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Predicting drug combination responses in cancer

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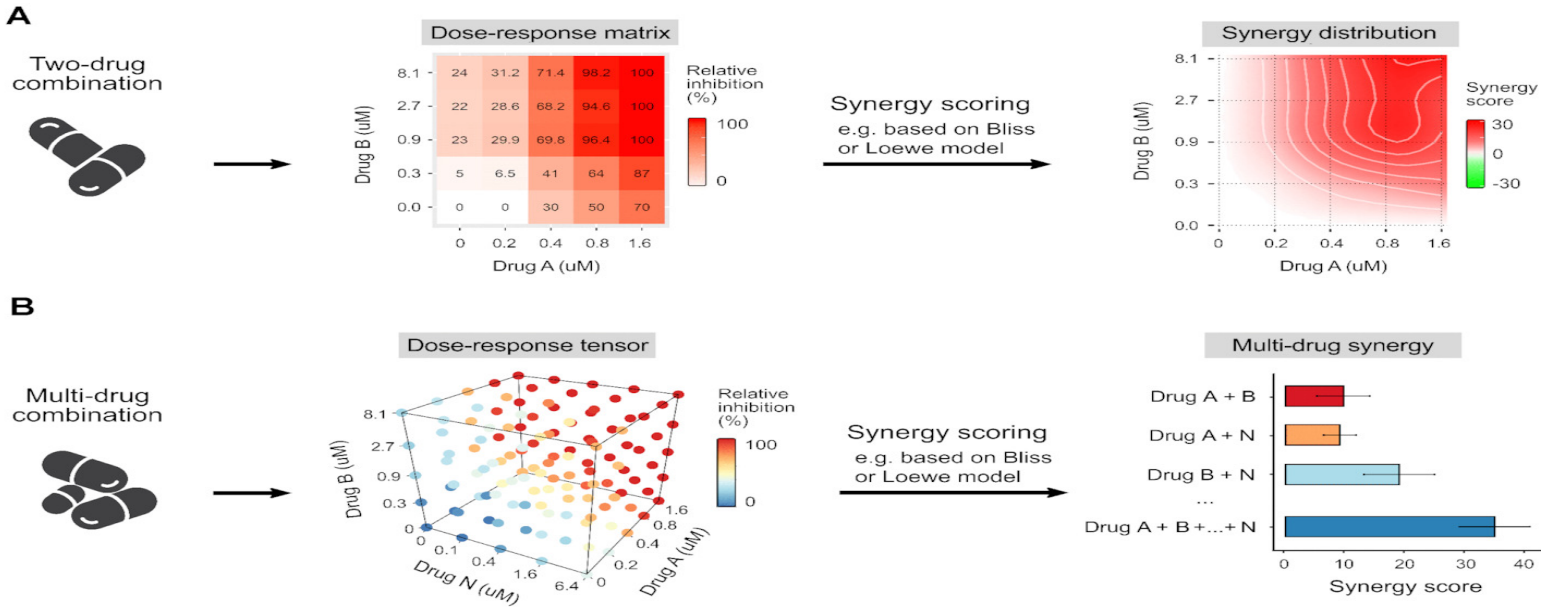
Combinatorial therapies in complex diseases

- Combinatorial treatments involving two or more drugs have become a standard of care for various complex diseases (tuberculosis, malaria, HIV, cancer)
- Their benefits include enhanced treatment efficacy, avoidance of drug resistance and fewer side-effects
- Promising drug combinations are typically search for by High-Throughput-Screening (HTS) in preclinical model systems (cancer cell lines, viral infection models)

Dose-response and synergy of drug combinations

- The quantities of interest are the **dose-response behavior** and the **synergy** of the drug combination – how much more effective the combination is compared to drugs acting alone



https://synergyfinder.fimm.fi/synergy/synfin_docs/

Ianevski, A., Giri, A.K. and Aittokallio, T., 2020. SynergyFinder 2.0: visual analytics of multi-drug combination synergies. *Nucleic Acids Research*.

Tackling the combinatorial explosion with machine learning

- The main challenge in finding promising drug combinations is the exponential size (in # combined drugs) of the search space
- To efficiently explore this space, we need **prioritization** of which drug combinations will be tested
- Machine learning is seen as a key tool for focusing the HTS efforts to most promising drug combinations
- NCI-Almanac dataset (Holbeck et al. 2017), with over 5000 drug pairs tested, is the first **large scale public combination response dataset** that enables accurate ML models to be developed

Holbeck et al., 2017. The National Cancer Institute ALMANAC: a comprehensive screening resource for the detection of anticancer drug pairs with enhanced therapeutic activity. *Cancer research*, *77*(13), pp.3564-3576.

Prediction scenarios

- Multiple prediction scenarios of different difficulty can be defined on drug combination response prediction
- Scenarios with out-of-tensor drugs and/or cell lines are generally the harder ones

Scenario	Title	Out of training tensor items in the test set			
		drugs	cell line	drug-drug	drug-drug-cell
NEW-ENTRY	Predicting new dose-response matrix entries	no	no	no	no
NEW-MATRIX	Predicting new dose-response matrices	no	no	no	yes
NEW-COMBO	Predicting new drug combinations	no	no	yes	yes
NEW COMBO-NO-MONO	Predicting new drug combinations with no monotherapy measurements	no	no	yes	yes
NEW-CELL-LINE	Predicting dose-response matrices on new cell lines	no	yes	no	yes
NEW-TISSUE-TYPE	Predicting dose-response matrices on new tissue types	no	yes	no	yes
NEW-DRUG	Predicting dose-response matrices on combos with one new drug	yes	no	yes	yes
2-NEW-DRUGs	Predicting dose-response matrices on combos with two new drugs	yes	no	yes	yes

Predicting multi-way interactions

Multi-way interaction problems

Consider prediction problems where the predicted target variable dependes on simultaneous interaction of m objects

- **Pairwise cases (m=2):**
  - Movie recommendation: f(user,movie) – predict if user will like a movies
  - Binding affinity between molecules (f(drug,target), f(protein,DNA), etc.)
- **Higher order interactions (m > 2):**
  - Genotype-phenotype interactions: m SNPs needed to explain a phenotype
  - Drug combination responses (this talk): 2 drugs x 2 doses x target = 5th order interaction

A first attempt of a predictive model

- Suppose we have large amounts of data on drugs and their responses on cancer cells
- Consider an additive model predicting the response of a cancer cell (c) to a drug (d):

$$F(d,c) = F_{Drug}(d) + F_{cell}(c)$$

- F_{drug} scores a drugs potency to kill cancer cells
- F_{cell} scores the cancer cells suceptibility to be killed by a drug
- Q: Would this model give a good basis for finding new drugs?

The need for non-linearity

- **An additive model can only recognize drugs that are effective regardless of the properties of the cancer cell**

  $F(d,c) = F_{Drug}(d) + F_{cell}(c)$

  - 'snake-oil' type cure for everything
  - cannot find targeted therapies for particular type of cancer cell
- **This is true even if F_{drug} and F_{cell} are highly non-linear**
- **Non-linear dependencies between the interacting objects need to be modelled**
- **Example: a polynomial of degree k can model interactions of k objects**
  - i.e. minimum quadratic model is needed for pairwise prediction

Factorization machines & latent tensor reconstruction

Starting point: polynomial regression

- Consider a quadratic regression model $f: R^d \rightarrow R$

$$f(x) = \sum_j w_j x_j + \sum_j \sum_k w_{jk} x_j x_k$$

- $O(d^2)$ parameters to estimate
- Generalize this to m'th degree polynomials

$$f(x) = \sum_j w_j x_j + \sum_j \sum_k w_{jk} x_j x_k + \cdots + \sum_{j_1,\ldots,j_m} w_{j_1,\ldots,j_m} \cdot x_{j_1} \cdot x_{j_2} \cdot x_{j_k}$$

- $O(d^m)$ parameters to estimate!
- Two-fold challenge:
  - Time complexity of estimating the model is exponential in **m**
  - Statistical challenge: in practical scenarios typically not enough data to estimate all parameters when **m** > 2

Factorization machines

- Factorization machines (Rendle, 2010) are an approach to make estimation of polynomial regression models from large dataset feasible
- The polynomial regression model is replaced by a factorized form

$$\hat{y}FM(x) = \sum_{j} w_j x_j + \sum_{j'>j} \langle p_j, p_{j'} \rangle x_j x_{j'}$$

- $p_j \in R^k$ is a vector representing contributions of variable x_j to k latent factors, where typically $k \ll d$ (low-rank)
- The interaction weight $w_{ij} \approx \langle p_j, p_{j'} \rangle = \sum_{s=1}^{k} p_{js}\, p_{j's}$ is represented as a inner product over the factor contributions
- O(dk) parameters to estimate, compare to original O(d^2)

Rendle, S., 2010, December. Factorization machines. In *2010 IEEE International Conference on Data Mining* (pp. 995-1000). IEEE.

Higher-order factorization machines

- Higher-order factorization machines (HOFM) (Blondel, 2016) can represent polynomial models of arbitrary maximum degree m

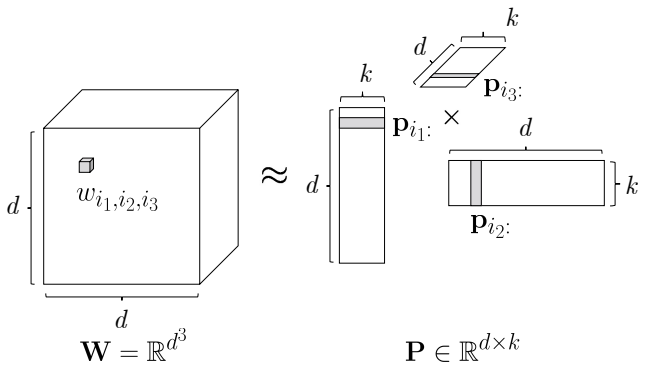
$$\hat{y}HOFM(x) = \sum_{j} w_j x_j + \sum_{j\prime>j} \langle p_j{}^{(2)}, p_{j\prime}{}^{(2)} \rangle x_j x_{j\prime} + \cdots + \sum_{j_m>\cdots>j_1} \langle p_{j_1}{}^{(m)}, \ldots, p_{j_m}{}^{(m)} \rangle x_{j_1} \cdots x_{j_m}$$

- The interaction weights are given by generalized inner products

$$\mathrm{w}_{\mathrm{j}_1 \ldots \mathrm{j}_\mathrm{m}} \approx \langle \mathrm{p}_{\mathrm{j}_1}{}^{(\mathrm{m})}, \ldots, \mathrm{p}_{\mathrm{j}_\mathrm{m}}{}^{(\mathrm{m})} \rangle = \sum_{\mathrm{s}=1}^{\mathrm{k}} \mathrm{p}_{\mathrm{j}_1 \mathrm{s}}{}^{(\mathrm{m})} \cdots \mathrm{p}_{\mathrm{j}_\mathrm{m} \mathrm{s}}{}^{(\mathrm{m})}$$

- O(dkm) parameters to estimate, compared to O(d^m) of the full model

Figure right: factorization of a 3rd order weight tensor



Blondel, M., Fujino, A., Ueda, N. and Ishihata, M., 2016. Higher-order factorization machines. In *Advances in Neural Information Processing Systems* (pp. 3351-3359).

Learning HOFMs

- The objective function of learning HOFMs is given by

$$\frac{1}{n}\sum_{i=1}^{n}\ell\left(y_i,\hat{y}HOFM(x_i)\right)+\frac{\beta_1}{2}\|w\|^2+\frac{\beta_2}{2}\|P\|^2$$

- It is a differentiable non-convex functional; can be trained by stochastic gradient descent (SGD)
- The challenging part is the exponential number of terms in the expression for $\hat{y}HOFM(x)$
- However by making use of the repetitive structure of the factor combinations, dynamic programming can be used to compute $\hat{y}HOFM(x)$ and its gradients in linear time
- The SGD algorithm runs in time O(dkmn) per epoch
- GPU acceleration can be used for further speed-up

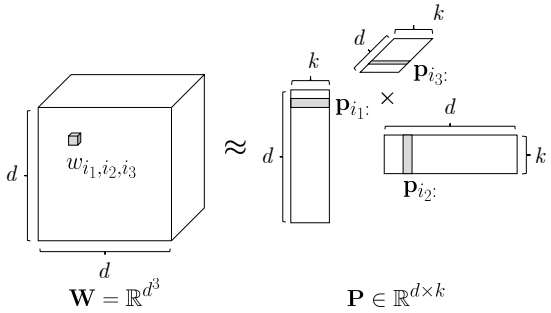
Blondel, M., Fujino, A., Ueda, N. and Ishihata, M., 2016. Higher-order factorization machines. In *Advances in Neural Information Processing Systems* (pp. 3351-3359).

Latent tensor reconstruction

- Latent tensor reconstruction (LTR) is another machine learning method for learning multi-way interaction models
- It is motivated by higher-order SVD problem
- The LTR model is given by

$$f(\mathbf{x}) = \sum_{t=1}^{n_t} \lambda_t \left\langle \mathbf{p}_1^{(t)} \otimes \cdots \otimes \mathbf{p}_{n_d}^{(t)}, \mathbf{x} \otimes \cdots \otimes \mathbf{x} \right\rangle .$$

$$= \sum_{t=1}^{n_t} \lambda_t \left\langle \mathbf{p}_1^{(t)}, \mathbf{x} \right\rangle \cdot \ldots \cdot \left\langle \mathbf{p}_{n_d}^{(t)}, \mathbf{x} \right\rangle ,$$



- <.> is the inner product of two tensors and $\otimes$ is the tensor product
- Enjoys a similar exponential reduction in the number of parameters as HOFM, but is a more flexible model

Wang, T., Szedmak, S., Wang, H., Aittokallio, T., Pahikkala, T., Cichonska, A. and Rousu, J., 2021. Modeling drug combination effects via latent tensor reconstruction. Bioinformatics, 37(Supplement_1), pp.i93-i101.

Learning LTR

The basic rank wise algorithm

Given: a sample: $\{(\mathbf{x}_i, y_i),\ i = 1, \ldots, m\}$,
Let $y_i^{(1)} = y_i,\ i = 1, \ldots, m$.
For $t = 1$ **to** n_t **do**
Solve rank-one subproblem

$$\begin{aligned} \min \quad & \sum_{i=1}^{m} ||y_i^{(t)} - \lambda_t f^{(t)}(\mathbf{x}_i)||^2 \\ & + \frac{C_p}{n_d n} \sum_{d=1}^{n_d} ||\mathbf{p}_d^{(t)}||^2 \\ \text{w.r.t.} \quad & \lambda_t,\ \mathbf{p}_1^{(t)}, \ldots, \mathbf{p}_{n_d}^{(t)}, \end{aligned}$$

Optimum solution:
$\lambda_t^*,\ \mathbf{p}_1^{(t)*}, \ldots, \mathbf{p}_{n_d}^{(t)*}$
Deflation of the output:

$$y_i^{(t+1)} = y_i^{(t)} - \lambda_t^* \prod_{d=1}^{n_d} \langle \mathbf{p}_d^{(t)*}, \mathbf{x}_i \rangle, \forall i$$

- **The LTR model can be estimated as a series of rank-one problems**
- **Each subproblem finds a rank-one parameter tensor that best fits the residuals of the output**
- **The subproblem can be solved by gradient approaches (e.g. ADAM)**

Wang, T., Szedmak, S., Wang, H., Aittokallio, T., Pahikkala, T., Cichonska, A. and Rousu, J., 2021. Modeling drug combination effects via latent tensor reconstruction. Bioinformatics, 37(Supplement_1), pp.i93-i101.

LTR vs HOFM

- HOFMs are limited to symmetric polynomials i.e. f(i,j) = f(j,i) while LTR is not → LTR is better as a general regression method
- In LTR, the input data can be fed through an activation function to give rise to a learnable embedding (e.g. non-linear dimensionality reduction): $\phi(\mathbf{x}) = \mathcal{A}(\mathbf{U}^{(d)T}\mathbf{x})$
- LTR requires more training data than HOFMs due to the more flexible function class
- LTR is arguably more interpretable due to the simpler functional form

LTR:

$$f(\mathbf{x}) = \sum_{t=1}^{n_t} \lambda_t \left\langle \mathbf{p}_1^{(t)} \otimes \cdots \otimes \mathbf{p}_{n_d}^{(t)}, \mathbf{x} \otimes \cdots \otimes \mathbf{x} \right\rangle .$$
$$= \sum_{t=1}^{n_t} \lambda_t \left\langle \mathbf{p}_1^{(t)}, \mathbf{x} \right\rangle \cdot \ldots \cdot \left\langle \mathbf{p}_{n_d}^{(t)}, \mathbf{x} \right\rangle ,$$

HOFM:

$$\hat{y}HOFM(x)$$
$$= \sum_j w_j x_j + \sum_{j\prime>j} \langle {p_j}^{(2)}, {p_{j\prime}}^{(2)} \rangle x_j x_{j\prime} + \cdots$$
$$+ \sum_{j_m>\cdots>j_1} \langle {p_{j_1}}^{(m)}, \ldots, {p_{j_m}}^{(m)} \rangle x_{j_1} \cdots x_{j_m}$$

Experiments on drug combination response prediction

Compared methods

- **ComboFM** (Julkunen et al., 2020): relies on a recent machine learning technology called **higher-order factorization machines** (HOFM) that allow capturing the multi-way interactions between drug combinations and their targets
- **ComboLTR** (Wang et al. Bioinformatics, 2021): a **latent tensor reconstruction** method, which removes some limitations of HOFMs
- **Random forest regressor (RF).** Strong baseline e.g. winner of the AstraZeneca-Sanger DREAM Challenge.

Julkunen, H., Cichonska, A., Gautam, P., Szedmak, S., Douat, J., Pahikkala, T., Aittokallio, T. and Rousu, J., 2020. Leveraging multi-way interactions for systematic prediction of pre-clinical drug combination effects. *Nature communications*, *11*(1), pp.1-11.

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Dataset

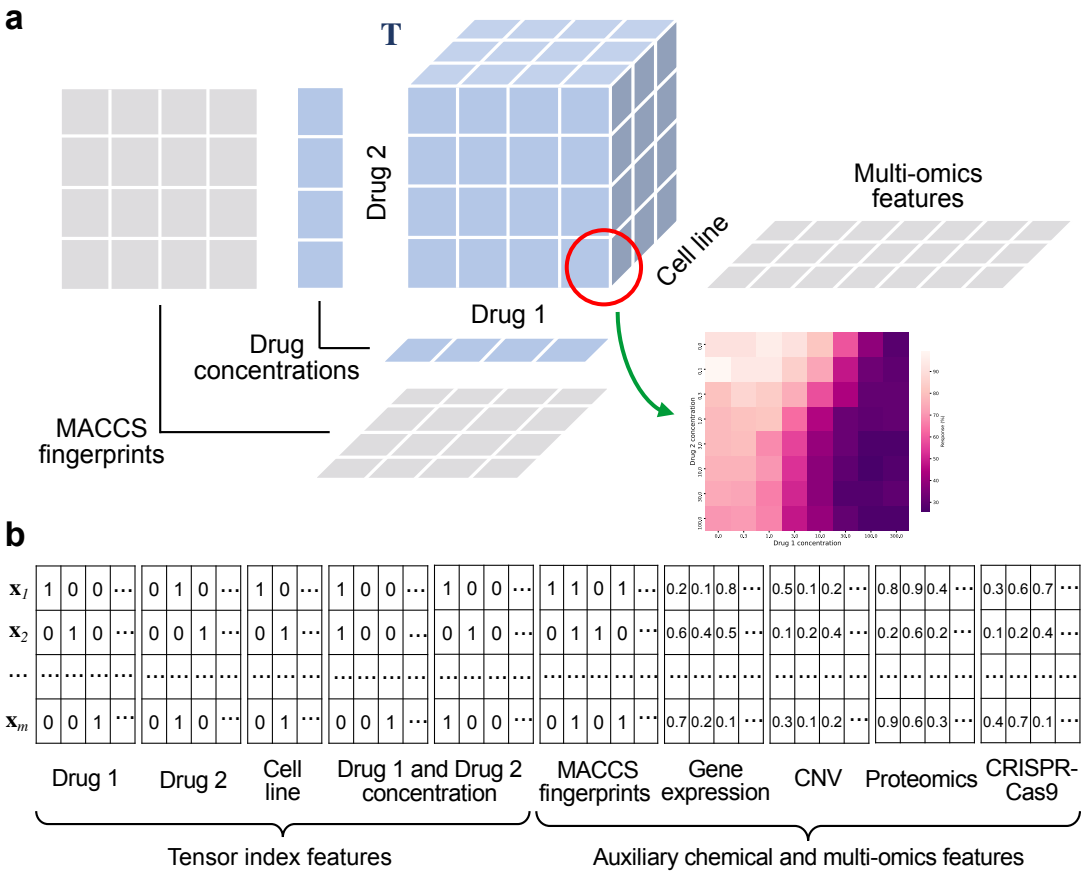
- We used the NCI-ALMANAC data, large drug combinations screening data by NCI
- We used a subset of this data where omics data for cell lines was availables:
  - 828 324 response measurements of 5 035 drug combinations and
  - 15 396 monotherapies in
  - 19 cancer cell lines originating from 9 tissue types.

https://dtp.cancer.gov/ncialmanac/

Holbeck et al., 2017. The National Cancer Institute ALMANAC: a comprehensive screening resource for the detection of anticancer drug pairs with enhanced therapeutic activity. *Cancer research*, *77*(13), pp.3564-3576.

Data structure

a. 5-order tensor containing the drug combination responses
b. flattened representation for the learning algorithms



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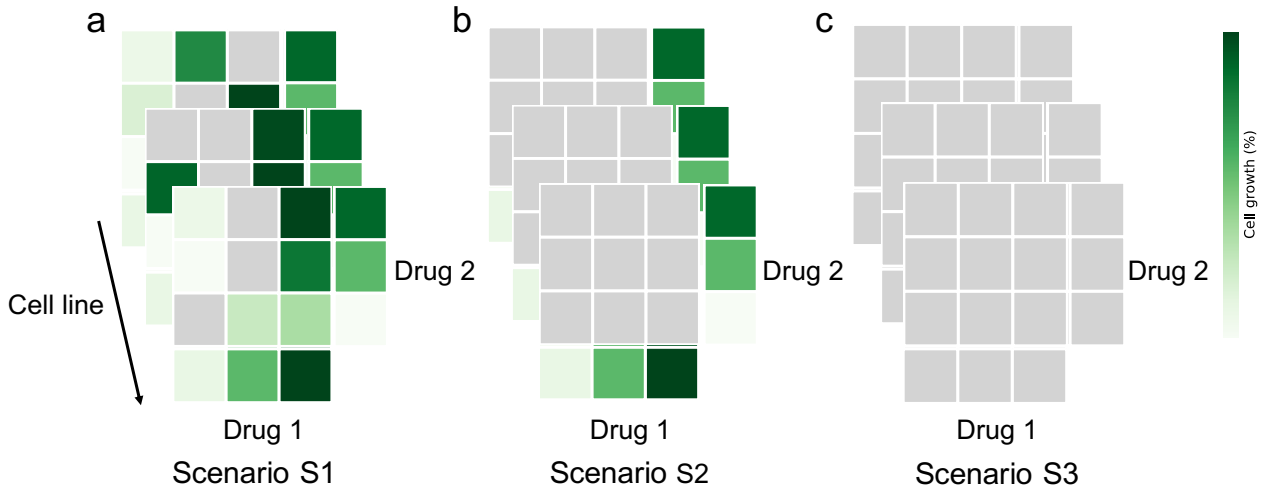
Prediction scenarios

- **Scenario S1: Predicting new response matrix entries**
- **Scenario S2: Predicting new drug combination responses (monotherapy responses known)**
- **Scenario S3: Predicting new combination responses w.o. monotherapy measurements**



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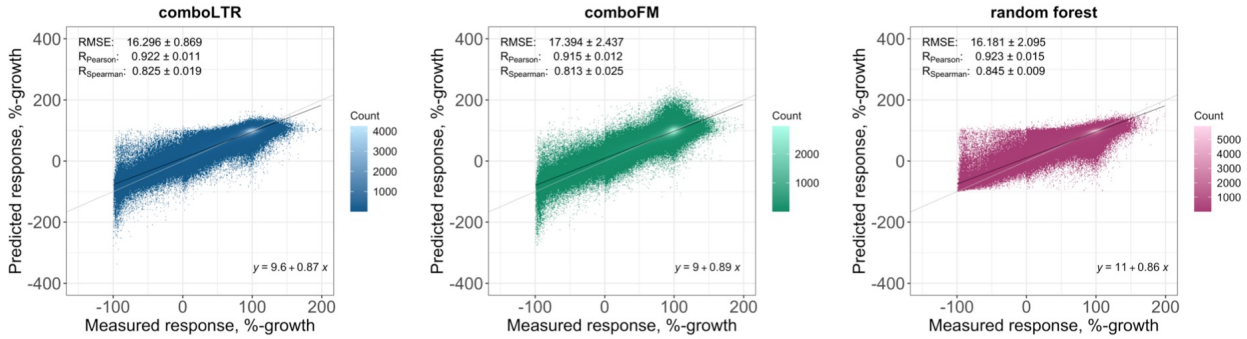
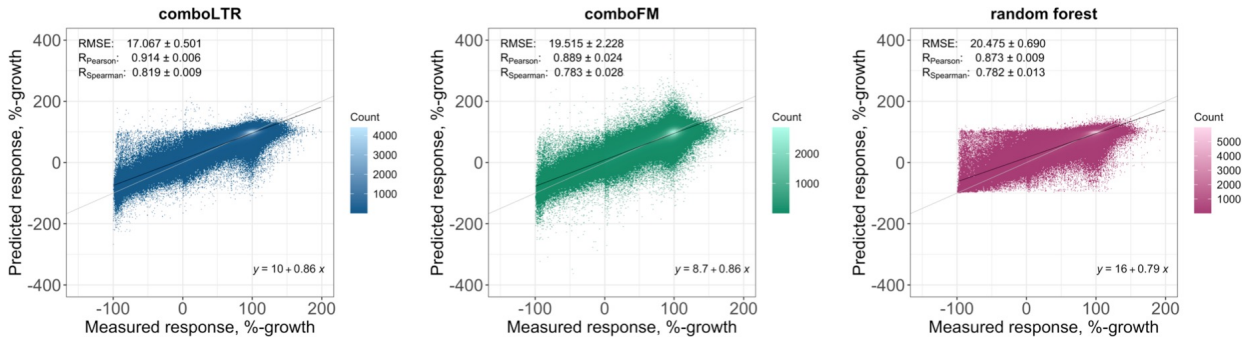
Prediction performance

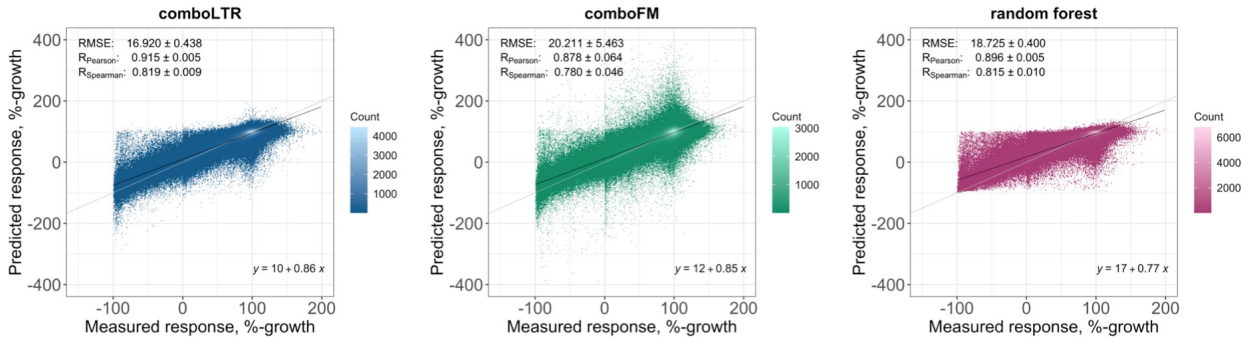
a **S1: Filling in the gaps in partially measured dose-response matrices**



b **S2: Predicting dose-response matrices of new drug combinations**



c **S3: Predicting dose-response matrices of new drug combinations w/o monotherapy responses**



Effect of different data sources

- The predictive performance of the models using different input data sources was studied
- In all prediction scenarios, the primary data (drug features, cell line features) was shown to be very small
- The response measurements from similar drugs and cell lines ('Tensor indices') dominates

Table 2. Performance of *comboLTR*, *comboFM*, and random forest (RF) under different prediction scenarios and using different features. Pearson correlations between predicted and measured drug combination responses, reported as averages across 5 cross validation folds ± standard deviations.

Features	Method	S1	S2	S3
Tensor indices	*comboLTR*	0.915±0.009	0.894±0.002	0.893±0.003
	comboFM	0.920±0.010	0.914±0.003	0.907±0.004
	RF	0.886±0.019	0.853±0.010	0.858±0.010
Tensor indices + MACCS	*comboLTR*	0.921±0.010	0.908±0.003	0.910±0.003
	comboFM	0.923±0.012	0.923±0.005	0.913±0.005
	RF	0.921±0.016	0.872±0.009	0.894±0.005
Tensor indices + Multi-omics	*comboLTR*	0.908±0.014	0.909±0.007	0.911±0.005
	comboFM	0.910±0.027	0.904±0.014	0.870±0.064
	RF	0.895±0.019	0.859±0.010	0.865±0.010
Tensor indices + MACCS + Multi-omics	*comboLTR*	0.922±0.011	0.914±0.006	0.915±0.005
	comboFM	0.915±0.012	0.889±0.024	0.878±0.064
	RF	0.923±0.015	0.873±0.009	0.896±0.005

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Time and space complexity

- **The time consumption of comboLTR is on par with RF, while comboFM is significantly less time-efficient**
- **All three methods have similar memory-requirements**

Table 3. The time (h) and memory (GB) usage of *comboLTR*, *comboFM* and random forest in 5-fold cross validation.

	Time (h) / Memory (GB)		
Features	*comboLTR*	*comboFM*	RF
One-hot encoding	1.1 / 24	1.2 / 20	1.2 / 24
One-hot encoding + MACCS	2.1 / 35	5.9 / 35	0.4 / 38
One-hot encoding + Multi-omics	3.2 / 44	31.5 / 63	5.6 / 54
One-hot encoding + MACCS + Multi-omics	3.1 / 74	39.0 / 73	2.1 / 74

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Summary

Summary

- **The search for new combinatorial therapies requires prioritization due to the huge search space of drug combinations**
- **Machine learning tools can be used to predict the drug combination responses and synergies, and thus help to prioritize the search**
- **The predictive accuracy of ML models depends strongly on the assumed prediction scenarios**
- **comboFM and comboLTR uses factorization machine technology to learn pairwise drug combination responses**
  - monotherapy responses of the drugs alone, and
  - responses of similar drug combinations in similar cell lines

Thank you for your attention!

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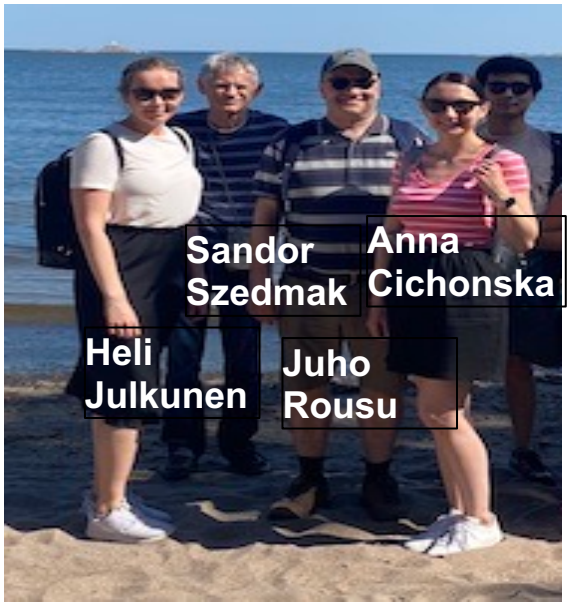

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comboFM: https://github.com/aalto-ics-kepaco/comboFM
comboLTR: https://github.com/aalto-ics-kepaco/ComboLTR