ParKCa: Causal Inference with Partially Known Causes

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Abstract

Causal Inference methods based on observational data are an alternative for applications where collecting the counterfactual data or realizing a more standard experiment is not possible. In this work, our goal is to combine several observational causal inference methods to learn new causes in applications where some causes are well known. We validate the proposed method on The Cancer Genome Atlas (TCGA) dataset to identify genes that potentially cause metastasis.

1. Introduction

Most of the traditional causal inference methods are based on a comparison between treatments and experimental design. Nowadays, however, there is a rise of methods that are more data-driven, based on observational data (Johansson et al., 2016; Louizos et al., 2017; Wang et al., 2017; Yao et al., 2018; Kallus et al., 2018; Wang & Blei, 2019; Syrkganis et al., 2019). The main motivations of these works are the lack of the full experiment and counterfactual data, either because it is too expensive or impossible to collect. Luckily, some of the traditional causal inference techniques work in both scenarios (Spirtes & Glymour, 1991; Spirtes et al., 2000; Pearl, 2000; Chipman et al., 2010).

Expanding the problem definition, some applications, such as Driver Gene Discovery (Stratton et al., 2009) or causation in Earth Systems (Runge et al., 2019), have a few causes that are well known. These causal inference applications with partially known causes are yet to be explored. So far, all the previously mentioned techniques use known causes from real-world applications or simulated experiments only for evaluation. To address this type of application, we propose ParKCa, a method that uses the few known causes to learn new causes, in a semi-supervised learning approach.

ParKCa has several advantages. First, leveraging several methods instead of using a single one can minimize bias from specific approaches and highlights patterns common across the methods. Second, it allows the use of known causes to help identify new causes. Third, this strategy is especially suitable for applications with many possible causes. And finally, it allows the combinations of several datasets that share the same set of possible causes but might differ in the datatype or set of rows.

The proposed method ParKCa for causal inference with partially known causes is validated in the driver gene discovery application. The existence of associations between cancer and certain genes is well accepted in the precision medicine field. However, the human body has more than 20,000 genes and not all genes are associated with cancer (Stratton et al., 2009). Hence, the challenge is to recognize those genes that are associated with cancer development through causal inference. In this context, these genes are known as driver genes and play an important role in cancer prevention and treatment.

A toy example of this application is shown below. Table 1 shows the input data, in the patient × gene format. Two causal models are fitted on this data: the BART (Chipman et al., 2010; Hill, 2011) and the Deconfounder Algorithm (DA) (Wang & Blei, 2019). These causal models produce a coefficient or an output for each gene in Table 1. These outputs are put together in Table 2, in the gene × causal model format. In our analysis, we refer to Table 2 as output data or $D_{out}$. In the output data, the current knowledge about the causes of the application is added, here referred as the known causes. The output data is separated into training and testing sets, and a binary classification model is fitted on the training data to predict other causal genes on the testing set.

| Gene 1 | ... | Gene V | Metastasis |
|--------|-----|--------|------------|
| Patient 1 | 7.39 | ... | 1.60 | 0 |
| ...   | ... | ...   | ... | ... |
| Patient J | 3.25 | ... | 2.73 | 1 |

Table 1. Example of input dataset for our application. The causal models are fitted using gene expression data of patients.

There are many challenges around driver gene discovery. Progress in sequencing technology has provided many good datasets, such as The Cancer Genome Atlas (TCGA). The cost to collect genetic information from cancer patients is decreasing, however, it is still an expensive process (Chen et al., 2016). The consequence of these costs is the small
Table 2. Example of output dataset constructed using the causal algorithms BART and Deconfounder Algorithm (DA). The classification model to identify new causes uses this data.

| Gene  | BART  | DA   | Known Cause |
|-------|-------|------|-------------|
| Gene 1| -1.2  | ...  | -2.4        |
|       |       |      | 1           |
| Gene V| 8.9   | ...  | 12.3        |
|       |       |      | 0           |

size of available datasets, which is a limitation in the use of certain machine learning methods that require large datasets. The number of columns (genes) is often much larger than the number of rows (patients), which poses an extra challenge for machine learning models. Another challenge is the partially known dependence between genes due to pathways. Pathways are sets of genes where the alteration or mutation in one gene can cause changes in other genes that share the same pathway (Vandin et al., 2012). Some pathways are established and well explored, but there is no guarantee that all existing pathways are known. Additionally, some elements that cause cancer might not be included in the dataset. Examples of elements not observed are the structured clinical information about the patient, such as their lab results, and lifestyle. Finally, the last challenge mentioned here is the lack of a well-defined training set, making evaluation of results tricky. There is no ‘true’ list of driver genes to evaluate the quality of the machine learning models (Dees et al., 2012; Schroeder et al., 2014; Tokheim et al., 2016).

The main contributions of this paper are as follows:

- We introduce the problem of causal inference from observational data with partially known causes.
- We propose the method ParKCa, which learns new causes from causal inference methods based on observational data with continuous treatments, multiple confounders, and partially known causes.
- For the predictive check necessary in some of the causal methods used, we propose a factor model agnostic score called $\gamma$.
- The proposed method is validated on the TCGA dataset, for identifying genes that are potential causes of cancer metastases.

2. Related Work

Our work combines several research areas, and we briefly discuss related work from these areas:

Causal Inference: Motivated by the need for models which are more robust, more reproducible and easier to explain, causality has been receiving a lot of attention. Some classical approaches such as the PC-algorithm (Spirtes & Glymour, 1991), FCI (Spirtes et al., 2000), do-calculus (Pearl, 2000) are still relevant and being used. New approaches to speed up some graph-based causal inference methods, such as the RFCI (Colombo et al., 2012) and GFCI (Ramsey et al., 2017), or to deal with confounders (Wang & Blei, 2019) have also been proposed. The number of causal methods based on other approaches, such as Random Forest (Wager & Athey, 2018; Hill, 2011), deep learning (Johansson et al., 2016; Louizos et al., 2017) or focused on data formats such as Times Series (Runge et al., 2019) is also growing.

Causal Inference from observational data: In this paper, we focus on applications with continuous treatments and multiple confounders and only observational data available. Some of the classical methods, such as PC-algorithm (Spirtes & Glymour, 1991), FCI (Spirtes et al., 2000) and RFCI (Colombo et al., 2012), can be used when only observational data is available. However, they do not scale easily for problems with thousands of possible causes, demanding techniques that deal better with the large number of columns. Also, because the application we are focused on, we aim to use methods that do not require a large number of examples, which excludes deep learning approaches (Johansson et al., 2016; Louizos et al., 2017). Hill (2011) proposed to use BART (Chipman et al., 2010) with CATE (Abadie & Imbens, 2002; Kallus et al., 2019) to do a causal inference analysis with binary or continuous treatments, observational data and a large number of possible causes. Another possible method is the Deconfounder Algorithm (DA) proposed by Wang and Blei (2019). This method is mainly focused on applications that have multiple confounders and is also agnostic regarding the type of treatment. While our method works with any causal model for observational data, for our application we will be focusing on BART and DA.

Learning from Positive and Unlabeled Data: The problem introduced in this paper requires learning new causes from positive and unlabeled examples, a sub-class of semi-supervised learning. The binary classification task is performed on the output dataset $D^\text{out}_{Y \times M}$, where each possible cause is a row and the columns are the coefficients/outputs of the causal models. The labels are $Y^\text{out} = 1$ for well-known causes and $Y^\text{out} = 0$ for non-causal or unknown causes. The most obvious classification model for this type of problem is PU-learning (Liu et al., 2002; Lee & Liu, 2003; Liu et al., 2003; Elkan & Noto, 2008; Fusilier et al., 2015; Du Plessis et al., 2015), which learns from positive (known causes) and unlabeled (not causal or unknown causes) data. While the interpretation is not the same, traditional binary classification models, such as Logistic Regression, Random Forest Classification (Breiman, 2001), Ensemble (Dietterich, 2000), and SVM (Suykens & Vandewalle, 1999), can still be used.

Driver Gene Discovery: Our approach is validated in the
context of driver gene discovery (Stratton et al., 2009). We want to find genes that contribute to cancer metastases development, where the cancer is spreading from the original site to other areas of the body. Therefore, each gene is a possible driver gene (cause). Previous methods that explored this application are: MuSiC (Dees et al., 2012), OncodriveFM (Gonzalez-Perez & Lopez-Bigas, 2012), ActiveDriver (Reimand & Bader, 2013), TUSON (Davoli et al., 2013), OncodriveCLUST (Tamborero et al., 2013), MutsigCV (Lawrence et al., 2014), OncodriveFML (Mularoni et al., 2016), 20/20+ (https://github.com/KarchinLab/2020plus), and others (Vandin et al., 2012; Schroeder et al., 2014). The first challenge of this application is the large number of genes (possible causes) along with the small sample size and the known (and unknown) dependencies among genes, which adds certain complexity to the problem. The existence of confounders, some possible to be observed (such as clinical information), others not (such as family history or lifestyle) (Stratton et al., 2009) poses another challenge. Finally, the limited and biased list of well-known driver genes (Futreal et al., 2004) also needs some attention (Tokheim et al., 2016). This list, here refereed as Cancer Gene Census (CGC), is the gold-standard of driver genes currently available, based on clinical or laboratory results and computational methods that aim to identify driver genes.

3. The ParKCa Method

Figure 1 shows an illustration of the proposed method. The main contribution is dealing with causal discovery from an ensemble perspective. So, instead of exploring causal methods individually and comparing the results, we take their outputs and use them as features in a binary classification model. Hence, we start with feature creation (See Figure 1 for reference), where coefficients/outputs are extracted from the dataset \( D_{J \times V} \) using a causal model \( f_m() \), \( \forall m \in [1, M] \), where \( J \) denotes the number of rows, \( V \) the number of features/possible causes and \( M \) the number of causal models available. Then, all the outputs are aggregated in the dataset \( D'_{V \times M} \). Each possible cause \( v \in \{1, \ldots, V\} \) receives a label \( Y'_v \in \{0, 1\} \), where \( Y'_v = 1 \) means that row \( v \) is a known cause and \( Y'_v = 0 \) if row \( v \) is an unknown cause or non-causal. Finally, a classification model from the partially known causes is fitted using \( 70\% \) of \( D'_{out} \) and \( Y'_{out} \) as training set and the other \( 30\% \) as testing set. These two sets are randomly selected. This problem can be extended for many initial datasets that share the same set of possible causes, as also shown in Figure 1.

The causal methods used to create features are described in Subsection 3.1 and the classification models used to learn the causes from positive and unlabeled examples are described in Subsection 3.2.

3.1. Causal Models

As previously mentioned, there are many methods available for causal inference on observational data. Our two assumptions (continuous-valued data and violation of ignorability) hold in many causal models, not only in the models used to validate our method in our application of driver gene discovery. Below, we will describe the two causal models used in our application: DA and BART. The DA model was chosen because it addresses the influence of multiple confounders and it scales to many possible causes. The BART model was chosen to deal with continuous treatments and also it scales to large datasets.

3.1.1. Deconfounder Algorithm

The main idea of the Deconfounder Algorithm (DA) proposed by Wang and Blei (2019) is to learn latent variables to use as substitute of unobserved confounders. Next, the latent variables along with the original data are used to do the causal inference. The use of proxies to replace true confounders in causal inference analysis was an idea also explored by Kallus at all (2018) and Bennett and Kallus (2019). This type of approach is designed mainly for applications where the ignorability assumption fails, meaning that the treatments or output are not independent of the missing (or unobserved) data.
The DA model can be summarized as follows: first, we need to define and fit a probabilistic factor model; then, we calculate the latent variables with the fitted factor model; finally, we perform a causal inference using the input data and the latent variables. One of DA’s assumptions is that the factor model captures not only the population distribution of the assigned causes but also their dependence structure. A predictive check is used to verify this assumption. In our work, one of our contributions is the proposal of \( \gamma \), a predictive check that is an alternative to the one used by Wang and Blei (2019). Its main advantage is being agnostic while the predictive check from Wang and Blei (2019) works only for probabilistic factor models.

Below, we describe the Factor Models, the Predictive Check \( \gamma \) and the Outcome Model used in our work.

**FACTOR MODEL:** For applications with many possible causes, like the one we are using to validate our proposed method, factor models robust to large datasets are needed. Furthermore, we want to consider the possibility that the factor models need to learn complex relationships (non-linear) from the input data. Thus, we will use three factor models: Principal Component Analysis (PCA) (Jolliffe, 1986), Matrix Factorization (MF) (Lee & Seung, 2001) and Autoencoder (A) (Rumelhart et al., 1986).

**PREDICTIVE CHECK:** In this step the quality of the factor models is checked. Here we propose \( \gamma \), a new predictive check score that is factor model agnostic.

Consider the input dataset \( D \) divided in two parts: the features/possible causes \( X_{J \times V} \) and the binary classification \( Y_{J \times 1} \). The predictive check used by Wang and Blei (2019) holds out a subset of the feature set \( X \), fits a probabilistic factor model with the remaining data \( p(Z|X_{\text{held}}) \) and then tries to replicate the \( X_{\text{held}} \) by computing \( p(X_{\text{held}}|Z) \). Then, the predictive score is calculated from a discrepancy function between the observed value and the predicted one. A predictive check score around the value 0.5 is ideal.

Our score \( \gamma \) also aims to verify how good the fitted factor model and the latent features \( Z \) can predict columns from the data \( X \). However, in our approach, we will use a Linear Regression Model \( X_v = f(Z), \forall v \in \{1, ..., V\} \) for the predictive check, instead of a probabilistic approach. We reserve 20% of each combination between a column \( X_v \) and \( Z \) for testing and train the linear model on the remaining data. Considering only the \( n \) data points from the testing set and the fitted model \( f() \), we calculate \( \gamma_v \) as follows:

\[
\gamma_v = \frac{\text{count}(X_{v,\text{test}} < f(Z_{v,\text{test}}))}{n}, \quad \gamma = \frac{\sum_v \gamma_v}{V}
\]

Where \( \gamma_v \in [0, 1] \) and \( \gamma \in [0, 1] \). The interpretation of \( \gamma \) is similar to the probabilistic predictive check: the closer the average value of \( \gamma \) is to 0.5, the better. However, as for the probabilistic predictive check, interpreting this value alone can be very challenging. Is \( \gamma = 0.4 \) a good value? And \( \gamma = 0.64? \)

In order to make its interpretation easier, we propose a test to verify if \( \gamma \) is at least as good as a model that only uses the average value of the training set to make predictions. This can be represented as:

\[
\gamma^*_v = \frac{\text{count}(X_{v,\text{test}} < X_{v,\text{train}})}{n}, \quad \gamma^* = \frac{\sum_v \gamma^*_v}{V}
\]

Using the weak law of large numbers, with a sufficient number of columns \( V \), the expected value \( E(\gamma^*) = 0.5 \). Then we calculate a confidence interval \( CI(\gamma^*) = [\gamma^*_l, \gamma^*_u] \) and check if \( \gamma \) is inside this confidence interval.

The scenarios where the score \( \gamma \) might produce poor results are as follows: \( X_v \) is a non-informative feature, or the Linear Model is not appropriate, or the fitted factor model is not good. In the first two scenarios, our assumption is that a sufficient amount of features \( V \) would solve the problem due the weak law of large numbers. The last situation is the one that we aim to identify with our score: if the factor model is not appropriate, the results are likely to be consistently worse than \( \gamma^* \), making \( \gamma \leq \gamma^*_l \) for any \( V \).

**OUTCOME MODEL:** To calculate the causal effects, a Logistic Regression is used as the Outcome Model. This model is represented by \( Y = f_o(X,Z) \), where \( X_{J \times V} \) has the original features and possible causes, and \( Z_{J \times K} \) the latent features fitted. If the ignorability assumption holds, the causal effects estimated using an Outcome Model with only \( Y \) and \( X \) would be enough. However, if the founders can not be ignored, then the causal effects from \( Y = f_o(X) \) are biased, but the model with the augmented data \( Y = f_o(X,Z) \) is unbiased (Wang & Blei, 2019).

This approach, however, does not scale for datasets with small sample size and a large number of columns. For this scenario, we first split the \( X_{J \times V} \) columns in \( M \) disjoint sets of size \( \left\lfloor \frac{J}{M} \right\rfloor \), where \( j \) is the number of rows in \( X \) and 25 is a constant; then, we define \( Y = f_o(X_{J \times m}, Z_{J \times K}), \forall m \in \{1, ..., M\} \). The coefficients estimated through the Logistic Regression of each set are then used as causal effects. This approach is valid because of the following theorem proposed and proved by Wang and Blei (2019):

**Theorem 1** (Identification of the average causal effect of subsets of the causes) Assume SUTVA\(^1\), single ignorability, and consistency of substitute confounders. Then, under the conditions of the substitute confounder being a piece-wise constant function of the causes and the outcome being separable, the deconfounder non-parametrically identifies the average causal effect of subsets of causes.

\(^1\)Stable Unit Treatment Value Assumption
Therefore, if \( Z \) is a good replacement for unobserved confounders, verified through the predictive check \( \gamma \), then the coefficients and \( p \)-value of the features set \( m \) in \( f_m(X_m, Z) \) and \( f_o(X, Z) \) should be approximately the same.

### 3.1.2. BART

The Bayesian “sum-of-trees(BART) model was originally proposed by Chipman at all (2010). A year later, Hill (2011) proposed a methodology to use BART to estimate causal effects. The main idea is to estimate causal effects using data interventions and comparing the potential outcomes.

Considering the features set \( X_{J \times V} \) and the binary variable response \( Y_{J \times 1} \), the goal is fit a BART model such that \( Y = f_b(X) + \epsilon \), where \( \epsilon \sim \text{Normal}(0, \sigma^2) \). From the fitted model, the next step is to calculate the conditional average treatment effect (CATE) (Abadie & Imbens, 2002; Kallus et al., 2019) individually for each possible cause \( v \in \{1, ..., V\} \) as follows:

\[
\text{CATE}_v = \sum_{j=1}^{J} E(Y_j(X_v = a) - Y_j(X_v = 0))
\]

where \( X_v = 0 \) represents the intervention component on the observed data \( X_a \). To calculate the two components, are used the predictive values \( \hat{Y}_j = f_b(X_v = a, X_{V-v}) \) and \( \hat{Y}_j = f_b(X_v = 0, X_{V-v}) \).

### 3.2. Classification with Positive and Unlabeled Examples

Given the features produced by the causal models, the next challenge is to develop a classification model using only positive and unlabeled data. The outputs of the causal models are saved on a new dataset \( D_{out} \), which will be used in the classification model. The dataset \( D_{out} \) contains \( V \) rows with the possible causes and \( M \times d \) columns, where \( M \) is the number of causal models used and \( d \) is the number of initial datasets/subsets as shown in Figure 1.

As an illustration, consider the hypothetical scenario where we have 2 initial datasets, the first dataset has dimensions \( 3000 \times 200 \) and the second dataset, \( 1500 \times 200 \). Also, suppose we are working with BART and DA causal models. \( D_{out} \) would have 200 rows and \( 2 \times 2 = 4 \) columns. Then, the prior knowledge about known causes is added in a new array \( Y_{out} \), where \( Y_{out} = 1 \) if \( v \) is a known cause of this application, and 0 otherwise. From this assignment, unless all the possible causes are known, some true causes, or positive examples, will be labeled as 0.

In total, 6 classification models are explored: Adapter-PU, Unbiased PU, Logistic Regression, Random Forest, Ensemble and random model. These models are described below. The Adapter-PU proposed by Elkan and Noto (2008) uses a traditional probabilistic classifier \( c^\alpha(X) \) such that \( c^\alpha(X) = p(Y = 1|X) \) is as close as possible. The assumption is that the labeled positive examples are chosen completely randomly. We used the implementation available on the python package ‘pu-adapter’ (Drouin, 2013).

Based on the work of du Plessis et al. (2015), Unbiased PU (UPU) is a convex classification method that is capable to cancel the bias by using a loss function for positive examples and another loss function for unlabeled examples. The bias that the algorithm aims to cancel is from the unlabeled data being a mix of positive and negative examples. We used the implementation available on the python package ‘pywsl’ (Sakai, 2018).

Logistic Regression (LR): LR models the probability of \( p(Y = 1) \). In this case, all the unlabeled examples are considered negative examples of the training set. We used the implementation available on python library ‘statsmodel’ (Seabold & Perktold, 2010).

Random Forest (RF) (Breiman, 2001) is an ensemble method, which means that multiple decision trees are constructed using the training set and the assigned label is the mode of the classification across the several trees built. As in the Logistic Regression, here the unlabeled examples are considered negative. The implementation used was the one from ‘scikit-learn’ python package (Pedregosa et al., 2011).

An ensemble from the four methods previously described is also adopted. In this case, if 2 or more classification models predict a label as positive (or 1), then the ensemble will also predict positive, and negative otherwise. Finally, the random model randomly assign the labels 1 and 0 according with the proportion of 1 and 0’s on the training data. In other words, if 30% of the training set is 1, this model will randomly assign the label 1 for 30% of the testing set.

The Adapter-PU and the UPU were chosen for being classification models for positive and unlabeled examples, which is the exact scenario we are dealing with. The LR and RF were adopted because they are commonly used for binary classification, and they are good baselines to verify if the PU-learning approaches are better than traditional binary classification models. Finally, SVM approaches (PU or traditional) were eliminated from the results of the experiments due to their poor performance.

### 4. Experiments

To evaluate the quality of the proposed method, we performed experiments on the TCGA dataset. The F1 score, a suitable metric to compare models in unbalanced datasets, is used to evaluate the classification models. The F1 score is defined as \( 2 \times \frac{\text{Precision} \times \text{Recall}}{\text{Precision} + \text{Recall}} \).
Figure 2. Plots $a - d$ show a comparison of the ROC curve for each causal model for metastases prediction. Darker colors in the $b, c$, and $d$ plots means larger $k \in \{10, 20, 40, 60\}$, where $k$ is the dimension of latent features. The larger the area under the ROC curve, the better. Plot $e$ shows the predictive check $\gamma$ and its 95% confidence interval. The plot $f$ shows the Recall and Precision in the testing set of all classification models tested.

4.1. Dataset

The genomic dataset used is The Cancer Genome Atlas Program (TCGA) and it was downloaded using the tools provided by Broad Institute (Center, 2016; Lawrence et al., 2014). The goal is to predict whether the patient has metastases based on their gene expression (RNA-seq) data. In our context, the RNA-seq is the continuous treatments. To create a more balanced dataset, 15 cancer types with the highest occurrence of metastases were selected.

The complete dataset has 20534 genes and 2854 patients. Many of these genes can be eliminated because of their low variance among patients or high correlation with other genes. The reduction of the dataset also decreases the complexity of our machine learning models, which is a positive point considering we only have 2854 patients. The process used to select relevant genes for further analysis is described below.

Consider the matrix $X_{J \times V}$ that records the gene expression of patients, and $Y$ is a binary array that has the label 1 if the patient had metastases and 0 otherwise:

1. Considering the list of known driver genes from Cancer Gene Census (CGC) (https://cancer.sanger.ac.uk/census, access: 10-25-2019), if $X_v \in CGC, \forall v \in \{1, \ldots, V\}$, then $X_v$ is an exception for the steps 2, 3 and 4 described below and it is not excluded from the data $X$;

2. We keep the column $X_v$ if $\text{var}(X_v) \geq th$, $\forall v \in \{1, \ldots, V\}$. In other words, we keep the gene column if its gene expression variance is above a certain threshold. This threshold is defined to eliminate the genes with the 10% lowest variances;

3. The matrix $X$ is divided into 2 parts: $X^1_v = X_v[Y == 1]$ and $X^0_v = X_v[Y == 0]$. We use the Wilcoxon test to calculate if $X^1_v$ is significantly different from $X^0_v \forall v \in \{1, \ldots, V\}$ with $\alpha = 0.01$. This means that we will keep the genes whose gene distribution among patients with metastases is significantly different from the patients without metastases;

4. We keep the genes whose absolute correlation $|\text{cor}(X_i, X_j)| \leq 0.7, \forall i, j \in \{1, \ldots, V\}$ and $i \neq j$. If a pair of genes $X_i$ and $X_j$ have a correlation greater than 0.7, then we randomly pick one to keep and eliminate the other.
After this feature/gene selection, the input dataset has 7066 genes and 2854 patients, of which 1039 (36%) have metastases. From the 7066 remaining genes, 681 (9%) are known driver genes (Futreal et al., 2004). These known driver genes will be our positive examples in the classification model described in Subsection 3.2.

Finally, while the set of genes used in all causal inference methods was the same, several combinations of the patients were tested to try to identify driver genes that are cancer or gender-specific. Therefore, we worked with the following datasets: complete data, male patients, female patients, and patients separated by cancer types with at least 100 patients.

4.2. Feature Creation - Causal Model Outputs

As described in Section 3, we worked with BART and three variations of the DA models, each one with a different factor model. While the causal discovery for driver genes will be evaluated in Subsection 4.3, here we will evaluate the causal models used to create the outputs that will be used as features in the classification model from positive and unlabeled examples. For the DA models, it is important to check if the latent features dimension $k$ and the Outcome model are good. For this, we will compare the results of several values of $k$ on the 3 DA models (DA with PCA, DA with A, DA with MF) that passed on the predictive check. The significance level of the predictive check was 5%.

These 4 causal models were fitted on 18 data subsets: 1 complete set, 2 gender-specific sets (male and female), 14 cancer-specific sets\(^2\). Therefore, we have in total $4 \times 3 \times 17 + 17 = 221$ causal models outputs to evaluate. The Figures 2.a, 2.b, 2.c and 2.d shows the ROC curve of the causal models. The DA+Autoencoder, DA+Matrix Factorization and DA+PCA plots show the ROC curve for the values $k = \{10, 20, 40, 60\}$. Darker colors are associated with larger $k$.

For DA+Autoencoder, the results are mostly independent of $k$, therefore, in the following analysis we will focus on $k = 10$ for this causal model. On the other hand, DA+Matrix Factorization and DA+PCA shows that larger values of $k$ produce better results (bigger area under the ROC curve). However, for some cancer types with fewer patients, the Outcome Model does not converge with $k = 60$. Therefore, for these two models, we will be working with $k = 40$. For the BART plot, we can see that the curves present a reasonable result and the fitted model is adequate for further analysis.

Figure 2.e shows the predictive check $\gamma$ of the latent features learnt for Autoencoder with $k = 10$, and Matrix Factorization and PCA with $k = 40$ for the full dataset and several subsets. For these combinations of factor models and data subsets, all values of $\gamma$ were inside the confidence interval constructed using the average model with $\alpha = 0.05$.

4.3. Driver Gene Discovery - Classification Models

After checking which $k$ is best for predicting if a patient has metastasis or not and the quality of the BART model, we can focus on the classification models used to finally identify the causes of metastasis.

Several combinations of $D^{out}$ were also tested in this part of the experiments. Figure 3.a, for example, considers only the full dataset with BART and DA+PCA as causal models, forming a $D^{out}$ with 2 features. Figure 3.b have the same causal models, but also includes the male and female subsets. Therefore, $D^{out}$ in the scheme $b$ has $3 \times 2 = 6$ features. In total, 98 different combinations of $D^{out}$ were tested.

Figure 2.f shows the recall and precision of all 98 possible combinations of $D^{out}$ for each one of the 6 classification models. For the evaluation, the gold-standard driver gene list CGC (Futreal et al., 2004) was used. The Adapter-PU, UPU and LR models have a larger recall, however, their precision is almost the same as the random model. This means that these models are excellent at predicting known driver genes but at the cost of many false positives. The RF and Ensemble models both have smaller recall, and larger precision, reflecting the smaller number of False Positives, but a larger number of False Negatives.

A comparison between the models with the largest F1-scores on the test set for each classifier developed using ParKCa and 8 other driver gene discovery methods is shown in Figure 4 and Figure 5. These baselines for driver gene discovery were previously compared with each other using the CGC list by Tokheim et al. (2016). They are: MutsigCV, ActiveDriver, MuSiC, OncodriveCLUST, OncodriveFM, OncodriveFML, TUSON and 20/20+. Their approaches vary from analysis of somatic point mutations, mutation significance, functional impact and clusters of somatic mutations, and Random Forest of previous driver genes methods.

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\(^2\)The TCGA cancer types used were: ACC, BLCA, CHOL, ESCA, HNSC, LGG, LIHC, LUSC, PAAD, PRAD, SARC, SKCM, TGCT, UCS
Before interpreting the final results, it is important to point out that the choice of what is considered a good driver gene discovery model is also an open question. Some of these methods, such as OncodriveFM and MuSiC, have larger recall/smaller precision, meaning that the model can recover many known driver genes at the cost of a large rate of False Positives (FP). One researcher can interpret this as a bad model because the true driver genes are lost in the middle of the FP, while others might think that this is an indication of a larger number of unknown driver genes, yet to be discovered and explored. On the other hand, we also have methods like 20/20+, TUSON, and MutsigCV, with high precision/low recall. These methods are good at identifying certain driver genes, however, they fail to identify a broader range of them, reflected by the large number of False Negatives (FN). The F1-score, a score to evaluate unbalanced classifications, and the harmonic mean of recall and precision, can summarize these measures by giving the same importance for both of them. Therefore, if we adopt the F1-score as a measure of the model quality, we are valuing models that do an average job in both recall and precision.

Figure 4 shows that the models learnt by ParKCa have a larger recall than all baselines. The ParKCa with Random Forest and Ensemble have the largest F1-score as Figure 5 shows, the largest and the third-largest precision respectively (See Figure 4). The best baseline was the model 20/20+, which is also an ensemble model that uses the other driver gene discovery baselines in its construction.

5. Discussion and Conclusion

Our proposed method ParKCa demonstrated excellent results in the experiments. The best classification models for partially known causes consider a $D_{out}$ composed by all possible subsets (full dataset, gender subsets, and cancer type subsets) and the causal model’s outputs of 3 to 4 of the 4 available models. This indicates that the use of several causal models instead of a single causal model and the augmentation of the data by using the outputs of the causal models in subsets of the dataset improves the causal discovery. Otherwise, the models with only one of the subsets and one of the causal model’s output for feature creation would be enough to have good experimental results.

Considering the classification models, there was no significant difference between PU models and traditional classification models. One possible explanation is the small percentage of positive examples among the unlabeled examples in our application. If the unlabeled examples are mostly negative examples, the contribution that PU models can offer is decreased and the PU classification can be reduced to a traditional binary classification. The quality of the experimental results crucially depends on the list of known driver genes or known causes. If this list is comprehensive and includes driver genes with different behaviors and types, the classification will likely be unbiased. On the other hand, if the list is biased towards the most common mutated driver genes in most common cancer types, our method might only identify driver genes with behavior similar to the known examples.
Finally, we believe our proposed method ParKCa makes important contributions to causal inference. Our proposed method is flexible, robust, easy to use and demonstrates promising results in practical problems.

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