Maximin-Projection Learning for Optimal Treatment Decision with Heterogeneous Data

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Sources of heterogeneity

- Data Integration (Meta analysis)
  - Results combined from different studies to identify similar patterns.
  - Heterogeneity due to different study populations.
  - Heterogeneity due to different study periods.
- Divide and conquer (Massive data)
  - Data too large to fit an overall model, a possible solution is divide and conquer.
  - Estimator for each group often differs.
  - Heterogeneity due to large-scale data.

Schizophrenia study (Tarrier et al., 2004)

- A multi-center, randomized controlled trial with an 18 month follow-up period.
- To examine the effectiveness of cognitive-behavioral therapy for patients with schizophrenia.
- Treatments: the cognitive-behavioural therapy plus treatment as usual (CBT); supportive counselling plus treatment as usual (SC); and treatment as usual (TAU).
- Y: the reduction of PANSS score.
- X: PANSS score at baseline; log duration of untreated psychosis.
- Over 400 patients initially enrolled in 11 mental health units in England; 165 patients finish the follow-up study and have completed information for both X and Y.
- Data are from three geographical locations (Manchester/Salford, Liverpool and North Nottinghamshire)

Schizophrenia study (Continued)

- We compare CBT ($A = 1$) vs. CS ($A = 0$).
- For each group, consider the following model

$$E(Y_{gj}|X_{gj}, A_{gj}) = h_g(X_{gj}) + A_{gj}\left(\beta_{g0} + \beta_{g1}X_{gj}^{(1)} + \beta_{g2}X_{gj}^{(2)}\right),$$

and estimate β_{g0}, β_{g1}, β_{g2} by A-learning.

Table: Estimators of groupwise optimal treatment regime (standard errors in paranthesis)

	Group 1	Group 2	Group 3
β_{g0}	$-8.51(6.96)$	$1.42(4.98)$	$0.47(5.74)$
β_{g1}	$-1.53(4.75)$	$0.05(6.55)$	$-4.89(5.74)$
β_{g2}	$2.65(5.70)$	$5.41(3.52)$	$-11.67(4.27)$

Health assessment questionnaire (HAQ) progression data

- An observational study to investigate the influence of early disease modifying antirheumatic drug (DMARD) treatment for patients with recent onset inflammatory polyarthritis (Farragher et al., 2010).
- 847 patients enrolled from 1990 to 2000.
- We focused on treatments: methotrexate ($A = 1$) and sulfasalazine ($A = 0$).
- Y: reduction in HAQ scores between baseline and 5 years.
- X: age, baseline HAQ score, number of swollen joints and number of tender joints.
- Patients enrolled at different times showing heterogeneity; we considered three groups: 1990 - 1992 ($G = 1$); 1993 - 1996 ($G = 2$); 1997 - 2000 ($G = 3$).

HAQ data (continued)

- We estimate the group-wise optimal treatment regime using A-learning based on the same models as in the previous example.

Table: Estimators of groupwise optimal treatment regime (standard errors in paranthesis)

	Group 1	Group 2	Group 3
$\hat{\beta}_{g0}$	−0.39(0.11)	−0.09(0.10)	0.48(0.33)
$\hat{\beta}_{g1}$	0.26(0.15)	0.24(0.11)	−0.17(0.14)
$\hat{\beta}_{g2}$	0.09(0.12)	0.18(0.13)	1.02(0.36)
$\hat{\beta}_{g3}$	0.03(0.12)	−0.34(0.15)	0.01(0.19)

- Heterogeneity inside the data

Questions:

- How to effectively combine different treatment regimes?
- How to take into account data heterogeneity?

Simple solutions:

- Combine the data together and find the optimal treatment regime based on the pooled data (ignore the data heterogeneity!).
- Take average of group-specific optimal treatment regimes (may work bad for some groups).

Our thinking:

- What else can we do with heterogeneous data?
- What is a good criteria for combining treatment regimes?

Model

- G different population groups:

$$Y_{gj} = h_g(X_{gj}) + A_{gj}\psi_g(X_{gj}^T\beta_g) + \varepsilon_{gj}$$

- $||\beta_g||_2 = 1, g = 1, \ldots, G, j = 1, \ldots, m$
- h_g arbitrary baseline function
- ψ_g arbitrary monotone increasing function

Objective

Find a decision rule

$$d : X \to \mathcal{A} = \{0, 1\}$$

that works well for patients of all G groups.

Idea

- Groupwise optimal regime: $I\{X_0^T\beta_g > \psi_g^{-1}(0)\}$
- Overall decision: $I(X_0^T\beta_0 > c_0)$ subject to $||\beta_0||_2 = 1$
- Two step strategy:
  - Step 1: Fix c_0, search some $\beta_0(c_0)$ achieves some "optimality"
  - Step 2: Optimize over c_0

How to define "optimality"

- For each β, define the reward function $R_g(\beta)$ given the decision

$$I(X_0^T\beta > c_0).$$

- Maximin effects $\beta_0 = \arg\max_\beta \min_g R_g(\beta)$
  - Maximize the minimum reward
  - Minimize the risk of the worst-case scenario

How to choose reward function

Example (Average Percentage of making Correct Decisions (PCD))

Using PCD,

$$R_g^{(1)}(\beta) = 1 - E|I(X_g^T\beta_g > \psi_g^{-1}(0)) - I(X_g^T\beta > c_0)|,$$

The maximin effects $\beta_0^{(1)} = \arg\max_{\beta:||\beta||_2=1} \min_g R_g^{(1)}(\beta)$.

Example (Value function)

Using value function,

$$R_g^{(2)}(\beta) = E\{Y_g^\star(d(X_g,\beta))\} - E\{Y_g^\star(0)\},$$

where $d(X_g,\beta) = I(X_g^T\beta > c_0)$.

The maximin effects $\beta_0^{(2)} = \arg\max_{\beta:||\beta||_2=1} \min_g R_g^{(2)}(\beta)$

An intuitive definition for the maximin effects

- Assume $\psi_1^{-1}(0) = \psi_2^{-1}(0) = \cdots = \psi_G^{-1}(0) = \bar{c}$, for each subgroup g, the optimal regime becomes

$$I(X_0^T \beta_g > \bar{c}),$$

- Note that $||\beta_g||_2 = 1$, each β_g represents the "direction".
- Intuitively, we can define the maximin effects through "angles":

$$\beta_0^{(3)} = \arg \min_{||\beta||_2=1} \max_g \angle(\beta, \beta_g).$$

- More formally, let

$$F(\beta) = \min_g \beta^T \beta_g,$$

and $\beta_0^{(3)}$ is defined as $\arg\max_{||\beta||_2=1} F(\beta)$ (Maximin correlation approach in Avi-Itzhak et al., 1995).

Theorem (Equivalence of $\beta_0^{(1)}$ and $\beta_0^{(3)}$)

Assume $\psi_1^{-1}(0) = \psi_2^{-1}(0) = \cdots = \psi_G^{-1}(0) = \bar{c}$, X_{ij} *i.i.d spherically distributed, then for any* c_0,

$$\beta_0^{(3)} = \arg\max_{||\beta||_2=1} \min_g R_g^{(1)}(\beta).$$

Theorem (Equivalence of $\beta_0^{(2)}$ and $\beta_0^{(3)}$)

Assume $\psi_1 = \psi_2 = \cdots = \psi_G = \psi$, X_{ij} *i.i.d spherically distributed, then for any* c_0,

$$\beta_0^{(3)} = \arg\max_{||\beta||_2=1} \min_g R_g^{(2)}(\beta).$$

Only need to focus on the third definition

Refinement

- $\beta_0^{(3)} = \arg\max_{||\beta||_2=1} F(\beta)$
- $\beta_0^{(3)}$ always exists: the maximin effect is well defined
- May not be unique when $F_0 \equiv \max_{||\beta||_2=1} F(\beta) < 0$
- The optimization problem

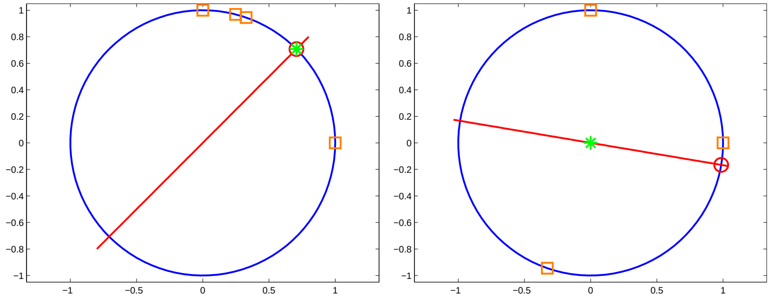
$$\arg \max_{||\beta||_2=1} F(\beta),$$

  is a quasi-concave problem (difficult to solve globally).
- Consider $\beta_0^{(4)} = \arg\max_{||\beta||_2\leq 1} F(\beta)$,
- Solving $\beta_0^{(4)}$ is a tractable concave programming (Seung-Jean et al., 2008).
- $\beta_0^{(4)}$ always exists, and is unique when $F_0 \neq 0$.

Graphical characterization

- When $F_0 > 0$, $\beta_0^{(4)} = \beta_0^{(3)}$,
- When $F_0 < 0$, $\beta_0^{(4)} = 0$.

Figure: Illustration of maximin effects $\beta_0^{(4)}$ (green star), $\beta_0^{(3)}$ (red circle), and subgroup parameters (orange square)



Estimating procedure

- Assume estimators $\hat{\beta}_1, \ldots, \hat{\beta}_G$ are available with $||\hat{\beta}_g||_2 = 1$ for any g.
- Concave optimization problem

$$\hat{\beta}_0 = \arg \max_{\beta : ||\beta||_2 \leq 1} \min_{g=1,\ldots,G} \beta^T \hat{\beta}_g.$$

- Equivalent to quadratic constraint linear programming (QCLP):

$$\begin{aligned} \text{maximize} \quad & t \in \mathbb{R} \\ \text{subject to} \quad & \beta^T \hat{\beta}_g \geq t, g = 1, \ldots, G \\ & \beta^T \beta \leq 1, \end{aligned}$$

- Obtain $\hat{c}_0$ by maximizing the estimated value function:

$$\hat{c}_0 = \arg \max_c \frac{1}{mG} \sum_i \sum_j \frac{Y_{ij} I(X_{ij}^T \hat{\beta}_0 > c)}{A_i \hat{\pi}_i + (1 - A_i)(1 - \hat{\pi}_i)}$$

Statistical property

Theorem (Consistency)

Define $\hat{B} = (\hat{\beta}_1, \ldots, \hat{\beta}_G)$. *Assume that* $F_0 \neq 0$, $G \geq 2$, *vectors in* B_{I_0} *are linearly independent, each* $\hat{\beta}_g$ *is consistent with* $||\hat{\beta}_g||_2 = 1$. *Then with probability going to* 1, *the estimated maximin effects* $\hat{\beta}_0$ *is equal to*

$$\begin{cases} [e^T(\hat{B}_{I_0}^T \hat{B}_{I_0})^{-1} e]^{-1/2} \hat{B}_{I_0} (\hat{B}_{I_0}^T \hat{B}_{I_0})^{-1} e & \text{if } F_0 > 0, \\ 0 & \text{if } F_0 < 0. \end{cases}$$

If $F_0 > 0$, *then*

$$||\hat{\beta}_0 - \beta_0||_2 = \sup_{g \in I_0} O(||\hat{\beta}_g - \beta_g||_2).$$

Statistical property

Theorem (Asymptotic normality)

Assume $F_0 > 0$ *and*

$$\sqrt{m}(\hat{\beta}_g - \beta_g) = \frac{1}{\sqrt{m}} \sum_{i=1}^{m} \psi_{ig} + o_p(1).$$

Under suitable conditions, $\sqrt{m}(\hat{\beta}_0 - \beta_0)$ *is asymptotically normally distributed with mean* 0 *and covariance matrix*

$$\frac{1}{||t_0||_2^2} \sum_{g \in I_0} \left(v_g^T t_0 N(B_{I_0}) - N(t_0) v_g t_0^T \right) \Sigma_g \left(v_g^T t_0 N(B_{I_0}) - N(t_0) v_g t_0^T \right)^T,$$

where $\Sigma_g = E(\psi_{ig}\psi_{ig}^T)$, $v_g = B_{I_0}(B_{I_0}^T B_{I_0})^{-1} e_g$, $t_0 = B_{I_0}(B_{I_0}^T B_{I_0})^{-1} e$, $N(\Phi) = I - \Phi(\Phi^T \Phi)^+ \Phi^T$.

Overall value function

For each threshold c, we define the overall value function under the regime $I(x^T\beta_0 > c)$ as

$$V(\beta_0, c) = \frac{1}{G}\sum_{g=1}^{G} \mathrm{E}\{h_g(X_{g0}) + \psi(X_{g0}^T\beta_0)I(X_{g0}^T\beta_0 > c)\},$$

and let $c_0 = \arg\max_c V(\beta_0, c)$.

Theorem

Under certain regularity conditions, we have

$$\hat{c}_0 - c_0 = O_p(m^{-1/3}).$$

Moreover, $\sqrt{m}\{\hat{V}_m(\hat{\beta}_0, \hat{c}_0) - V(\beta_0, c_0)\}$ *is asymptotically normal with mean* 0 *and variance* v_0^2*.*

Simulation settings

- Four groups of patients, each generated according to

$$Y_{gj} = h(X_{gj}) + 2A_{gj}X_{gj}^T\beta_g + \varepsilon_{gj},$$

$X_{gj} \overset{i.i.d}{\sim} N(0, I_2)$ and $\varepsilon_{gj} \overset{i.i.d}{\sim} N(0, 0.25)$.
- Two baseline models for h: linear and nonlinear.
- Two propensity score models: constant and probit.
- For each setting: subgroup estimator obtained using A-learning based on a linear model for h and logistic model for π:

1. S1: π correct, h correct,
2. S2: π correct, h wrong,
3. S3: π wrong, h correct,
4. S4: π wrong, h wrong.

Simulation settings (continued)

- Two scenarios for the subgroup parameters (representing different degrees of heterogeneity):
  - (I) (large heterogeneity) $\beta_1 = (1, 0), \beta_2 = (\cos(10^\circ), \sin(10^\circ))$, $\beta_3 = (\cos(70^\circ), \sin(70^\circ))$, $\beta_4 = (0, 1)$;
  - (II) (small heterogeneity) $\beta_1 = (\cos(30^\circ), \sin(30^\circ))$, $\beta_2 = (\cos(45^\circ), \sin(45^\circ))$, $\beta_3 = (\cos(54^\circ), \sin(54^\circ))$, $\beta_4 = (\cos(60^\circ), \sin(60^\circ))$;
- The maximin effects parameter $\beta_0 = (\cos(45^\circ), \sin(45^\circ))$ for both scenarios.

Results for estimated maximin regimes

Table: Bias, standard deviation (in parenthesis) of $\hat{\beta}_0$ and coverage probability for confidence intervals of β_0.

		$\hat{\beta}_0^1$	$\hat{\beta}_0^2$	CP for $\hat{\beta}_0^1$	CP for $\hat{\beta}_0^2$
Sce I	S1	$-0.018(0.037)$	$-0.028(0.051)$	95.0%	97.4%
	S2	$-0.015(0.045)$	$-0.025(0.053)$	98.6%	95.0%
	S3	$-0.016(0.048)$	$-0.024(0.055)$	96.6%	97.2%
	S4	$-0.010(0.061)$	$-0.020(0.069)$	98.2%	97.0%
Sce II	S1	$3.6 \times 10^{-4}(0.018)$	$-0.001(0.018)$	96.0%	95.0%
	S2	$-0.006(0.033)$	$0.003(0.031)$	96.8%	96.8%
	S3	$-0.008(0.045)$	$0.002(0.042)$	96.6%	97.4%
	S4	$-0.012(0.064)$	$0.004(0.063)$	96.6%	97.8%

Results for estimated value functions

Table: Bias, standard deviation of $\hat{V}_m(\hat{\beta}_0, \hat{c}_0)$ and coverage probability for confidence intervals of $V(\beta_0, c_0)$

Sce I	Bias	SD	CI	Sce II	Bias	SD	CI
S1	0.017	0.083	93.6%	S1	0.007	0.099	95.4%
S2	0.018	0.074	93.6%	S2	0.005	0.075	95.2%
S3	0.018	0.134	95.4%	S3	0.011	0.101	95.2%
S4	0.027	0.137	96.8%	S4	0.003	0.115	95.2%

Comparisons with simple methods

- Methods to compare:
  - "maximin treatment regime" $d(x) = I(x^T\hat{\beta} > \hat{c}_0)$
  - "pooled treatment regime" $d(x) = I(x^T\tilde{\beta} > \tilde{c}_0)$
  - "simple average treatment regime" $d(x) = I(x^T\bar{\beta} > \bar{c})$
- Evaluation:
  - obtain the estimated regime based on three groups and apply it to the remaining group;
  - compute PCD (using the estimated group-specific regime as the truth) and estimated value function (using A-learning) of the estimated regime for each group.

Table: PCD and value function (in parenthesis) for the first scenario under estimated "maximin treatment regime", "pooled treatment regime" and "simple average treatment regime"

Testing group		First group	Second group	Third group	Fourth group
	pooled	67.8%(1.42)	74.9%(1.56)	78.1%(1.61)	64.3%(1.35)
S1	maximin	71.7%(1.50)	79.8%(1.64)	85.0%(1.71)	68.9%(1.45)
	average	67.4%(1.41)	74.3%(1.55)	77.0%(1.60)	63.9%(1.34)
	pooled	67.8%(1.42)	74.8%(1.56)	78.3%(1.62)	64.2%(1.34)
S2	maximin	72.0%(1.51)	79.8%(1.64)	84.5%(1.71)	68.8%(1.44)
	average	67.5%(1.42)	73.8%(1.54)	77.0%(1.59)	63.8%(1.34)
	pooled	68.0%(1.43)	74.9%(1.56)	78.1%(1.61)	63.9%(1.34)
S3	maximin	71.3%(1.49)	79.0%(1.62)	83.8%(1.69)	68.6%(1.44)
	average	67.3%(1.41)	73.4%(1.53)	76.0%(1.57)	63.6%(1.33)
	pooled	68.0%(1.42)	74.8%(1.55)	78.0%(1.61)	64.1%(1.34)
S4	maximin	71.3%(1.49)	79.0%(1.63)	83.7%(1.69)	68.2%(1.43)
	average	67.1%(1.40)	73.2%(1.53)	76.2%(1.58)	63.9%(1.34)

Table: PCD and value function (in parenthesis) for the second scenario under estimated "maximin treatment regime", "pooled treatment regime" and "simple average treatment regime"

Testing group		First group	Second group	Third group	Overall
S1	pooled	87.2%(1.73)	98.0%(1.80)	95.0%(1.79)	90.5%(1.76)
	maximin	87.0%(1.73)	96.7%(1.79)	94.0%(1.78)	89.4%(1.75)
	average	86.9%(1.73)	96.2%(1.79)	94.2%(1.78)	89.8%(1.76)
S2	pooled	87.2%(1.73)	97.7%(1.80)	94.8%(1.79)	90.4%(1.76)
	maximin	86.9%(1.73)	96.3%(1.79)	93.8%(1.78)	89.3%(1.75)
	average	86.7%(1.73)	96.1%(1.79)	93.8%(1.78)	89.9%(1.76)
S3	pooled	87.1%(1.73)	97.5%(1.79)	95.1%(1.79)	90.7%(1.76)
	maximin	86.7%(1.73)	95.6%(1.79)	93.4%(1.78)	89.4%(1.75)
	average	86.5%(1.72)	95.4%(1.79)	93.5%(1.78)	89.5%(1.75)
S4	pooled	87.0%(1.73)	96.6%(1.79)	90.4%(1.78)	90.5%(1.76)
	maximin	85.8%(1.71)	94.4%(1.78)	92.3%(1.77)	88.9%(1.75)
	average	85.9%(1.72)	94.1%(1.78)	92.9%(1.77)	89.0%(1.74)

Schizophrenia study

Table: Maximin and pooled treatment regimes, and the estimated value functions under these regimes

Testing group	Group 1		Group 2		Group 3	
	maximin	pooled	maximin	pooled	maximin	pooled
$\hat{\beta}_{g0}$	-1.00	-0.92	1.00	4.29	0.95	2.67
$\hat{\beta}_{g1}$	-0.98	-0.21	-1.00	-1.70	-0.26	-0.80
$\hat{\beta}_{g2}$	0.20	-0.14	-0.06	-5.11	0.97	3.95
$\hat{\mathrm{E}} Y_g^\star(d)$	24.99	23.73	30.11	28.25	21.00	20.31

HAQ data

Table: Maximin and pooled treatment regimes, and the estimated value functions under these regimes

Testing group	Group 1		Group 2		Group 3	
	maximin	pooled	maximin	pooled	maximin	pooled
$\hat{\beta}_{g0}$	1.625	0.023	2.900	−0.393	1.150	−0.198
$\hat{\beta}_{g1}$	0.838	0.204	0.513	−0.026	0.224	0.276
$\hat{\beta}_{g2}$	0.406	−0.264	0.855	0.084	0.861	0.109
$\hat{\beta}_{g3}$	−0.365	−0.104	0.077	0.045	−0.458	−0.152
$\hat{\mathrm{E}} Y_g^{\star}(d)$	0.092	−0.001	−0.037	−0.058	−0.026	−0.028

Future work

- Is it possible to extend the idea of maximin treatment decision under more general model setting?
- What if the covariates are not spherically distributed?
- Is it possible to extend the idea of maximin treatment decision to multiple stages?

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