Estimating Heterogeneous Treatment Effects in Randomized Control Trials

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September 26 2014

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Adjuvant Stage III Colon Cancer Therapy (All patients)
We conclude that adjuvant therapy with levamisole and fluorouracil should be standard treatment for Stage C colon carcinoma. Since most patients in our study were treated by community oncologists, this approach should be readily adaptable to conventional medical practice. (N Engl J Med 1990; 322:352-8.)
Adjuvant Stage III Colon Cancer Therapy (Under 61)
Adjuvant Stage III Colon Cancer Therapy (61 and Over)
In exploratory subset analyses, levamisole–fluorouracil treatment appeared to have the greatest advantage among male patients (in both survival and recurrence), older patients (recurrence), patients with tumors that were well differentiated to moderately well differentiated (survival and recurrence), patients in whom more than four nodes were involved (survival), and patients treated 21 to 35 days after surgery (recurrence). These results show two striking contradictions to those of subset analyses reported in the NCCTG study, in which levamisole plus fluorouracil was found to be most effective in reducing the risk of recurrence among female patients and younger patients. This underscores the importance of the statement by the authors of that study, that “subset analyses must be interpreted with great caution.”³
Overview

- Identification of HTEs
  - 1-Signal Model
  - 3-Signal Models
  - 2-Signal Models
- Estimator
  - Additivity Constrained NMF
  - Monte Carlo Simulation
- Adjuvant Therapy for S3 Colon Cancer
- Returns to Schooling
- Instrumental Variables (if time)
Identification
Causal Graph
Mediated Causal Graph

\[ X \quad U \quad Y \]
1-Signal Graph
1-Signal Model

- Finite Mixture Model

\[
Pr(y < Y) = \sum_{k=1}^{K} \pi(u_k)F(Y|u_k)
\]  

(1)

- If \( Y \) has \( I \) elements

\[
p_y = F\pi
\]  

(2)

where

- \( p_y \) is a \( I \times 1 \) vector
- \( \pi \) is a \( K \times 1 \) vector
- \( F \) is a \( I \times K \) matrix
1-Signal Model

Example

\[
\begin{bmatrix}
    p_1 \\
    p_2 \\
    p_3
\end{bmatrix}
= 
\begin{bmatrix}
    F_{11} & F_{12} \\
    F_{21} & F_{22} \\
    F_{31} & F_{32}
\end{bmatrix}
\times 
\begin{bmatrix}
    \pi_1 \\
    \pi_2
\end{bmatrix}(3)
\]

where

\[\sum_{i=1}^{3} p_i = 1\]

\[\sum_{i=1}^{3} F_{ik} = 1 \text{ for all } k \in \{1, 2\}\]

\[\sum_{k=1}^{2} \pi_k = 1\]
1-Signal Model

- Finite Mixture Model

\[
Pr(y < Y) = \sum_{k=1}^{K} \pi(u_k)F(Y|u_k)
\] (4)

- \( F(.|u_k) \) and \( \pi(u_k) \) are not identified (in general)
3-Signal Graph

U

Y  W  Z
3-Signal Model

- Finite Mixture Model

\[ Pr(y < Y, w < W, z < Z) = \sum_{k=1}^{K} F(Y|u_k) G(W|u_k) H(u_k, Z) \]  \hfill (5)

- If \( \mathcal{Y} \) has \( I \) elements, \( \mathcal{W} \) has \( J \) elements, \( \mathcal{Z} \) has \( L \) elements.

\[ P_z = F D_z G^T \]  \hfill (6)

- where
  - \( P_z \) is a \( I \times J \) prob. matrix conditional on \( Z = z \)
  - \( D_z \) is a \( K \times K \) diagonal matrix conditional on \( Z = z \)
  - \( G^T \) is a \( K \times J \) matrix
3-Signal Model

Example

\[
\begin{bmatrix}
  P_{11z} & P_{12z} \\
  P_{21z} & P_{22z} \\
  P_{31z} & P_{32z}
\end{bmatrix}
= \begin{bmatrix}
  F_{11} & F_{12} \\
  F_{21} & F_{22} \\
  F_{31} & F_{33}
\end{bmatrix}
\begin{bmatrix}
  \pi_{1z} & 0 \\
  0 & \pi_{2z}
\end{bmatrix}
\begin{bmatrix}
  G_{11} & G_{21} & G_{31} \\
  G_{12} & G_{22} & G_{32}
\end{bmatrix}
\]

\[(7)\]

where

\[\sum_{i=1}^{3} P_{ijz} = 1 \text{ for all } j \in \{1, 2\}\]
\[\sum_{i=1}^{3} F_{ik} = 1 \text{ for all } k \in \{1, 2\}\]
\[\sum_{k=1}^{2} \pi_{kz} = 1\]
\[\sum_{j=1}^{2} G_{kj} = 1 \text{ for } k \in \{1, 2\}\]
3-Signal Model

\[ P_z = FD_zG^T \] (8)

- If
  - \( L \geq 2 \) (num of Z’s)
  - certain rank conditions hold
- then \( F, D_z, D_z', \) and \( G \) are identified.
- Kruskal (1977), An et al (2010), etc.
NMF
2-Signal Graph
2-Signal Model

- Exclusion restriction

\[ F(Y|u_k, W) = F(Y|u_k, W') \] (9)

- for all \( Y, W \neq W' \) and \( u_k \)

- Henry et al. (2014, 2013)
2-Signal Model

- Finite Mixture Model

\[ Pr(y < Y, w < W) = \sum_{k=1}^{K} \pi(u_k)F(Y|u_k)G(W|u_k) \]  \hspace{1cm} (10)

- As matrices

\[ P = FD\pi G^T \]  \hspace{1cm} (11)

- or

\[ P = WH \]  \hspace{1cm} (12)
2-Signal Model

- In general, bi-linear matrix decompositions are not unique

\[ P = WH = WAA^{-1}H \]  \hspace{1cm} (13)

- or

\[ P = \tilde{W}\tilde{H} \]  \hspace{1cm} (14)

- where \( \tilde{W} = WA \) and \( \tilde{H} = A^{-1}H \)

- for all \( A \) of full-rank.
2-Signal Model

- If
  - \( P, W, H, \tilde{W} \) and \( \tilde{H} \) are non-negative
  - \( W, H \) rank conditions hold
  - \( A \) is diagonal
- then \( W \) and \( H \) are “essentially unique” (up to scaling and permutation).
- Huang et al (2013)
2-Signal Model

- When is $A$ diagonal?
  - Given certain “sparsity conditions.”
  - Also if
    - $\sum_{j=1}^{I} F_{ik} = 1$,
    - $\sum_{j=1}^{J} G_{jk} = 1$, and
    - certain (possibly less strong) sparsity conditions.
Set and Point Identification
Sufficient Conditions for Uniqueness

If $A$, $W$, $\tilde{W}$, $H$ and $\tilde{H}$ are matrices with the following properties,

1. $\tilde{H} = A^{-1}H$,
2. $\tilde{W} = WA$,
3. $\sum_{j=1}^{J} H_{kj} = 1$ for all $k \in \{1, \ldots, K\}$,
4. $\sum_{j=1}^{J} \tilde{H}_{kj} = 1$ for all $k \in \{1, \ldots, K\}$,
5. $H > 0$, $W > 0$, and
6. $\tilde{H} \geq 0$, $\tilde{W} \geq 0$

then as $W_{ik_k} \to 0$ and $H_{jk_k} \to 0$ for at least one $i_k \in \{1, \ldots, I\}$ and $j_k \in \{1, \ldots, J\}$, where $i_k \neq i_{k'}$ and $j_k \neq j_{k'}$ for all $k \neq k' \in \{1, \ldots, K\}$, $A \to Q$ where $Q \in \mathcal{Q}$. 
The Set $\mathcal{A}$

- Given the conditions we can write

$$ A = \begin{bmatrix} 1 + a & -a \\ -b & 1 + b \end{bmatrix} \tag{15} $$

- where $a, b \in \mathbb{R}$.

- Let $\{a, b\} \in \mathcal{A}$ for all vectors associated with $\mathbf{W}$ and $\mathbf{H}$ such that the inequalities in the theorem hold.
The Set $\mathcal{A}$

1. $b \leq (1 + a) \frac{W_1}{W_2}$
2. $b \geq a \frac{W_1}{W_2} - 1$
3. $b \geq -a \frac{H_2}{H_1} - 1$
4. $b \geq -(1 + a) \frac{H_2}{H_1}$
The set $\mathcal{A}$
Necessary and Sufficient Conditions for Point Identification

If $A$, $F$, $\tilde{F}$, $D_\pi$, $\tilde{D}_\pi$, $G$ and $\tilde{G}$ are matrices with the following properties,

1. $\tilde{G}^T = A^{-1}G^T$,
2. $\tilde{F}\tilde{D}_\pi = FD_\pi A$,
3. $G^T \geq 0$, $F\tilde{D}_\pi \geq 0$,
4. $\tilde{G}^T \geq 0$, $\tilde{F}\tilde{D}_\pi \geq 0$
5. $\sum_{i=1}^I F_{i,k} = 1$ and $\sum_{i=1}^I \tilde{F}_{i,k} = 1$ for all $k \in \{1, \ldots, K\}$,
6. $\sum_{k=1}^K D_\pi k = 1$ and $\sum_{k=1}^K \tilde{D}_\pi k = 1$ and
7. $\sum_{j=1}^J G_{k,j}^T = 1$ and $\sum_{j=1}^J \tilde{G}_{k,j}^T = 1$ for all $k \in \{1, \ldots, K\}$,

and define

$$I_k = \{i \in \{1, \ldots, I\} | F_{i,k} \neq 0\}$$

$$J_k = \{j \in \{1, \ldots, J\} | G_{k,j}^T \neq 0\}$$

(16)

then $P = FD_\pi G^T$ is unique up to relabeling if and only if there do not exist $k_1, k_2 \in \{1, \ldots, K\}$, $k_1 \neq k_2$ such that $I_{k_1} \subseteq I_{k_2}$ or $J_{k_1} \subseteq J_{k_2}$.
Proof.

- Necessary: Huang et al. (2013) Theorem 3.
- Sufficient: Result above.
Estimator
Constrained NMF

\[
\min_{F, D_{\pi}, G} \|P - FD_{\pi}G^T\|_F^2
\]

s.t. \(F_{ik} \geq 0\) for all \(i, k\)
\(D_{\pi kk} \geq 0\) for all \(k\)
\(G_{jk} \geq 0\) for all \(j, k\)
\(\sum_{i=1}^IF_{ik} = 1\) for all \(k\)
\(\sum_{j=1}^JG_{jk} = 1\) for all \(k\)
\(\sum_{k=1}^K\pi_k = 1\)

Implemented using continuously updating GMM.
Monte Carlo Results \( (N = 30,000) \)
Monte Carlo Results

\[
F = \begin{bmatrix}
0.29 & 0.95 \\
0 & 0.05 \\
0.71 & 0
\end{bmatrix} \quad (18)
\]

\[
G = \begin{bmatrix}
0 & 0.2 \\
0.19 & 0.8 \\
0.81 & 0
\end{bmatrix} \quad (19)
\]
<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Mean</th>
<th>SD</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi_1$</td>
<td>0.7500</td>
<td>0.7337</td>
<td>(0.0862)</td>
<td>0.7493</td>
<td>(0.0032)</td>
</tr>
<tr>
<td>$\pi_2$</td>
<td>0.2500</td>
<td>0.2663</td>
<td>(0.0862)</td>
<td>0.2507</td>
<td>(0.0032)</td>
</tr>
<tr>
<td>$F_{11}$</td>
<td>0.2900</td>
<td>0.3522</td>
<td>(0.1648)</td>
<td>0.2891</td>
<td>(0.0034)</td>
</tr>
<tr>
<td>$F_{21}$</td>
<td>0.0001</td>
<td>0.0607</td>
<td>(0.1487)</td>
<td>0.0001</td>
<td>(0.0001)</td>
</tr>
<tr>
<td>$F_{31}$</td>
<td>0.7099</td>
<td>0.5871</td>
<td>(0.2316)</td>
<td>0.7109</td>
<td>(0.0034)</td>
</tr>
<tr>
<td>$F_{12}$</td>
<td>0.9499</td>
<td>0.8184</td>
<td>(0.2581)</td>
<td>0.9488</td>
<td>(0.0026)</td>
</tr>
<tr>
<td>$F_{22}$</td>
<td>0.0500</td>
<td>0.1229</td>
<td>(0.1847)</td>
<td>0.0506</td>
<td>(0.0025)</td>
</tr>
<tr>
<td>$F_{32}$</td>
<td>0.0001</td>
<td>0.0558</td>
<td>(0.1043)</td>
<td>0.0006</td>
<td>(0.0007)</td>
</tr>
<tr>
<td>$G_{11}$</td>
<td>0.0001</td>
<td>0.0689</td>
<td>(0.1752)</td>
<td>0.0001</td>
<td>(0.0001)</td>
</tr>
<tr>
<td>$G_{21}$</td>
<td>0.1899</td>
<td>0.2588</td>
<td>(0.1806)</td>
<td>0.1903</td>
<td>(0.0030)</td>
</tr>
<tr>
<td>$G_{31}$</td>
<td>0.8100</td>
<td>0.6723</td>
<td>(0.2566)</td>
<td>0.8096</td>
<td>(0.0030)</td>
</tr>
<tr>
<td>$G_{12}$</td>
<td>0.1999</td>
<td>0.2108</td>
<td>(0.1094)</td>
<td>0.1998</td>
<td>(0.0044)</td>
</tr>
<tr>
<td>$G_{22}$</td>
<td>0.8000</td>
<td>0.6841</td>
<td>(0.2201)</td>
<td>0.7980</td>
<td>(0.0051)</td>
</tr>
<tr>
<td>$G_{32}$</td>
<td>0.0001</td>
<td>0.0892</td>
<td>(0.1722)</td>
<td>0.0023</td>
<td>(0.0027)</td>
</tr>
<tr>
<td>SOS</td>
<td>0.0000</td>
<td>0.2507</td>
<td>(0.4348)</td>
<td>0.00003</td>
<td>(0.00003)</td>
</tr>
<tr>
<td>T</td>
<td>100</td>
<td>56</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
RCT-2-Signal Graph

\[ \begin{align*}
X & \rightarrow U \\
Y & \rightarrow W
\end{align*} \]
Adjuvant Chemotherapy for S3 Colon Cancer
RCT Data

- Moertel (1990)
- NEJM study on adjuvant therapy for stage III colon cancer patients
- R dataset called "colon" in the "survival" package
## Heterogeneous Treatment Effect of Colon Cancer Drugs

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th></th>
<th>Type 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\pi_1 = 0.77$</td>
<td></td>
<td>$\pi_2 = 0.23$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Obs</td>
<td>Lev</td>
<td>Lev+5FU</td>
<td>Obs</td>
</tr>
<tr>
<td>&lt; 1 Yr</td>
<td>0.04</td>
<td>0.04</td>
<td>0.05</td>
<td>0.20</td>
</tr>
<tr>
<td>1-3 Yrs</td>
<td>0.14</td>
<td>0.20</td>
<td>0.13</td>
<td>0.71</td>
</tr>
<tr>
<td>3-4 Yrs</td>
<td>0.09</td>
<td>0.05</td>
<td>0.07</td>
<td>0.09</td>
</tr>
<tr>
<td>&gt; 4 Yrs</td>
<td>0.73</td>
<td>0.71</td>
<td>0.75</td>
<td>0.00</td>
</tr>
<tr>
<td>&lt; 4, MW</td>
<td>0.65</td>
<td></td>
<td></td>
<td>0.00</td>
</tr>
<tr>
<td>&lt; 4, W or P</td>
<td>0.16</td>
<td></td>
<td></td>
<td>0.54</td>
</tr>
<tr>
<td>&gt; 4, MW</td>
<td>0.18</td>
<td></td>
<td></td>
<td>0.11</td>
</tr>
<tr>
<td>&gt; 4, W or P</td>
<td>0.02</td>
<td></td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>SOS</td>
<td>0.0418</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Treatment Effect for Type 1 [5th percentile, 95th percentile]

<table>
<thead>
<tr>
<th></th>
<th>Obs</th>
<th>Lev</th>
<th>Lev &amp; 5-Fu</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type 1</strong></td>
<td>0.77</td>
<td>[0.66, 0.89]</td>
<td></td>
</tr>
<tr>
<td><strong>Less 1 Year</strong></td>
<td>0.04</td>
<td>[0.00, 0.08]</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>1-3 Years</strong></td>
<td>0.14</td>
<td>0.20</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>3-4 Years</strong></td>
<td>0.09</td>
<td>[0.07, 0.27]</td>
<td>0.07</td>
</tr>
<tr>
<td><strong>More 4 Years</strong></td>
<td>0.73</td>
<td>0.71</td>
<td>0.75</td>
</tr>
<tr>
<td></td>
<td>Obs</td>
<td>Lev</td>
<td>Lev &amp; 5-Fu</td>
</tr>
<tr>
<td>------------------</td>
<td>---------</td>
<td>-------------</td>
<td>------------</td>
</tr>
<tr>
<td>Type 2</td>
<td>0.23</td>
<td>[ 0.11,0.34 ]</td>
<td></td>
</tr>
<tr>
<td>Less 1 Year</td>
<td>0.20</td>
<td>[ 0.00,0.29 ]</td>
<td>0.17</td>
</tr>
<tr>
<td>1-3 Years</td>
<td>0.71</td>
<td>[ 0.52,1.00 ]</td>
<td>0.47</td>
</tr>
<tr>
<td>3-4 Years</td>
<td>0.09</td>
<td>[ 0.00,0.18 ]</td>
<td>0.11</td>
</tr>
<tr>
<td>More 4 Years</td>
<td>0.00</td>
<td>[ 0.00,0.12 ]</td>
<td>0.15</td>
</tr>
</tbody>
</table>
## Observed Patient Characteristics By Type for Nodal Involvement and Histological Differentiation [5th percentile, 95th percentile]

<table>
<thead>
<tr>
<th></th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>&lt; 4, Mod. Well</strong></td>
<td>0.65</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td>[ 0.56, 0.67 ]</td>
<td>[ 0.00, 0.30 ]</td>
</tr>
<tr>
<td><strong>&lt; 4, Well &amp; Poor</strong></td>
<td>0.16</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>[ 0.13, 0.23 ]</td>
<td>[ 0.38, 0.67 ]</td>
</tr>
<tr>
<td><strong>&gt; 4, Mod. Well</strong></td>
<td>0.18</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>[ 0.14, 0.21 ]</td>
<td>[ 0.00, 0.19 ]</td>
</tr>
<tr>
<td><strong>&gt; 4, Well &amp; Poor</strong></td>
<td>0.02</td>
<td>0.35</td>
</tr>
<tr>
<td></td>
<td>[ 0.00, 0.06 ]</td>
<td>[ 0.11, 0.45 ]</td>
</tr>
<tr>
<td><strong>Sum of Squares</strong></td>
<td>0.04512</td>
<td></td>
</tr>
<tr>
<td></td>
<td>[ 0.05, 0.38 ]</td>
<td></td>
</tr>
</tbody>
</table>
Adjuvant Stage III Colon Cancer Therapy (< 4, WM)
Adjuvant Stage III Colon Cancer Therapy (> 4, WM)
Conclusion

- Estimate HTEs with mixture models
- Matrix factorization used to identify types
- Treatment effect varies across types
- Similar method for unconfounded and confounded data.
