Proportional Hazards Models With Continuous Marks
Yanqing Sun, Peter B. Gilbert, and Ian W. McKeague
*Annals of Statistics* 37(1), Feb 2009

Presented by Jason Shao

University of Washington Biostatistics
Stat/Biost 572

Jun 6, 2013
Scientific Motivation

- Randomized HIV vaccine trials
- **Major difficulty**: Differential vaccine efficacy (VE)
- Vaccines don’t protect as well against unfamiliar viruses
- Can quantify genetic diversity using Hamming distance (continuous)

GAG fragment alignment

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4</td>
<td>0</td>
<td>-2</td>
<td>-1</td>
<td>-2</td>
<td>0</td>
<td>-2</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>9</td>
<td>-3</td>
<td>-4</td>
<td>-2</td>
<td>-3</td>
<td>-3</td>
</tr>
<tr>
<td>D</td>
<td>-2</td>
<td>-3</td>
<td>6</td>
<td>2</td>
<td>-3</td>
<td>-1</td>
<td>-1</td>
</tr>
<tr>
<td>E</td>
<td>-1</td>
<td>-4</td>
<td>2</td>
<td>5</td>
<td>-3</td>
<td>-2</td>
<td>0</td>
</tr>
<tr>
<td>F</td>
<td>-2</td>
<td>-2</td>
<td>-3</td>
<td>-3</td>
<td>6</td>
<td>-3</td>
<td>-1</td>
</tr>
<tr>
<td>G</td>
<td>0</td>
<td>-3</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
<td>-1</td>
<td>-2</td>
</tr>
<tr>
<td>H</td>
<td>-2</td>
<td>-3</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
<td>-1</td>
<td>-2</td>
</tr>
</tbody>
</table>

Part of the Hamming substitution matrix
Want to perform inference on vaccine efficacy, accounting for infecting type in the model.

Measures on infecting type **only observed in infected subjects** - *cannot* be treated as ordinary covariates!

<table>
<thead>
<tr>
<th>i</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>...</th>
</tr>
</thead>
<tbody>
<tr>
<td>T</td>
<td>13.3</td>
<td>7.4</td>
<td>4.8</td>
<td>16.3</td>
<td>1.5</td>
<td>14.2</td>
<td>16.3</td>
<td>7.0</td>
<td>...</td>
</tr>
<tr>
<td>δ</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>V</td>
<td>0.72</td>
<td>0.80</td>
<td>0.51</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.06</td>
<td>...</td>
</tr>
<tr>
<td>X</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>...</td>
</tr>
</tbody>
</table>

- **T**: follow-up time
- **δ**: failure indicator
- **V**: mark variable
- **X**: Vaccine (1) or placebo(0). Could be a vector, including other covariates of interest (possibly time-varying).
Parameter of interest…sort of

- We are interested in the **strain-specific vaccine efficacy**:  
  \[ VE(v) = 1 - \frac{\lambda(t, v|X_1 = 1)}{\lambda(t, v|X_1 = 0)} \]

- \( \lambda(t, v|X) \) is a conditional **strain-specific hazard**.
  - Interpretable as instantaneous failure rate due to type \( v \) at time \( t \), conditional on having survived up to \( t \).
  - Also conditional on \( X \), which includes vaccination status.

- Gilbert (2000) demonstrates the above, based on two assumptions:
  - A.1) Vaccination reduces **strain-specific** transmission probability per exposure uniformly.
  - A.2) Risk behavior and exposure equal among participants regardless of vaccination status.
Estimation of $\beta(\nu)$ using partial likelihood

- Proportional hazards assumption (Cox [1972]):
  \[
  \lambda(\nu, t | X) = \lambda_0(t, \nu) \exp(\beta(\nu)^T X)
  \]

- Localized log partial likelihood:
  \[
  \ell_\nu(\beta_\nu) = \sum_{i=1}^{n} \int_{0}^{1} \int_{0}^{T} K_h(u - \nu) \times \left[ \beta^T(\nu)X_i(t) - \log \left( \sum_{j=1}^{n} Y_j(t)e^{\beta^T(\nu)X_j} \right) \right] \times N_i(dt, du)
  \]

- Counting process $N_i = I(X_i \leq t, \delta_i = 1, V_i \leq \nu)$: jumps from 0 to 1 at $u = V_i$ and $t = T_i$ if $i$th subject is uncensored.
- Weighted by risk set of all subjects at time $T_i$ ["At risk" $Y_j(t)$].
- ...and by $V_i$ being close to $\nu$ of interest [Kernel function $K_h(\cdot)$].
- For $\nu \in [0, 1]$, the MPLE is $\hat{\beta}(\nu) = \arg \max_{\beta} \mathcal{L}(\beta(\nu))$
Other quantities of interest based on the MPLE

- In the PH model, $\beta_1(v)$ is the hazard ratio for vaccinees vs. non-vaccinees
- Thus, $\hat{VE}(v) = 1 - \exp(\hat{\beta}_1(v))$
- Calculations of asymptotic variance: (similar to Cox ['72]):

\[
S^{(j)}(t, \beta) = n^{-1} \sum_{i=1}^{n} Y_i(t) e^{\beta_T Z_i} Z_i^j
\]

\[
J_n(t, \beta) = \frac{S^{(2)}(t, \beta)}{S^{(0)}(t, \beta)} - \left( \frac{S^{(1)}(t, \beta)}{S^{(0)}(t, \beta)} \right)^{\otimes 2}
\]

\[
\hat{\ell}_\beta(v, \beta(v)) = -\sum_{i=1}^{n} \int_0^1 \int_0^\tau K_h(u - v) J_n(t, \beta) N_i(dt, du)
\]
More asymptotic properties of the MPLE

$$\sqrt{nh}(\hat{\beta}(v) - \beta(v)) \to_d N(0, \nu_0\Sigma^{-1}(v))$$

$$\nu_0 = 3/5$$ (integral of squared kernel function)

$$\sqrt{nh}(\hat{VE}(v) - VE(v)) \to_d N(0, \nu_0\sigma_1^2(v)e^{2\beta_1(v)})$$

Pointwise estimates and confidence bands for VaxGen004 dataset:

\[ n = 5403; \text{2:1 randomization; 336 failures with observed marks} \]
The *real* quantity of interest

- Cumulative vaccine efficacy

\[
\hat{CV}(v) = \int_a^b \hat{VE}(u)du, \quad [a, b] \in [0, 1]
\]

- \(\sqrt{n}(\hat{CV}(v) - CV(v))\) converges to a mean-zero Gaussian process.
- Naive variance estimate: \(\int_a^b \hat{\Sigma}^2(u)(1,1)e^{2\hat{\beta}_1(u)}du\)
  - Ignores correlations at discrete values of \(v\) in finite samples.
- Instead use \(\hat{\rho}^2(v) = \hat{\Sigma}_{\hat{A}}(v)(1,1)\), where

\[
\Sigma_{\hat{A}}(v) = n^{-1} \sum_{i=1}^n \int_a^v \int_0^\tau \hat{A}(u)J_n(t, \hat{\beta}(u))\hat{A}(u)^T N_i(dt, du)
\]

\[
\hat{A}(v) = e^{\hat{\beta}_1(v)}\hat{\Sigma}(v)^{-1}
\]
(1-\(\alpha\)) confidence bands for \(\hat{CV}(v)\)

Pointwise: 
\[
\hat{CV}(v) \pm n^{1/2} Z_{\alpha/2} \hat{\rho}(v)
\]

Simultaneous: 
\[
\hat{CV}(v) \pm n^{1/2} U_{\alpha} \left( \frac{\hat{\rho}(v) + \hat{\rho}(b)}{\hat{\rho}(b)} \right)
\]

\(U_{\alpha}\) is the upper \(\alpha\)-quantile of \(\sup_{v \in [0,0.5]} |B(v)|\), where \(B(v)\) is a Brownian bridge.

Estimate of cumulative VE with pointwise (---) and simultaneous (···) confidence bands for VaxGen004 dataset
Hypothesis testing

Goal: Test overall and differential vaccine efficacy on $v \in [a, b]$ 

- $H_{10}$ (Overall Null): vaccine efficacy zero for all $v$
  - $H_{1a}$ (General alternative): VE nonzero for some $v$
  - $H_{1m}$ (Monotone alternative): VE non-negative for all $v$, and positive for some $v$.

- $H_{20}$ (Differential Null): vaccine efficacy does not depend on $v$
  - $H_{2a}$ (General alternative): VE depends on $v$
  - $H_{2m}$ (Monotone alternative): VE decreases with increasing $v$. 
Defining test processes and statistics

Define: test processes \( \hat{Z} \) and test statistics \( T \) for each alternative:

- \( H_{10} \): \( \hat{Z}^{(1)}(v) = \sqrt{n} \frac{\widehat{CV}(v)}{\hat{\rho}(b)} \) and \( \hat{t}(v) = \frac{\hat{\rho}^2(v)}{\hat{\rho}^2(b)} \)
  - \( H_{1a} \): \( T_{a}^{(1)} = \int_{a}^{b} (\hat{Z}^{(1)}(v))^2 d\hat{t}(v) \)
  - \( H_{1m} \): \( T_{m1}^{(1)} = \int_{a}^{b} \hat{Z}^{(1)}(v) d\hat{t}(v) \)

- \( H_{20} \): \( \hat{Z}^{(2)}(v) = \sqrt{n} \frac{\overline{CV}(v)_{v-a} - \overline{CV}(b)_{b-a}}{\hat{\rho}(b)} \)
  - \( H_{2a} \): \( T_{a}^{(2)} = \int_{a}^{b} (\hat{Z}^{(2)}(v))^2 d\hat{t}(v) \)
  - \( H_{2m} \): \( T_{m1}^{(2)} = \int_{a}^{b} \hat{Z}^{(2)}(v) d\hat{t}(v) \)
Some simplified examples

\[ \begin{align*}
\text{VE}(v) &= 1 \\
\text{CV}(v) &= v \\
Z^{(1)} \propto \hat{\text{CV}}(v) &= v \\
Z^{(2)} \propto \frac{\hat{\text{CV}}(v)}{v} - \hat{\text{CV}}(1) &= 0
\end{align*} \]

\[ \begin{align*}
\text{VE}(v) &= v \\
\text{CV}(v) &= v^2 / 2 \\
\hat{Z}^{(1)} \propto \hat{\text{CV}}(v) &= \frac{v^2}{2} \\
\hat{Z}^{(2)} \propto \frac{\hat{\text{CV}}(v)}{v} - \hat{\text{CV}}(1) &= \frac{v - 1}{2}
\end{align*} \]

\[ \begin{align*}
\text{VE}(v) &= 1 - v \\
\text{CV}(v) &= v - v^2 / 2 \\
\hat{Z}^{(1)} \propto \hat{\text{CV}}(v) &= v - \frac{v^2}{2} \\
\hat{Z}^{(2)} \propto \frac{\hat{\text{CV}}(v)}{v} - \hat{\text{CV}}(1) &= \frac{1 - v}{2}
\end{align*} \]
Test statistic distributions

- Under their respective nulls, the test processes $\hat{Z}^{(1)}(v)$ and $\hat{Z}^{(2)}(v)$ converge to Wiener processes indexed by $t(v) = \rho^2(v)/\rho^2(b)$.
- Test statistics $T_{a}^{(1)}$, $T_{m1}^{(1)}$, $T_{a}^{(2)}$, $T_{m1}^{(2)}$ converge to the respective functionals, so their null distributions can be simulated.
- Discretized versions of the monotone alternative test statistics $T_{m2}^{(2)}$, $T_{m2}^{(2)}$ also exist.
Simulation study

- Generate time-to-failure data from given hazard function:
  \[ \lambda(t, v|x) = \exp(\gamma v + (\alpha + \beta v)x) \quad t \geq 0, \, v \in [0,1] \]

- \( v \) generated from uniform distribution
- \( x \) vaccination status 0 or 1 with probability 0.5
- \( t \) simulated from exponential distribution, using the hazard function conditional on \( v, x \)
- Censoring simulated from an independent exponential distribution with rates of 20 to 30 %

- Results in true \( \beta(v) = \alpha + \beta v \) and \( VE(v) = 1 - \exp(\alpha + \beta v) \)
Simulation setup

- $H_{10} : VE(v) = 0$ for all $v \in [a, b]$
  - Model 1: $(\alpha, \beta, \gamma) = (0.0, 0.0, 0.3)$ (Null)
  - Model 2: $(\alpha, \beta, \gamma) = (-0.5, 0.5, 0.3)$ (Alternative)
  - Model 3: $(\alpha, \beta, \gamma) = (-0.6, 0.6, 0.3)$ (Alternative)
  - Model 4: $(\alpha, \beta, \gamma) = (-0.6, 0.0, 0.3)$ (Alternative)

- $H_{20} : VE(v)$ does not depend on $v \in [a, b]$
  - Model 5: $(\alpha, \beta, \gamma) = (-0.7, 0.0, 0.3)$ (Null)
  - Model 6: $(\alpha, \beta, \gamma) = (-1.2, 1.2, 0.3)$ (Alternative)
  - Model 7: $(\alpha, \beta, \gamma) = (-1.5, 1.5, 0.3)$ (Alternative)
  - Model 8: $(\alpha, \beta, \gamma) = (-1.8, 1.8, 0.3)$ (Alternative)

Models 1, 2, 5, 8: 1,000 simulations each with $n = 500, 800$; $h = 0.05, 0.10, 0.15$

Models 3, 4, 6, 7: $n = 500$ and $h = 0.10$ only.
Simulation results: estimation

For selected models with $n=500$ and $h = 0.1$, random sample of 50 point estimates for $\beta_1(v)$ and $\text{CV}(v)$ (—), true values (—) and mean of 1000 estimates (···)
## Selected results: coverage and power

### Tests of overall vaccine efficacy

<table>
<thead>
<tr>
<th>Model</th>
<th>$(\alpha, \beta, \gamma)$</th>
<th>$n$</th>
<th>$h$</th>
<th>$T_a^{(1)}$</th>
<th>$T_{m1}^{(1)}$</th>
<th>$T_{m2}^{(1)}$</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1</td>
<td>(0.0, 0.0, 0.3)</td>
<td>500</td>
<td>0.10</td>
<td>7.0</td>
<td>2.8</td>
<td>9.6</td>
<td>96.5</td>
</tr>
<tr>
<td>M2</td>
<td>(-0.5, 0.5, 0.3)</td>
<td>500</td>
<td>0.05</td>
<td>49.0</td>
<td>57.3</td>
<td>69.0</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
<td>58.7</td>
<td>68.6</td>
<td>70.0</td>
<td>99.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800</td>
<td>0.05</td>
<td>63.7</td>
<td>69.8</td>
<td>74.5</td>
<td>98.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
<td>74.7</td>
<td>81.5</td>
<td>87.1</td>
<td>99.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>800</td>
<td>0.15</td>
<td>70.2</td>
<td>71.8</td>
<td>86.4</td>
<td>98.8</td>
</tr>
<tr>
<td>M3</td>
<td>(-0.6, 0.6, 0.3)</td>
<td>500</td>
<td>0.10</td>
<td>75.4</td>
<td>82.2</td>
<td>84.7</td>
<td>96.5</td>
</tr>
<tr>
<td>M4</td>
<td>(-0.6, 0.0, 0.3)</td>
<td>500</td>
<td>0.10</td>
<td>96.5</td>
<td>98.4</td>
<td>99.8</td>
<td>96.7</td>
</tr>
</tbody>
</table>
## Selected results: coverage and power

**Tests of differential vaccine efficacy**

<table>
<thead>
<tr>
<th>Model</th>
<th>$\alpha, \beta, \gamma$</th>
<th>$n$</th>
<th>$h$</th>
<th>$T_a^{(1)}$</th>
<th>$T_m^{(2)}$</th>
<th>$T_m^{(2)}$</th>
<th>Coverage (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M5</td>
<td>(-0.7, 0.0, 0.3)</td>
<td>500</td>
<td>0.10</td>
<td>4.2</td>
<td>3.3</td>
<td>12.1</td>
<td>98.4</td>
</tr>
<tr>
<td>M6</td>
<td>(-1.2, 1.2, 0.3)</td>
<td>500</td>
<td>0.10</td>
<td><strong>38.0</strong></td>
<td>42.3</td>
<td>48.8</td>
<td>96.7</td>
</tr>
<tr>
<td>M7</td>
<td>(-1.5, 1.5, 0.3)</td>
<td>500</td>
<td>0.15</td>
<td>61.7</td>
<td>66.0</td>
<td>73.0</td>
<td>94.8</td>
</tr>
<tr>
<td>M8</td>
<td>(-1.8, 1.8, 0.3)</td>
<td>500</td>
<td>0.10</td>
<td>60.7</td>
<td>60.7</td>
<td>77.2</td>
<td>95.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>800</td>
<td>0.05</td>
<td>92.5</td>
<td>87.1</td>
<td>92.0</td>
<td>93.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
<td>96.2</td>
<td>94.1</td>
<td>96.9</td>
<td>93.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.15</td>
<td>96.2</td>
<td>94.4</td>
<td>97.6</td>
<td>96.0</td>
</tr>
</tbody>
</table>
Criticisms & Conclusions

Many calculation details weren’t explicitly stated - needed author code to clarify:
- Integrals implemented differently from paper text
- Bandwidth-dependent measures to avoid the lower boundary - not mentioned in text
- Simulation results difficult to reproduce from details in paper

Possible next steps:
- Simulate from more complex distributions (distinguish between monotone and general alternatives)
- Compare to finite competing risks (Prentice et al. 1975)
- Clarify calculation details and justify the additional procedures.
Thank you!

HIV plushie from www.giantmicrobes.com
Discretized monotone alternative test statistics

- Defined by inverting covariance estimates of Wiener processes on a finite grid:

\[ T_{m2}^{(1)} = (K - 1)^{1/2} \sum_{k=2}^{K} \frac{Z^{(1)}(v_k) - Z^{(1)}(v_{k-1})}{\sqrt{t(v_k) - t(v_{k-1})}} \]

\[ T_{m2}^{(2)} = \hat{\Pi}_{K}^{-1} \sum_{k=2}^{K} Z^{(2)}(v_k) - Z^{(2)}(v_{k-1})/\hat{\pi}_k \]

\[ \hat{\pi}_k^2 = \hat{\pi}_{k-1,k} - 2\hat{\pi}_{k-1,k} + \hat{\pi}_{k,k} \]

\[ \hat{\tau}_{i,j} = \hat{\text{Cov}}(Z^{(2)}(v_i), Z^{(2)}(v_j)) \]

\[ = \frac{\hat{t}(v_i)}{(v_i - a)(v_j - a)} - \frac{\hat{t}(v_i)}{(v_i - a)(b - a)} - \frac{\hat{t}(v_j)}{(b - a)(v_j - a)} + \frac{1}{(b - a)^2} \]

\[ \Gamma = (\hat{\tau}_{i,j})_{K \times K} \]

\[ \xi = (\hat{\pi}_2^{-1}, \hat{\pi}_3^{-1} - \hat{\pi}_2^{-1}, ..., \hat{\pi}_K^{-1} - \hat{\pi}_{K-1}^{-1}, \hat{\pi}_K^{-1}) \]

\[ \hat{\Pi}_K = \xi^T \Gamma \xi \]