C5)NC(=O)C6=CC=CC=C6)O)O)OC(=O)C7=CC=CC=C7)(CO4)OC(=O)C)O)C)OC(=O)C

- **trametinib**:

  CC1=C2C(=C(N(C1=O)C)NC3=C(C=C(C=C3)I)F)C(=O)N(C(=O)N2C4=CC=CC(=C4)NC(=O)C)C5CC5

- **gemcitabine-50mpk**:

  C1=CN(C(=O)N=C1N)[C@H]2C([C@@H]([C@H](O2)CO)O)(F)FS

- **CLR457**:

  C[C@@H]1[C@@H](N(C(=O)O1)C2=NC(=NC(=C2)C3=CN=C(N=C3C(F)(F)F)N)N4CCOCC4)CO

- **erlotinib**:

  COCCOC1=C(C=C2C(=C1)C(=NC=N2)NC3=CC=CC(=C3)C#C)OCCOC

- **binimetinib**:

  CN1C=NC2=C1C=C(C(=C2F)NC3=C(C=C(C=C3)Br)F)C(=O)NOCCO

- **INC424**:

  C1CCC(C1)[C@@H](CC#N)N2C=C(C=N2)C3=C4C=CNC4=NC=N3

- **BKM120**:

  C1COCCN1C2=NC(=NC(=C2)C3=CN=C(C=C3C(F)(F)F)N)N4CCOCC4

- **LDK378**:

  CC1=CC(=C(C=C1C2CCNCC2)OC(C)C)NC3=NC=C(C(=N3)NC4=CC=CC=C4S(=O)(=O)C(C)C)Cl

- **BYL719**:

  CC1=C(SC(=N1)NC(=O)N2CCC[C@H]2C(=O)N)C3=CC(=NC=C3)C(C)(C)C(F)(F)F

- **5FU**:

  C1=C(C(=O)NC(=O)N1)F

- **encorafenib**:

  C[C@@H](CNC1=NC=CC(=N1)C2=CN(N=C2C3=C(C(=CC(=C3)Cl)NS(=O)(=O)C)F)C(C)C)NC(=O)OC

- **tamoxifen**:

  CC/C(=C(\C1=CC=CC=C1)/C2=CC=C(C=C2)OCCN(C)C)/C3=CC=CC=C3

- **HSP990**:
  `CC1=C2C(=NC(=N1)N)C[C@@H](NC2=O)C3=C(C=C(C=C3)F)C4=NC(=CC=C4)OC`
- **HDM201**:
  `CC(C)N1C2=C(C(=O)N([C@H]2C3=CC=C(C=C3)Cl)C4=CC(=CN(C4=O)C)Cl)N=C1C5=CN=C(N=C5OC)OC`
- **WNT974**:
  `CC1=CC(=CN=C1C2=CC(=NC=C2)C)CC(=O)NC3=NC=C(C=C3)C4=NC=CN=C4`

How we train on PDX dataset

For fairness, we trained the basic model and domain adaptation model for both PANCDR and MY on the prepared PDXdataset. We several reasonable combinations of hyperparameters to find the optimal hyperparameters for each method, and the specific results are shown in Table **??** and 2.

Table 2: The Result of Trainning on PDX Dataset without Domain Adaptation.

Model	Hyperparameters	AUC	ACC	Precision	Recall	F1
PANCDR-	128;100;0.0001;0.0001;0.01;128	0.5026	0.6737	0.2619	0.3235	0.2895
PANCDR-	128;100;0.0001;0.0001;0.01;256	0.5389	0.7583	0.3571	0.2206	0.2727
PANCDR-	128;100;0.0003;0.0003;0.01;256	0.4903	0.7372	0.3061	0.2206	0.2564
PANCDR-	128;100;0.0003;0.0003;0.01;128	0.4947	0.6314	0.2404	0.3676	0.2907
PANCDR-	128;128;0.0001;0.0001;0.01;256	0.5374	0.4048	0.2346	0.8382	0.3666
PANCDR-	128;128;0.0001;0.0001;0.01;128	0.5330	0.4532	0.2347	0.7353	0.3559
PANCDR-	128;128;0.0003;0.0003;0.01;128	0.4530	0.2749	0.2152	0.9559	0.3514
PANCDR-	128;128;0.0003;0.0003;0.01;256	0.5413	0.7372	0.3273	0.2647	0.2927
PANCDR-	128;100;0.0001;0.0001;0.02;128	0.5029	0.6737	0.2619	0.3235	0.3895
PANCDR-	128;100;0.0001;0.0001;0.02;256	0.5389	0.7583	0.3571	0.2206	0.2727
PANCDR-	128;128;0.0001;0.0001;0.02;128	0.5330	0.4532	0.2347	0.7353	0.3559
MY-	0.0003;768;0	0.5029	0.5377	0.2293	0.5294	0.3200
MY-	0.0003;512;0	0.5417	0.5045	0.2391	0.6471	0.3492
MY-	0.0001;512;0	0.5219	0.3353	0.2246	0.9112	0.3605
MY-	0.0001;768;0	0.4908	0.4532	0.2244	0.6765	0.3370
MY-	0.0003;512;0.2	0.4934	0.4985	0.2216	0.5735	0.3197
MY-	0.0001;512;0.2	0.5042	0.5650	0.2467	0.5441	0.3394
MY-	0.0001;768;0.2	0.4825	0.5347	0.2208	0.5	0.3063

References

[1] Hui Gao, Joshua M Korn, Stéphane Ferretti, John E Monahan, Youzhen Wang, Mallika Singh, Chao Zhang, Christian Schnell, Guizhi Yang, Yun Zhang, et al. High-throughput screening using patient-derived tumor xenografts to predict clinical trial drug response. *Nature medicine*, 21(11):1318–1325, 2015.

[2] John G Tate, Sally Bamford, Harry C Jubb, Zbyslaw Sondka, David M Beare, Nidhi Bindal, Harry Boutselakis, Charlotte G Cole, Celestino Creatore, Elisabeth Dawson, et al. Cosmic: the catalogue of somatic mutations in cancer. *Nucleic acids research*, 47(D1):D941–D947, 2019.

[3] Bharath Ramsundar, Peter Eastman, Pat Walters, and Vijay Pande. *Deep learning for the life sciences: applying deep learning to genomics, microscopy, drug discovery, and more.* " O'Reilly Media, Inc.", 2019.