How to Predict Effective Drug Combinations? - Moving beyond Synergy Scores!

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Read the paper!

Relevance

- Combination therapy is widely used in cancer treatment
- Methods for predicting cell line-specific (patient-specific) treatment response to combination therapies are required

Background

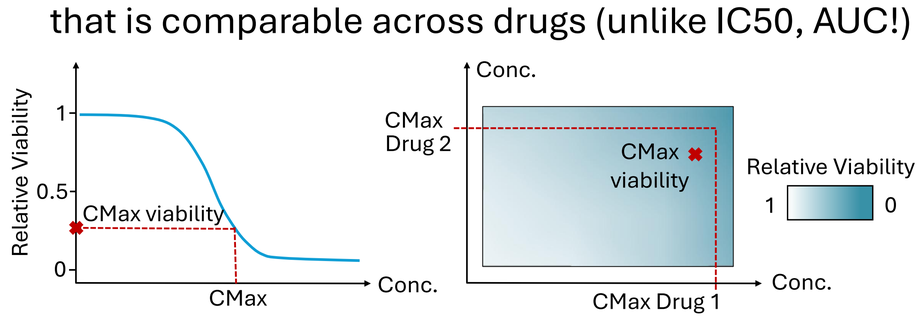
- Existing ML approaches for drug combination data focus on **synergy prediction**
- A drug combination is *synergistic* if the actual effect of the combination treatment exceeds the expected effect
- Expected effect is derived from monotherapy data via a baseline model (e.g., Loewe, Bliss)

Problems

- **Drug synergy does not imply treatment effectiveness!**
- Assumptions of baseline models vary and are often violated
- Synergy scores are aggregated over multiple (sometimes arbitrary) drug concentrations

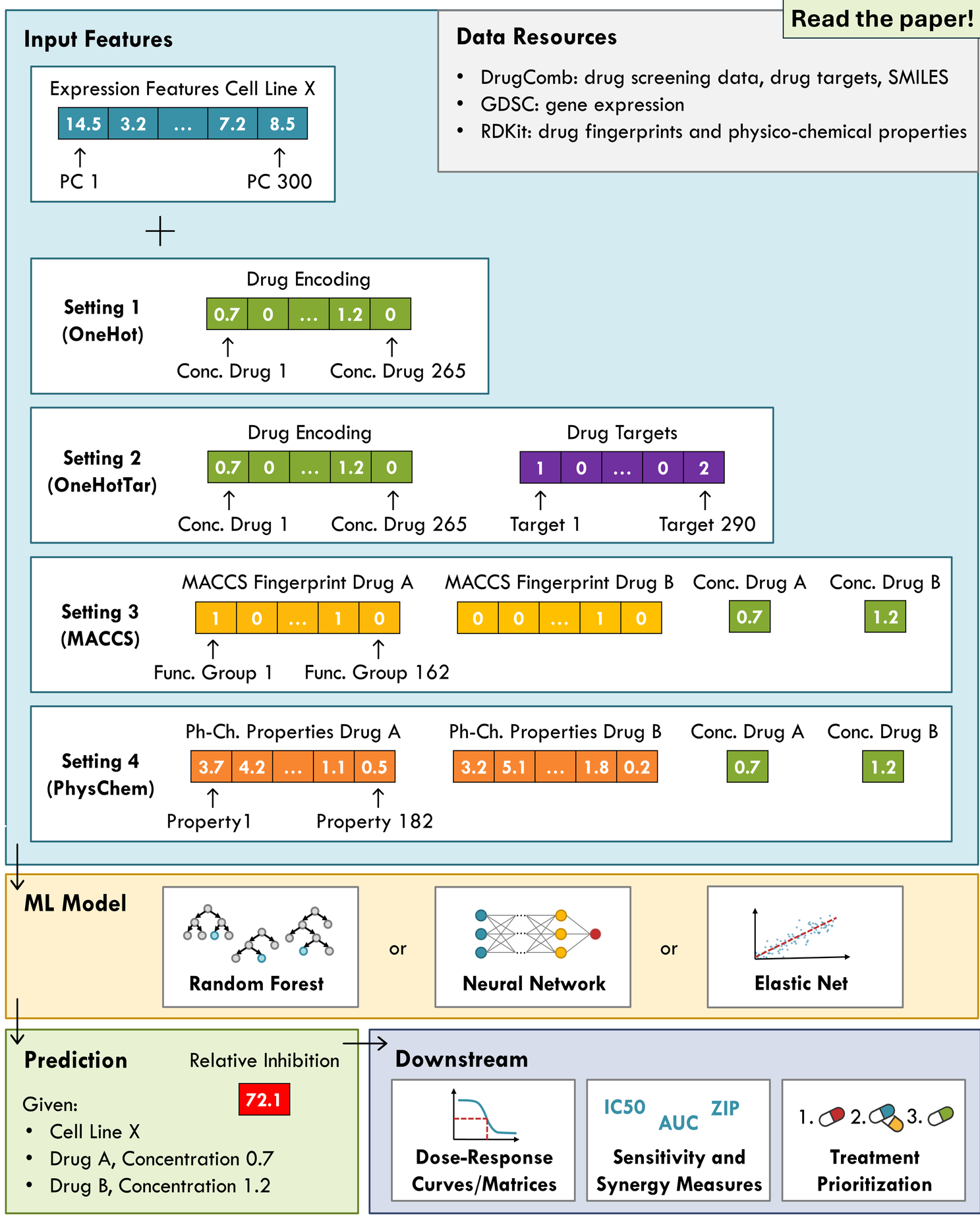
Our Approach

- Our ML models **predict sensitivity instead of synergy**
- They are suited for mono- and combination therapies
- We make dose-specific predictions, based on which we can then reconstruct
  (1) dose-response curves and matrices
  (2) various drug sensitivity (and synergy) measures,
  including our **novel sensitivity measure** (CMax viability) that is comparable across drugs (unlike IC50, AUC!)



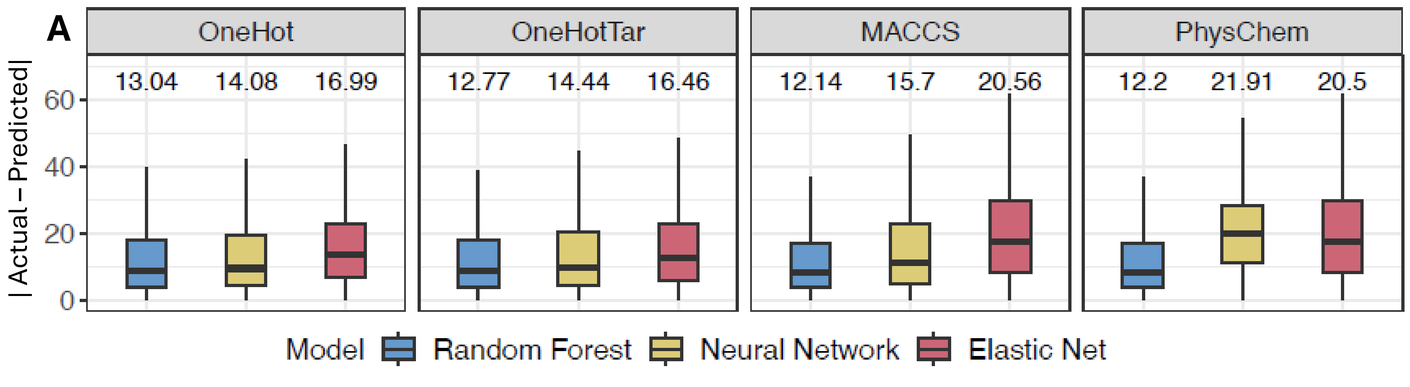
- Our models can be applied to cell lines (and drugs) **unseen during training**, mimicking the treatment of a new patient
- Our novel measure enables **jointly prioritizing mono- and combination therapies**

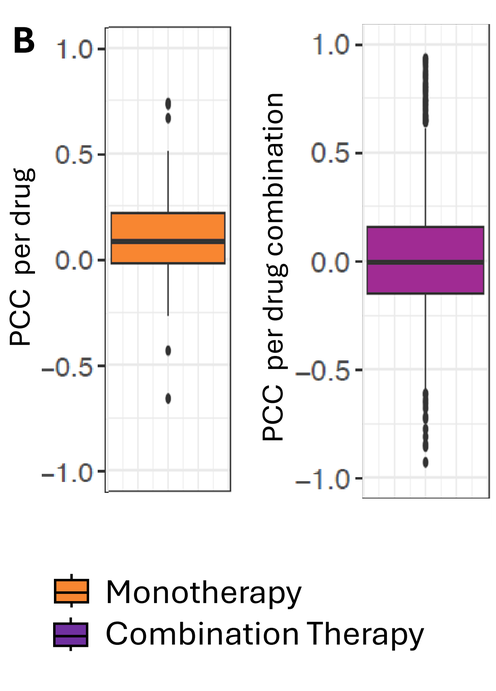


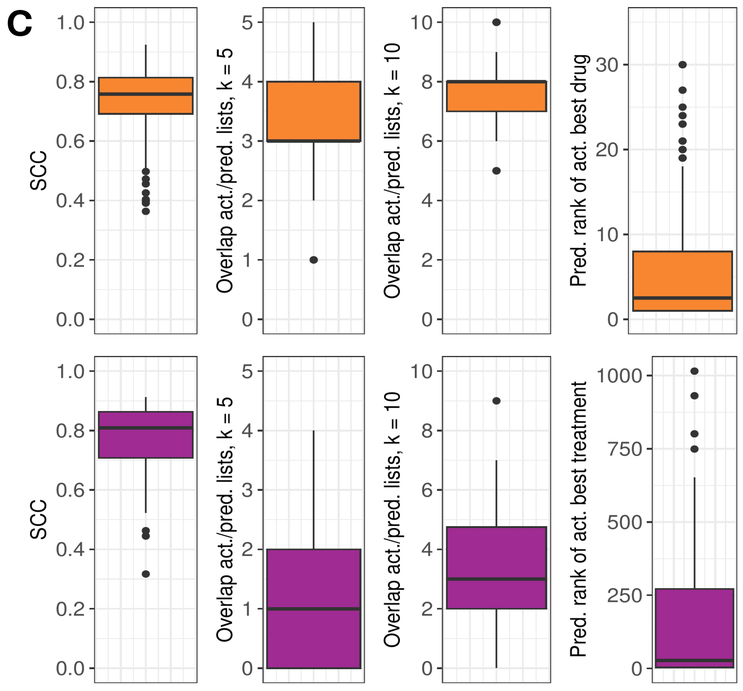


Data Resources

- DrugComb: drug screening data, drug targets, SMILES
- GDSC: gene expression
- RDKit: drug fingerprints and physico-chemical properties







Results

- Random forests using MACCS fingerprints performed best, see Figure **A** (test errors and test MAE)
- Neural networks with drug features **did not improve over simple mean baseline** (MAE=19.72) , see Figure **A**
- Reconstruction of dose-response curves works relatively well (mean RMSE 0.13, GDSC required RMSE < 0.3)
- Reconstructing sensitivity measures from predictions remains challenging, see Figure **B** (Pearson correlation of actual and predicted CMax viabilities)

→ **Issue of multi-drug models** learning mean response per drug/combination instead of actual sensitivity patterns

- Actual and predicted treatment prioritization rankings are well correlated, see Figure **C**

Take Home Messages

- Systems for drug prioritization must (1) be applicable to unseen samples and predict measures that (2) truly reflect treatment sensitivity and (3) are comparable across drugs
- Baseline models are essential to contextualize performance
- Performance evaluation per drug (combination) is crucial to unveil issues of multi-drug models

Who are we?

We are the *Integrative Bioinformatics* (*AI & Multi-Omics Data*) group at University Medical Center Göttingen and the *Lower Saxony Center for AI & Causal Methods in Medicine* (CAIMed). We are interested in applying **trustworthy machine learning** to questions within the medical domain, investigating not only the technical impact but also ethical and legal considerations.
Currently, our main research topics are (single-cell) drug sensitivity prediction in cancer and antimicrobial resistance prediction.

Connect with us!