NCoRE: Neural Counterfactual Representation Learning for Combinations of Treatments

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Abstract

Estimating an individual’s potential response to interventions from observational data is of high practical relevance for many domains, such as healthcare, public policy or economics. In this setting, it is often the case that combinations of interventions may be applied simultaneously, for example, multiple prescriptions in healthcare or different fiscal and monetary measures in economics. However, existing methods for counterfactual inference are limited to settings in which actions are not used simultaneously. Here, we present Neural Counterfactual Relation Estimation (NCoRE), a new method for learning counterfactual representations in the combination treatment setting that explicitly models cross-treatment interactions. NCoRE is based on a novel branched conditional neural representation that includes learnt treatment interaction modulators to infer the potential causal generative process underlying the combination of multiple treatments. Our experiments show that NCoRE significantly outperforms existing state-of-the-art methods for counterfactual treatment effect estimation that do not account for the effects of combining multiple treatments across several synthetic, semi-synthetic and real-world benchmarks.

1. Introduction

Understanding the causal effects of an intervention is a key question in many applications, such as personalised medicine (e.g. Wager & Athey (2017); Alaa & van der Schaar (2017)), advertisement (Bottou et al., 2013), or in education (Zhao & Heffernan, 2017) or economics (Athey & Imbens, 2017). While in some applications, only one intervention is possible at a time or actions can be performed sequentially, especially in healthcare applications such as polypharmacology, the concurrent use of multiple interventions is necessary. As a concrete example, consider the case of treating patients with human immunodeficiency virus (HIV), where the standard of care is to prescribe synergistic combinations of antiretrovirals concurrently to prevent viral escape. Similarly, again in the healthcare setting, patients may be affected by multiple co-morbidities who may have to be addressed concurrently with multiple prescriptions. In economics, multiple fiscal and monetary measures might have to be applied at the same time, while in digital marketing multiple ads are typically shown at the same time on websites. In Figure 1, we outline two illustrative application scenarios in healthcare and marketing, respectively.

Whilst existing methods are focused on estimating the effects of continuous or categorical treatments, we examine the setting where a unit has a set of potentially multiple concurrent treatments applied. This setting is particularly challenging for learning algorithms since, for exam-
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In these situations, methods for estimating causal effects from observational data are of paramount importance. This is an important but challenging problem since the data is likewise often confounded.

Propensity Score-based Methods. Since their introduction, propensity scores (Rosenbaum & Rubin, 1983) have been widely used to control for pre-treatment imbalances on observed variables in observational studies. Several approaches use these scores to perform matching (Stuart, 2010; Rosenbaum, 2002; Kallus, 2020), stratification (Rosenbaum & Rubin, 1984) or weighting of samples from similar treatment and control groups (McCaffrey et al., 2004) to reduce the effects of confounding. They offer several advantages to standard regression-based covariate adjustment techniques and have also been extended to settings with multiple treatments of interest. Specifically, Imbens (2000); Robins et al. (2000); Imai & Van Dyk (2004); McCaffrey et al. (2013) and Lopez et al. (2017) use inverse probability of treatment weighting (IPTW) for modelling treatment effects in multi-treatment settings. Further works by Lechner (2001), Zanutto et al. (2005) and Spreeuwenberg et al. (2010) demonstrate application of propensity scores for matching and stratification. However, none of these works provides practical guidance on the use of propensity scores in a multi-treatment setting, nor are any of these methods applicable for use with multiple concurrent treatments as we propose here.

Latent Variable Models for Estimating Treatment Effects. Deep latent variable models such as (Louizos et al., 2017; Johansson et al., 2016b; Yoon et al., 2018; Bica et al., 2020) are popular tools for individualised treatment effect estimation. These methods all learn latent representations on the basis of observed confounders or noisy proxies, and condition on these representations for inferring treatment outcomes. Alternative methods such as Parbhoo et al. (2017) model the effects of a series of treatments as a Markov Decision Process, where treatments are treated as independent actions and can influence one another only via changes to the state. Additional work from Schwab et al. (2020) also explores how to reason about effects in continuous settings, where different dosages of treatments produce different patient outcomes. In contrast to these methods, NCoRE focuses on estimating effects of multiple concurrent treatments where we explicitly model the cross-interactions between treatments.

Treatment Combinations. Several other works examining the effects of combinations of treatments (e.g. Parbhoo et al., 2020) have been proposed from a reinforcement learning perspective where each treatment combination constitutes a different action. Unlike these methods, our work explicitly focuses on modelling the interactions between various treatments to deduce their combined effects. Similar causal

Contributions. We present the following contributions:

- We introduce NCoRE, a novel approach for training neural networks for counterfactual inference that, in contrast to existing methods, is suitable for estimating the effects for combinations of treatments.
- We extend several existing approaches for treatment effect estimation from the binary to the multiple treatment setting. In contrast to existing approaches and naïve extensions thereof, NCoRE leverages relationships between interventions and is able to extrapolate to unseen combinations in real-world situations (presented in an evaluation on experimental CRISPR-Cas9 Three-way Knockout data).
- We perform extensive experiments on synthetic, semi-synthetic and real-world data settings. The experiments show that NCoRE significantly outperforms a number of more complex state-of-the-art methods for counterfactual treatment effect estimation that do not account for the effects of combining multiple treatments.

2. Related Work

Background. Inferring the causal effects of interventions is a central pursuit in many important domains, such as healthcare, economics, and public policy. In medicine, for example, treatment effects are typically estimated via rigorous prospective studies, such as randomised controlled trials (RCTs), and their results are used to regulate the approval of treatments. However, in many settings of interest, randomised experiments are too expensive or time-consuming to execute, or not possible for ethical reasons (Carpenter, 2014; Bothwell et al., 2016). Observational data, i.e. data that has not been collected in a randomised experiment, on the other hand, is often readily available in large quantities.

To address this challenging setting, we introduce Neural Counterfactual Relation Estimation (NCoRE), a novel method for learning meaningful counterfactual representations for combinations of treatments. Our approach is based on a new conditional neural representation containing treatment interaction modulators that model the way in which combinations of treatments may interact at a time. On several synthetic, semi-synthetic and real-world benchmarks, NCoRE significantly outperforms existing methods for counterfactual treatment effect estimation that do not account for the effects of combining multiple treatments.

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interaction methods for application in conjoint analysis have been explored in (Luce & Tukey, 1964; Green et al., 2001). Recently, Egami & Imai (2018) also studied the problem of causal interaction in factorial experiments, where several factors at differing levels may be randomised to produce a large number of treatment combinations. Specifically, the authors focus on estimating a metric known as the Average Marginal Interaction Effect (AMIE) to reason about the choice of treatments. The authors use a penalised regression model this purpose. Unlike these studies, the work we present in this paper focuses on estimating individual treatment effects rather than average treatment effects and introduces a new conditional neural architecture containing treatment interaction modulators to model cross-treatment interactions.

3. Methodology

Problem Setting. We consider a setting where we are given \( n \) observed samples, or units, \( x \) with pre-treatment covariates \( x_i \) for \( i \in [1..p] \) with \( p \) being the number of available per-unit covariates. For each sample, the potential outcomes \( y_T(x) \) are the responses to a subset of treatments \( T \) where constituent treatments \( t_j \) are chosen out of the complete available set of treatments \( T_{\text{complete}} = \{t_0, t_1, \ldots, t_{k-1}\} \) with \( j \in [0..k-1] \) and \( k \) being the number of available treatment options. For training, we receive observed samples \( x \) with outcomes \( y_T(x) \) for only one particular set of treatments \( T \) that may be different for each sample. We subsequently use the training data to train a model to produce counterfactual estimates \( \hat{y}_T(x) \) of the potential outcome after applying treatment set \( T \). This corresponds to the Rubin-Neyman potential outcomes framework extended to multiple treatments that may be applied concurrently. Three causal directed acyclic graphs (DAGs) exemplifying this setting are presented in Figure 2. Note that, depending on the modelling context, not all possible combinations of treatments in \( T_{\text{complete}} \) may be permissible. For example, the empty treatment set \( T = \{\} \) considering the effect of non-intervention may not in all settings be an available option.

We make the following standard assumptions in order to infer treatment effects from observational data:

**Assumption 1. (Ignorability.)** We assume unconfoundedness i.e. the distribution of the treatment is independent of potential outcomes when given the observed variables.

**Assumption 2. (Overlap).** Every unit has non-zero probability of receiving either treatment given their observed covariates.

**Assumption 3. (Stable Unit Treatment Value.)** We assume the distribution for the potential outcomes of a particular unit are unaffected by treatment assignments of another unit when given the covariates \( X \).

Neural Counterfactual Relation Estimation (NCoRE). An important design consideration when performing counterfactual inference is model structure (Johansson et al., 2016b; Alaa & van der Schaar, 2017). In the combination treatment setting, we would ideally aim to explicitly model interactions between various treatments such that the effects of applying combinations of concurrent interventions can estimated. We therefore propose the use of a Neural Counterfactual Relation Estimation (NCoRE) model, a fully differentiable neural network model that consists of a variable number of base layers that operate on the unit covariates \( x \) followed by \( k \) treatment arms, one for each base treatment \( t_j \) with a variable number of per-treatment interaction subnetwork layers (Figure 3). During training, shared base layer parameters are updated for every observed sample, whereas the parameters of a treatment arms are only updated if the respective treatment \( t_j \) is part of the treatment set \( T \) applied to that sample. Mathematically, the interaction subnetworks \( h_T(x) \) operating on an input \( x \in \mathbb{R}^n \) (either passed from the shared base layers or another subnetwork depending on location) that make up the base layers of the treatment arms are recursively defined as:

\[
h_T(x) = \begin{cases} W_0 x + b_0, & \text{if } T = \{\} \\ W_j h_T(x, t_j) + b_j, & \text{if } t_j \in T \end{cases}
\]

With \( W_0 \) and \( W_j \) and \( b_0 \) and \( b_j \) being weight matrices, biases of the base feedforward layers and the per-treatment interaction submodules that are jointly optimised with the other model parameters during training for each available treatment \( t_j \) respectively. Using this formulation, NCoRE ensures concurrent treatment arms all sequentially influence the learnt hidden representation and thereby explicitly models potential cross-treatment interactions (see Figure 3 for an unrolled illustration). In contrast to NCoRE, existing methods that, for example, naively utilise separate models for each treatment combination tend to suffer from data sparsity since only units that receive a specific treatment combination of may be used to train each arm. As the number of treatment combinations grows, there may not be adequate samples available to train a separate combination model.

Figure 2. Three exemplary directed acyclic graphs (DAGs) in which (a) only one treatment is applied (left), (b) two treatments are applied concurrently (centre) or (c) all treatments are applied concurrently (right). Note the potential for cross-treatment interactions when multiple treatments are applied concurrently.
NCoRE overcomes this issue by enabling information to be shared across treatments through the base layers of our architecture and by explicitly modelling cross-treatment interactions via the interaction subnetworks.

**Treatment Assignment Bias.** Beyond structural deliberations, another important factor in learning counterfactual models is treatment assignment bias. Treatment assignment bias refers to systematic differences in the covariate distributions of observed unit samples between groups treated with different sets of treatments \( T \). Such observed or hidden confounding can preclude the disentanglement of causal effects between differences in outcomes that can be attributed to differences in the underlying covariate distribution and differences in outcomes that can be attributed to the actual effect of treatment set \( T \). As outlined in Section 2, in the well-studied setting with only two available treatments that may not be used concurrently, researchers have proposed the use of balancing scores (Rosenbaum & Rubin, 1984; Stuart, 2010; Rosenbaum, 2002; Kallus, 2020; Schwab et al., 2018) or distribution matching (Johansson et al., 2016b; Shalit et al., 2017) to address observed confounding under assumptions of no hidden or unobserved confounding. In the combination treatment setting, the direct application of balancing scores is however, in general, computationally not tractable as the number of matched controls that would have to be included grows exponentially with the number of treatment options available in \( T_{\text{complete}} \). We therefore introduce a new randomised algorithm for approximate batch matching to address observed confounding in the combination treatment setting. The algorithm, starting from a randomly selected seed unit’s covariates out of the available training data, iteratively builds a batch \( B \) consisting of a pre-specified number \( s \) of samples that is approximately balanced across the included treatment combinations. At each iteration, the algorithm randomly selects from the remaining training data the closest matching unit with an observed treatment combination also randomly chosen from those not yet represented in the batch \( B \). Closest matches are determined by matching on an appropriate balancing score, such as for example a lower dimensional representation of the covariates \( x \). We note that, in practice, an appropriate spatial search structure may be used to computationally accelerate the search of closest matches in the balancing score space, and a dimensionality reduction algorithm such as principal components analysis (PCA) may be used to construct a lower dimensional covariate space for matching.

**Metrics.** In order to enable a meaningful comparison of models in the presented setting, we use metrics that cover desirable aspects of models trained for estimating treatment responses. Specifically, we evaluate models by calculating the root mean squared error (RMSE)

\[
\text{RMSE}(y, \hat{y}) = \frac{1}{2^k - 1} \sum_{j \in \{1, \ldots, 2^k - 1\}} (y_j - \hat{y}_j)^2
\]

between the true counterfactual outcomes \( y \) and the estimated counterfactual outcomes \( \hat{y} \) for all \( 2^k - 1 \) possible

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1In principle, matching on the propensity score vector (Lechner, 2001) instead of a balancing score determined by dimensionality reduction is also an option in the combination treatment setting. However, since the dimensionality of the propensity score vector grows exponentially with the number of treatments in \( T_{\text{complete}} \), using a balancing score based on dimensionality reduction is typically preferable as the dimensionality of the balancing score is then independent of the number of treatments available.
combinations of treatments in the set of all available treatments \( T_{\text{complete}} \) across all patients in the test fold.

4. Experiments

To evaluate NCoRE, we conducted an experimental evaluation that aimed to answer the following questions:

1. How does NCoRE compare to existing state-of-the-art approaches to inferring counterfactual outcomes in settings with multiple available treatments that can be used in conjunction?

2. How is the counterfactual estimation performance of NCoRE and existing state-of-the-art baselines impacted by varying (i) the number of available treatments, (ii) the number of samples available for training and evaluation, and (iii) the treatment assignment bias with which treatments are assigned to units?

Datasets. To empirically answer the above questions, we utilised three datasets consisting of synthetic and semi-synthetic real-world data collected in different environments (Table 1). Using the three datasets, we created an open suite of benchmark tasks that are aimed to represent a variety of relevant use cases for counterfactual inference in settings with multiple available treatments that may be combined. For all experiments, datasets were randomly split into training (\(60\%\)), validation (\(20\%\)) and test folds (\(20\%\) of all samples) in strata of key baseline features using the scikit-multilearn package (Szymański & Kajdanowicz, 2017) (version 0.2.0).

Human Immunodeficiency Virus (HIV) Simulator. To enable testing of the sensitivity of NCoRE and other state-of-the-art methods for counterfactual inference to the number of available treatments, the number of samples available, and treatment assignment bias, we constructed a fully simulated setting for modelling treatment response to pharmacological interventions targeting patient populations with human immunodeficiency virus (HIV) infections and acquired immunodeficiency syndrome (AIDS). HIV/AIDS treatment is well-suited for evaluating counterfactual estimators that include combination effects because treatment with combination antiretroviral therapy (cART) - a combined cocktail of multiple antiretroviral drugs with different mechanisms of action - is the standard of care for treating HIV (Friedberg et al., 2001). The design of our simulator consisted of a first stage in which we generated baseline pre-treatment HIV/AIDS patient characteristics \( x \), including age, sex, ethnicity, membership in risk groups, AIDS status, prior treatment history, mutation status, and pre-treatment CD4 cell counts and viral load (VL) measures. The first stage of the simulator was designed to generate baseline characteristics of HIV/AIDS patients that match baseline characteristic distributions observed in real-world observational studies. We then, at random and with uniform probability, selected \( k \) patient archetypes \( a_k \) for each available treatment option that were used to assign \( T_i \sim \text{Poisson}(2) + 1 \) with \( t \in [1 \ldots k] \) treatments to patient \( i \) (truncated to a maximum of \( k \)). To assign treatments to patients, we calculated the distance

\[
\text{MixedDistance}(x_1, x_2) = \frac{|I_{\text{discrete}}|}{p} \text{Jaccard}(x_1, I_{\text{discrete}}, x_2, I_{\text{discrete}}) + \frac{|I_{\text{continuous}}|}{p} \sum_{l \in I_{\text{continuous}}} |x_{1,l} - x_{2,l}|
\]

consisting of the weighted sum of Jaccard and mean absolute distances of the continuous baseline demographics with \( I_{\text{discrete}} = \{ q | x_q = \text{discrete} \} \) and \( I_{\text{continuous}} = \{ q | x_q = \text{continuous} \} \) respectively as the sets of indices of discrete and continuous covariates in \( x \) between each patient’s pre-treatment covariates \( x \) and each treatment archetype \( c_k \).

Treatment assignments for treatment \( j \) and a patient with covariates \( x \) were then defined as \( t_j \sim \text{Uniform}(0, 1) > p_{ij} \) with \( p_{ij} = \text{softmax}(\kappa d(x, a_j)) \) as the assignment treatment probability for treatment indicator \( t_j \in [0 \ldots k - 1] \) and with \( \kappa \) as the variable treatment assignment bias strength coefficient. \( \kappa = 0 \) corresponds to no treatment assignment bias and higher numbers correspond to stronger assignment biases based on the patient covariates \( x \). We generated counterfactual outcomes \( y_{T} \) for each possible combination \( T \) of treatments using a two-step process with the first step consisting of sampling a Gaussian outcome model \( M_j \) that defines the outcome \( y_{T}(t_j) \) for each treatment \( j \) used by itself. The per-treatment Gaussian outcome models \( M_j \) calculated outcomes for a patient with pre-treatment covariates \( x \) using

\[
y_{T}(t_j) = \hat{y}_{T}(t_j) \cdot \text{MixedDistance}(x, c_l)
\]

with unscaled outcomes \( \hat{y}_{T}(t_j) \sim \mathcal{N}_{\text{truncated}}(\mu_{c_l}, \sigma_{c_l}) \) truncated to \( \hat{y}_{T}(t_j) \in (L_{\text{initial,min}}, L_{\text{initial,max}}) \), mean \( \mu_{c_l} \sim \text{Uniform}(L_{\text{initial,min}}, L_{\text{initial,max}}) \), standard deviation \( \sigma_{c_l} \sim 0.5 \), minimum and maximum initial viral loads \( L_{\text{initial,min}} = 0.84 \frac{1}{\text{ml}} \) and \( L_{\text{initial,max}} = 7.69 \frac{1}{\text{ml}} \) respectively and centroids \( c_l = x_l \) with centroid indices \( l \) selected at random from the entire training set \( l \sim \text{Uniform}(0, N - 1) \) consisting of \( N \) patients. The second step in the outcome generating process then generated outcomes

\[
y_{T} = \mathcal{P}_d(T)\mathcal{P}_d(y_{T}(t_j)) \cdot B^T
\]

for all possible combinations \( T = \{ j | t_j = 1 \} \) of assigned base treatments \( t_j \) with the ordered set of all possible polynomial interactions \( \mathcal{P}_d(\theta) \) of degree \( d = \min(|T|, 5) \).
Table 1. Comparison of the datasets used in our experimental evaluation. We evaluated one synthetic and two semi-synthetic datasets with varying numbers of samples, features and treatments.

| Dataset       | Samples | Features | Treatments | Type     |
|---------------|---------|----------|------------|----------|
| Simulator     | any     | 2870     | any        | synthetic|
| Europe 1      | 3161    | 266      | 20         | semi-synthetic |
| Europe 2      | 3116    | 105      | 18         | semi-synthetic |
| CRISPR KO     | 3185    | 2424     | 15         | experimental |

with coefficients $\theta$, combination coefficients $B_o \sim s_{B_o} \cdot \mathcal{N}(1.02^d_o - 1 \mu_B, 1.02^d_o - 2 \sigma_B)$, scarcity coefficient $s_{B_o} \sim \text{Uniform}(0, 1) < 0.2$, means of combination coefficients $\mu_B = -0.03$, standard deviations of combination coefficients $\sigma_B = 0.015$ and degree $d(\cdot)$ of the interaction $P_d(T)_o$ at index $o \in [0 \ldots |P_d(T)| - 1]$. 

**EuResist Integrated Database Cohorts (Europe 1 and Europe 2).** Europe 1 is a subset of data from HIV-infected individuals between 18 and 72 years of age obtained from the EuResist Integrated Database (Zazzi et al., 2012). The database contains the genotype (mutation) data, CD4 count, viral load and therapy data for individuals that have been administered HIV therapies since 1988. The therapy data records the number of prior treatment lines a patient was administered and treatment history. We focus on a subset of these patients that have at least 3 prior treatment lines. Europe 2 is a set of data from Antiretroviral Resistance Cohort Analysis (ARCA) (ARCA, 2014) database with the same set of features. For both Europe 1 and Europe 2, treatment assignments and outcomes (viral load after treatment) were generated analogously to the Simulator dataset using a semi-synthetic approach based on the real-world observed pre-treatment covariates $x$ and the observed treatments as treatment assignments.

**CRISPR Three-way Knockout (CRISPR KO).** The CRISPR Three-way Knockout (CRISPR KO) benchmark dataset consists of real-world experimental data collected in a systematic multi-gene knockout screen conducted by Zhou et al. (2020). In their screen, Zhou et al. (2020) used a CRISPR-Cas9-based multi-gene knockout system to experimentally quantify the synergistic or antagonistic causal genetic interaction of a total of 3185 combinations (up to three-way interactions) of 15 genes $T = \{\text{CDK4}, \text{DNMT1}, \text{EGFR}, \text{ERBB2}, \text{FGF2}, \text{HDAC1}, \text{HPRT1}, \text{MAP2K1}, \text{MTO1}, \text{PIK3C3}, \text{POLA1}, \text{TGFBI1}, \text{TOP1}, \text{TUBA1A}, \text{TYMS}, \text{VKORC1}\}$ that are targets of existing ovarian cancer treatments in a cell line representative for high-grade serous ovarian cancer (HGSOC). To measure the causal effect $y_{T'}$ of targeting a set $T'$ of genes, Zhou et al. (2020) compared the $\log_2$ fold change in barcoded guide ribonucleic acid (gRNA) counts in cells cultured for 15 and 26 days as a measure for the degree to which cancer cell growth was modulated by the knockout - where an increased inhibition of cell growth was assumed to be associated with a potential synergistic causal effect of targeting the respective genes using a combination therapy. To estimate the relationship between sets of genes and the causal effect of targeting those genes on inhibiting ovarian cancer cell growth in vitro, we used a feature set $X = \{X_{G_1}, X_{G_2}, X_{G_3}\}$ consisting of three 808-dimensional gene descriptors $X_{G_1}, X_{G_2}, X_{G_3}$ where each gene descriptor contained the as determined using data from genome-wide single knockout CRISPR-Cas9 essentiality screens in 808 cell lines (Dempster et al., 2019) and computed using the CERES algorithm (Meyers et al., 2017) for genes $G_1, G_2,$ and $G_3$ included in the set $T$ of genes that were intervened on$^3$. $X_{G_2}$ and $X_{G_3}$ were zero-imputed to indicate missingness for single or two-way gene knockouts with a total of only one or two genes involved, respectively. The CRISPR KO benchmark is particularly challenging for causal inference methods because of the complex underlying biological process that determines causal effects on cancer cell growth in a realistic model system of a heterogenous disease, the large number of potential treatment combinations, high-dimensional covariate space, and the sparsity of labelled data available (at most one outcome for each combination). Due to only one sample being available for each evaluated gene combination, the CRISPR KO benchmark also tests the ability of counterfactual inference methods to extrapolate beyond treatment sets $T$ observed in the training data, as the randomly split off test set consisted entirely of novel combinations not present in the training or validation data, i.e. it could, for example, tests the ability of counterfactual estimators to estimate the causal effect of intervening on genes $\{G_1, G_2, G_3\}$ based on data observed after intervening on genes $\{G_1\}, \{G_3\}, \{G_2, G_3\}$, and experimental data from other genes with potentially similar gene descriptors $X$.

$^3$The data is freely available from the DepMap project at https://ndownloader.figshare.com/files/25494359 (DepMap, 2020).

Table 2. Hyperparameters. Hyperparameter ranges used for hyperparameter optimisation of Ridge Regression (RR), Deconfounder (DC) and Neural Network (NN; includesGANITE, TARNET, and NCoRE) models for all benchmark tasks. Comma-delimited lists indicate discrete choices sampled with equal selection probability.

| Hyperparameter | Choices          |
|----------------|------------------|
| Regularization strength $C$ | 0.1, 1.0, 10.0 |
| Latent dimension $D$ | 3, 5, 10, 15 |
| Number of hidden units $N$ | 8, 16, 32, 64 |
| Number of layers $L$ | 1, 2, 3 |
| Batch size $B$ | 16, 32, 64, 128 |
| L2 regularisation $\lambda_2$ | 0.0, 0.00001, 0.0001 |
| Learning rate $\alpha$ | 0.003, 0.03 |
| Dropout percentage $p$ | 0, 10, 15, 25% |
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**Baselines.** We included the following state-of-the-art counterfactual estimators developed for the multiple treatment setting in the presented experimental evaluation: A composite model consisting of a separate ridge regression model for each possible treatment set $T$ (Kallus, 2017), a composite ridge regression model (Kallus, 2017) with the input data preprocessed using a Deconfounder (Wang & Blei, 2019), composite models consisting of a separate nearest neighbour predictor (kNN) and Gaussian Process (GP) regressors for each possible treatment set, Treatment Agnostic Regression Network (TARNET) (Johansson et al., 2016a) adapted to the multiple treatment setting (Schwab et al., 2018) modelling each possible treatment interaction as an additional, separate treatment path, and Generative Adversarial Nets for inference of Individualised Treatment Effects (GANITE) (Yoon et al., 2018) with an outcome prediction node $y_T$ for each possible treatment interaction set and loss weights $\alpha = \beta = 1$. In addition to unregularized NCoRE, we also tested a version of NCoRE (Balanced) that employed randomised batch matching to train on the data in a manner that controls for observed confounding using low-dimensional balancing scores.

**Hyperparameters.** We took an unbiased, systematic approach to hyperparameter search in which we used a fixed hyperparameter optimisation budget of at most 30 hyperparameter optimisation runs for all compared methods. For each of the runs, we selected hyperparameters from predefined ranges with uniform probability (Table 2). After hyperparameter optimisation, we selected the model with the highest validation set performance in terms of root mean squared error (RMSE) in predicting the factual, observed outcomes on the validation fold for each model type.

**Metrics.** We evaluate models by calculating the root mean squared error (RMSE)

$$\text{RMSE}(y, \hat{y}) = \frac{1}{2^{|T_{\text{complete}}|} - 1} \sum_{j \in [1, 2^{|T_{\text{complete}}|} - 1]} (y_j - \hat{y}_j)^2$$

between the true counterfactual outcomes $y$ and the estimated counterfactual outcomes $\hat{y}$ for all $2^{|T|} - 1$ possible combinations of treatments in the set of all available treatments $T_{\text{complete}}$ across all patients in the test fold. Note that a set of treatments $T$ has $2^{|T|} - 1$ possible combinations and that RMSE can only be evaluated in synthetic or semi-synthetic settings where the true underlying outcome generating process is known. We additionally used bootstrap resampling with 100 bootstrap resamples to compute uncertainty bounds for each presented result, and used two-sided Mann-Whitney-Wilcoxon tests to test whether the observed results met the pre-specified significance level of $\alpha = 0.05$.

**5. Results and Discussion**

**Counterfactual Estimation Performance.** We compared the performance in terms of RMSE of all the baselines for counterfactual inference on the simulated data, Europe 1, Europe 2 and CRISPR KO (Fig. 4). Across all the datasets, we find that NCoRE outperforms all existing state-of-the-art methods in terms of the RMSE. On simulated data there is a significant performance gap to all the baselines where TARNET, RIDGE and Deconfounder perform equally well and at least slightly better than GANITE, GP and kNN baselines. On Europe 1, NCoRE offers the smallest gap in performance improvement compared to all other baselines, which might be explained by the fact that the variance in the results (dotted points on top of the bars) is likewise significantly higher compared to the simulated data and Europe 2. On the real-world CRISPR Three-way Knockout only NCoRE, kNN and Ridge return results after a reasonable time frame. All methods show performance levels in the same range while balancing seems to have a positive effect on NCoRE. On the other datasets, the effect of balancing is small and only slightly positive with respect to RMSE on Europe 1. It is thus unclear if randomised batch matching for training on the data whilst controlling for confounding with balancing scores, has a positive effect for NCoRE. Finally, our results show that NCoRE improves upon Deconfounder and other baselines by a large margin across all data sets demonstrating that the interaction subnetworks introduced by NCoRE are important for learning meaningful representations for counterfactual inference.

**Performance by Number of Treatments $k$.** To assess the impact of the number of treatments on the performance

![Figure 4: Performance comparison in terms of RMSE (y-axis) of several state-of-the-art methods (x-axis) for counterfactual treatment across various synthetic (left), semi-synthetic (middle, Europe1 and Europe2) and real-world datasets (right). For simulated data and semi-synthetic data NCoRE outperforms all competitive baselines in most cases with a significant margin. For the real-world experiment (CRISPR Three-way Knockout), less baselines are shown since due to the computational complexity most baseline approaches did not converge within reasonable time.](image-url)
of NCoRE we measured the RMSE trained with varying numbers of treatments on the simulated dataset (Fig. 5). With all other hyperparameters held equal, we found that a larger number of treatments, in general, worsens estimation performance across all baselines. However, NCoRE has the lowest RMSE regardless of the number of treatments because of its ability to model and account for interactions between treatments. In particular, NCoRE seems to scale better than the other baselines, since the difference between performance becomes more pronounced as the number of treatments grows. Unlike all the other baselines, by explicitly modelling interactions between treatments using interaction subnetworks, information can be shared that allows NCoRE to extrapolate more easily to effects of less-frequently occurring treatment combinations as the number of treatments grows.

Performance by Number of Samples \( n \). To determine the efficiency of our model in terms of the influence of the number of samples available for training and evaluation, we compared the performance of NCoRE against each of the other baselines on the simulated data (Figure 5). Unlike the other baselines, our method improves in accuracy with an increase in the number of samples. We also find that NCoRE requires significantly fewer samples for training and evaluation to achieve a lower RMSE. We attribute this efficiency to the inclusion of interaction subnetworks in our model that enable knowledge to be shared across common treatments.

Performance by Treatment Assignment Bias \( \kappa \). To assess the robustness of NCoRE and existing methods to increasing levels of treatment assignment bias in observational data, we compared the performance of NCoRE to each of the baselines on the simulated test set with varying choices of treatment assignment bias \( \kappa \in [5, 20] \) (Fig. 5). We found that NCoRE outperformed existing methods across the entire range of evaluated treatment assignment biases.

Limitations. Like other methods that attempt to estimate causal effects from observational data, our method is based on certain assumptions that are untestable in practice. In our work, we assume unconfoundedness which means that our covariate set \( X \) contains the most relevant information inferring treatment effects. Without knowledge of the underlying causal process, this is difficult to assess or justify. In addition, we assumed that all treatments have non-zero probability of being observed in the data. In practice, certain combinations may not observable for instance, if the number of available treatments is high, or, in the healthcare setting, if clinical guidelines prevent certain treatments from being applied concurrently.

6. Conclusion

We presented NCoRE, a new method for learning counterfactual representations to estimate treatment effects of multiple concurrent treatments. Our approach used a new conditional neural architecture containing treatment interaction subnetworks to model the way in which combinations of treatments may interact when applied in conjunction. Our experiments demonstrated that the model structure is key to learning neural representations for counterfactual inference with multiple treatments from observational data. Overall, NCoRE significantly outperforms existing state-of-the-art baselines for estimating effects of interventions across several challenging benchmarks, including combination therapy selection in HIV patients and in-vitro causal effect estimation of multi-gene interventions on cancer cell growth based on experimental CRISPR-Cas9 data. Promising future directions include generalising the approach to hidden confounders, extending NCoRE for modelling sequential treatments, as well as combining observational and interventional data to assess the quality of estimation. Broadly, we see our approach as a means of bridging the long-standing gap between classical methods for reasoning about combination treatment effects and practical applica-
tions in medicine, advertising and economics.

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