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# Personalizing Treatment for ICU Patients with ARDS Using Meta-Learning Algorithms

Comparing the S-, T-, and X-learner to Estimate the CATE for High versus Low PEEP in Mechanical Ventilation

## 1. Introduction

- **Mechanical ventilation** is a vital supportive measure for patients suffering from Acute Respiratory Distress Syndrome (ARDS) in the Intensive Care Unit (ICU) [1].
- **An important setting** of the mechanical ventilator is the positive end-expiratory pressure (PEEP)
  - High PEEP regime
  - Low PEEP regime
- **It is hypothesized** that some patients benefit more from high PEEP than others, based on patient characteristics
- **In this research**, we examine whether we can personalize treatment by estimating the conditional average treatment effect (CATE) on the MIMIC-IV dataset [2] using machine-learning methods
- **More specifically,** we compare different meta-algorithms (S-, T-, and X-learner) to estimate the CATE

***Main Research Question:***
How do the S-learner, T-learner, and X-learner perform in estimating the CATE to predict which ICU patients suffering from ARDS benefit from high PEEP compared to low PEEP in mechanical ventilation, based on patient characteristics?

***Sub Question:***
Does the X-learner perform particularly well in estimating the CATE when the treatment assignment in the data is significantly unbalanced?

## 2. Definitions

**Problem Description**
The problem we are addressing is the heterogeneity of treatment effects in mechanical ventilation for ICU patients with ARDS.

- **MIMIC-IV dataset**
  - Data from an observational study (ICU patients with ARDS)
  - *Treatment variable T:* PEEP regime
  - *Outcome variable Y:* 28-day mortality
  - *Feature vector X:* includes demographic data and medical data
- **Causal Inference**
  - Difference in outcomes when comparing the result of giving treatment (high PEEP) versus not giving treatment (low PEEP)
  - **CATE**: estimating the treatment effect, conditional on patient characteristics

$$\tau(x) = E[Y(1) - Y(0) | X = x]$$

## 3. Methodology

**S-learner**
Uses a *single* ML model to estimate the combined response function:

$$\mu(x,t) = E[Y|X=x, T=t]$$

Estimated CATE is calculated as follows:

$$\hat{\tau}(x) = \hat{\mu}(x,1) - \hat{\mu}(x,0)$$

**T-learner**
Uses *two* ML models to estimate the response functions for *T=0* and *T=1*:

$$\mu_0(x) = E[Y|X=x, T=0]$$
$$\mu_1(x) = E[Y|X=x, T=1]$$

Estimated CATE is calculated as follows:

$$\hat{\tau}(x) = \hat{\mu}_1(x) - \hat{\mu}_0(x)$$

**X-learner**
- Use *two* ML models to estimate the response functions for *T=0* and *T=1*
- Impute missing values:

$$\hat{\tau}_0(x) = \hat{\mu}_1(x) - Y \quad \text{for } T = 0$$
$$\hat{\tau}_1(x) = Y - \hat{\mu}_0(x) \quad \text{for } T = 1$$

Fit two more ML models to estimate the imputed treatment effects:

$$\hat{\tau}_0(x) \sim M_{\tau 0}$$
$$\hat{\tau}_1(x) \sim M_{\tau 1}$$

- Combine the estimated treatment effects with the propensity score e(x):

$$\hat{\tau}(x) = \hat{e}(x)\hat{\tau}_0(x) + (1 - \hat{e}(x))\hat{\tau}_1(x)$$

**Confounders *L***
All variables affecting the treatment assignment and the outcome variable must be correctly identified (will be used as *x*)
- Age
- Weight
- PF_ratio
- PaO2
- Driving Pressure
- FIO2
- HCO3
- Plateau Pressure
- Respiratory Rate

## 4. Experimental Setup and Results

**Simulations**
- Generating MIMIC-like data
- Confounded + unbalanced
- Simulating Y(0) and Y(1)
- Applying S-, T-, and X-learner (using different base models)
- Repeat 30 times

Results
- Comparing predicted CATE to actual CATE, plot MSE
- For S-, T-, X-learner:
  - Low MSE (around 0.35)
  - No significant difference between models

**MIMIC-IV dataset**
1. Pre-processing (imputation)
2. Split into 70% training and 30% testing
3. Applying S-, T-, and X-learner (using different base models)
4. Repeated 100 times to gain average Cumulative Gain Curve (AUC scores shown below)

Table 4: AUC scores using LGBM as base model(s).

| Learner | Mean | SD |
|---|---|---|
| S-learner (test) | 0.90 | 1.49 |
| T-learner (test) | 0.29 | 1.19 |
| X-learner (test) | 0.69 | 1.38 |
| S-learner (train) | 12.18 | 1.65 |
| T-learner (train) | 21.00 | 1.13 |
| X-learner (train) | 15.10 | 1.30 |

Table 7: AUC scores using SVR as base model(s).

| Learner | Mean | SD |
|---|---|---|
| S-learner (test) | 2.90 | 1.66 |
| T-learner (test) | 2.81 | 1.79 |
| X-learner (test) | 2.98 | 1.46 |
| S-learner (train) | 4.34 | 1.02 |
| T-learner (train) | 4.47 | 0.92 |
| X-learner (train) | 4.17 | 0.78 |

Table 6: AUC scores using RF as base model(s).

| Learner | Mean | SD |
|---|---|---|
| S-learner (test) | 0.44 | 1.34 |
| T-learner (test) | 0.15 | 1.26 |
| X-learner (test) | 1.06 | 1.75 |
| S-learner (train) | 25.22 | 1.18 |
| T-learner (train) | 27.55 | 0.40 |
| X-learner (train) | 20.93 | 1.36 |

Table 5: AUC scores using LR as base model(s).

| Learner | Mean | SD |
|---|---|---|
| S-learner (test) | 0.36 | 1.23 |
| T-learner (test) | 0.85 | 1.31 |
| X-learner (test) | 0.92 | 1.32 |
| S-learner (train) | 0.20 | 0.79 |
| T-learner (train) | 2.78 | 0.98 |
| X-learner (train) | 2.33 | 0.69 |

**RCT dataset**
1. Training S-, T-, and X-learner on MIMIC-IV dataset
2. Pre-process RCT dataset (imputation and normalization)
3. Apply trained models (using SVR) to RCT dataset
4. Resulting Cumulative Gain Curve (shown below)

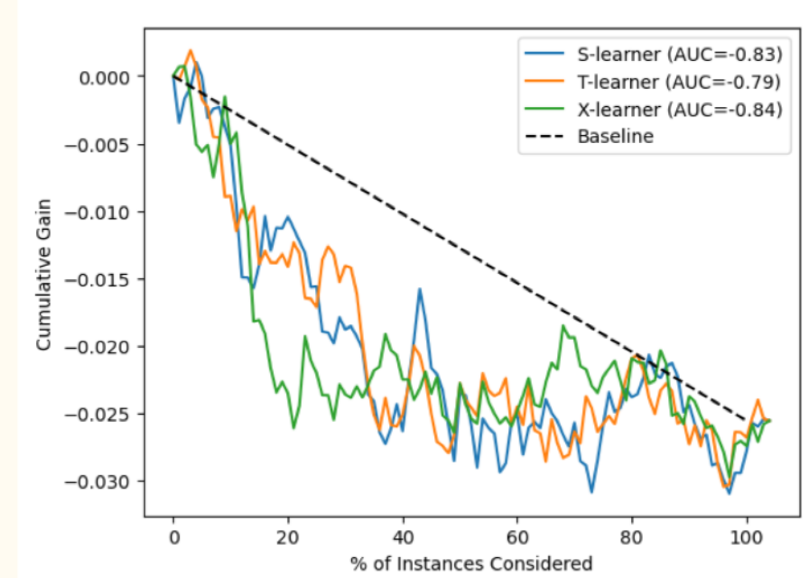


Figure 3: Cumulative gain curve for the RCT dataset.

## 5. Discussion

**Simulation Results**
- Meta-learners performed well under unbalanced and confounded conditions.
- Based only on a single simulation setup
- Simulation setup does not fully capture MIMIC-IV complexity

**MIMIC-IV results**
- Meta-learners overfitted with LGBM and RF
- No significant performance on the MIMIC-data: results are close to random + high variation
  - Meta-learners struggle with complex relationships in MIMIC data
  - Potential hidden confounders might have biased results

**RCT data results**
- Meta-learners performed poorly on RCT data
- Might be due to difference in data distribution
- Might be due to missing important features in RCT data
- Training on unbalanced data and applying to balanced data may have biased CATE estimates

## 6. Conclusion and Future Research

**Key findings**
- *Simulated data*:
  - meta-learners performed well in MSE using different base models.
- *MIMIC-IV data*:
  - LGBM and RF overfitted on training data
  - Meta-learners did not identify a patient subgroup benefiting from high PEEP
- *RCT data:*
  - Meta-learners performed worse than the randomized base model

**X-learner**
Slightly outperformed S-, and T-learner under unbalanced conditions, but with high variability, the hypothesis cannot be verified

**Future research**
- Generate simulation data with more complex response functions
- Look into a broader range of base-models
- Combine different base-models
- Look into methods to identify hidden confounders
- Ensure external validation data distribution aligns with training data

**References:**
[1] Tobin, Martin J. "Advances in mechanical ventilation." New England Journal of Medicine 344.26 (2001): 1986-1996.

[2] Johnson, A. E. W. et al. MIMIC-IV, a freely accessible electronic health record dataset. Sci. Data 10, 1–9 (2023).