Use of mechanistic models for in Silico trials: Evaluating new strategies design for HAART in HIV infected patients

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Motivating example

Short-cycle therapies (SCT) for HIV infected patients

Strategies on-off with x/7 designs. During a week the patient is on treatment x consecutive days.

Many trials realized and on going (FOTO, Breather, 4D, QUATUOR…)

→ Reduces toxicity
→ Reduces drug costs
→ Improve patients’ quality of life
Motivating example

Short-cycle therapies (SCT) for HIV infected patients

- Strategies on-off with x/7 designs. During a week the patient is on treatment x consecutive days.
- Many trials realized and on going (FOTO, Breather, 4D, QUATUOR…)
  - Reduces toxicity
  - Reduces drug costs
  - Improve patients’ quality of life

In silico trials

- Available data
- In vitro assays
- Pre-clinical models
- Clinical trials
- Observational data …

Propose new strategies to evaluate (e.g. SCT)
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2. Simulate in silico trials
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Estimate causal treatment of cART in observational data
Available Information

Sparse Longitudinal data (Patients \( i \), time \( j \)):

- Biomarkers \( (Y_{ij}) \) – Viral load (VL) and CD4
- Population characteristics \( (X_{ij}) \)
- Treatment antiretroviral (ART) schedule \( (TRT_{ij}) \)
- Multiple treatments cART in combination \( (TRT_{ij}^1, \ldots, TRT_{ij}^N) \)

\[ VL_{ij} = Y_{ij1} \]
\[ CD4_{ij} = Y_{ij2} \]
HIV treatment initiation depends on CD4 history

CD4 (t) → TRT (t+1) → CD4 (t+1) → ... → TRT (t+k) → CD4 (t+k)

Mechanistic models
Marginal Structural models (MSM)

Outcome of interest

Time Varying confounders

[Prague et al. (2017) Biometrics]
[Hernan et al. (2002) Biometrics]
[Robins et al. (2000) Epidemiology]
[Diggle et al. (2007) JRSS-C]
Marginal structural models (MSM)

Step 1:

• Calculate $p_{ij} = P(TRT_{ij} = 1 | X_{ij})$
• Assign Weights $w_{ij} = \frac{A_{ij}}{p_{ij}} + \frac{1-A_{ij}}{1-p_{ij}}$

Step 2:

• Run a weighted regression
  
  $$E(CD4_{ij}|F_{j-1}) = \beta_0 + \beta_{Y1} \sum_{k=1}^{j-1} TRT_{ik} + \beta_{Y2} \sum_{k=1}^{j-2} TRT_{ik} + \beta_t t(j) + \beta_{CD4} CD4(0)$$

→ Implementation in R package ipw and geepack

[Cole et al. (2005) Am. J. Epidemiology]
**Dynamical Modelling**

**Non linear mixed effect model** based on **ordinary differential equations**

**NLME-ODE**: Mathematical, statistical & observation models

\[
\begin{align*}
\dot{Q} &= \lambda_i - \mu_Q Q - \alpha Q + \rho T \\
\dot{T} &= \alpha Q - \rho T - \mu_T T - \gamma_i(A)V_T \\
\dot{T}^* &= \gamma_i(A)V_T - \mu_T^* T^* \\
\dot{V} &= \pi T^* - \mu_V V
\end{align*}
\]

\[
Y_{ij} = f\left(t_{ij}, \xi_{ij}(A_{t_{ij}}, X_{t_{ij}})\right) + \epsilon_{ij} \\
\xi_{ij} = \xi_0 + \beta_A T_{RT}(t_{ij}) + u_i^\xi \\
u_i^\xi \sim N(0, \Sigma_\xi) \\
\epsilon_{ij} \sim N(0, \Sigma_Y) \\
\theta = (\xi, \beta, \Sigma_\xi, \Sigma_Y)
\]

[Guedj et al. (2006) Biometrics]
[Prague et al. (2013) Advanced Drug and delivery review]
**Dynamical Modelling**

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\begin{align*}
\dot{Q} &= \lambda^i - \mu_Q Q - \alpha Q + \rho T \\
\dot{T} &= \alpha Q - \rho T - \mu_T T - \gamma_i(A)VT \\
\dot{T^*} &= \gamma_i(A)VT - \mu^i_{T^*}T^* \\
\dot{V} &= \pi T^* - \mu_V V
\end{align*}
\]

\[
Y_{ij} = f\left(t_{ij}, \xi_{ij}(A_{t_{ij}}, X_{t_{ij}})\right) + \epsilon_{ij}
\]

\[
\xi_{ij} = \xi_0 + \beta_A TRT(t_{ij}) + u^\xi_i
\]

\[
u^\xi_i \sim N(0, \Sigma^\xi)
\]

\[
\epsilon_{ij} \sim N(0, \Sigma^\epsilon)
\]

\[
\theta = (\xi, \beta, \Sigma^\xi, \Sigma^\epsilon)
\]

![Diagram of CD4, T, T*, and VL with arrows and labels indicating relationships between variables such as \(\lambda\), \(\alpha\), \(\gamma\), \(\mu_Q\), \(\mu_T\), \(\mu_{T^*}\), \(\mu_V\), and \(\pi\).]

**Average treatment effect:**

\[
\beta_{Y1} = E(Y_{ij}(1\ year, A_{ij}, X_{ij})|A_{ij} = 1) - E(Y_{ij}(1\ year, A_{ij}, X_{ij})|A_{ij} = 0)
\]

\[
\beta_{Y2} = E(Y_{ij}(2\ year, A_{ij}, X_{ij})|A_{ij} = 1) - E(Y_{ij}(2\ year, A_{ij}, X_{ij})|A_{ij} = 0) - \beta_{Y1}
\]

[**Guedj et al. (2006) Biometrics**]

[**Prague et al. (2013) Advanced Drug and delivery review**]
Estimation of parameters (NIMROD)

**NIMROD** (Fortran parallel code)

**NLME-ODE model**
\[
y_i \sim f_{ODE}(\theta(t, TRT), u_i)
\]
\[
u_i \sim h(.)
\]

**Likelihood**
\[
L(\theta) = \prod_{i} \left( \int_{R^q} p(y_i | \theta) h(u) du \right)
\]

**Bayesian** (penalized likelihood)
\[
L^P(\theta) = L(\theta) - J(\theta)
\]

**MAP**

**Convergence criteria**

**Identifiability**

**Numeric integration**

Download at:
http://www.isped.u-bordeaux.fr/NIMROD.aspx

[Prague et al. (2013) Computer Methods and Programs in Biomedicine]
Simulation Study (1)

\[ P(\text{TRT}_{ij}|\text{CD4}_{ij}) = \begin{cases} 
28\% & \text{if } \text{CD4}_{ij} > 400 \\
47\% & \text{if } \text{CD4}_{ij} \leq 200 \\
2\% & \text{otherwise} 
\end{cases} \]

## Simulation Study (2)

<table>
<thead>
<tr>
<th>Method</th>
<th>$\hat{\beta}_A$</th>
<th>Sd ($\hat{\beta}_A$)</th>
<th>Z-stat</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>325</td>
<td>11</td>
<td>28.81</td>
<td>&lt; 1 min</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>-7</td>
<td>4</td>
<td>-1.56</td>
<td></td>
</tr>
<tr>
<td>∞ CD4</td>
<td>-∞</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NLME-ODE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>312</td>
<td>7</td>
<td>44.5</td>
<td>10 hours</td>
</tr>
<tr>
<td>&gt; 1 year</td>
<td>2</td>
<td>3</td>
<td>0.53</td>
<td>100 cores</td>
</tr>
<tr>
<td>∞ CD4</td>
<td>306</td>
<td>8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- MSM and NLME-ODE are unbiased under correct specification of the model.
- NLME-ODE is more efficient to detect ATE than MSM and give access to more information.
- NLME-ODE is time consuming.
Simulate in silico trials
The ANRS CO3 Aquitaine HIV cohort
(N=2550, selected=248 patients)

Real Data

 Improve identifiability:
→ Use in vitro information as priors
  • Instantaneous inhibitory potentials (IIP).
→ Use posteriors from previous mechanistic analysis of clinical trials
  • Sequential Bayesian analysis

Estimate with NLME-ODE: \( \theta \)

[Thiébaut et al. (2000) JAIDS]
[Siliciano et al. (2011), Lancet]
[Prague et al. (2016) Journal de la statistique française]
Methods to generate in silico trials

Generate pseudo-patients:
Sample \( r = 1, \ldots, N \) parameters from the posterior distribution of \( \theta \)
\[
\theta^P_r \sim N(\theta_{MAP}, H(\theta_{MAP}))
\]
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Set distribution of the target population:
\((X^P, A^P)\)

In silico trajectories:
Simulate biomarkers trajectories under various treatment strategies \((A^P(t_{ij}))\)
\[Y^P_r = f(\theta^P_r, A^P, X^P, t_{ij})\]
Methods to generate in silico trials

Generate pseudo-patients:
Sample \((r = 1, \ldots, N)\) parameters from the posterior distribution of \(\theta\)
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\theta_r^P \sim N(\theta_{MAP}, H(\theta_{MAP}))
\]

Set distribution of the target population:
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Y_r^P = f(\theta_r^P, A^P, X^P, t_{ij})
\]

In silico outcome at 48 weeks:
→ Virological failure (50 copies/mL)
\[
P \left( V^P > 50 \frac{\text{copies}}{\text{mL}} \right)
\]

Additional features:
→ First virus replication \(P \left( V^P > 1 \frac{\text{copies}}{\text{mL}} \right)\)
→ Basic reproduction number
\[
R_0 = \frac{\lambda \pi a \gamma}{\mu_T^* \mu_V^* (\rho \mu_Q + \alpha \mu_T + \mu_Q \mu_T)}
\]

[Prague et al. (2012) Biometrics]
The basic reproduction number $R_0$ of an infection can be thought of as the number of cases one case generates on average over the course of its infectious period, in an otherwise uninfected population.
<table>
<thead>
<tr>
<th>HAART</th>
<th>Probability virological failure (&gt;1cp/mL)</th>
<th>Probability virological failure (&gt;50cp/mL)</th>
<th>Mean R0 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV + TEN + 3TC</td>
<td>0.9% [0%; 5%]</td>
<td>0.5% [0%; 4%]</td>
<td>0.77 [0.59; 0.92]</td>
</tr>
<tr>
<td>EFV + ABC + 3TC</td>
<td>1.1% [0%; 14%]</td>
<td>0.6% [0%; 11%]</td>
<td>0.82 [0.64; 0.99]</td>
</tr>
<tr>
<td>EFV + AZT + 3TC</td>
<td>2.4% [0%; 19%]</td>
<td>1.0% [0%; 16%]</td>
<td>0.84 [0.65; 1.02]</td>
</tr>
<tr>
<td>BREATHER trial</td>
<td>1.7% [0%; 15%]</td>
<td>1% [0%; 11.9%]</td>
<td>0.82 [0.63; 0.99]</td>
</tr>
</tbody>
</table>

Real outcome in BREATHER trial: in SCT arm 6% [2%; 10%]
→ Model misspecification ?
→ Adherence ?
→ Mutations?

[Butler et al. (2017) Lancet HIV]
## In silico QUATUOR trial (4/7 design)

<table>
<thead>
<tr>
<th>CART</th>
<th>4/7 designs</th>
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</tr>
</thead>
<tbody>
<tr>
<td><strong>Probability virological failure (&gt;1cp/mL)</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>EFV+ Tenofovir + Lamivudine</strong></td>
<td>5.3% [2.2%; 9.0%]</td>
<td>2.0% [0.0%; 4.0%]</td>
<td>0.91 [0.71; 1.11]</td>
</tr>
<tr>
<td><strong>EFV+ Abacavir+ Lamivudine</strong></td>
<td>17.1% [11%; 23%]</td>
<td>11.9% [6%; 17%]</td>
<td>0.96 [0.74; 1.16]</td>
</tr>
<tr>
<td><strong>EFV+ Zidovudine+ Lamivudine</strong></td>
<td>21.4% [16%; 28%]</td>
<td>16.4% [10%; 23%]</td>
<td>0.97 [0.75; 1.18]</td>
</tr>
</tbody>
</table>

→ 4/7 designs based on EFV-HAART are likely to be more difficult to maintain
Conclusion
Going further

From a methodological perspective:
→ Account for mutations
→ Account for pharmacometrics

From an application perspective:
→ Personalize SCT (x/7) with approaches that are:
  • HAART-specific
  • Patient-specific
  • Based on optimal control theory

[Bertrand et al. (2015) Pharmacokinetics and genomics]
[Sampah et al. (2011), PNAS]
Thanks

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