Dynamic Treatment of Children with Leukaemia

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ALL and data

Methods

Results
Acute Lymphoblastic Leukaemia (ALL)

ALL is treated with intensive chemotherapy. 75-80% cured by first-line chemotherapy.

No general rules on how to optimise treatment.

NOPHO ALL-92:

Nordic randomised study.
(Follow-up until 23.01.2008.)
The treatment

2-2.5 years of treatment:
Induction therapy
Consolidation therapy

**Maintenance therapy** (9-27 months)

**Drugs:**
- Methotrexate weekly.
- 6-Mercaptopurine daily.

**Measurements:**
- Weekly White Blood Counts (WBC) and Thrombocyte Counts (TC).

**Target:**
- Keep WBC within $1.5-3.5 \times 10^9$/L.
The protocol

Control group

Pharmacology group

- Increase
- Increase if drug concentrations are low
- Decrease (50%)
- Pause

Thrombocyte Count

WBC

0 100 200 300 400

0 1 2 3 4 5 6
Result of the NOPHO study

Probability of staying in remission (opdateres...):

- Probability of staying in remission
- Years since diagnosis

Graph showing the probability of staying in remission over years since diagnosis.
Goal

Estimation of an optimal dynamic treatment strategy:

• Murphy (2003), *JRSS. B.*


Estimation of a statically-optimal treatment strategy:

• Van der Laan, Petersen and Joffe (2005), *Int J Biostat.*
The setup

\( K + 1 \) measurements, \( j = 1, \ldots, K + 1 \).

\( S_j = (WBC_j, TC_j, \cdots) \): State variable.

\( D_j \): Dose.

\[ \begin{array}{cccccc}
S_1 & \rightarrow & D_1 & \rightarrow & S_2 & \rightarrow & D_2 & \rightarrow & \cdots & \rightarrow & S_K & \rightarrow & D_K & \rightarrow & S_{K+1} \\
\end{array} \]

Notation:
\( \bar{D}_j = (D_1, \ldots, D_j) \)
\( \underline{D}_j = (D_j, \cdots, D_K) \)
Counterfactuals

Counterfactual variables:

\[
\begin{align*}
\text{Observed} & \quad \rightarrow \quad \text{Counterfactual} \\
D_1 & \rightarrow d_1 \\
S_2 &= S_2(D_1) \quad \rightarrow \quad S_2(d_1)
\end{align*}
\]

Counterfactual process:

\[
\bar{S}(\bar{d}_K) = (S_1, S_2(d_1), S_3(\bar{d}_2), \ldots, S_{K+1}(\bar{d}_K)), \quad \bar{d}_K = (d_1, \ldots, d_K).
\]

Counterfactual outcome:

\[
Y_{K+1}(\bar{d}_K) = f(\bar{S}(\bar{d}_K)) \quad (\text{eg. } S_{K+1}(\bar{d}_K))
\]
Optimal treatments

\[
\begin{aligned}
S_1 & \rightarrow D_1 \rightarrow S_2 \rightarrow D_2 \rightarrow \cdots \rightarrow S_K \rightarrow D_K \rightarrow Y_{K+1}
\end{aligned}
\]

\(Z_0\) baseline covariates.
Searching for decision rules \(d_j(\bar{S}_j, \bar{D}_{j-1}; Z_0), j = 1, \cdots, K:\)

Optimal (Murphy(2003) and Robins (2004)):
\[
E(Y_{K+1}(\bar{d}_K)|Z_0) \text{ is maximised.}
\]

Statically-optimal (van der Laan, Petersen and Joffe (2005)):
\[
E(Y_{j+m}(\bar{D}_{j-1}, \bar{d}_j)|(S_j, \bar{D}_{j-1}), Z_0) \text{ is maximised, } m \geq 1.
\]
d\(j\) is found as \(\arg \max_{d_j(\cdot)} \) [1]
History-Adjusted-Marginal Structural Models

Model conditional on $V_j \subseteq (S_j, \bar{D}_{j-1})$ and $Z_0$:

$$E(Y_{j+m}(\bar{D}_{j-1}, d_j)|V_j, Z_0) = \alpha + \beta' V_j + \gamma' d_j + \delta' Z_0.$$ 

A naive regression analysis will fail.

→

Inverse Probability of Treatment Weighted (IPTW) regression. 

Weights:

$$\frac{1}{P(D_j = d_j|\bar{S}_j, \bar{D}_{j-1}, Z_0)P(D_j = d_j|V_j, Z_0)}.$$ 

Easy! Only requires modeling of the distribution of the doses (discrete).
Modeling the decision on the dose

$D_j$ product dose.
$D_{j-1} > 0$.
Control group.

$\bar{S}_j, \bar{D}_{j-1}$

- **Increase:**
  \[ D_j > D_{j-1} \]
  \[ D_j = d_j^I(\bar{D}_{j-1}, \bar{S}_j) \]

- **No changes:**
  \[ D_j = D_{j-1} \]

- **Decrease:**
  \[ D_j < D_{j-1} \]
  \[ D_j = d_j^P(\bar{D}_{j-1}, \bar{S}_j) \]

- **Pause:**
  \[ D_j = 0 \]
A HA-MSM model

At least 2 weeks between consecutive measurements. \( m = 1 \).

Dose \( d_j \) = change of dose \( (D_j/D_{j-1}) \).

The model conditional on \( V_j \subseteq (\bar{S}_j, \bar{D}_{j-1}) \) and \( Z_0 \):

\[
E \left( \log(WBC_{j+1}(\bar{D}_{j-1}, d_j)) \mid V_j, Z_0 \right) \\
\sim 1 \times \log(WBC)_j + \{\text{mean dose up to } (j - 1)\} \\
+ D_{j-1} + D_{j-1} \times \begin{cases} \\
I(d_j \in (0.0, 0.5)) \\
I(d_j \in (0.5, 1.0)) \\
I(d_j = 1.0) \\
I(d_j \in (1.0, 1.5)) \\
I(d_j > 1.5) \\
\end{cases}
\]

2904 measurements on 250 patients.
Estimates of the HA-MSM model

\[ E\left( \log(WBC_{j+1}(D_{j-1}, d_j)) \mid V_j, Z_0 \right): \]

<table>
<thead>
<tr>
<th>Parameter (( V_j ))</th>
<th>Estimate</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>0.0419</td>
<td>0.0151</td>
<td>0.0055</td>
</tr>
<tr>
<td>( \log(WBC_j) )</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>mean dose up to ((j - 1))</td>
<td>0.5968</td>
<td>0.1218</td>
<td>\textless .0001</td>
</tr>
<tr>
<td>( D_{j-1} \times I(d_j \in (0.0, 0.5)) )</td>
<td>1.3726</td>
<td>0.1170</td>
<td>\textless .0001</td>
</tr>
<tr>
<td>( D_{j-1} \times I(d_j \in (0.5, 1.0)) )</td>
<td>0.4061</td>
<td>0.0887</td>
<td>\textless .0001</td>
</tr>
<tr>
<td>( D_{j-1} \times I(d_j = 1) )</td>
<td>0</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>( D_{j-1} \times I(d_j \in (1.0, 1.5)) )</td>
<td>-0.5263</td>
<td>0.0656</td>
<td>\textless .0001</td>
</tr>
<tr>
<td>( D_{j-1} \times I(d_j &gt; 1.5) )</td>
<td>-1.3748</td>
<td>0.2352</td>
<td>\textless .0001</td>
</tr>
</tbody>
</table>
A statically-optimal decision

An example

Third measurement \((j = 3)\) of a Danish patient (girl, age 4.5):

\(WBC_3 = 4.20,\ TC_j=254.\)

6-months mean dose before \(j = 1= .2509\)

\(D_1 = D_2 = .30933.\)

<table>
<thead>
<tr>
<th>(d_3)</th>
<th>(EWBC(\bar{D}_2, d_3))</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0.0,0.5)</td>
<td>6.33</td>
<td>0.2125</td>
</tr>
<tr>
<td>(0.5,1.0)</td>
<td>4.69</td>
<td>0.1130</td>
</tr>
<tr>
<td>1.0</td>
<td>4.14</td>
<td>0.0365</td>
</tr>
<tr>
<td>(1.0,1.5)</td>
<td>3.52</td>
<td>0.0647</td>
</tr>
<tr>
<td>1.5+</td>
<td>2.70</td>
<td>0.1949</td>
</tr>
</tbody>
</table>

Observe \(d_3 = 1.0\) and \(WBC_4 = 3.0.\)

Further elaboration on the HA-MSM-model is needed...
Summary

NOPHO data:
Common setting in the treatment of many types of patients.

The search for optimal dynamic treatment strategies is difficult:
Available methods suffer from estimation difficulties.

Statically-optimal treatment regimes provide a useful alternative.