Proposing a Change to the Assignment Mechanism in Precision Oncology Programs to enable Causal Inference and Conditional Average Treatment Effect estimation

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Problem - Causal inference in Precision Oncology programs

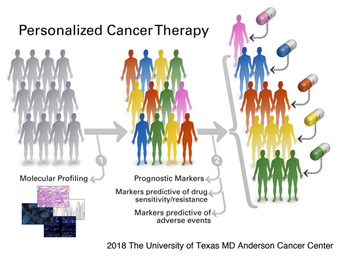
The goal of precision medicine is providing the right treatment to the right patient at the right time. Despite a number of successes, assigning patients to adequate treatments remains a challenge until today. The current best practice in precision oncology is to base the treatment decision on published and frequently used therapeutic protocols that consider the patient's clinical characteristics and cancer biomarkers. For example, based on the status of a single mutation, such as a BRAF V600E, a treatment decision can be made.

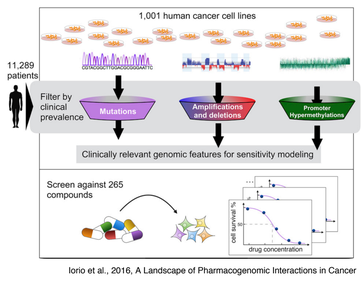
Current therapeutic protocols in precision oncology evaluate one biomarker and one targeted therapeutic at a time. This limits the ability to make high-confidence clinical decisions in a real world scenario with a large number of biomarkers to measure and potential treatments to choose from. The current limitations include:

(I) high selectiveness
(II) high unsystematic compassionate use
(III) limited continuous development
(IV) limited predictive availability

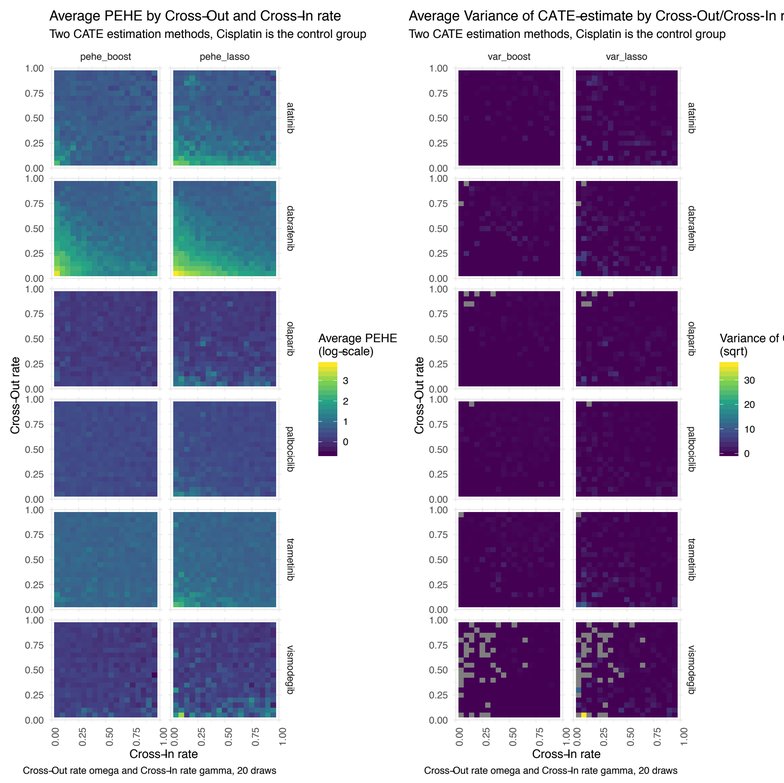
We hypothesized that an assignment mechanism in precision oncology programs that sustained the positivity assumption could be used for conditional treatment effect (CATE) estimation. This could allow a less selective, more systematic, continuously evolving practice of precision oncology.

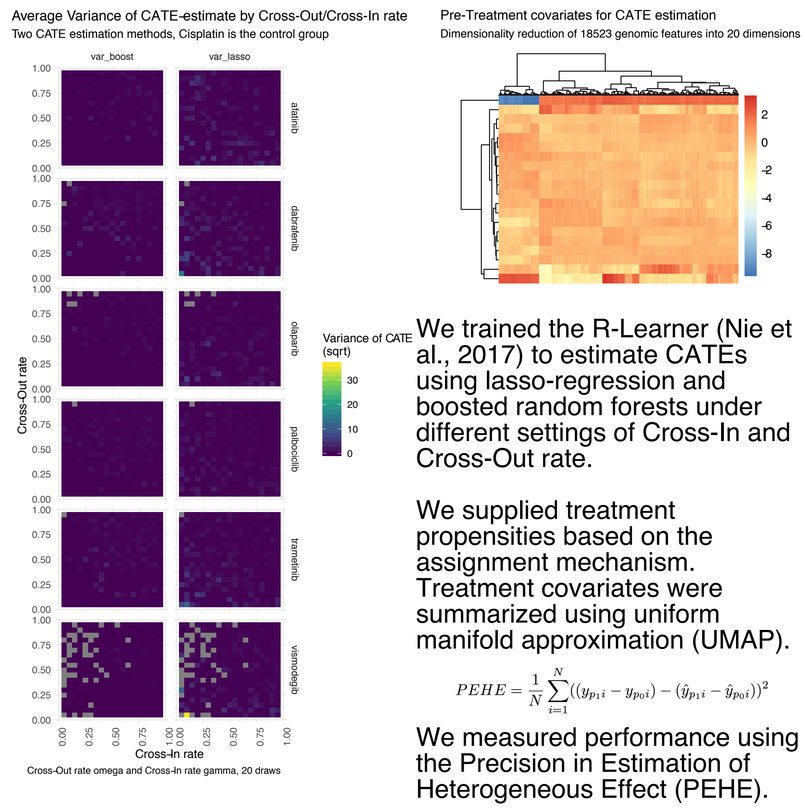
To this end we prepared a public dataset of drug vulnerability measurements from >1000 cancer cell lines for causal inference. The dataset contains genomic information for every cell line and complete observations for more then 7 drugs.





Results - CATE estimation





We trained the R-Learner (Nie et al., 2017) to estimate CATEs using lasso-regression and boosted random forests under different settings of Cross-In and Cross-Out rate.

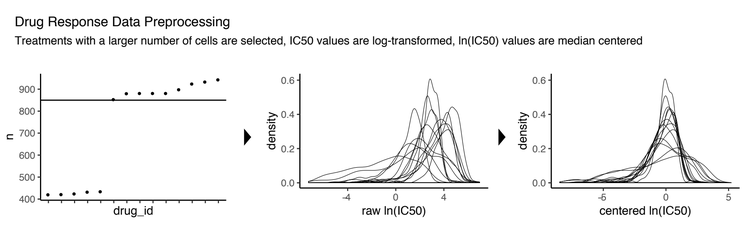
We supplied treatment propensities based on the assignment mechanism. Treatment covariates were summarized using uniform manifold approximation (UMAP).

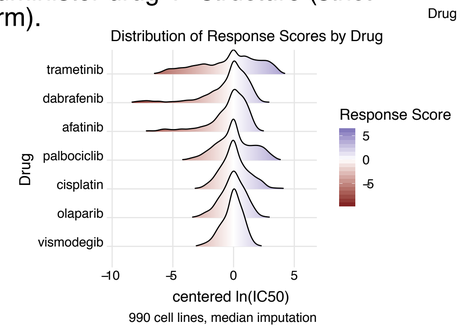
$$PEHE = \frac{1}{N}\sum_{i=1}^{N}((y_{p_1 i} - y_{p_0 i}) - (\hat{y}_{p_1 i} - \hat{y}_{p_0 i}))^2$$

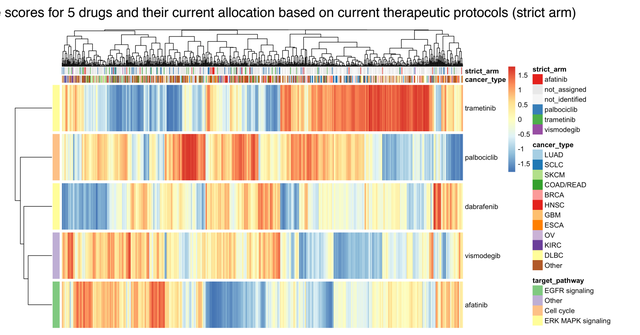
We measured performance using the Precision in Estimation of Heterogeneous Effect (PEHE).

Methods - Dataset synthesis

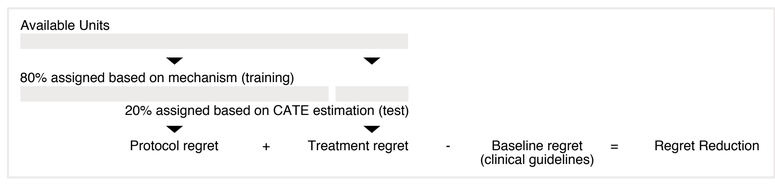
Next to data pre-processing, we searched clinical guidelines and trial protocols to identify FDA approved targeted therapeutics that have genetic biomarkers of an evidence level >2A. We defined a set of therapeutic protocols that follow a "IF gene X is altered THEN administer drug Y" structure (strict arm).



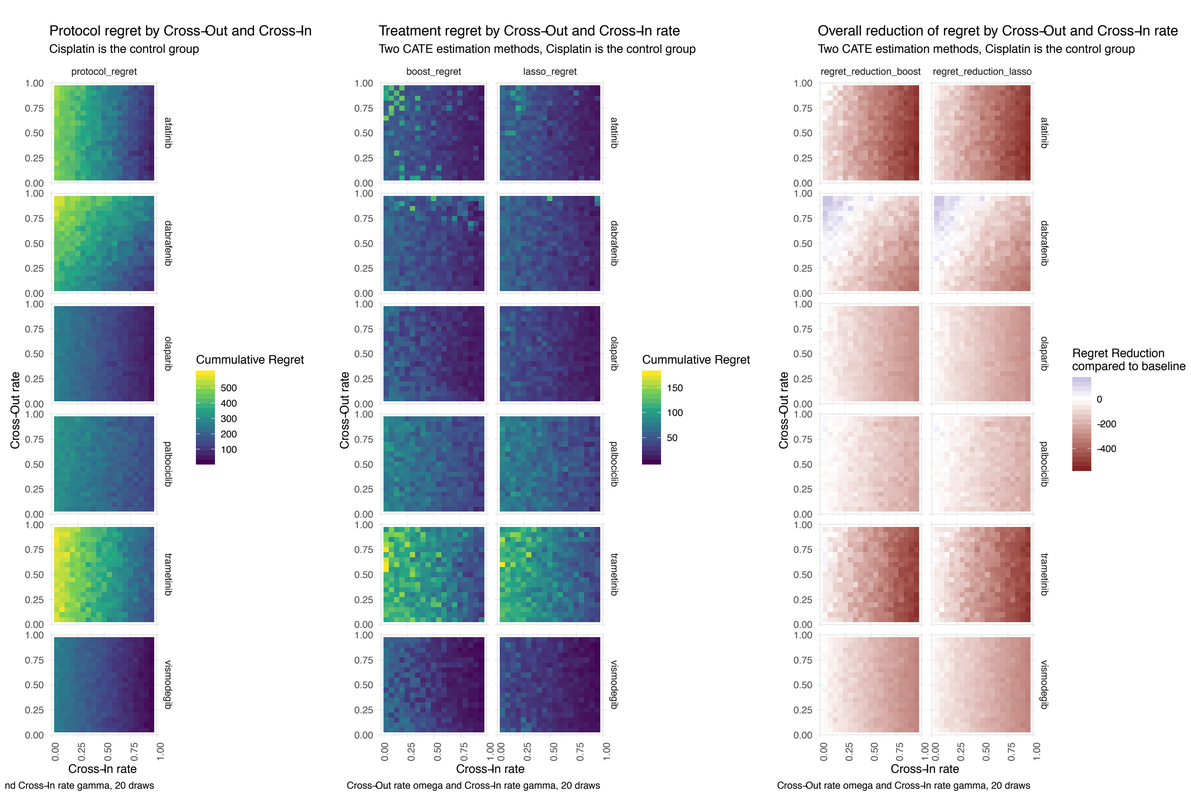




Results - CATE guided Treatment



We evaluated PEHE (above) and CATEs (below) on a 20% holdout set of units after fitting the R-Learner on 80% of available units.



To estimate the feasibility of introducing the proposed modified assignment mechanism to precision oncology programs, we introduced regret as a measure for the impact of changes to the assignment mechanism (Protocol regret) and CATE guided treatment assignment (Treatment regret).

Regret is defined as the Sum of absolute response scores for units that have not been treated with the optimal agent. The sum of Protocol regret and Treatment regret is compared with the Baseline regret, which is experienced when adhering strictly to current therapeutic protocols.

Methods - Assignment Mechanism

To preserve the positivity assumption, we expand the current therapeutic protocol based treatment assignment mechanisms.

First, units are assigned to a mutually exclusive treatment arm (or control, T=0) based on pre-treatment covariate depending therapeutic protocols.

Next, units are mixed between treatment arms (Cross-Over, controlled by epsilon), assigned from the control arm into a treatment arm (Cross-In, controlled by gamma) or reassigned into the control arm (Cross-Out, controlled by omega).

Most parameters are weighted by a parameter proportional to the prevalence of a treatment's biomarker.

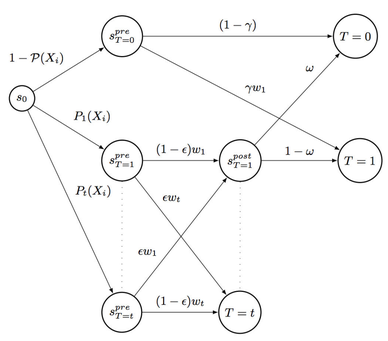
We performed CATE estimation in a "star-schema", comparing a single treatment arm to the common control treatment, Cisplatin.

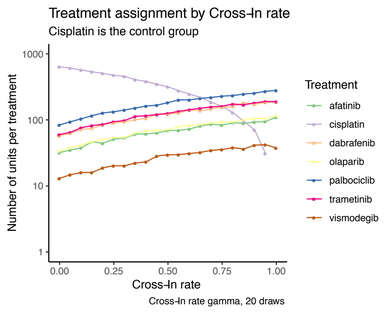
We keep the Cross-Over rate epsilon=0 for the rest of the study.

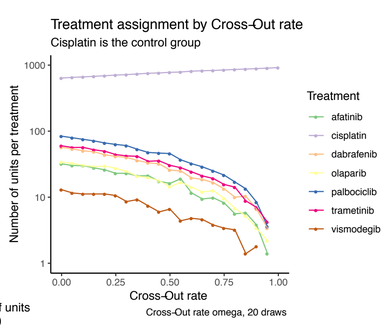
Proposed Assignment Mechanism to conserve the positivity assumption
Current mechanism can be used for CATE estimation (Treatment vs. Control T=0)

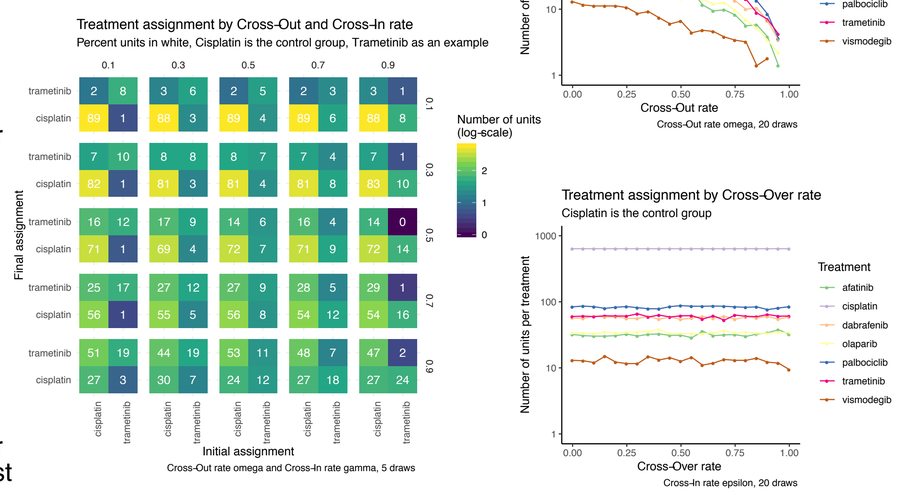
$$P_t(X_i) \in \{0;1\} \qquad w_t = \frac{\hat{l}(P_t(X))}{\hat{l}(\mathcal{P}(X))}$$

$$p(T = t|X_i) = P_t(X_i)(1-\omega) + (1-\mathcal{P}(X))\gamma w_t$$









Conclusion

Assignment mechanisms in precision oncology programs can be modified to allow causal inference.

The Precision in Estimation of Heterogeneous Effect (PEHE) metric is optimized in configurations with maximal Cross-In and Cross-Out. Still, the limited sample size and covariate complexity leads to CATE predictions with low variance, decreasing with Cross-In and Cross-Out rate.

In contrast, the regret caused by the assignment mechanism alone (Protocol regret) is highest in conditions of high Cross-In rate and low Cross-Over rate, which may be linked to the on average higher response scores in treatments vs. control.
Of note, the regret caused by wrong predictions of the CATE (Treatment regret) shows the same behavior.
In the current study, treatment assignment according to the proposed mechanism (80% of units) paired with subsequent CATE based treatment assignment (20% of units) reduces the overall regret compared to the Baseline regret.

This study has several limitations including: (I) In-vitro drug response data of cancer models has limited transferability into a clinical context, (II) The response scores are on average lower in treatments vs. controls, (III) Cisplatin is a limited reference treatment for all considered cancer types.

In the future, it would be interesting to evaluate this problem as a contextual bandit problem.

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