Cure models based on univariate and bivariate random effects

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Introduction

What is special in survival analysis?

- non-negative values, censored observations
- mixture of discrete and continuous variables: \((T, \Delta)\)
- \(T = \min(T^*, C), \Delta = I(T^* \leq C)\)
- \(T\) observation time, \(T^*\) event time, \(C\) censoring time, \(\Delta\) censoring indicator

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Introduction

Two typical assumptions in survival analysis:

- All individuals are susceptible to the event under study.
- All observations are independent.
cure models

Cure models

- mixture cure models
  \[ S(t) = (1 - \phi) + \phi S_0(t) \]
- nonmixture cure models
  \[ S(t) = (1 - \phi)^{1 - S_0(t)} \]

\( S_0(t) \) proper survival function
\( 1 - \phi \) size of the cure fraction

A. Wienke, Cure models based on univariate and bivariate random effects, ROeS 2013

mixture cure models

- assumption: not everybody is susceptible to the event under study and will eventually experience the event if follow-up is sufficiently long
- sometimes individuals are not expected to experience the event of interest
- those individuals are cured or non-susceptible
- two sub-populations

A. Wienke, Cure models based on univariate and bivariate random effects, ROeS 2013
individuals are either cured with probability $1 - \phi$ or have proper survival function with probability $\phi$

- examples: genetically influenced diseases or individuals may be vaccinated against infectious diseases
- often used model (Farewell 1982, Sy and Taylor 2000)
- incidence and latency

$$S(t | X) = (1 - \phi(X)) + \phi(X) S_0(t | X)$$

$$= \frac{1}{1 + e^{\alpha X}} + \frac{e^{\alpha X}}{1 + e^{\alpha X}} S_0(t) e^{\beta X}$$

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cure models

- $Y$ susceptible status (binary 0/1) – random effect

\[ \mu(t | Y) = Y \mu_0(t) \]

\[ P(Y = 1) = \varphi, \quad P(Y = 0) = 1 - \varphi \]

\[ \mu(t | Y, Z) = YZ \mu_0(t) \]

compound Poisson frailty model

univariate compound Poisson frailty by Aalen (1992)

$N$ Poisson distributed r.v.
$V_i$ gamma distributed r.v.
$Z = V_1 + V_2 + \ldots + V_N$

\[ \mu(t | Z) = Z \mu_0(t) \]

\[ S(t) = e^{\frac{1-\gamma}{\gamma} ((1 + \frac{\gamma s^2}{1 - \gamma}) \mu_0(t) - 1)} \]

\[ S(\infty) = e^{\frac{1-\gamma}{\gamma}}, \text{ if } \gamma < 0 \]
correlated compound Poisson frailty model

\[ S(t_1, t_2) = S(t_1)^{1-p} S(t_2)^{1-p} e^{-\frac{p(1-p)\gamma^2}{\gamma^2(1-(1-\frac{\gamma^2}{1-\gamma}\ln S(t_1))^\gamma+(1-\frac{\gamma^2}{1-\gamma}\ln S(t_2))^\gamma-1)^\gamma}} \]

correlated PVF (three parameter family) frailty model
Yashin et al. (1999) when \( 0 \leq \gamma \leq 1 \)

\[
\begin{array}{|c|c|}
\hline
\text{gamma} & \gamma = 0 \\
\text{inverse Gaussian} & \gamma = 0.5 \\
\text{PVF} & 0 \leq \gamma \leq 1 \\
\text{compound Poisson} & -\gamma \leq \gamma \leq 0 \\
\hline
\end{array}
\]

Vaupel et al. 1979
Hougaard 1984
Hougaard 1986a
Aalen 1992
correlated compound Poisson frailty model

\[ S(t_1, t_2) = S(t_1)^{1-\rho} S(t_2)^{1-\rho} e^{\frac{\rho(1-\gamma)}{\gamma(1-\gamma)} \left( 1 - \left( 1 + \frac{\gamma^2}{1-\gamma} \ln(S(t_1)) \right)^{1/\gamma} + \left( 1 - \frac{\gamma^2}{1-\gamma} \ln(S(t_2)) \right)^{1/\gamma} - 1 \right)^{\gamma} } \]

\[ \rho = 1 \text{ (shared frailty model)} \]

\[ S(t_1, t_2) = e^{\frac{1-\gamma}{\gamma(1-\gamma)} \left( 1 - \left( 1 + \frac{\gamma^2}{1-\gamma} \ln(S(t_1)) \right)^{1/\gamma} + \left( 1 - \frac{\gamma^2}{1-\gamma} \ln(S(t_2)) \right)^{1/\gamma} - 1 \right)^{\gamma} } \]

**frailty distribution**

<table>
<thead>
<tr>
<th>gamma</th>
<th>( \gamma = 0 )</th>
<th>Clayton 1978</th>
</tr>
</thead>
<tbody>
<tr>
<td>inverse Gaussian</td>
<td>( \gamma = 0.5 )</td>
<td></td>
</tr>
<tr>
<td>PVF</td>
<td>( 0 \leq \gamma \leq 1 )</td>
<td>Hougaard 1992</td>
</tr>
<tr>
<td>compound Poisson</td>
<td>( -\infty &lt; \gamma &lt; 0 )</td>
<td>Hougaard 2000</td>
</tr>
</tbody>
</table>

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correlated compound Poisson frailty model

\[ S(t_1, t_2) = S(t_1)^{1-\rho} S(t_2)^{1-\rho} e^{\frac{\rho(1-\gamma)}{\gamma(1-\gamma)} \left( 1 - \left( 1 + \frac{\gamma^2}{1-\gamma} \ln(S(t_1)) \right)^{1/\gamma} + \left( 1 - \frac{\gamma^2}{1-\gamma} \ln(S(t_2)) \right)^{1/\gamma} - 1 \right)^{\gamma} } \]

\[ 0 \leq \rho \leq 1 \text{ (correlated frailty model)} \]

**frailty distribution**

<table>
<thead>
<tr>
<th>gamma</th>
<th>( \gamma = 0 )</th>
<th>Yashin et al. 1993</th>
</tr>
</thead>
<tbody>
<tr>
<td>inverse Gaussian</td>
<td>( \gamma = 0.5 )</td>
<td>Zahl 1994</td>
</tr>
<tr>
<td>PVF</td>
<td>( 0 \leq \gamma \leq 1 )</td>
<td>Yashin et al. 1999</td>
</tr>
<tr>
<td>compound Poisson</td>
<td>( -\infty \leq \gamma \leq 0 )</td>
<td>Wienke et al. 2010</td>
</tr>
</tbody>
</table>
twin example

Swedish Twin Registry

- study population: all Swedish twin pairs born 1886-1925, both partners were still alive in 1961
- data include age at death and information about whether the twin developed breast cancer or not
- pairs with incomplete information about zygosity or breast cancer were excluded
- follow-up: January 1, 1961 - October 27, 2000
- data are bivariate right censored
- n=5857 female pairs, 715 cases of breast cancer

Breast cancer of Swedish twins (n=5857 pairs)
715 cases (Wienke et al. 2006, 2010)

<table>
<thead>
<tr>
<th></th>
<th>gamma frailty</th>
<th>inverse Gaussian frailty</th>
<th>compound Poisson frailty</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\gamma$</td>
<td>0</td>
<td>0.5</td>
<td>-0.62 (0.90)</td>
</tr>
<tr>
<td>$\sigma^2$</td>
<td>32.78 (7.78)</td>
<td>17.62 (14.22)</td>
<td>15.94 (8.27)</td>
</tr>
<tr>
<td>$\rho_{MZ}$</td>
<td>0.15 (0.05)</td>
<td>0.34 (0.13)</td>
<td>0.15 (0.05)</td>
</tr>
<tr>
<td>$\rho_{DZ}$</td>
<td>0.13 (0.04)</td>
<td>0.30 (0.11)</td>
<td>0.13 (0.04)</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>1.00</td>
<td>1.00</td>
<td>0.15</td>
</tr>
<tr>
<td>log-L</td>
<td>-5122.32</td>
<td>-5130.59</td>
<td>-5121.23</td>
</tr>
</tbody>
</table>
discussion

- Chatterjee and Shih (2001) and Wienke et al. (2003) found 22% woman to be susceptible to breast cancer.
- Overall lifetime risk of breast cancer is 8 - 12% in current western population (Harris et al. 1992; Feuer et al. 1993; Rosenthal and Puck 1999; Ries et al. 1999).
- Overall lifetime risk of breast cancer is increasing (less competing risks).
- Influence of genetic factors on susceptibility to breast cancer is small (5 - 10%).

discussion

correlated compound Poisson/PVF frailty model

- More elegant than frailty cure models.
- Very flexible and general.
- Includes gamma, inverse Gaussian and PVF frailty models as special cases.
- Explicit form of the survival function allows traditional ML parameter estimation.
- Identifiability problems as in all cure models.
- Parametric model.
**references**


A. Wienke, Cure models based on univariate and bivariate random effects, ROeS 2013

**correlated compound Poisson frailty model**

compound Poisson Frailty ($-\infty < \gamma \leq 1$)

PVF Frailty ($0 \leq \gamma \leq 1$)

Gamma Frailty ($\gamma = 0$)

inverse Gauss Frailty ($\gamma = 0.5$)

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twin example

Methodology for genetic studies of twins

- twin data provide a powerful tool to assess the overall genetic influence in the variation of specific traits
- separation of the impact of genetic and environmental factors
- comparing MZ and DZ twins
- if MZ twins are more similar than DZ twins this indicates the influence of genetic factors (heritability)
- Neale & Cardon (1992)
twin example

phenotypic variance

\[ V = V_A + V_C + V_D + V_E \]
\[ a^2 = \frac{V_A}{V}, \quad c^2 = \frac{V_C}{V}, \quad d^2 = \frac{V_D}{V}, \quad e^2 = \frac{V_E}{V} \]

\[ \rho_{MZ} = a^2 + c^2 + d^2 \]
\[ \rho_{DZ} = 0.5a^2 + c^2 + 0.25d^2 \]
\[ 1 = a^2 + c^2 + d^2 + e^2 \]

genetic models: ACE, ADE, AE, DE, CE

Simulation study 1000 runs, 5000 twin pairs each

<table>
<thead>
<tr>
<th>true value</th>
<th>mean of estimates</th>
<th>standard error</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>2.00e-5</td>
<td>2.07e-5</td>
</tr>
<tr>
<td>b</td>
<td>0.100</td>
<td>0.100</td>
</tr>
<tr>
<td>γ</td>
<td>-0.600</td>
<td>-0.638</td>
</tr>
<tr>
<td>σ</td>
<td>4.000</td>
<td>3.991</td>
</tr>
<tr>
<td>ρ_{MZ}</td>
<td>0.150</td>
<td>0.152</td>
</tr>
<tr>
<td>ρ_{DZ}</td>
<td>0.150</td>
<td>0.153</td>
</tr>
</tbody>
</table>
frailty cure models

bivariate extensions by Chatterjee & Shih (2001), Wienke et al. (2003)

\[
\mu(t_1 \mid Y_1, Z_1) = Y_1 Z_1 \mu_0(t_1)
\]

\[
\mu(t_2 \mid Y_2, Z_2) = Y_2 Z_2 \mu_0(t_2)
\]