Predictive and Causal Inference of Cervical Cancer

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Table of contents

Introduction

Predictions using classification models

Causal inference using Bayesian networks

Appendix: Mathematical details of Bayesian networks

Introduction

The problem

- A + test $\Rightarrow$ found (pre)cancerous cells; may need treatment
  - https://www.healthline.com/health/cervical-biopsy#results
- Can we predict biopsy result using demographic data, lifestyle, and medical history?
- Dataset: Cervical cancer dataset with patient details (2017)
  - from UCI ML Repository

The data set (2017)

From UCI ML Repository

- $N = 858$
- Originally 32 independent vars + 4 targets
- Deleted 3 targets out of concern
- Deleted 2 vars only w/ 0 values
- Deleted 2 vars w/ 91.7% missing values
- Impute the missing data by mode
- The target response: `Biopsy` (binary $\Rightarrow$ classificaton)
  - $+ : - = 55{:}803$
  - $+$ accounts for $< 7\%$ of all available cases

Variables

Attribute	Type
Age	Integer
Number of sexual partners	Integer
First sexual intercourse (age)	Integer
Num of pregnancies	Integer
Smokes	Boolean
Smokes (years)	Boolean
Smokes (packs/year)	Boolean
Hormonal Contraceptives	Boolean
Hormonal Contraceptives (years)	Integer
IUD	Boolean
IUD (years)	Integer
STDs	Boolean
STDs (number)	Integer
STDs:condylomatosis	Boolean
STDs:cervical condylomatosis	Boolean
STDs:vaginal condylomatosis	Boolean
STDs:vulvo-perineal condylomatosis	Boolean
STDs:syphilis	Boolean

Attribute	Type
STDs:pelvic inflammatory disease	Boolean
STDs:genital herpes	Boolean
STDs:molluscum contagiosum	Boolean
STDs:AIDS	Boolean
STDs:HIV	Boolean
STDs:Hepatitis B	Boolean
STDs:HPV	Boolean
STDs: Number of diagnosis	Integer
STDs: Time since first diagnosis	Integer
STDs: Time since last diagnosis	Integer
Dx:Cancer	Boolean
Dx:CIN	Boolean
Dx:HPV	Boolean
Dx	Boolean
Hinselmann: target variable	Boolean
Schiller: target variable	Boolean
Cytology: target variable	Boolean
Biopsy: target variable	Boolean

Tasks

(1) Prediction
- accurate prediction save biopsy cost (insurance companies like it)

(2) Further: Causal inference.
- More interesting
- Not only of interpreting Biopsy. e.g. IUD (contraceptive device) vs Dx.Cancer
- Figure out potential risk factors $\Longrightarrow$ prevention!

Do what?

- Yuki: Predictions using different classification models
- Lupe: Predictions and causal inference using Bayesian networks

Predictions using classification models

About the classification models

Before feeding these models with the training set ($N = 686$)

- Standardize the data according to the training set
- maybe over-/under-sampling a bit

Over-/under-sampling

We use

- SMOTE – over-sample the + cases
- Near Miss – under-sample the – cases

For the classification models, we tried

- SMOTE + cases to have the same count as – cases
- Near Miss the other way
- SMOTE + cases & Near Miss – cases to their geometric mean
- Nothing only for the random forest

Existing (classification) models

To compare the results with Al-Wesabi et al's (2018), we feed the over-/under-sampled training set into

- Gaussian Naive Bayes
- Decision Tree
- Logistic regression
- SVM
- kNN ($k = 5$)
- Random forest that Al-Wesabi et al didn't try

using Python with `scikit-learn` and `imbalanced-learn`

Metrics to measure and compare the performance

Given tp, fn, tn, fp are True $+$, False $-$, True $-$, False $+$

- Overall accuracy

$$\frac{tp + tn}{tp + fn + tn + fp} \tag{1}$$

- Weighted precision

$$\left[\frac{tp(tp + fn)}{tp + fp} + \frac{tn(tn + fp)}{tn + fn}\right] \div (tp + fn + tn + fp) \tag{2}$$

- $+$ recall

$$\frac{tp}{tp + fn} \tag{3}$$

Metrics to measure and compare the performance

Numbers

- Weighted specificity

$$\left[\frac{tp(tn+fp)}{tp+fn}+\frac{tn(tp+fn)}{tn+fp}\right]\div(tp+fn+tn+fp) \tag{4}$$

- Weighted F_1 & F_2 score ($\beta = 1, 2$)

$$\begin{aligned}&\frac{(1+\beta^2)tp}{(1+\beta^2)tp+\beta^2 fn+fp}\times\frac{tp+fn}{tp+fn+tn+fp}\\ +&\frac{(1+\beta^2)tn}{(1+\beta^2)tn+\beta^2 fp+fn}\times\frac{tn+fp}{tp+fn+tn+fp}\end{aligned} \tag{5}$$

Results on GNB, DT, LR, SVM & 5NN

	GNB	Tree	LR	SVM	kNN
Accuracy	9.4	87.0	76.8	83.3	76.9
Recall	97.2	15.9	35.4	26.1	42.8
Specificity	91.2	20.7	38.1	30.1	45.1
Precision	89.7	89.0	89.4	89.4	90.1
F_1 score	6.9	87.9	82.0	86.0	82.2
F_2 score	5.6	87.3	78.5	84.2	78.6

Table: SMOTE-ed

Results on GNB, DT, LR, SVM & 5NN

	GNB	Tree	LR	SVM	kNN
Accuracy	63.5	34.5	44.5	53.8	60.1
Recall	63.9	82.0	76.2	70.2	63.7
Specificity	63.8	78.7	74.0	69.0	63.4
Precision	90.9	90.5	90.7	90.8	90.6
F_1 score	72.7	44.7	55.8	64.4	70.0
F_2 score	65.7	35.5	46.5	56.0	62.5

Table: Near Miss-ed

Results on GNB, DT, LR, SVM & 5NN

	GNB	Tree	LR	SVM	kNN
Accuracy	70.8	60.5	51.1	58.9	59.7
Recall	56.1	57.7	68.2	63.0	67.4
Specificity	57.1	57.8	67.0	62.7	66.9
Precision	90.7	90.0	90.4	90.5	91.0
F_1 score	78.2	70.3	62.2	69.0	69.7
F_2 score	72.8	63.0	53.4	61.3	62.0

Table: SMOTE-ed and Near Miss-ed

Results on GNB, DT, LR, SVM & 5NN

After repeating the workflow from p. 10 to p. 12 for 100 times,

- GNB is better and decision tree is worse c.f. Al-Wesabi
  - esp. in SMOTE followed by Near Miss
  - from different train–test split
    - us: 80:20, Al-Wesabi et al: 88:12
  - Near Miss instead of Tomek Links

With all the above metrics, which models work the best?

- SMOTE (+ Near Miss): 5NN
- Near Miss: GNB

Random forest

Tune hyper-parameters by grid searching with stratified 7-fold CV

- look at the $+$ recall of the SMOTE-ed and Near Miss-ed standardized training set
- Highest recall $\Rightarrow$ get the parameters $\Rightarrow$ plant the forest with
  - Neither
  - SMOTE-ed
  - Near Miss-ed
  - Both

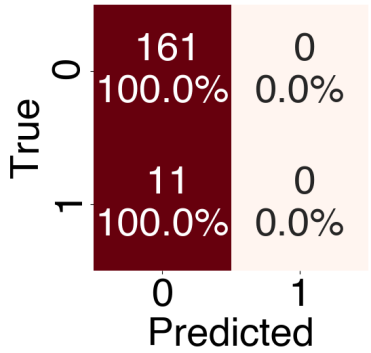
  standardized training set

$\Rightarrow$ compare the confusion matrices on the test set

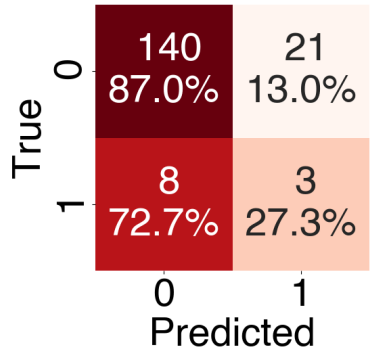
How are the fruit from the forests?

The confusion matrices with the same stdized training set w/(o) over-/under-sampling

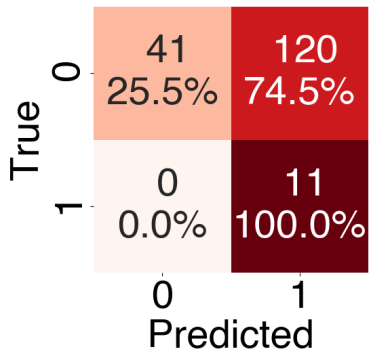
- `max_features` $= \lceil \log_2 28 \rceil = 5$
- `n_estimators` $= 10$
- `max_depth` $= 5$
- `min_samples_split` $= 2$



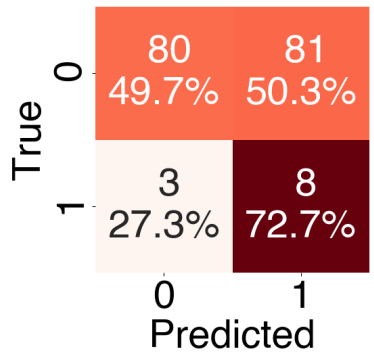
(a) Nothing



(b) SMOTE



(c) Near Miss



(d) Both

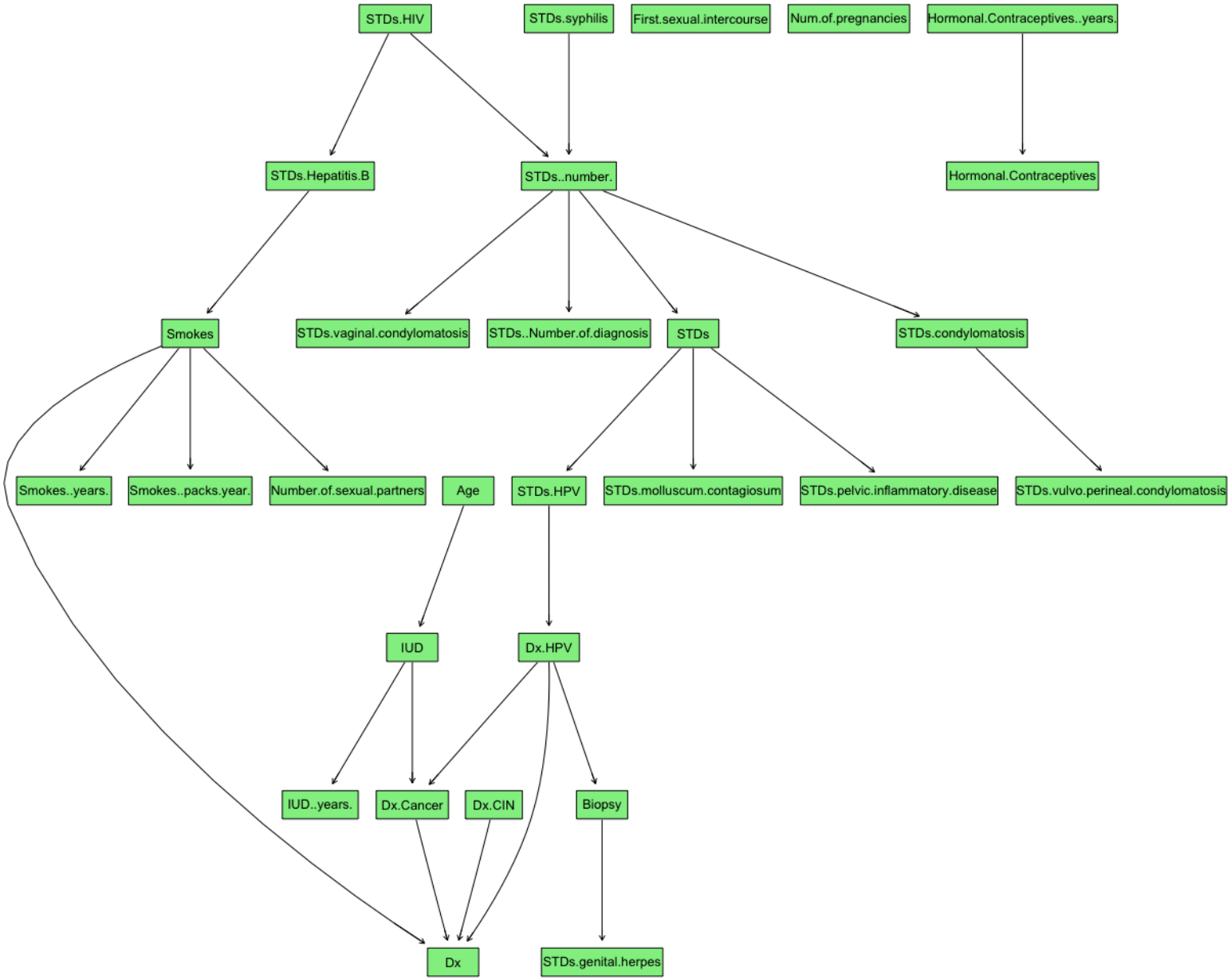
Use which to do the prediction?

Would suggest SMOTE on the standardized training set $\Rightarrow$ predict

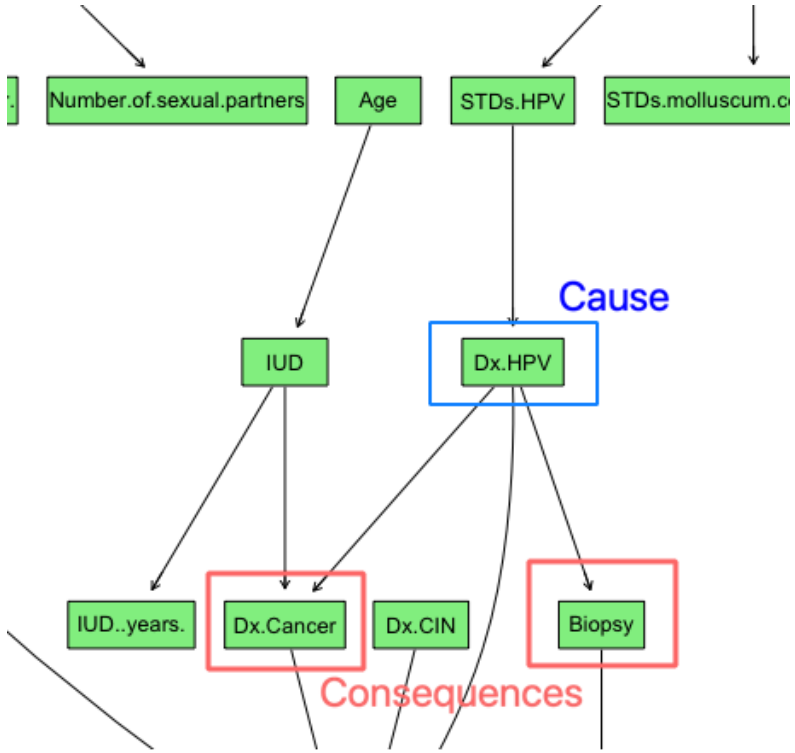
- at least identified some (not much though) $+$ cases
- the overall accuracy (83.1%) is okay
- not giving too many false alarms ($fp/(tn + fp) = 13.0\%$)

Causal inference using Bayesian networks

Bayesian networks: Introduction



Bayesian networks: Introduction



- `Dx.HPV` $\rightarrow$ `Dx.Cancer`: Probabilistic causal relationship
- Conditional independence: `Dx.Cancer` $\perp\!\!\!\perp$ `Biopsy` $\mid$ `Dx.HPV`
- Unsupervised learning usually

Bayesian networks: Definition

- $V = (X_1, \ldots, X_n)$: variable set/vertex set. x_i discrete, with supports $\{1, 2, \ldots, q_i\}$
- E: arc set; e.g. $X_1 \to X_2 \in E$
- $G = (V, E)$ defines a directed acyclic graph: directed graph without cycles

Causal inference: Overall idea

- Procedures
  - Given the dataset D, learn structure G
  - Assign posterior score $P(G|D)$ to G
  - MCMC approach: G is random. Sample $\mathcal{G} = \{G_1, G_2, \ldots, G_N\}$ based on $P(G|D)$; Sample from posterior modes
  - Estimate the edge feature, $P(X_i \to X_j|D)$ using $\mathcal{G}$ (Model averaging)
  - Estimate $P(X = x|Y = y)$ for interesting relationship, for some X and Y using $G^* = \arg\max_{G \in \mathcal{G}}\{P(G|D)\}$ (Maximum a posteriori, MAP)

Results: Prediction

- Can be used to predict; not our main goal
- Calculate $P(\texttt{Biopsy} = 1|X)$ by simulation

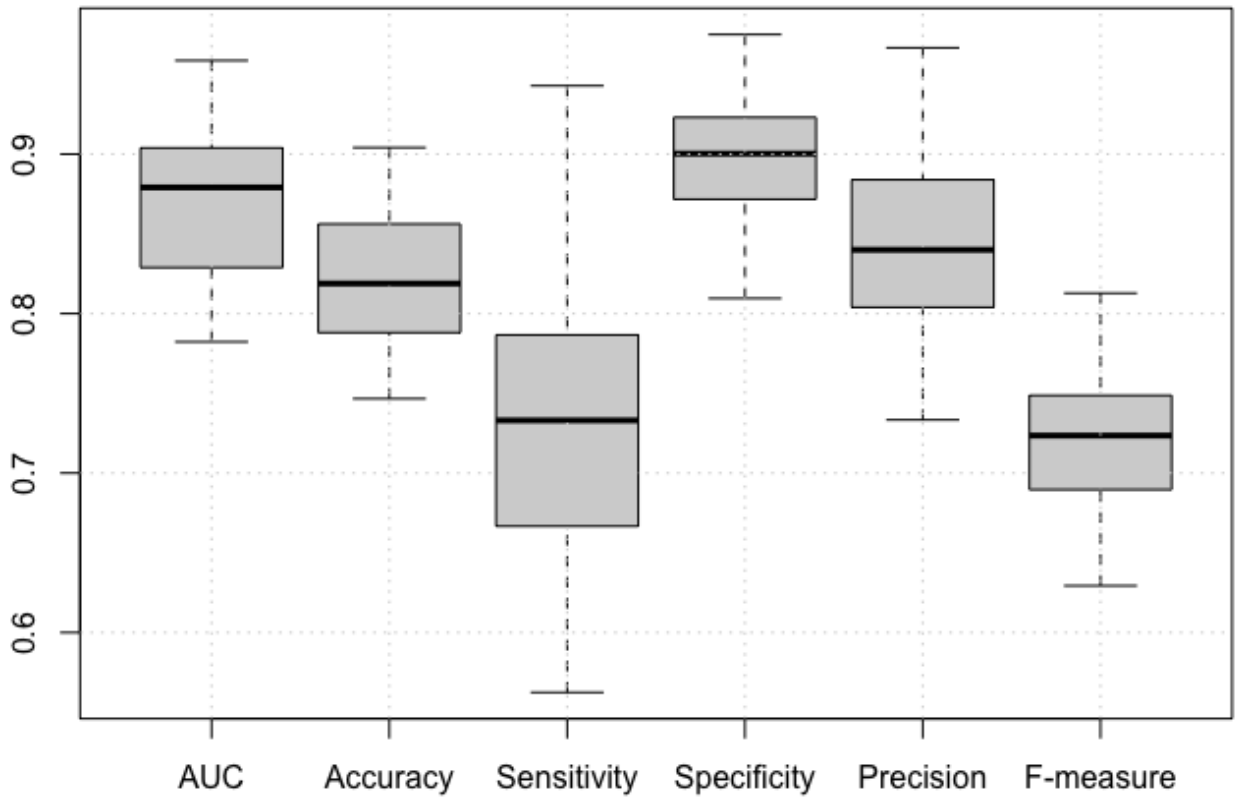
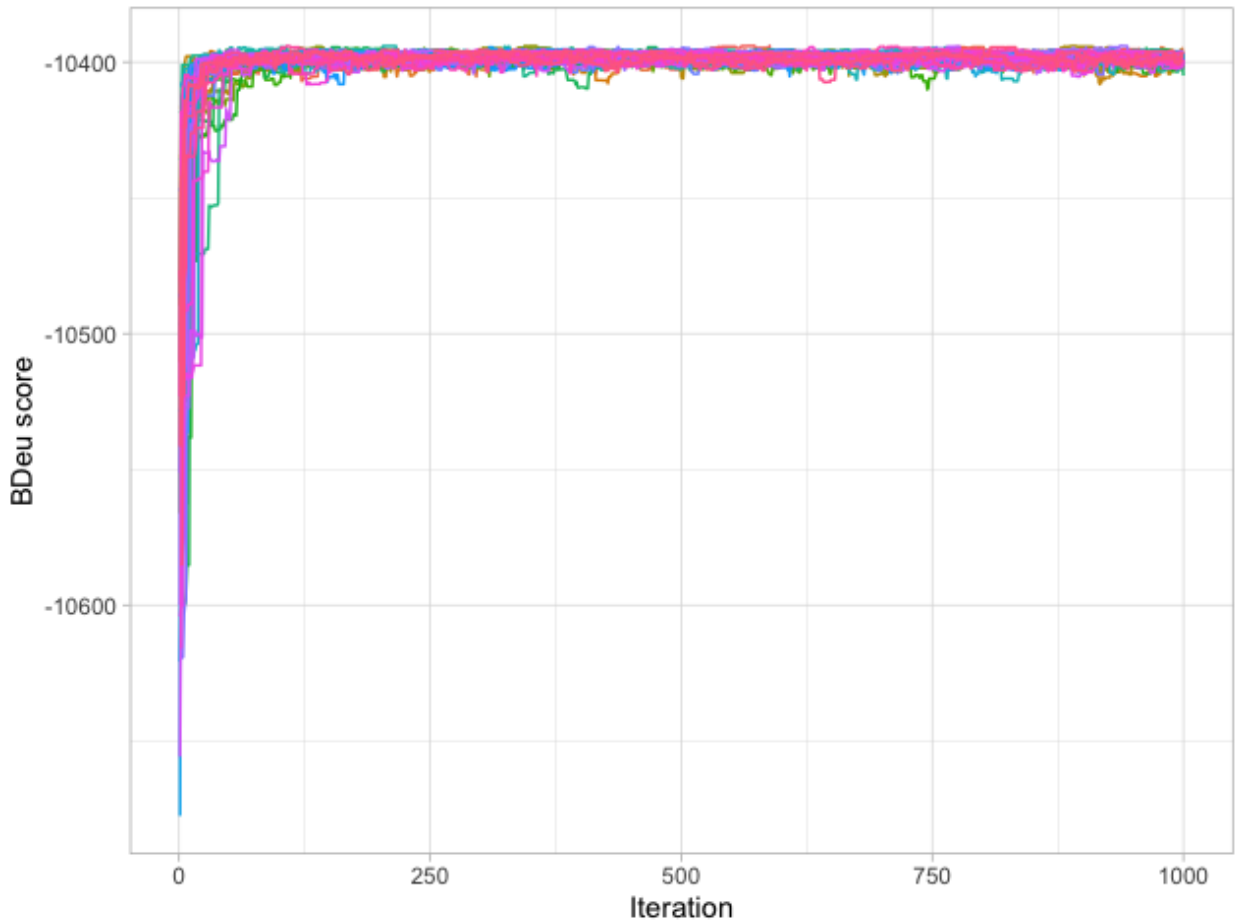
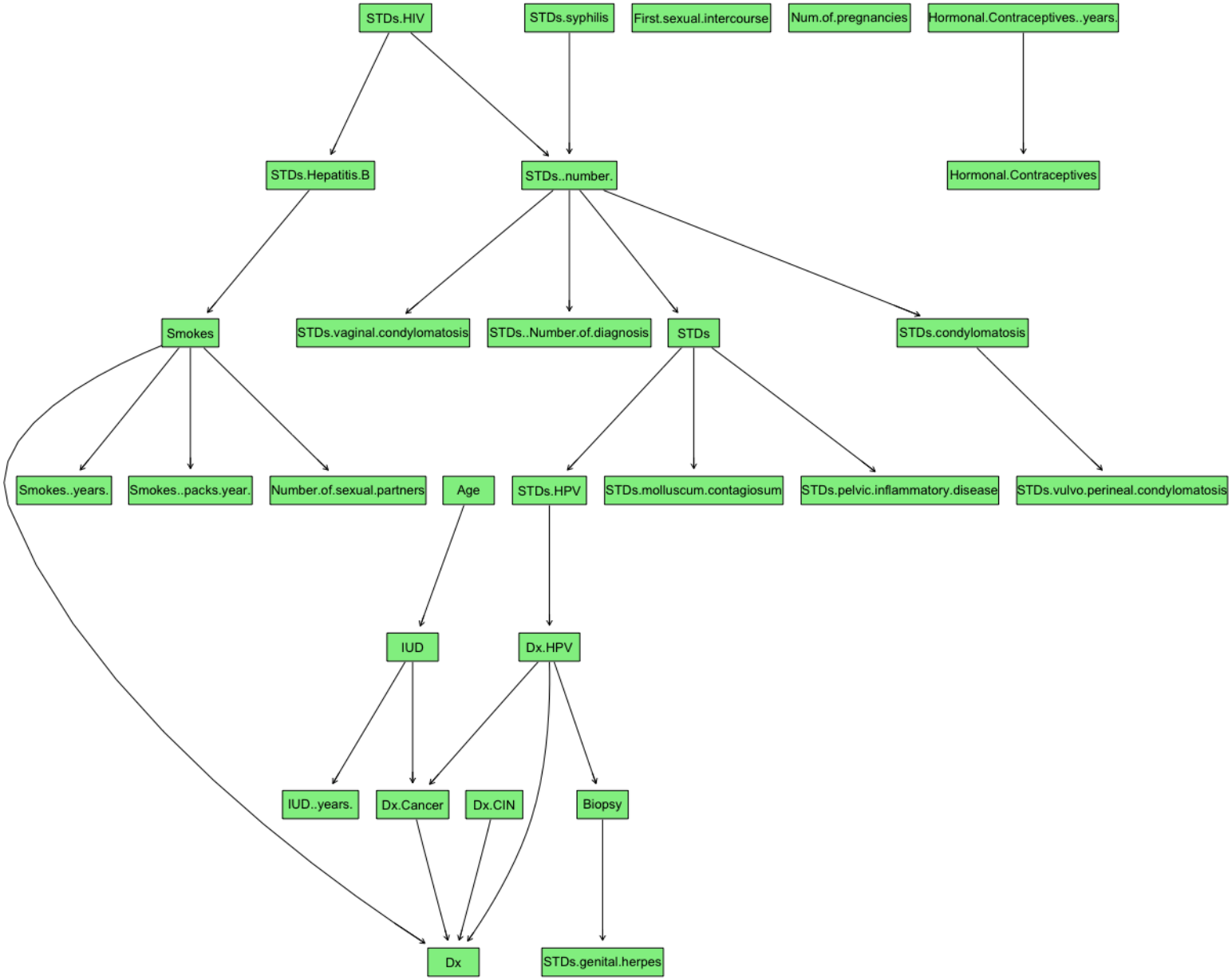


Figure: Boxplot of the AUCs of the ROC curves of 20 replications with SMOTE oversampled dataset.

Results: MCMC convergence of 50 replications



Results: MAP graph



Results: MAP graph

- Correct patterns almost
- IUD:Intrauterine device
- Age $\rightarrow$ IUD? More averaging is better

Results: Edge features

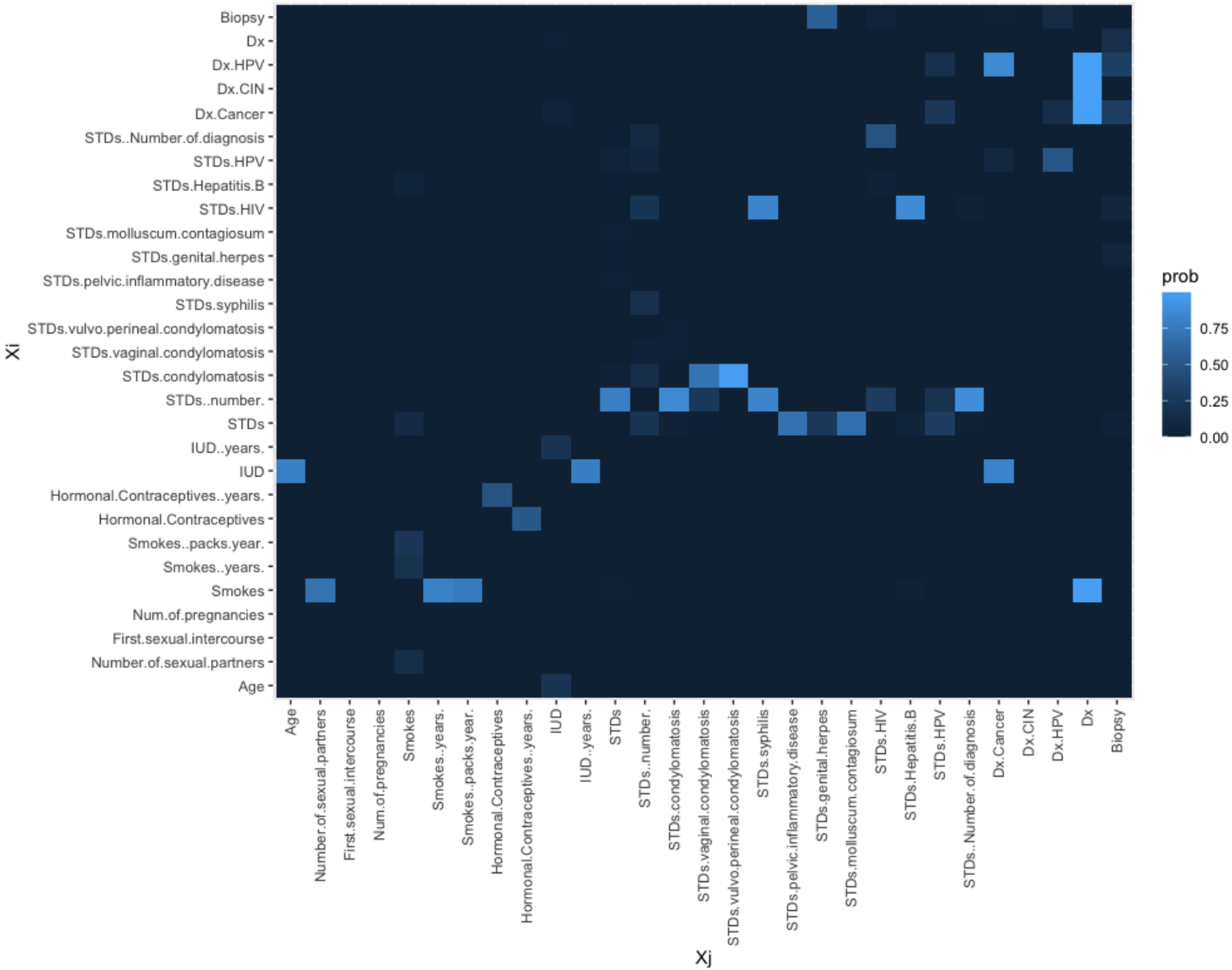
- Edge features:

$$\hat{P}(X_i \to X_j | D) = \frac{1}{M - B} \sum_{m=B+1}^{M} 1_{X_i \to X_j}(G_m), \qquad (6)$$

  B: Burn-in size of MCMC

- "Strength" of the causal relationship

Results: Edge features



Results: Edge features

- $\hat{P}(\text{Dx.HPV} \rightarrow \text{Dx.Cancer}|D) = 0.8601$
- $\hat{P}(\text{IUD} \rightarrow \text{Dx.Cancer}|D) = 0.82518$
- $\hat{P}(\text{Dx.HPV} \rightarrow \text{Biopsy}|D) = 0.3126$
- $\hat{P}(\text{Smokes} \rightarrow \text{Dx.HPV}|D) = \hat{P}(\text{IUD} \rightarrow \text{Dx.HPV}|D) = 0$

Results: Probability Estimation

- $\hat{P}(\text{Dx.HPV} \rightarrow \text{Dx.Cancer}|D) = 0.8601$
  - $P(\text{Dx.Cancer}|\text{Dx.HPV} = 0) = 0.00246$
  - $P(\text{Dx.Cancer}|\text{Dx.HPV} = 1) = 0.86858$
  - Odds ratio $= 2680$
  - Relative risk $= 353.1$
- Signficiant risk increases in cancer with HPV infection

Results: Probability Estimation

- Use the MAP network to estimate (easier to interpret)
- $\hat{P}(\text{IUD} \rightarrow \text{Dx.Cancer}|D) = 0.82518$
  - $P(\text{Biopsy} = 1|\text{Dx.HPV} = 0) = 0.05846$
  - $P(\text{Biopsy} = 1|\text{Dx.HPV} = 1) = 0.33486$
  - Odds ratio $= 8.1$
  - Relative risk $= 5.728$
- The use of IUD increases risk of cervical cancer

Results: Probability Estimation

- $\hat{P}(\text{Dx.HPV} \rightarrow \text{Biopsy}|D) = 0.3126$
  - $P(\text{Biopsy} = 1|\text{Dx.HPV} = 0) = 0.05846$
  - $P(\text{Biopsy} = 1|\text{Dx.HPV} = 1) = 0.33486$
  - Odds ratio $= 85.6$
  - Relative risk $= 5.72$
- Well-known

Results: Probability Estimation

- $\hat{P}(\text{Smokes} \rightarrow \text{Dx.HPV}|D) = \hat{P}(\text{IUD} \rightarrow \text{Dx.HPV}|D) = 0$
  - $P(Dx.HPV = 1|\text{Smokes}= 1) = 0.02112072$
  - $P(Dx.HPV = 1|\text{Smokes}= 0) = 0.02107726$
  - Odds ratio $= 1.00210$
  - Relative risk $= 1.00206$
- Smoking or not does not affect HPV diagnosis

Summary

Causal inference using Bayesian network

Apply to any other datasets

One model, multiple predictions

Good interpretation:

- MAP: A clear network for the relationship of variables
- Stregnth of causal relationship
- Predict risks

Appendix: Mathematical details of Bayesian networks

Score-based structure learning: Posterior likelihood

- Conditional independence: Joint density function decomposition

$$P(X_1, \ldots, X_2) = \prod_{i=1}^{n} P(X_i | pa(X_i)), \tag{7}$$

$pa(X_i)$: parent set of X_i

- The likelihood function is

$$P(D|\Theta) = \prod_{i=1}^{n} \prod_{j=1}^{q_i} \prod_{k=1}^{r_i} \theta_{ijk}, \tag{8}$$

N_{ijk}: Number of case in D that $\{X_i = j | pa(X_i) = k\}$; r_i: Number of possible parent configuration.

Score-based structure learning: Posterior likelihood

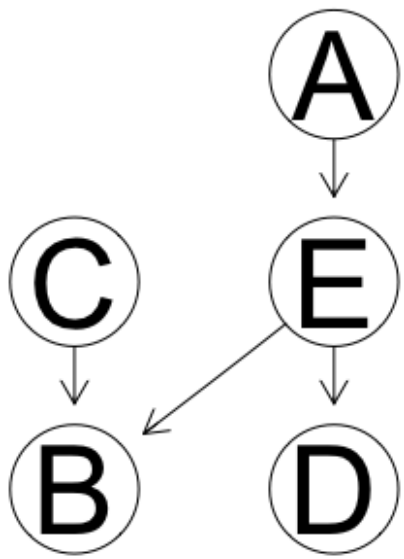
- Assume that $p(\Theta|G) \propto \prod_{i=1}^{n} \prod_{j=1}^{q_i} \prod_{k=1}^{r_i} \theta_{ijk}^{\alpha_{ijk}}$, i.e., product Dirichlet distribution with parameters α
- Assume $P(G) \propto 1$
- Apply Bayes' theorem, the posterior is

$$\log P(G|D) \propto \int P(D|\theta, G) P(\theta|G) d\Theta P(G)$$

$$\propto \sum_{i=1}^{n} \left[\log \frac{\Gamma(\alpha_{i.k})}{\Gamma(\alpha_{i.k} + N_{i.k})} + \sum_{j=1}^{q_i} \prod_{j=1}^{r_i} \frac{\Gamma(N_{ijk} + \alpha_{ijk})}{\Gamma(\alpha_{ijk})} \right] \tag{9}$$

Score-based structure learning: Order MCMC

- Sample on the partial ordering space.
- Define $\prec = (\prec_{(1)}, \ldots, \prec_{(n)})$ be the ordering of nodes, which are the permutation of nodes in V
- $\prec_{(i)}$ has higher order than $\prec_{(j)}$ iff the nodeAs corresponding to $\prec_{(j)}$ can only be non-ancestor of $\prec_{(i)}$
- e.g. $\prec = (A, E, C, B, D)$



Score-based structure learning: Order MCMC

- Initialize an order $\prec_0 = (\prec_{(1)}, \ldots, \prec_{(n)})$
- Interchange two orders. New order: $\prec'$
- Accept $\prec'$ (i.e. set $\prec_1 = \prec'$, else $\prec_1 = \prec_0$) with probability

$$\min\left\{1, \frac{P(\prec' | D)}{P(\prec | D)}\right\}, \tag{10}$$

where

$$P(\prec | D) = \prod_{i=1}^{n} \sum_{\Pi \in \Pi_i^{\prec}} P(X_i | \Pi_i) \tag{11}$$

- Then, sample a graph consistent to order $\prec_1$, name it G_1
- Repeat, until the chain converges

Probability Estimation

- Target: Estimate $P(X_i = x|E = e)$; E: evidences

Algorithm 1: Likelihood-Weighted (LW) sampling

Result: Write here the result
Input: A graph G, an event $Y = y$ and an evidence with k vairables, $E = e \equiv (e_1, \ldots, e_k)$;
Initialize $w \leftarrow 1$;
for $i = 1, 2, \ldots, n$ **do**
  if $X_i \in E$ **then**
    Set $x_i \leftarrow e_i$;
    Update $w \leftarrow w \times P(e_i|\Pi_i)$, where Π_i is the parent set of X_i in the graph G ;
  else
    Sample x_i from $P(X_i|\Pi_i)$;
  end
end
return $(x_1, \ldots, x_n), w$

Probability Estimation

- Conduct Algorithm 1 for L times.

$$\hat{P}(Y = y|E = e) = \frac{\sum_{\ell=1}^{L} w_\ell I\{y = y_\ell\}}{\sum_{\ell=1}^{L} w_\ell}, \tag{12}$$

Thank you! Q&A