Using Machine Learning Models to Accelerate Drug Discovery Process

Maheep Brar, Allen Chang, Sarah Firestone, Camille Goenawan, Zhixian Han, Christian Leidholm, Sean Lee, Hector Lozano Perez, Yazan Meqbil, Pratim Moulik, Imrul Shahriar, Rosalie Wilfong, Andres Urbina, Rohit Varansay, Keishi Vannithamby, Kyle Zheng

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ATOM

ATOM INTRODUCTION

- **ATOM:** Accelerating Therapeutics for Opportunities in Medicine
- Open public-private partnership for accelerating drug design using computation-driven drug design
- Use of computational modeling to speed up long drug discovery process
- Create machine learning models using AMPL software and tutorials that can learn from how different compounds interact with targets (opioid receptors, hERG, and histamine receptors)
- **Goals:**
  - Accelerate drug discovery process
  - Improve success rate in translation to patients
  - Transforming drug discovery from slow, high-failure process into rapid, patient-centric model

QUESTIONS

- Can we create multi-task models that learn across several protein targets?
- Are multi-task models better at predicting compounds than single-task models are?
- Can we find new makeable compounds that meet our design criteria?

Hypothesis

- Multi-task models are better at ranking compounds than single-task models.

MACHINE LEARNING VOCAB

- Single-task: train to do one task
- Multi-task: learn by training on multiple tasks, using similarities and differences to generalize better

RESEARCH METHODOLOGY

Fall 2021: Single-Task Models

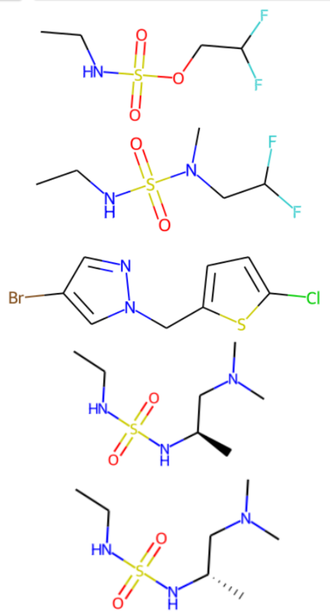
- **Split type**
  - Scaffold split
- **Model Selection**
  - Random forest
  - Graph convolutional neural network (GCNN)
- **Hyperparameter optimization**
  - Random search
  - Grid search
  - Bayesian search
  - Utilized these techniques to find hyperparameters that yielded the highest validation score

Spring 2022: Multi-Task Models

- **Split type**
  - Multi-task split (scaffold)
- **Model selection**
  - Graph convolutional neural network (GCNN)
- **Utilized SLURM**
  - Train models for increased efficiency
- **Hyperparameter optimization**
  - Added multiple layers (layer sizes)
  - Learning rate, early stop
- Compared single-task and multi-task models

ANALYSIS AND RESULTS

- Split into 3 teams:
- **Team 1:** Opioid Receptors
  - GCNN multi-task vs GCNN single-task:
    - Multi-task model has slightly higher testing (R^2 score) than the single task model
  - GCNN multi-task vs Random Forest single task:
    - Multi-task model still has slightly lower testing R^2 than the single task model
- **Team 2**: hERG
  - GCNN multi-task vs GCNN and Random Forest single-task:
    - Multi-task model has better testing R^2 scores for certain assays compared to the single-task model
    - *However, it has lower scores in other assays.
- **Team 3**: Histamine Inhibitors
  - GCNN multi-task vs GCNN and Random Forest single-task:
    - Trained on the highly correlated CHRM targets:
      - Multi-task model has better testing R^2 scores than our single task models for all five targets.
    - Trained on the HRH1, HTR2A, and DRD2 targets:
      - Multi-task GCNN model only performed better for HRH1.



Top 5 Compounds Identified by the Blood-Brain-Barrier Team Multi-task Model Calculated by the Cost-Score Function and Screening 924,890 SMILEs Strings.

CONCLUSIONS

- Our multi-task models did not surpass our single-task models in performance across the board.
- Identified new molecules for multi-task models by screening Enamine libraries.
- Overall, we cannot conclude with certainty whether multi-task models are better at predicting compounds in all cases.

FUTURE GOALS

- Further improve model performance
- Continue model testing on holdout datasets

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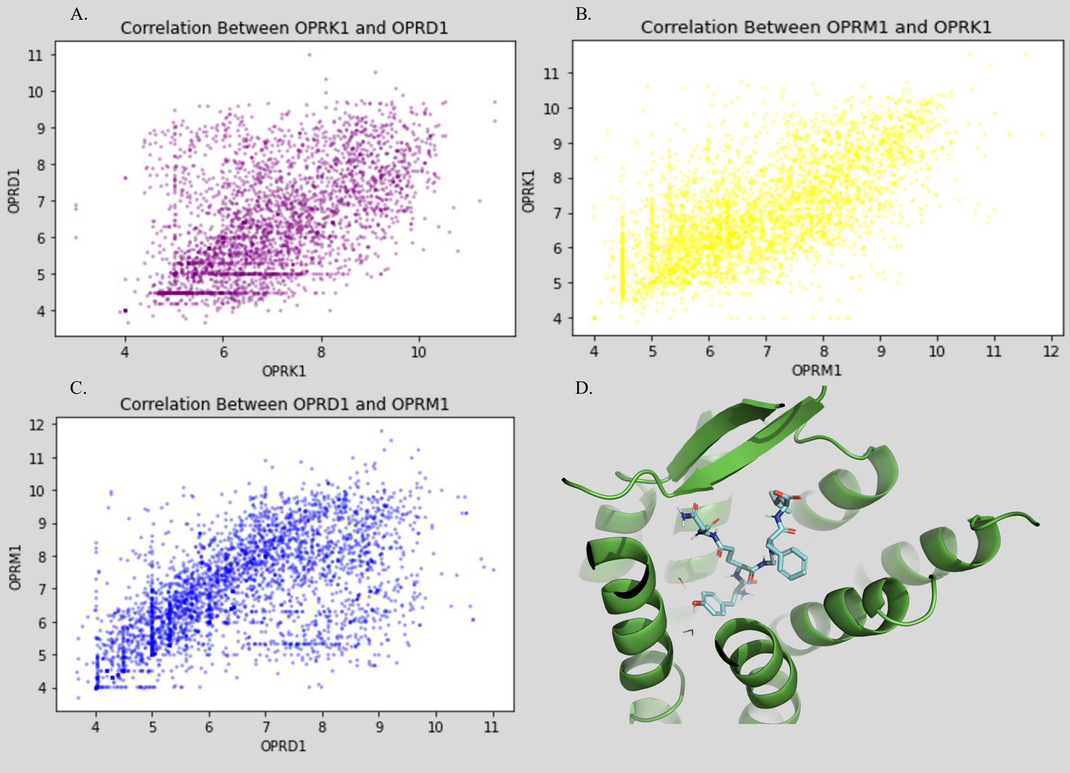
Team 1

	Single Task Random Forest	Single Task GCNN		Multitask GCNN	
Opioid Receptor	Validation	Validation	Testing	Validation	Testing
OPRD1	0.76	0.71	0.56	0.73	0.60
OPRK1	0.66	0.59	0.60	0.58	0.61
OPRM1	0.73	0.69	0.66	0.71	0.65

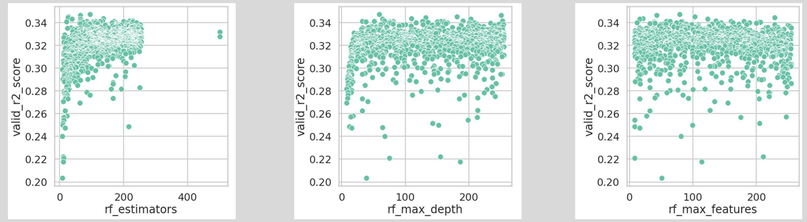


Correlational plots between pIC50 values for the three opioid receptor targets. **A.** OPRK1 vs. OPRD1 **B.** OPRM1 vs. OPRK1 **C.** OPRD1 vs. OPRM1 **D.** Docking pose for the highest scoring compound docked into the delta opioid receptor (OPRD1).

Team 2

DBA = Displacement binding
PCA = Patch clamp
TFA = Thallium flux

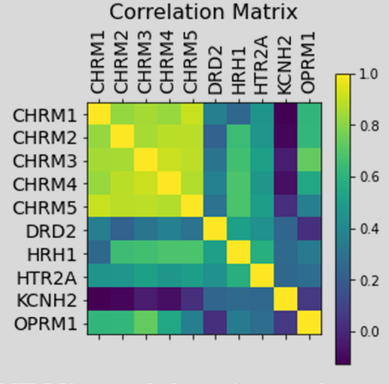
Single Task Random Forest Parameters



HERG Overall Results

Tasks	Testing r^2			
	RF Single-Task	GCNN Single-Task (5 layers)	GCNN Multi-Task (5 layers)	Multi-Task Delta
DBA	0.47	0.42	0.42	-0.05
PCA	0.25	0.33	0.38	+0.05
TFA	-0.04	-0.17	0.44	+0.48
Other	0.36	0.41	0.32	-0.05

Team 3



Virtual Screening with MT machine learning model

compound_id	H1 (>9)	M2 (<5)	hERG (<5)	cost
compound_026981	9.3	4.8	4.9	-1.81
compound_005764	9.2	4.1	4.3	-1.46
compound_251713	9.2	5.5	4.9	-1.29
compound_067674	9.2	4.5	4.2	-1.28
compound_067675	9.2	4.5	4.2	-1.28

MT-ML model performs better for HRH1

Target	Single Task Model (test_r^2_score)	Multitask Model (test_r^2_score)
HRH1	0.410	0.493
HTR2A	0.462	0.378
DRD2	0.405	0.370

MT-ML model performs better for all the CHRM receptors

Target	Single Task Model (test_r^2_score)	Multitask Model (test_r^2_score)
CHRM1	0.185	0.394
CHRM2	0.308	0.389
CHRM3	0.354	0.518
CHRM4	0.198	0.305
CHRM5	0.345	0.392