Proposing an assignment mechanism optimization in precision oncology programs for conditional average treatment effect estimation

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1 Introduction

The goal of precision medicine is providing the right treatment to the right patient at the right time. Oncology has been one of the central fields in modern precision medicine [1], with an increasing number of targeted compounds available, that are hypothesized to show activity in a very specific subset of patients (among the most popular examples being Imatinib for BCR-ABL positive CML).

Despite these early 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 genetics. For example, based on the status of a single biomarker, such as a BRAF V600E mutation, a treatment decision can be made [3].

These decision rules, or therapeutic protocols, are constantly evolving and used to link patients to optimal potential outcomes. Most therapeutic protocols in precision medicine are the result of biological reasoning that was validated in prospective [3] or retrospective [5] analysis of clinical trials. However, most clinical trials 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 consequences of strict therapeutic "if..when" protocols in precision medicine can be (I) high selectiveness - where only a small number of patients are assigned to a treatment with robust clinical evidence, (II) high compassionate use - where a majority of patients are left with limited treatment options that, if treated outside of a therapeutic protocol, do not contribute systematically to the development of new clinical evidence and (III) limited predictive ability - where due to a reduced number of new observations, therapeutic protocols can not improve beyond their initial version. For example, in recent precision medicine trials less than 50% of all screened patients were assigned to a treatment [10] and only a third of treated patients showed signs of increased progression-free-survival relative to their prior treatment [11].

Causal inference is an increasingly popular statistical method for estimating treatment effects from observational data. The fundamental problem of causal inference and precision oncology are the same: We can only observe the realized outcome of one treatment for a given patient. Estimating the potential outcomes for other treatments for a very similar patient becomes increasingly complex, especially as our definition of similar patients becomes more narrow.

The primary goal of precision medicine, when re-framed in into causal inference terminology, is to assign a patient with the observable attributes X_i to the ideal treatment $T = t_{ideal}$ with the greatest conditional average treatment effect $Y(T = t_{ideal}|X_i)$, also referred to as CATE. At the basis of this primary goal rests the assumption, that we are able to estimate the potential outcomes Y for a large set of currently available treatment options T. The ability to estimate the potential outcomes of multiple treatments is not only desirable because of differences in patient preference, side-effect

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tolerability or financial implications, but also because the number of new treatment options and diagnostic methods is constantly increasing, making it unfeasible to perform direct comparisons to every potential treatment option as new therapeutics enter clinical practice.

However, currently most assignment mechanisms in precision oncology programs limit the use of causal inference methods, due to reasons such as a violation of the positivity assumption. After developing a theoretical model of therapeutic protocol based treatment assignments in precision medicine, we aim to show how small changes to this assignment mechanism can enable the use of causal inference methods for conditional average treatment effect (CATE) estimation.

To this end we introduce a new synthetic causal inference benchmark dataset for precision oncology. We synthesized a cancer cell line drug-response dataset that contains more than 1000 genetically characterized cancer cell lines treated with 10 frequently used targeted therapeutics and assigned them to treatments based on current state-of-the-art therapeutic protocols [8].

To estimate conditional average treatment effects (CATE) we propose using a two-step approach based on the R-learner algorithm for causal inference. Finally, we plan to evaluate how the error of CATE estimation as well as the treatment recommendation quality are influenced by changes to the assignment mechanism model.

2 Related Work

Recently the number of targeted therapeutics tested in clinical trials has grown rapidly, prompting the introduction of modern master trial designs, such as baskets, umbrellas and platforms, thereby improving the throughput of efficacy testing [14]. Of note, first master protocols such as the I-SPY2 trial for neoadjuvant breast cancer therapy have employed an adaptive design based on bayesian hierarchical models to guide treatment assignment and treatment arm discontinuation [6, 15]. Despite these changes in clinical trial design, most studies still violate the positivity assumption of causal inference, which states that a patient's probability to be assigned to any given treatment must not be zero.

Multiple models for heterogeneous treatment effect estimation in causal inference have been reported. These include lasso [4], boosting [13] and neural network based estimators [9]. All the above models follow the unconfoundedness assumption. In practical terms this means, that once we control for a patient's features X_i (for example tumor genetics or demographic covariates) the treatment assignment should be random.

Of particular relevance for this study is the R-learner, a two-step estimator of heterogeneous treatment effects [12]. The R-learner uses the Robinson's transformation to decompose the estimation of the CATE into two subsequent loss-optimizing steps. (I) Estimating the treatment propensity (the probability to be assigned to a specific treatment t given the features X_i) and conditional mean outcome (the average treatment effect for a patient with features X). (II) Estimating the CATE based on the estimated treatment propensity, the conditional mean outcome and features X_i. While the R-learner model has been implemented using penalized regression and boosted random forests, in theory it can be used with every loss-based machine learning model, including deep learning methods.

3 Problem Definition

In the following section we describe three scenarios of personalized treatment assignment and their implications for CATE estimation. As mentioned above, being able to estimate the CATE of all available treatment options would enable clinicians to potentially treat more patients with targeted therapeutics, even if they would no be included by current therapeutic protocols. We describe this desired scenario as the high-inclusion, optimal assignment scenario.

In contrast, the current assignment mechanisms in most precision oncology programs do not allow us to estimate the CATE due to strict therapeutic protocols. We refer to this scenario as the low-inclusion, strict assignment scenario. Due to ethical, medical and financial constraints, most program exploit the best available therapeutic protocols. However, following strict therapeutic protocols does not open up opportunities to estimate potential outcomes outside of the permitted treatments and identify potentially superior therapeutic protocols.

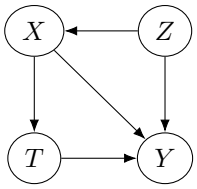

Figure 1: Proposed causal graph for precision oncology programs

We propose a scenario for precision oncology programs that follows a moderate inclusion, relaxed assignment strategy. In this scenario, similar to the low inclusion, strict assignment scenario, the assignment mechanism is grounded on a therapeutic protocol which represents the current optimal evidence for clinical decision making. However, this constantly developing therapeutic protocol is supplemented with random exploratory assignment of patients to a given treatment independent of the therapeutic protocol. The introduction of an exploratory treatment assignment preserves the positivity assumption of causal inference and is thus required for estimating the effect of unrealized, potential outcomes.

We hypothesize that assigning patients to therapeutic strategies outside the given therapeutic protocol at a rate ϵ will over time allow us to estimate the conditional average treatment effect for currently available treatment options.

4 Model Definition

4.1 Proposed Causal Graph

In this section we describe a simplified causal directed acyclic graph (DAG) for a moderate inclusion, relaxed assignment scenario and develop a theoretical model of therapeutic protocol based treatment assignments, that builds the foundation for later dataset synthesis and CATE modeling.

We hypothesize that the response Y to a treatment T is influenced by patient attributes Z, which are not observed. Based on Z we can measure a set of patient features X (such as tumor genetics and clinical variables) which guide the treatment assignment and also influence the treatment effect Y. In order to sustain the unconfoundedness assumption, we assume that given X we can fully understand the assignment mechanism and no unobserved patient attributes contained in Z influence treatment assignment. Furthermore, we adhere to the stable unit treatment variable assumption which, in medical terms, states that every treatment is only administered at one dose.

4.2 Assignment Mechanism

Based on this simplified causal graph and in order to maintain positivity we can describe the assignment mechanism in a precision oncology program as a Markov decision process. This framework is also able to represent classic randomized controlled trials.

We can describe the therapeutic protocols P for a given treatment t as a function of patient features X with a binary inclusion probability.

In this study we assume P_t to be a previously known logical function of a patient's features X_i and thus trivial to learn. However, the following model is also applicable in scenarios in which P_t is defined by either a more complex function or unknown confounding variables that are included in X_i.

$$P_t(X_i) \in \{0; 1\} \tag{1}$$

Every therapeutic protocol P is part of a set of protocols $\mathcal{P}\,\{P_1, P_2, .., P_t\}$ that are mutually exclusive, such that:

$$P_j(X_i) \neq P_k(X_i) \quad \forall\, j, k \in T \tag{2}$$

As mentioned above, the common practice in precision medicine programs includes assigning patients to a given treatment based on strict application of a set of therapeutic protocols. This practice does not

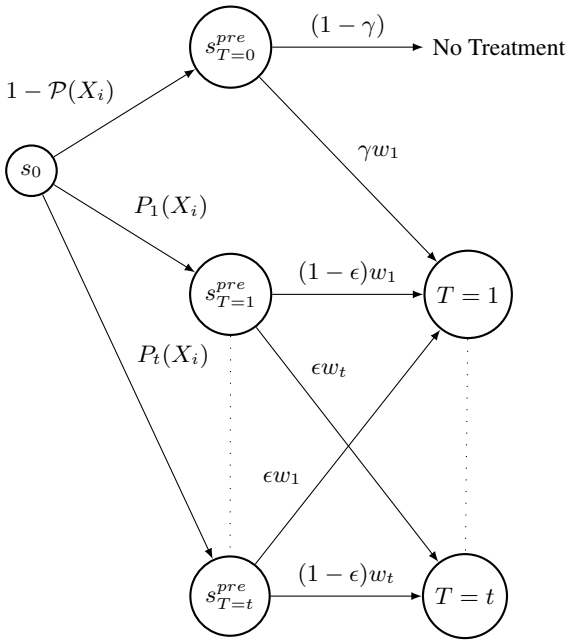

Figure 2: Proposed assignment mechanism

fulfill the positivity requirement of causal inference which demands that the probability $p(T = t|X_i)$ for a given unit X_i to be assigned every available treatment $t \in T\,\{1, 2, .., t\}$ is greater than 0.

To preserve the positivity assumption, we construct an intermediate state $s^{pre}_{T=t}$ in the assignment mechanism for every patient from which there is a cross-over probability $\epsilon \in (0, 1)$ to be assigned to any other treatment $T \neq t$.

In order to adjust ϵ to the overall probability of a patient being included to a given state $s^{pre}_{T=t}$ we introduce a weight w_t that is defined:

$$w_t = \frac{\hat{l}(P_t(X))}{\hat{l}(\mathcal{P}(X))} \tag{3}$$

where $\hat{l}(P_t(X))$ is the number of participants that are estimated to be included in the therapeutic protocol of P_t and $\hat{l}(\mathcal{P}(X))$ is the total number of participants that are estimated to be included in any available protocol.

In addition to a cross-over probability ϵ, we also introduce a cross-in probability γ that describes the rate at which patients that were not included in any protocol are allocated to treatments. Of note, there is no path linking the intermediate state $s^{pre}_{T=t}$ for any $t \in T$ to the state "No Treatment".

For the sake of simplicity, we fix γ to be a function of ϵ weighted by the estimated risk of patients not to be included in any protocol:

$$\gamma = \frac{\hat{l}(1 - \mathcal{P}(X))}{\hat{l}(\mathcal{P}(X))}\epsilon \tag{4}$$

Based on these definitions we can describe the probability of a given patient i to be assigned a given treatment t as a function of the program's protocol set $\mathcal{P}$, the patient's features X_i and the cross-over rate ϵ:

$$p(T = t|X_i) = P_t(X_i)(1 - \epsilon)w_t + (1 - \mathcal{P}(X))\gamma w_t \tag{5}$$

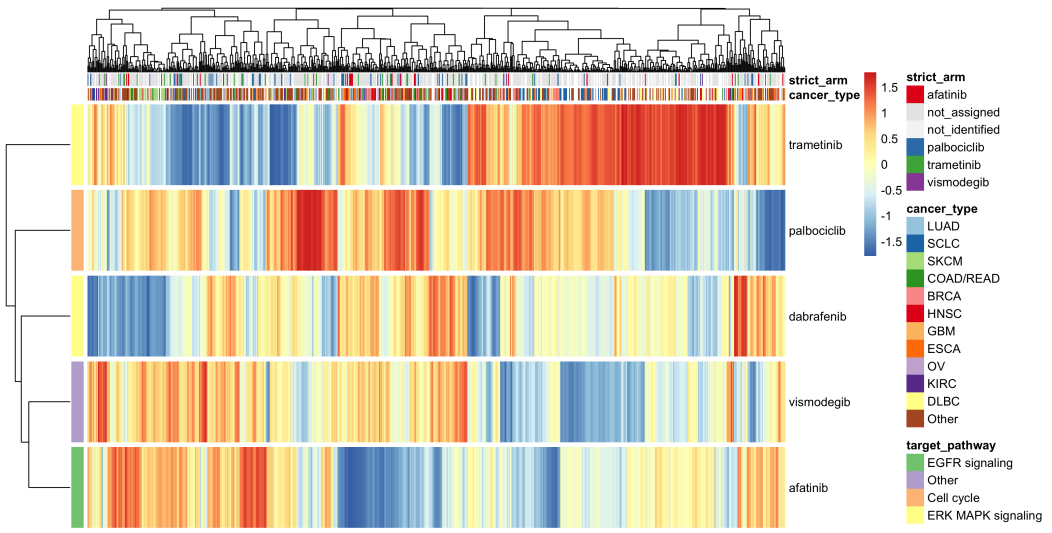

Figure 3: Drug vulnerability data for 1000 cell lines and 5 drugs

5 Dataset

We synthesized a public dataset of in-vitro cancer cell-line drug sensitivity for the purpose of causal inference evaluation [8]. In this dataset a complete matrix of treatment effects for >1000 cell-lines and >50 drugs has been measured and the IC50 values were recorded. Moreover, the dataset contains gene expression data as well as mutation status for most cell-lines.

In a first pre-processing step we focused on a set of 10 drugs that are currently used in clinical practice. We then log transformed the $IC50$ values and normalized them relative to the median $ln(IC50)$ across cell-lines for each drug.

As we are comparing the effectiveness of potential outcomes on a cell-line level, the latter step might seem counter-intuitive. However, the pharmacokinetics and phamacodynamics of therapeutic substances ex-vivo does, in general, not match in-vivo conditions. Thus, it is safer to estimate a treatment's in-vitro effect by comparing the transformed $IC50$ of a drug in a given cell-line relative to the median transformed $IC50$ of the same drug across the whole population of cell-lines.

Next we manually curated therapeutic protocols based on current clinical evidence and trial protocols with selected simplifications: (I) we excluded any protocols involving combination treatments, (II) we excluded any protocols that are based on the presence of oncogenic gene-fusions, (III) we did not include tissue type restrictions into any protocols.

We plan to use the collected therapeutic protocols according to the proposed treatment assignment model to synthesize an incomplete dataset that simulates potential observations in a precision oncology program. Figure 3 shows an example, in which the response to 5 treatments in visualized for 1000 cell lines. The *strict arm* bar underneath the dendrogram shows the results of the assignment mechanism for $\epsilon = 0$.

For the start, we propose to reduce the complexity of the cell-line features X into larger subgroups defined by (I) tissue type and (II) mutation status. Depending on the time, we will try to incorporate gene expression data as well.

6 CATE Estimation

We will estimate the CATE on the synthetic dataset using the R-learner. As described by Nie et al. [12], we can define the CATE τ in a two-step process after independently estimating the treatment propensity e and the conditional mean outcome m.

Based on this decomposition, we can perform a loss-based optimization of the CATE function. In other words, we can train a set of two machine learning algorithms to estimate the CATE on our

dataset by (I) training a model to predict m and e and (II) training a model to predict the CATE after fixing m and e. The loss of step (II) is described as the R-loss. The R-learner is trained by cross-fitting [7] both models according to the R-loss.

We propose to evaluate lasso and boosting for both modeling steps. The authors have published their code and an accompanying R package which will facilitate implementation.

7 Objective

We will evaluate the overall ability to recover conditional average treatment effects from a synthetic drug vulnerability dataset by using a modified version of the original Precision in Estimation of Heterogeneous Effect [2] (mPEHE) that has no fixed reference treatment:

$$mPEHE = \frac{1}{M}\sum_{p=1}^{M}\frac{1}{N}\sum_{i=1}^{N}((y_{p_1 i} - y_{p_0 i}) - (\hat{y}_{p_1 i} - \hat{y}_{p_0 i}))^2 \tag{6}$$

Where M is the number of unique and unordered pairs of available treatments T given by $M = \binom{t}{2}$ with t being the number of available treatments T.

An optional experiment would be to assess the estimated treatment effects in terms of a clinical recommendation system after learning the CATE model. This simple recommendation system would always pick the treatment with the highest estimated CATE for a given unit. Based on this system we could study two measures of potential clinical relevance: (I) treatment regret, which we define to be the proportion of instances in which the recommendation system does not identify the optimal treatment for a given unit and (II) treatment deviation, which we define to be the proportion of instances in which the system recommends a treatment which would not have been administered by strictly adhering to therapeutic protocols.

Finally, we are interested to measure to what extent variation of ϵ changes our model's mPEHE as well as, if time allows, regret and deviation.

8 Limitations

The current study uses in-vitro drug response data. Thus, no conclusions over clinical practice should be drawn.

The current method uses a retrospective approach to estimate assignment proportions. These proportions can only be estimated if prior information about biomarkers and the study population are available.

9 Outlook

The findings of this study should be validated with a second independent drug vulnerability dataset and other means of perturbation and biological models. Along these lines, the number of treatments under evaluation, as well as the number of features m in X could be increased.

The proposed assignment mechanism uses a fixed parameter ϵ to control the cross-over rate. In a subsequent project it would be interesting to see if ϵ or a more complex assignment mechanism can be learned and to what extent the overall task of controlling a precision oncology program with optimal CATE estimation capability can be framed as a policy learning problem that optimizes exploration against exploitation.

10 Discussion

One source of non-adherence to current therapeutic protocols are medical constraints such as side-effects and financial constraints such as limited insurance coverage of a recommended treatment. While these deviations might enable estimating the conditional average treatment effect for a set of possible interventions, it is not clear if they are going to be sufficient to minimize the precision of

estimation of heterogeneous treatment effects to a sufficient degree. Thus, depending on the results of this study, we want to encourage the community to engage in a continuous discussion for optimal trial design and data collection strategies that enable the estimation of conditional treatment effects, while respecting ethical, medical, scientific and financial boundaries.

References

[1] David Blumenthal and Marilyn Tavenner. "A New Initiative on Precision Medicine". In: *The New England journal of medicine* 363.1 (2010), pp. 1–3. ISSN: 15334406. DOI: 10.1056/NEJMp1002530. arXiv: arXiv:1011.1669v3. URL: http://scholar.google.com/scholar?hl=en%7B%5C&%7DbtnG=Search%7B%5C&%7Dq=intitle:New+engla+nd+journal%7B%5C#%7D0.

[2] Jennifer L. Hill. "Bayesian Nonparametric Modeling for Causal Inference". In: *Journal of Computational and Graphical Statistics* 20.1 (Jan. 2011), pp. 217–240. ISSN: 1061-8600. DOI: 10.1198/jcgs.2010.08162. URL: http://www.tandfonline.com/doi/abs/10.1198/jcgs.2010.08162.

[3] Jeannie Hou et al. "Improved Survival with Vemurafenib in Melanoma with BRAF V600E Mutation". In: *New England Journal of Medicine* 364.26 (2011), pp. 2507–2516. ISSN: 0028-4793. DOI: 10.1056/nejmoa1103782.

[4] Kosuke Imai and Marc Ratkovic. "Estimating treatment effect heterogeneity in randomized program evaluation". In: *Annals of Applied Statistics* 7.1 (2013), pp. 443–470. ISSN: 19326157. DOI: 10.1214/12-AOAS593. arXiv: arXiv:1305.5682v1.

[5] Jonathan Ledermann et al. "Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: A preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial". In: *The Lancet Oncology* 15.8 (2014), pp. 852–861. ISSN: 14745488. DOI: 10.1016/S1470-2045(14)70228-1. URL: http://dx.doi.org/10.1016/S1470-2045(14)70228-1.

[6] Rajeshwari Sridhara et al. "Current Statistical Challenges in Oncology Clinical Trials in the Era of Targeted Therapy". In: *Statistics in Biopharmaceutical Research* 7.4 (2015), pp. 348–356. ISSN: 19466315. DOI: 10.1080/19466315.2015.1094673.

[7] Victor Chernozhukov et al. "Double/Debiased Machine Learning for Treatment and Causal Parameters". In: *arxiv* Ml (2016), pp. 1–30. ISSN: 0002-8282. DOI: 10.1920/wp.cem.2016.4916. arXiv: 1608.00060. URL: http://arxiv.org/abs/1608.00060.

[8] Francesco Iorio et al. "A Landscape of Pharmacogenomic Interactions in Cancer". In: *Cell* 166.3 (2016), pp. 740–754. ISSN: 10974172. DOI: 10.1016/j.cell.2016.06.017. arXiv: NIHMS150003.

[9] Uri Shalit, Fredrik D. Johansson, and David Sontag. "Estimating individual treatment effect: generalization bounds and algorithms". In: (June 2016). ISSN: 0272-3638. DOI: 10.1146/annurev-pathol-011811-132457. arXiv: 1606.03976. URL: https://arxiv.org/abs/1606.03976%20http://arxiv.org/abs/1606.03976.

[10] Anthony Letai. *Functional precision cancer medicine-moving beyond pure genomics*. 2017. DOI: 10.1038/nm.4389. URL: http://dx.doi.org/10.1038/nm.4389.

[11] Christophe Massard et al. "High-throughput genomics and clinical outcome in hard-to-treat advanced cancers: Results of the MOSCATO 01 trial". In: *Cancer Discovery* 7.6 (2017), pp. 586–595. ISSN: 21598290. DOI: 10.1158/2159-8290.CD-16-1396.

[12] Xinkun Nie and Stefan Wager. "Quasi-Oracle Estimation of Heterogeneous Treatment Effects". In: *arxiv* 2017 (2017), pp. 1–46. arXiv: 1712.04912. URL: http://arxiv.org/abs/1712.04912.

[13] Scott Powers et al. "Some methods for heterogeneous treatment effect estimation in high-dimensions". In: *arxiv* (2017), pp. 1–28. arXiv: arXiv:1707.00102v1.

[14] Janet Woodcock and Lisa M LaVange. "Master Protocols to Study Multiple Therapies, Multiple Diseases, or Both." In: *The New England journal of medicine* 377.1 (2017), pp. 62–70. ISSN: 1533-4406. DOI: 10.1056/NEJMra1510062. URL: http://www.ncbi.nlm.nih.gov/pubmed/28679092.

[15] Shinjo Yada and Chikuma Hamada. "Application of Bayesian hierarchical models for phase I/II clinical trials in oncology". In: *Pharmaceutical Statistics* 16.2 (2017), pp. 114–121. ISSN: 15391612. DOI: 10.1002/pst.1793.