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Using Semiparametric NMME Models

HIV Dynamics Modelling
Conclusions

Model Comparison

Semi-parametric NLMEM Models

Models for Individual Subjects

The Data

OUTLINE
Figure 1: Viral load of 4 subjects.

The Data

Viral load: a surrogate marker used to accelerate AIDS clinical trials.

ACTG 315, 48 subjects, 2 ~ 13 obs per subject. Response: Viral

The Data
How to model?

Complete Viral Load Stages 1 + 2 + 3

Stage 3: Day 80 ~ 300, including rebounding data

Stage 2: Day 20 ~ 80, 2-exp Model (Wen, et al., 1995)

Stage 1: Day 0 ~ 20, 1-exp Model (Ho, et al., 1995)

Viral Load’s 3 Stages
Remark: used only to model earlier viral load data (Stage 1 data)

\( p \): positive viral load decay rate; indicating viral load dropping

\( \Lambda(0) \): baseline viral load

\( \exp \{ H_0, t \}, t \geq 1995, \forall t \geq 1995 \)

\( \exp \{ H_p - (t) \} \Lambda(0) \Lambda = (t) \Lambda \)

I. Unexp Models: Models for Individual Subjects
union Model (4)p nonparametrically

\[ a^d + \cdots + a^2 + a + a^0 = (4)p \quad \text{poly} \]
\[ \{a^g - a\} \exp a + \{a^g - a\} \exp a = (4)p \quad \text{uniexp} \]
\[ a^g + a^g + \{a^g - a\} \exp a = (4)p \quad \text{uniexp} \]
\[ a + \{a^g - a\} \exp a = (4)p \quad \text{uniexp} \]

Possible parametric models for (4)p

\[ \{4(4)p - a\} \exp a^0 = (4)a \quad \text{uniexp Models with time-varying decay rate} \]

Extensions
Remark: used only to model earlier viral load data (Stages 1 and $p_1$ and $p_2$: 1st and 2nd positive decay rates terms $P_1$ and $P_2$: baseline viral loads for first/second exponential

\[
\frac{P_2 e^{rt}}{P_2} + \frac{P_1 e^{rt}}{P_1} = (t) \Lambda
\]

2. Brief Modes:
\[
(\text{Dim.} 1999) \left\{ t^p \right\} \exp \gamma t^p + \cdots + \left\{ t^p \right\} \exp \gamma t^p = (t) \Lambda
\]

\text{Multiexp model:}

\[
(\text{Zhang } 2000) \left\{ t(t) \right\} \exp \gamma t^p + \left\{ t^p \right\} \exp \gamma t^p = (t) \Lambda
\]

\text{Exponential semi-parametric model: allow } d \text{ to be a smooth function over time.}

\text{Rebound model: allow } d \text{ to be negative, rebounding load.
\{(t) \Lambda\} \delta \eta = (t) \varphi \ 	ext{known, known, non-linear, e.g.}\ 
\text{time: } t
\text{non-parametric mixed-effects}
\text{coordinates for } \gamma
\text{parametric mixed-effects}
\begin{align*}
  u, \cdots, \eta \mid I = \gamma, \epsilon + (t) \varphi \gamma \epsilon \varphi \gamma x \varphi = \gamma \eta
\end{align*}

\text{Vector form:}

\text{Semi-parametric NLMEM models}
\begin{align*}
\langle \tau, \sigma \rangle \delta_{\mathcal{C}}^{\mathcal{B}} \rho &= (\langle \tau \rangle \delta^{\mathcal{B}} \delta \langle \sigma \rangle \delta^{\mathcal{B}} \rho)_{\text{cov}} \\
\langle \tau \rangle \mathcal{H}_{\mathcal{C}}^{\mathcal{B}} \rho &= (\langle \tau \rangle \delta^{\mathcal{B}} \delta \rho)_{\text{cov}} \\
\text{Covariance Structure:} \\
\text{Random:} & \quad \langle \tau \rangle \delta^{\mathcal{B}} \delta \quad \text{Fixed:} \quad \langle \tau \rangle \delta^{\mathcal{B}} \quad \langle \tau \rangle \delta^{\mathcal{B}} \rho + (\tau) \delta^{\mathcal{B}} = (\tau) \delta^{\mathcal{B}} \\
\text{Nonparametric Mixed-effects:} \\
\text{Random:} & \quad \langle \tau \rangle \delta^{\mathcal{B}} \delta \quad \text{Fixed:} \quad \langle \tau \rangle \delta^{\mathcal{B}} \quad \langle \tau \rangle \delta^{\mathcal{B}} \rho + (\tau) \delta^{\mathcal{B}} \rho = (\tau) \delta^{\mathcal{B}} \\
\text{Parametric Mixed-effects:} \\
\end{align*}
\[ d \] 
\[ \begin{align*} 
&= \begin{pmatrix}
\phi_1 & \phi_2 & \cdots & \phi_d
\end{pmatrix} \\
&= \begin{pmatrix}
\phi_1 & \phi_2 & \cdots & \phi_d
\end{pmatrix}
\end{align*} \]

Choice of \( \phi \) : see Ramsey and Silverman (1996) and Wu

\[ L(\frac{d\phi}{\phi}, \ldots, \frac{d\phi}{\phi} \phi, \frac{d\phi}{\phi} \phi) = \phi \Phi \]

where

\[ L(\frac{d\phi}{\phi}, \ldots, \frac{d\phi}{\phi} \phi, \frac{d\phi}{\phi} \phi) = \phi \Phi \]

The basis method is the simplest nonparametric method.

\( \text{Model Estimation} \)
Remark: AIC and BIC can be used to compare different models.

number of observations.

where \( h \): number of independent parameters in the model,

\[ b(N) \log + \text{likelihood} = \text{BIC} \]

\[ b(N) \log + \text{likelihood} = \text{AIC} \]

The number of basis functions can be chosen by AIC or BIC.

which can be solved by existing algorithms for a given \( \Phi \).

\[ \sum_{u} \cdots \sum_{u} I_{i} = I \quad \sum_{u} \cdots \sum_{u} I_{i} = \int_{\Omega} + \int_{\Omega} \Phi \sum_{i} \int \Phi \sum_{i} \int \approx \int \]

parametric mixed-effects model.

Then the semi-parametric NIME model (1) becomes a...
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<th>Model</th>
<th>BIC</th>
<th>AIC</th>
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<td>1.925</td>
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Table 1: Model comparisons for ACG 315.

Results: including rebounding data

Model Selection Rules: AIC and BIC

Model Comparison
Load of 9 subjects from ACTG 315.

Short-dashed, unindexed; Long-dashed, unid)poly

Figure 2: Parametric fits (solid, unindexed; dotted, unindexed)
of the viral load of 9 subjects from ACTG 315. This includes the solid (dotted, dashed, and semi-parametric) curves for each subject. Figure 3: Non-parametric (dotted, solid, and dashed) curves for each subject.
| Model | AIC | BIC | Results: excluding redundant data for ACTG 315.

Table 2: Model comparisons for ACTG 315.
All models considered gave similar results.

- Biexp semi-parametric NLME model as good as biexponential model.

For stages 1+2 viral load:

- Non/semi-parametric models improve parametric models.

All semi-parametric NLME is the best among all models.

Conclusions for the complete (stages 1+2+3) viral load.
THANK YOU