Learning Counterfactual Representations for Estimating Individual Dose-Response Curves

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Abstract

Estimating what would be an individual’s potential response to varying levels of exposure to a treatment is of high practical relevance for several important fields, such as healthcare, economics and public policy. However, existing methods for learning to estimate such counterfactual outcomes from observational data are either focused on estimating average dose-response curves, limited to settings in which treatments do not have an associated dosage parameter, or both. Here, we present a novel machine-learning framework towards learning counterfactual representations for estimating individual dose-response curves for any number of treatment options with continuous dosage parameters. Building on the established potential outcomes framework, we introduce new performance metrics, model selection criteria, model architectures, and open benchmarks for estimating individual dose-response curves. Our experiments show that the methods developed in this work set a new state-of-the-art in estimating individual dose-response curves.

1. Introduction

Estimating dose-response curves from observational data is an important problem in many domains. In medicine, for example, we would be interested in using data of people that have been treated in the past to predict which treatments and associated dosages would lead to better outcomes for new patients (Imbens, 2000). This question is, at its core, a counterfactual one, i.e. we are interested in predicting what would have happened if we were to give a patient a specific treatment at a specific dosage in a given situation.

Answering such counterfactual questions is a challenging task that requires either further assumptions about the underlying data-generating process or prospective interventional experiments, such as randomised controlled trials (RCTs) (Stone, 1993; Pearl, 2009; Peters et al., 2017). However, performing prospective experiments is expensive, time-consuming, and, in many cases, ethically not justifiable (Schafer, 1982). Two aspects make estimating counterfactual outcomes from observational data alone difficult (Yoon et al., 2018; Schwab et al., 2018): Firstly, we only observe the factual outcome and never the counterfactual outcomes that would potentially have happened had we chosen a different treatment option. In medicine, for example, we only observe the outcome of giving a patient a specific treatment at a specific dosage, but we never observe what would have happened if the patient was instead given a potential alternative treatment or a different dosage of the same treatment. Secondly, treatments are typically not assigned at random in observational data. In the medical setting, physicians take a range of factors, such as the patient’s expected response to the treatment, into account when choosing a treatment option. Due to this treatment assignment bias, the treated population may differ significantly from the general population. A supervised model naively trained to minimise the factual error would overfit to the properties of the treated group, and therefore not generalise to the entire population.

To address these problems, we introduce a novel framework for training neural networks for counterfactual inference that extends to any number of treatments with continuous dosage parameters. In order to control for the biased assignment of treatments in observational data, we combine our method with a variety of regularisation schemes originally developed for the discrete treatment setting, such as distribution matching (Johansson et al., 2016; Shalit et al., 2017), propensity dropout (PD) (Alaa et al., 2017), and matching on balancing scores (Rosenbaum & Rubin, 1983; Ho et al., 2007; Schwab et al., 2018). In addition, we devise new performance metrics, model selection criteria and open benchmarks for estimating individual dose-response curves. Our experiments demonstrate that the methods developed in this work set a new state-of-the-art in inferring individual dose-response curves. The source code for this work is available at https://github.com/d909b/drnet.
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Contributions. We present the following contributions:

- We introduce a novel framework for training neural networks for counterfactual inference that, in contrast to existing methods, is suitable for estimating counterfactual outcomes for any number of treatment options with associated exposure parameters.
- We develop new performance metrics, model selection criteria, model architectures, and open benchmarks for estimating individual dose-response curves.
- We extend state-of-the-art methods for counterfactual inference for two non-parametric treatment options to the multiple parametric treatment options setting.
- We perform extensive experiments that show that our method sets a new state-of-the-art in inferring individual dose-response curves from observational data across several datasets with varying characteristics.

2. Related Work

Background. Causal analysis of treatment effects with rigorous experiments is, in many domains, an essential tool for validating interventions. In medicine, prospective experiments, such as RCTs, are the de facto gold standard to evaluate whether a given treatment is efficacious in treating a specific indication across a population (Carpenter, 2014; Bothwell et al., 2016). However, performing prospective experiments is expensive, time-consuming, and often not possible for ethical reasons (Schafer, 1982). Historically, there has therefore been considerable interest in developing methodologies for performing causal inference using readily available observational data (Granger, 1969; Angrist et al., 1996; Rosenbaum & Rubin, 1983; Robins et al., 2000; Pearl, 2009; Hernán & Robins, 2016; Lake et al., 2017). The naïve approach of training supervised models to minimise the observed factual error is in general not a suitable choice for counterfactual inference tasks due to treatment assignment bias and the inability to observe counterfactual outcomes. To address the shortcomings of unsupervised and supervised learning in this setting, several adaptations to established machine-learning methods that aim to enable the estimation of counterfactual outcomes from observational data have recently been proposed (Johansson et al., 2016; Shalit et al., 2017; Wager & Athey, 2017; Alaa & van der Schaar, 2017; Alaa et al., 2017; Louizos et al., 2017; Yoon et al., 2018; Schwab et al., 2018). In this work, we build on several of these advances to develop a novel machine-learning framework for estimating individual dose-response.

Estimating Individual Treatment Effects\(^1\) (ITE). Matching methods (Ho et al., 2007) are among the simplest, and most widely used, approaches to causal inference from observational data. Matching methods estimate the counterfactual outcome of a sample \(X\) to a treatment \(t\) using the observed factual outcome of its nearest neighbours that have received \(t\). Propensity score matching (PSM) (Rosenbaum & Rubin, 1983) combats the curse of dimensionality of matching directly on the covariates \(X\) by instead matching on the scalar probability \(p(t|X)\) of receiving a treatment \(t\) given the covariates \(X\). Another category of approaches uses adjusted regression models that receive both the covariates \(X\) and the treatment \(t\) as inputs. The simplest such model is Ordinary Least Squares (OLS), which may use either one model for all treatments, or a separate model for each treatment (Kallus, 2017). More complex models based on neural networks, like Treatment Agnostic Representation Networks (TARNETs), may be used to build non-linear regression models (Shalit et al., 2017). Estimators that combine a form of adjusted regression with a model for the exposure, such as PSM or PD (Alaa et al., 2017), are referred to as doubly robust (Funk et al., 2011). In addition to OLS and neural networks, tree-based estimators, such as Bayesian Additive Regression Trees (BART) (Chipman et al., 2010; Chipman & McCulloch, 2016) and Causal Forests (CF) (Wager & Athey, 2017), and distribution modelling methods, such as Causal Multi-task Gaussian Processes (CMGP) (Alaa & van der Schaar, 2017), Causal Effect Variational Autoencoders (CEVAEs) (Louizos et al., 2017), and Generative Adversarial Nets for inference of Individualised Treatment Effects (GANITE) (Yoon et al., 2018), have also been proposed for ITE estimation.\(^2\) Other approaches, such as balancing neural networks (BNNs) (Johansson et al., 2016) and counterfactual regression networks (CFRNET) (Shalit et al., 2017), attempt to achieve balanced covariate distributions across treatment groups by explicitly minimising the empirical discrepancy distance between treatment groups using metrics such as the Wasserstein distance (Cuturi, 2013). Most of the works mentioned above focus on the simplest setting with two available treatment options without associated dosage parameters. A notable exception is the generalised propensity score (GPS) (Imbens, 2000) that extends the original PSM methodology to treatments with associated continuous dosage parameters.

In contrast to existing methods, we present the first doubly-robust, non-linear machine-learning approach to learn to estimate individual dose-response curves for multiple available treatments with a continuous dosage parameter from observational data. We address treatment assignment bias using several known regularisation schemes for counterfactual inference. To facilitate future research in this important

\(^1\) The ITE is sometimes also referred to as the conditional average treatment effect (CATE).

\(^2\) See (Knaus et al., 2018) and (Schwab et al., 2018) for empirical comparisons of large-numbers of machine-learning methods for ITE estimation for two and more available treatment options.
area, we introduce new performance metrics, model selection criteria, and open benchmarks. We believe this work could be particularly important for applications in precision medicine, where the current state-of-the-art of estimating the average dose response across the entire population does not take into account individual differences, even though large differences in dose-response between individuals are well-documented for many diseases (Zaske et al., 1982; Oldenhof et al., 1988; Campbell et al., 2007).

3. Methodology

**Problem Statement.** We consider a setting in which we are given \( N \) observed samples \( X \) with \( p \) pre-treatment covariates \( x_i \) and \( i \in [0, p] \). For each sample, the potential outcomes \( y_t(n,s) \) are the response of the \( n \)th sample to a treatment \( t \) out of the set of \( k \) available treatment options \( T = \{0, \ldots, k-1\} \) each associated with a dosage parameter \( s_t \in \{s_t \in \mathbb{R}, a_t > 0 \mid a_t \leq s \leq b_t \} \), where \( a_t \) and \( b_t \) are the minimum and maximum dosage for treatment \( t \), respectively. The set of treatments \( T \) can have two or more available treatment options. As training data, we receive factual samples \( X \) and their observed outcomes \( y_f(n,s) \) after applying a specific treatment \( f \) at a specific dosage \( s_f \). Using the training data with factual outcomes, we wish to train a predictive model to produce accurate estimates \( \hat{y}_t(n,s) \) of the potential outcomes across the entire range of \( s \) for all available treatment options \( t \). We refer to the range of potential outcomes \( y_t(n,s) \) across \( s \) as the individual dose-response curve of the \( n \)th sample. The presented setting is a direct extension of the Rubin-Neyman potential outcomes framework (Rubin, 2005).

**Assumptions.** Following (Imbens, 2000; Lechner, 2001), we assume unconfoundedness, which consists of three key parts: (1) Conditional Independence Assumption: The assignment to treatment \( t \) is independent of the outcome \( y_t \) given the pre-treatment covariates \( X \), (2) Common Support Assumption: For all values of \( X \), it must be possible to observe all treatment options with a probability greater than 0, and (3) Stable Unit Treatment Value Assumption: The observed outcome of any one unit must be unaffected by the assignments of treatments to other units.

**Metrics.** To enable a meaningful comparison of models in the presented setting, we propose new metrics that cover several desirable aspects of models trained for estimating individual dose-response curves. Our proposed metrics respectively aim to measure a predictive model’s ability (1) to recover the dosage-response curve across the entire range of dosage values, (2) to determine the optimal dosage point for each treatment, and (3) to deduce the optimal treatment policy overall, including selection of the right treatment and dosage point, for each individual case. To measure to what degree a model covers the entire range of individual dose-response curves, we use the mean integrated square error (MISE) between the true dose-response curve and the predicted dose-response \( \hat{y} \) as estimated by the model over \( N \) samples, all treatments \( T \), and the entire range \([a_t, b_t]\) of dosages \( s \).

\[
\text{MISE} = \frac{1}{N} \sum_{t=1}^{T} \sum_{n=1}^{N} \int_{s=a_t}^{b_t} \left( y_t(n,s) - \hat{y}_t(n,s) \right)^2 ds \quad (1)
\]

To further measure a model’s ability to determine the optimal dosage point for each individual case, we calculate the mean dosage policy error (DPE). The mean dosage policy error is the mean squared error in outcome \( y \) associated with using the optimal dosage point \( \hat{s}_t \) according to the predictive model to determine the true optimal dosage point \( s_t \) over \( N \) samples and all treatments \( T \).

\[
\text{DPE} = \frac{1}{N} \sum_{t=1}^{T} \sum_{n=1}^{N} \left( y_t(n,s_t) - y_t(n,\hat{s}_t) \right)^2 \quad (2)
\]

where \( \hat{s}_t \) and \( s_t \) are the optimal3 dosage point according to the true dose-response curve and the estimated dose-response curve, respectively.

\[
\hat{s}_t = \arg \max_{s \in [a_t, b_t]} y_t(n, s) \quad(3) \quad s_t = \arg \max_{s \in [a_t, b_t]} \hat{y}_t(n, s) \quad (4)
\]

Finally, the policy error (PE) measures a model’s ability to determine the optimal treatment policy for individual cases, i.e. how much worse the outcome would be when using the estimated best optimal treatment option compared to the true optimal treatment option and dosage.

\[
\text{PE} = \frac{1}{N} \sum_{n=1}^{N} \left( y_t(n,\hat{s}_t) - y_t(n,s_t) \right)^2 \quad (5)
\]

where

\[
\hat{s}_t = \arg \max_{t \in T} y_t(n, \hat{s}_t) \quad(6) \quad s_t = \arg \max_{t \in T} y_t(n, s_t) \quad (7)
\]

are the optimal treatment option according to the ground truth \( y \) and the predictive model, respectively. In general, we cannot calculate the MISE, DPE or PE without knowledge of the outcome-generating process, since the true dose-response function \( y_t(n,s) \) is unknown.

**Model Selection.** Given multiple models, it is not trivial to decide which model would perform better at counterfactual tasks, since we in general do not have access to the true dose-response to calculate error metrics like the ones listed above. We therefore propose the use of a nearest neighbour approximation of the MISE to perform model selection using observed factual data only. We calculate the nearest neighbour approximation NN-MISE of the MISE using:

\[
\text{NN-MISE} = \frac{1}{N} \sum_{t=1}^{T} \sum_{n=1}^{N} \int_{s=a_t}^{b_t} \left( y_{NN,t}(n,s) - \hat{y}_t(n,s) \right)^2 ds \quad (8)
\]

3We follow the convention that a higher outcome value is better.
where we substitute the true dose-response $y_t$ with the outcome $y_{NN,t}$ of an observed factual nearest neighbour of the $t$th sample at a dosage point $s$ from the training set. Using the nearest neighbour approximation of the MISE, we are able to perform model selection without access to the true counterfactual outcomes $y$.

**Model Architecture.** Model structure plays an important role in learning representations for counterfactual inference with neural networks (Shalit et al., 2017; Schwab et al., 2018; Alaa & Schaar, 2018). A particularly challenging aspect of training neural networks for counterfactual inference is that the influence of the treatment indicator variable $t$ may be lost in high-dimensional hidden representations (Shalit et al., 2017). To address this problem for the setting of two available treatments without dosage parameters, Shalit et al. (2017) proposed the TARNET architecture that uses a shared base network and separate head networks for both treatment options. In TARNETs, the head networks are only trained on samples that received the respective treatment. Schwab et al. (2018) extended the TARNET architecture to the multiple treatment setting by using $k$ separate head networks, one for each treatment option. In the setting with multiple treatment options with associated dosage parameters, this problem is further compounded because we must maintain not only the influence of $t$ on the hidden representations throughout the network, but also the influence of the continuous dosage parameter $s$. To ensure the influence of both $t$ and $s$ on hidden representations, we propose a hierarchical extension to the TARNET architecture for multiple treatments called dose response network (DRNet, Figure 1). DRNets ensure that the dosage parameter $s$ maintains its influence by assigning a head to each of $E \in \mathbb{N}$ equally-sized dosage strata that subdivide the range of potential dosage parameters $[a_t, b_t]$. The hyperparameter $E$ defines the trade-off between computational performance and the resolution $\frac{(b-a)}{E}$ at which the range of dosage values is partitioned. To further attenuate the influence of the dosage parameter $s$ within the head layers, we additionally repeatedly append $s$ to each hidden layer in the head layers. We motivate the proposed hierarchical structure with the effectiveness of the regress and compare approach to counterfactual inference (Kallus, 2017), where one builds a separate estimator for each available treatment option. Separate models for each treatment option suffer from data-sparsity, since only units that received each respective treatment can be used to train a per-treatment model and there may not be a large number of samples available for each treatment. DRNets alleviate the issue of data-sparsity by enabling information to be shared both across the entire range of dosages through the treatment layers and across treatments through the base layers.

**Regularisation Schemes.** DRNets are doubly-robust estimators if they are used with regularisation schemes developed to further address treatment assignment bias. We therefore evaluated DRNets using distribution matching (Shalit et al., 2017), propensity dropout (Alaa et al., 2017), matching on the entire dataset (Ho et al., 2007), and on the batch level (Schwab et al., 2018) (Details in Appendix A).

4. Experiments

Our experiments aimed to answer the following questions:

1. What is the comparative performance of our proposed approach compared to state-of-the-art methods for estimating individual dose-response?
2. How do varying choices of $E$ influence counterfactual inference performance?
3. How does increasing treatment assignment bias affect the performance of dose-response estimators?
4. How does the presence of hidden confounding affect the performance of DRNets?
Table 1. Comparison of the benchmark datasets used in our experiments. We evaluate on three semi-synthetic datasets with varying numbers of treatments and samples.

| Dataset      | Type        | # Samples | # Features | # Treatments |
|--------------|-------------|-----------|------------|--------------|
| News         | semi-synthetic | 5000     | 2870       | 2/4/8/16     |
| MVICU        | semi-synthetic | 8040     | 49         | 3            |
| TCGA         | semi-synthetic | 9659     | 20531      | 3            |

4.1. Datasets

Using real-world data, we performed experiments on three semi-synthetic datasets with two and more treatment options to gain a better understanding of the empirical properties of our proposed approach. In order to cover a broad range of settings, we chose datasets with different outcome and treatment assignment functions and varying numbers of samples, features and treatments (Table 1).

**News.** The News benchmark consisted of 5000 randomly sampled news articles from the NY Times corpus and was introduced as an benchmark for counterfactual inference in the setting with two treatment options without an associated dosage parameter (Johansson et al., 2016). We extended the original dataset specification (Johansson et al., 2016; Schwab et al., 2018) to enable the simulation of any number of treatments with associated dosage parameters. The samples $X$ were news articles that consist of word counts $x_t \in \mathbb{N}$, outcomes $y_{s,t} \in \mathbb{R}$ that represent the reader’s opinion of the news item, and a normalised dosage parameter $s_t \in \{0, 1\}$ that represents the viewer’s reading time. There was a variable number of available treatment options $t$ that corresponded to various devices that could be used to view the News items, e.g. smartphone, tablet, desktop, television or others (Johansson et al., 2016). We trained a topic model on the entire NY Times corpus to model that consumers prefer to read certain media items on specific topics. We assigned a random Gaussian outcome distribution with mean $\mu$ and standard deviation $\sigma$ to each centroid. For each sample, we drew ideal potential outcomes from that Gaussian outcome distribution $\tilde{y}_t \sim \mathcal{N}(\mu_t, \sigma_t) + \epsilon$ with $\epsilon \sim \mathcal{N}(0, 0.15)$. The dose response $\tilde{y}_s$ was drawn from a distance-weighted mixture of two Gaussians $\tilde{y}_s \sim d_0\mathcal{N}(\mu_{s,0}, \sigma_{s,0}) + d_1\mathcal{N}(\mu_{s,1}, \sigma_{s,1})$ using topic space distances $d = \text{softmax}(D(z(X), z_s, i))$ and the Euclidean distance as distance metric $D$. We assigned the observed treatment $t$ using $t|x \sim \text{Bern} (\text{softmax}(\kappa \tilde{y}_t \tilde{y}_s))$ with a treatment assignment bias coefficient $\kappa$ and an exponentially distributed observed dosage $s_t$ using $s_t \sim \text{Exp}(\beta)$ with $\beta = 0.25$. The true potential outcomes $y_{s,t} = C \tilde{y}_t \tilde{y}_s$ were the product of $\tilde{y}_t$ and $\tilde{y}_s$ scaled by a coefficient $C = 50$. We used four different variants of this dataset with $k = 2, 4, 8, \text{and} 16$ viewing devices, and $\kappa = 10, 10, 10, \text{and} 7$, respectively. Higher values of $\kappa$ indicate a higher expected treatment assignment bias depending on $\tilde{y}_t \tilde{y}_s$, with $\kappa = 0$ indicating no assigned bias.

**Mechanical Ventilation in the Intensive Care Unit (MVICU).** The MVICU benchmark models patients’ responses to different configurations of mechanical ventilation in the intensive care unit. The data was sourced from the publicly available MIMIC III database (Saeed et al., 2011). The samples $X$ consisted of the last observed measurements $x_i$ of various biosignals, including respiratory, cardiac and ventilation signals. The outcomes were arterial blood gas readings of the ratio of arterial oxygen partial pressure to fractional inspired oxygen $PaO_2/FiO_2$ which, at values lower than 300, are used as one of the clinical criteria for the diagnosis Acute Respiratory Distress Syndrome (ARDS) (Ferguson et al., 2012). We modelled a mechanical ventilator with $k = 3$ adjustable treatment parameters: (1) the fraction of inspired oxygen, (2) the positive end-expiratory pressure in the lungs, and (3) tidal volume. To model the outcomes, we use the same procedure as for the News benchmark with a Gaussian outcome function and a mixture of Gaussian dose-response function, with the exception that we did not make use of topic models and instead performed the similarity comparisons $D$ in covariate space. We used a treatment assignment bias $\kappa = 10$ and a scaling coefficient $C = 150$. Treatment dosages were drawn according to $s_t \sim \mathcal{N}(\mu_{dose,t}, 0.1)$, where the distribution means were defined as $\mu_{dose} = (0.6, 0.65, 0.4)$ for each treatment.

**The Cancer Genomic Atlas (TCGA).** The TCGA project collected gene expression data from various types of cancers in 9659 individuals (Weinstein et al., 2013). There were $k = 3$ available clinical treatment options: (1) medication, (2) chemotherapy, and (3) surgery. We used a synthetic outcome function that simulated the risk of cancer recurrence after receiving either of the treatment options based on the real-world gene expression data. We standardised the gene expression data using the mean and standard deviations of gene expression at each gene locus for normal tissue in the training set. To model the outcomes, we followed the same approach as in the MVICU benchmark with similarity comparisons done in covariate space using the cosine similarity as distance metric $D$, and parameterised with $\kappa = 10$ and $C = 50$. Treatment dosages in the TCGA benchmark were drawn according to $s_t \sim \mathcal{N}(0.65, 0.1)$. 

[^4]: https://archive.ics.uci.edu/ml/datasets/bag-of-words
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4.2. Experimental Setup

Models. We evaluated DRNet, ablations, baselines, and all relevant state-of-the-art methods: k-nearest neighbours (kNN) (Ho et al., 2007), BART (Chipman et al., 2010; Chipman & McCulloch, 2016), CF (Wager & Athey, 2017), GANITE (Yoon et al., 2018), TARNET (Shalit et al., 2017), and GPS (Imbens, 2000) using the "causaldrf" package (Galagate, 2016). We evaluated which regularisation strategy for learning counterfactual representations is most effective by training DRNets using a Wasserstein regulariser between treatment group distributions (+ Wasserstein) (Shalit et al., 2017), PD (+ PD) (Alaa et al., 2017), batch matching (+ PM) (Schwab et al., 2018), and matching the entire training set as a preprocessing step (Ho et al., 2011) using the PM algorithm (+ PSM_PM) (Schwab et al., 2018). To determine whether the DRNet architecture is more effective than its alternatives at learning representations for counterfactual inference in the presented setting, we also evaluated (1) a multi-layer perceptron (MLP) that received the treatment index $t$ and dosage $s$ as additional inputs, and (2) a TARNET for multiple treatments that received the dosage $s$ as an extra input (TARNET) (Johansson et al., 2016; Schwab et al., 2018) with all other hyperparameters beside the architecture held equal. As a final ablation of DRNet, we tested whether appending the dosage parameter $s$ to each hidden layer in the head networks is effective by also training DRNets that only receive the dosage parameter once in the first hidden layer of the head network (- Repeat). We naively extended CF, GANITE and BART by adding the dosage as an additional input covariate, because they were not designed for parametric treatments.

Hyperparameters. To ensure a fair comparison of the tested models, we took a systematic approach to hyperparameter search. Each model was given exactly the same number of hyperparameter optimisation runs with hyperparameters chosen at random from predefined hyperparameter ranges (Appendix B) for each dataset. We used 5 hyperparameter optimisation runs for each model on TCGA and 10 on all other benchmarks. Furthermore, we used the same random seed for each model, i.e. all models were evaluated on exactly the same sets of hyperparameter configurations. After computing the hyperparameter runs, we chose the best model based on the validation set NN-MISE. Note that this setup does not ensure optimality for any model. However, it does ensure that each model received the same degree of hyperparameter optimisation. For all DRNets and ablations, we used a fixed number $E = 5$ of dosage strata.

Metrics. For each dataset and model, we calculated the $\sqrt{\text{MISE}}$, $\sqrt{\text{DPE}}$, and $\sqrt{\text{PE}}$. We used Romberg integration with 64 equally spaced samples from $y_t$ and $\hat{y}_t$ to compute the inner integral over the range of dosage parameters necessary for the MISE metric. To compute the optimal dosage points and treatment options in the DPE and PE, we used Sequential Least Squares Programming (SLSQP) to determine the respective maxima of $y_t(n, s)$ and $\hat{y}_t(n, s)$ numerically.

Figure 2. Analysis of the effect of choosing various numbers of dosage strata $E$ (x-axis) on MISE (red), DPE (blue), PE (orange) and Time needed for training and evaluation (black) as calculated on the test set of the MVICU benchmark. Metrics were normalised to the range $[0, 1]$. All hyperparameters besides $E$ were held equal. We found that performance improves significantly across MISE, DPE and PE as we increase the resolution at which the dosage range is partitioned. However, a higher $E$ also consistently increased the computation time used for training and prediction.

Figure 3. Comparison of DRNet (red), TARNET (blue), MLP (yellow) and GPS (purple) in terms of their $\sqrt{\text{MISE}}$ (top) and $\sqrt{\text{DPE}}$ (bottom) for varying levels of treatment assignment bias $\kappa$ (x-axis) on News-2. DRNet performs significantly better than other methods across the entire evaluated range of treatment assignment bias values, and is more robust to increasing levels of $\kappa$. 
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Table 2. Comparison of methods for counterfactual inference with multiple parametric treatments on News-2, News-4 and News-8. We report the mean value ± standard deviation of \( \sqrt{\text{MISE}} \), \( \sqrt{\text{DPE}} \), and \( \sqrt{\text{PE}} \) on the respective test sets over 5 repeat runs with new random seeds. \( \dagger \) = significantly different from DRNet (\( \alpha < 0.05 \)).

| Method     | News-2 \( \sqrt{\text{MISE}} \) | News-2 \( \sqrt{\text{DPE}} \) | News-2 \( \sqrt{\text{PE}} \) | News-4 \( \sqrt{\text{MISE}} \) | News-4 \( \sqrt{\text{DPE}} \) | News-4 \( \sqrt{\text{PE}} \) | News-8 \( \sqrt{\text{MISE}} \) | News-8 \( \sqrt{\text{DPE}} \) | News-8 \( \sqrt{\text{PE}} \) |
|------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| DRNet      | 8.0 ± 0.1                       | 14.0 ± 0.1                      | 15.7 ± 0.2                      | 14.3 ± 0.2                      | 15.5 ± 0.4                      | 10.2 ± 0.1                      | 17.2 ± 0.6                      | 15.1 ± 0.2                      |                                  |
| - Repeat   | 9.0 ± 0.1                       | 17.5 ± 0.1                      | 20.4 ± 9.6                      | 18.5 ± 3.8                      | 20.0 ± 10.0                     | 10.3 ± 0.1                      | 16.8 ± 2.9                      | 24.3 ± 12.0                     |                                  |
| + Wasserstein | 7.7 ± 0.2                      | 13.8 ± 0.1                      | 15.2 ± 0.1                      | 14.2 ± 0.3                      | 15.4 ± 0.5                      | 10.0 ± 0.0                      | 16.7 ± 0.6                      | 15.6 ± 1.1                      |                                  |
| + PD       | 9.0 ± 0.2                       | 13.7 ± 0.1                      | 15.3 ± 0.6                      | 14.3 ± 0.2                      | 12.8 ± 0.0                      | 10.6 ± 0.2                      | 17.6 ± 0.0                      | 14.9 ± 0.0                      |                                  |
| + PM       | 8.4 ± 0.3                       | 13.7 ± 0.1                      | 15.1 ± 0.1                      | 13.9 ± 0.5                      | 12.4 ± 0.5                      | 11.4 ± 0.3                      | 21.3 ± 2.7                      | 29.3 ± 7.2                      |                                  |
| + PSM\(_{PM}\) | 8.6 ± 0.1                      | 14.0 ± 0.1                      | 16.2 ± 0.4                      | 14.3 ± 0.1                      | 15.3 ± 0.3                      | 11.5 ± 0.2                      | 19.5 ± 1.3                      | 23.7 ± 7.3                      |                                  |
| MLP        | 15.3 ± 0.1                      | 49.5 ± 0.1                      | 14.5 ± 0.0                      | 43.2 ± 0.1                      | 49.6 ± 0.0                      | 13.9 ± 0.1                      | 39.8 ± 0.4                      | 48.5 ± 0.7                      |                                  |
| TARNET     | 15.5 ± 0.1                      | 45.0 ± 0.1                      | 15.4 ± 0.0                      | 41.5 ± 1.1                      | 48.0 ± 1.8                      | 14.7 ± 0.1                      | 38.6 ± 1.1                      | 47.7 ± 1.1                      |                                  |
| GANITE     | 16.8 ± 0.1                      | 39.4 ± 0.1                      | 15.6 ± 0.1                      | 35.5 ± 0.1                      | 40.3 ± 0.3                      | 14.8 ± 0.1                      | 32.6 ± 0.2                      | 42.7 ± 0.4                      |                                  |
| kNN        | 16.2 ± 0.0                      | 44.6 ± 0.0                      | 14.7 ± 0.0                      | 41.4 ± 0.0                      | 42.1 ± 0.0                      | 15.0 ± 0.0                      | 39.2 ± 0.0                      | 45.5 ± 0.0                      |                                  |
| GPS        | 14.7 ± 0.1                      | 42.3 ± 0.0                      | 24.7 ± 0.1                      | 34.7 ± 0.0                      | 13.3 ± 0.0                      | 22.9 ± 0.0                      | 22.5 ± 0.0                      | 13.3 ± 0.0                      |                                  |
| CF         | 19.2 ± 0.0                      | 32.5 ± 0.0                      | 18.2 ± 0.0                      | 38.7 ± 0.0                      | 45.9 ± 0.0                      | 19.2 ± 0.0                      | 40.2 ± 0.0                      | 49.0 ± 0.0                      |                                  |
| BART       | 13.8 ± 0.2                      | 31.6 ± 1.4                      | 14.0 ± 0.1                      | 25.0 ± 1.5                      | 34.6 ± 4.2                      | 13.0 ± 0.1                      | 23.1 ± 0.4                      | 44.5 ± 1.2                      |                                  |

5. Results and Discussion

Counterfactual Inference. In order to evaluate the relative performances of the various methods across a wide range of settings, we compared the performances of the listed models for counterfactual inference on the News-2, News-4 and News-8 benchmarks (Table 2) and the News-16, MVICU and TCGA benchmarks (Table 3). Across the benchmarks, we found that DRNets significantly outperformed all existing state-of-the-art methods in terms of all three metrics with the exception of the PE on News-8, where DRNets achieved the second-best result after GPS. We also found that DRNets that used additional regularisation strategies outperformed vanilla DRNets on News-2, News-4, News-8 and News-16. However, on MVICU and TCGA, DRNets that used additional regularisation performed similarly as standard DRNets. Where regularisation was effective, Wasserstein regularisation between treatment groups (+ Wasserstein) and batch matching (+ PM) were generally slightly more effective than PSM\(_{PM}\) and PD. In addition, not repeating the dosage parameter for each layer in the per-dosage range heads of a DRNet (- Repeat) performed worse than appending the dosage parameter on News-2, News-4 and News-8, and had a significantly higher standard deviation in terms of both DPE and PE on all but News-16. Lastly, the results showed that DRNet improved upon both TARNET and the MLP baseline by a large margin across all datasets - demonstrating that the hierarchical subdivision introduced by DRNets is effective, and that an optimised model structure is indeed an important aspect when learning representations for counterfactual inference.

Number of Dosage Strata \( E \). To determine the impact of the choice of the number of dosage strata \( E \) on DRNet performance, we analysed the estimation performance and computation time of DRNets trained with various numbers of dosage strata \( E \) on the MVICU benchmark (Figure 2). With all other hyperparameters held equal, we found that a higher number of dosage strata in general significantly improves estimation performance, because the resolution at which the dosage range is partitioned is increased. However, there is a trade-off between resolution and computational performance, as higher values of \( E \) consistently increased the computation time necessary for training and prediction.

Treatment Assignment Bias. To assess the robustness of DRNets and existing methods to increasing levels of treatment assignment bias in observational data, we compared the performance of DRNet to TARNET, MLP and GPS on the test set of News-2 with varying choices of treatment assignment bias \( \kappa \in [5, 20] \) (Figure 3). We found that

![Figure 4. Comparison of DRNets trained under varying percent-ages of hidden confounding (x-axis) in terms of their \( \sqrt{\text{MISE}} \) (red), \( \sqrt{\text{DPE}} \) (blue), and \( \sqrt{\text{PE}} \) (yellow) on TCGA with all other hyperparameters held equal. 10% of hidden confounding corresponded to 2053 hidden confounders out of the original set of 20531 co-variates. The dashed lines indicate the reference performance of GPS without any hidden confounding. DPE and PE are slightly more sensitive to hidden confounding than MISE, but all metrics are adversely affected by hidden confounding to a small degree.](image-url)
Table 3. Comparison of methods for counterfactual inference with multiple parametric treatments on News-16, MVICU and TCGA. We report the mean value ± the standard deviation of \( \sqrt{\text{MISE}} \), \( \sqrt{\text{DPE}} \), and \( \sqrt{\text{PE}} \) on the respective test sets over 5 repeat runs with new random seeds. n.r. = not reported for computational reasons (excessive runtime). \( ^\dagger \) = significantly different from DRNet (\( \alpha < 0.05 \)).

| Method  | \( \sqrt{\text{MISE}} \) | \( \sqrt{\text{DPE}} \) | \( \sqrt{\text{PE}} \) | \( \sqrt{\text{MISE}} \) | \( \sqrt{\text{DPE}} \) | \( \sqrt{\text{PE}} \) | \( \sqrt{\text{MISE}} \) | \( \sqrt{\text{DPE}} \) | \( \sqrt{\text{PE}} \) |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| DRNet  | 10.3 ± 0.0      | 19.1 ± 2.1      | 19.2 ± 14.9     | 31.1 ± 0.4      | 12.9 ± 1.2      | 9.6 ± 0.0       | 2.1 ± 0.4       | 2.1 ± 0.1       |
| - Repeat | 10.4 ± 0.1    | 16.1 ± 3.0      | 5.3 ± 8.8       | 31.0 ± 0.3      | 5.4 ± 3.1       | 13.7 ± 2.5      | 5.4 ± 3.9       | 2.9 ± 1.3       |
| + Wasserstein  | 10.2 ± 0.0    | 18.7 ± 2.4      | 19.2 ± 14.9     | 32.9 ± 2.9      | 20.3 ± 19.0     | 13.6 ± 1.3      | 10.2 ± 0.9      | 2.9 ± 1.3       | 2.2 ± 0.0       |
| + PD  | 10.3 ± 0.1      | 16.5 ± 2.0      | 9.0 ± 0.0       | 36.9 ± 0.9      | 38.9 ± 19.6     | 48.1 ± 27.1     | 11.9 ± 1.4      | 12.7 ± 5.4      | 21.8 ± 9.2      |
| + PM  | 12.3 ± 0.3      | 21.0 ± 0.7      | 33.0 ± 11.7     | 31.2 ± 0.4      | 12.5 ± 3.5      | 12.1 ± 1.9      | 9.7 ± 0.2       | 1.8 ± 0.1       | 2.3 ± 0.4       |
| + PSM  | 12.2 ± 0.3      | 19.2 ± 1.6      | 1.3 ± 0.8       | 32.5 ± 0.5      | 28.3 ± 8.6      | 14.3 ± 23.3     | 11.1 ± 0.6      | 2.5 ± 1.1       | 2.3 ± 0.1       |
| MLP  | 14.0 ± 0.0      | 40.7 ± 0.0      | 48.3 ± 0.3      | 49.5 ± 5.1      | 42.8 ± 22.8     | 23.7 ± 9.8      | 15.3 ± 0.2      | 31.1 ± 0.1      | 37.1 ± 2.3      |
| TARNET  | 14.7 ± 0.1      | 38.1 ± 1.4      | 44.8 ± 3.2      | 58.0 ± 4.8      | 106.8 ± 8.8     | 102.7 ± 44.0    | 14.7 ± 0.1      | 38.6 ± 1.1      | 47.7 ± 1.1      |
| GANITE  | 14.8 ± 0.0      | 32.0 ± 0.3      | 34.4 ± 0.6      | 59.5 ± 0.8      | 103.8 ± 9.1     | 96.7 ± 9.9      | 15.4 ± 0.2      | 26.6 ± 0.5      | 25.9 ± 1.1      |
| kNN  | 14.5 ± 0.0      | 38.1 ± 0.0      | 46.4 ± 0.0      | 54.9 ± 0.0      | 60.5 ± 0.0      | 59.1 ± 0.0      | n.r.    | n.r.    | n.r.    |
| GPS  | 15.5 ± 0.1      | 17.3 ± 0.1      | 16.1 ± 0.0      | 78.3 ± 0.0      | 81.6 ± 0.0      | 140.0 ± 0.0     | 26.3 ± 0.0      | 23.8 ± 0.0      | 20.0 ± 0.0      |
| CF  | 18.8 ± 0.0      | 22.0 ± 0.0      | 35.8 ± 0.0      | 84.5 ± 0.0      | 57.7 ± 0.0      | 80.5 ± 0.0      | n.r.    | n.r.    | n.r.    |
| BART  | n.r.    | n.r.    | n.r.    | 47.1 ± 0.8      | 39.9 ± 2.4      | 13.2 ± 1.0      | n.r.    | n.r.    | n.r.    |

DRNet significantly outperformed existing methods across the entire range of evaluated treatment assignment biases.

**Hidden Confounding.** To analyse the sensitivity of DRNets to hidden confounding, we retrained the models on a reduced set of covariates \( X \) in the TCGA benchmark (Figure 4). Specifically, we removed 50% (= 10265 gene loci) and 80% (= 16424 gene loci) of the covariates included in the original TCGA benchmark. To simulate hidden confounding, we kept the removed covariates for computing treatment assignments and outcomes. The experimental results showed that a larger number of hidden confounders negatively influenced the counterfactual estimation performance across all metrics to a small degree. However, the differences between GPS and DRNet were larger than the performance loss induced by hidden confounding. We reason that our models were robust to hidden confounding because some gene loci in the retained covariate set were correlated with gene loci in the set of hidden confounders.

**Limitations.** A general limitation of methods that attempt to estimate causal effects from observational data is that they are based on untestable assumptions (Stone, 1993). In this work, we assume unconfoundedness (Imbens, 2000; Lechner, 2001), which implies that one must have reasonable certainty that the available covariate set \( X \) contains the most relevant variables for the problem setting being modelled. Making this judgement can be difficult in practice, particularly when one does not have much prior knowledge about the underlying causal process. Even without such certainty, the presented approach may nonetheless be a justifiable starting point to generate hypotheses when experimental data is not available (Imbens, 2004), as our empirical results show that the presented approach may be robust to even large amounts of hidden confounders if the hidden confounders are sufficiently correlated with variables in the covariate set.

**6. Conclusion**

We presented a novel framework to train neural networks to learn to estimate individual dose-response to multiple treatments with associated continuous dosage parameters based on observational data. We extended several existing regularisation strategies to this setting and combined them with our approach in order to further address treatment assignment bias inherent in observational data. In addition, we introduced new performance metrics, model selection criteria, model architectures, and open benchmarks for counterfactual inference in this setting. Our experiments demonstrated that model structure plays an important role in learning neural representations for counterfactual inference from observational data, that there is a trade-off between model resolution and computational performance in DRNets, and that DRNets are robust against hidden confounding if correlated variables are observed. The methods developed in this work set a new state-of-the-art in inferring individual dose-response curves across several heterogenous datasets.

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A. Treatment Assignment Bias Regularisation

To address treatment assignment bias in DRNets, we evaluated four different regularisation strategies: (1) distribution matching between treatment groups using the Wasserstein regulariser (+ Wasserstein), (2) propensity dropout (+ PD), (3) matching on the entire dataset, and (4) matching on the batch level. Because neither of these regularisation strategies were originally developed for the setting with parametric treatment options, we implemented naïve extensions thereof for this setting. To extend (1) to this setting, we followed Schwab et al. (2018) and penalised pair-wise differences between treatment group distributions in the top-most shared hidden layer using the first treatment option as the control treatment. For (2), we applied PD for each treatment option to both the corresponding per-treatment layers and to the respective treatment option’s head layers in each dosage stratum. To use (3) dataset-wide and (4) per-batch matching with parametric treatments, we followed the PM algorithm outlined in Schwab et al. (2018), and matched directly on the covariates $X$ with the dosage parameter $s$ added to the covariate set. For datasets of dimensionality higher than 200, we matched on a low-dimensional representation obtained via Principal Components Analysis (PCA) using 50 principal components in order to reduce the computational requirements.

B. Hyperparameters

We used a standardised approach to hyperparameter optimisation for all methods. Each method was given exactly the same amount of hyperparameter optimisation runs (5 on TCGA, and 10 on all other benchmarks). We also fixed the random seed such that all methods were evaluated on exactly the same random hyperparameter configurations.

For the methods based on neural network models (DRNet, + Repeat, + Wasserstein, + PD, + PM, + PSM, MLP, TAR-NET, GANITE), we chose hyperparameters at random from predefined ranges (Table S1). For "+ Wasserstein", we additionally chose an imbalance penalty weight at random from 0.1, 1.0, or 10.0. For GANITE, we also randomly chose the supervised loss weights $\alpha$ and $\beta$ from 0.1, 1.0, and 10.0 (Yoon et al., 2018) as an additional hyperparameter. For BART and CF, we used the default hyperparameters from their respective implementations in the R-packages "bartMachine" (Kapelner & Bleich, 2013) and "grf" (Athey et al., 2016). For KNN, we used 5 nearest neighbours to compute the potential outcomes matching on the covariates $X$ with the dosage parameter $s$ added as an additional covariate. For GPS, we used the implementation in the "causaldrf" R-package (Galagate, 2016) with a normal treatment model, a linear treatment formula, and a polynomial of degree 2 as the outcome formula. To reduce the computational requirements for GPS to a manageable level, we additionally preprocessed the covariates $X$ using PCA dimensionality reduction with 16 principal components for benchmarks with a covariate-space dimensionality higher than 200.

Table S1. Hyperparameter ranges used in our experiments.

| Hyperparameter                  | Values       |
|--------------------------------|--------------|
| Batch size $B$                  | 32, 64, 128  |
| Number of units per hidden layer $M$ | 24, 48, 96   |
| Number of hidden layers $L$     | 2, 3         |
| Dropout percentage $p_{\text{dropout}}$ | [0.0, 0.2]   |

For GPS, we used the implementation in the "causaldrf" R-package (Galagate, 2016) with a normal treatment model, a linear treatment formula, and a polynomial of degree 2 as the outcome formula. To reduce the computational requirements for GPS to a manageable level, we additionally preprocessed the covariates $X$ using PCA dimensionality reduction with 16 principal components for benchmarks with a covariate-space dimensionality higher than 200.