A new bivariate survival model including a non-susceptible fraction

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Overview

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- Frailty cure models
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- Breast cancer in Swedish twins
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Introduction

Cox proportional hazards model (1972)

- to assess the relationship of covariates to time to event (regression model)
- semi-parametric model

$$\lambda(t \mid X) = \lambda_0(t) e^{\beta' X}$$

two often made assumptions in survival analysis:

- all individuals are susceptible to the event under study
- all observations are independent

Cure models

Cure models

- often unstated assumption in survival analysis: everybody is susceptible to the event under study and will eventually experience this event if follow-up is sufficiently long
- for example total mortality - everybody will die
- sometimes individuals are not expected to experience the event of interest
- those individuals are cured or non-susceptible
- two sub-populations

Cure models

- individuals are either cured with probability 1-φ or have proper survival function with probability φ
- examples: genetically influenced diseases or individuals may be vaccinated against infectious diseases

$$\lambda(t \mid X, Y) = Y\lambda_0(t)e^{\beta' X}$$

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

Unconditional survival function (population):

$$S(t \mid X) = (1 - \varphi) + \varphi S_0(t \mid X)$$

Frailty models

random effects model (frailty)

$$\lambda(t \mid X, Z) = Z\lambda_0(t)e^{\beta' X}$$

Z follows some distribution (gamma, log-normal, positive stable, etc.)

$$S(t \mid X) = ES(t \mid X, Z) = Ee^{-\Lambda(t,X,Z)} = Ee^{-Z\Lambda_0(t)e^{\beta' X}} = L_Z(\Lambda_0(t)e^{\beta' X})$$

Frailty cure models

frailty cure models by Halloran et al. (1996), Longini & Halloran (1996), Price & Manatunga (2001)

$$\lambda(t \mid X, Y, Z) = YZ\lambda_0(t)e^{\beta' X}$$

multivariate extensions by Chatterjee & Shih (2001), Wienke et al. (2003), Locatelli (2004)

$$\lambda(t_1 \mid X_1, Y_1, Z_1) = Y_1 Z_1 \lambda_0(t_1)e^{\beta' X_1}$$
$$\lambda(t_2 \mid X_2, Y_2, Z_2) = Y_2 Z_2 \lambda_0(t_2)e^{\beta' X_2}$$

Frailty cure models

Shared gamma frailty model (Clayton 1978)

(drop observable covariates X, register data)

$$S(t_1, t_2 \mid Z) = S_0(t_1)^Z S_0(t_2)^Z$$

$$S(t_1, t_2) = \mathbf{E} S(t_1, t_2 \mid Z)$$

$$= \mathbf{E} e^{-Z(\Lambda_0(t_1) + \Lambda_0(t_2))}$$

$$= \ \ldots$$

$$= (S(t_1)^{-\sigma^2} + S(t_2)^{-\sigma^2})^{-1/\sigma^2}$$

Frailty cure models

Correlated gamma frailty model

$\lambda = k_0 + k_1$ V_0, V_1, V_2 independent gamma distributed r. v.

$V_0 \sim \Gamma(k_0, \lambda)$ $V_1 \sim \Gamma(k_1, \lambda)$ $V_2 \sim \Gamma(k_1, \lambda)$

with

$$Z_1 = V_0 + V_1 \sim \Gamma(k_0 + k_1, \lambda) = \Gamma(\lambda, \lambda)$$

$$Z_2 = V_0 + V_2 \sim \Gamma(k_0 + k_1, \lambda) = \Gamma(\lambda, \lambda)$$

Z_1 and Z_2 are correlated, $\rho = \mathbf{corr}(Z_1, Z_2)$

Frailty cure models

Correlated gamma frailty model

(Yashin et al. (1993), Pickles et al. (1994))

$$S(t_1, t_2 \mid Z_1, Z_2) = S_0(t_1)^{Z_1} S_0(t_2)^{Z_2}$$

$$S(t_1, t_2) = \mathbf{E} S(t_1, t_2 \mid Z_1, Z_2)$$

$$= \mathbf{E} e^{-Z_1 \Lambda_0(t_1) + Z_2 \Lambda_0(t_2)}$$

$$= \mathbf{E} e^{-Y_0(\Lambda_0(t_1) + \Lambda_0(t_2)) - Y_1 \Lambda_0(t_1) + Y_2 \Lambda_0(t_2)}$$

$$= \ldots$$

$$= S(t_1)^{1-\rho} S(t_2)^{1-\rho} \left(S(t_1)^{-\sigma^2} + S(t_2)^{-\sigma^2}\right)^{-\rho/\sigma^2}$$

Compound Poisson frailty model

PVF frailty model by Hougaard (1986) when $0 \leq \gamma \leq 1$

$$\lambda(t \mid Z) = Z\lambda_0(t)$$

$$S(t) = ES(t \mid Z) = Ee^{-\Lambda(t,Z)} = Ee^{-Z\Lambda_0(t)} = L_Z(\Lambda_0(t))$$

$$S(t) = e^{-\frac{1-\gamma}{\gamma\sigma^2}\left(\left(1+\frac{\gamma\sigma^2}{1-\gamma}\Lambda_0(t)\right)^{\gamma}-1\right)}$$

special cases: gamma ($\gamma=0$) and inverse Gaussian ($\gamma=0.5$) frailty

Compound Poisson frailty model

univariate **compound Poisson frailty** by Aalen (1992)

N Poisson distributed random variable

V_i gamma distributed random variables

$Z=V_1+V_2+ \ldots +V_N$

$$S(t) = e^{-\frac{1-\gamma}{\gamma\sigma^2}((1+\frac{\gamma\sigma^2}{1-\gamma}\Lambda_0(t))^{\gamma}-1)}$$

$$S(\infty) = e^{\frac{1-\gamma}{\gamma\sigma^2}} \text{ when } \gamma < 0$$

Correlated compound Poisson frailty model

$Z_1=V_0+V_1$, $Z_2=V_0+V_2$,

V_0, V_1, V_2 univariate compound Poisson distributed r.v.

$$\lambda(t_1 \mid Z_1) = Z_1 \lambda_0(t_1)$$

$$\lambda(t_2 \mid Z_2) = Z_2 \lambda_0(t_2)$$

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

correlated PVF (three parameter family) frailty model

Yashin et al. (1999) when $0 \leq \gamma \leq 1$

Univariate compound Poisson frailty model

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

$\rho = 0$ (univariate frailty model)

$$S(t_1,t_2)=S(t_1)\,S(t_2)\quad \text{with}\quad S(t)=e^{-\frac{1-\gamma}{\gamma\sigma^2}\left(\left(1+\frac{\gamma\sigma^2}{1-\gamma}\Lambda_0(t)\right)^{\gamma}-1\right)}$$

frailty distribution		
gamma	$\gamma = 0$	Vaupel et al. 1979
inverse Gaussian	$\gamma = 0.5$	Hougaard 1984
PVF	$0 \le \gamma \le 1$	Hougaard 1986a
compound Poisson	$-\infty \le \gamma \le 1$	Aalen 1992

Shared compound Poisson frailty model

$$S(t_1,t_2)=S(t_1)^{1-\rho}S(t_2)^{1-\rho}e^{-\frac{\rho(1-\gamma)}{\gamma\sigma^2}(1-((1-\frac{\gamma\sigma^2}{1-\gamma}\ln(S(t_1)))^{1/\gamma}+(1-\frac{\gamma\sigma^2}{1-\gamma}\ln(S(t_2)))^{1/\gamma}-1)^{\gamma})}$$

$\rho = 1$ (shared frailty model)

$$S(t_1,t_2)=e^{-\frac{1-\gamma}{\gamma\sigma^2}(1-((1-\frac{\gamma\sigma^2}{1-\gamma}\ln(S(t_1)))^{1/\gamma}+(1-\frac{\gamma\sigma^2}{1-\gamma}\ln(S(t_2)))^{1/\gamma}-1)^{\gamma})}$$

frailty distribution		
gamma	$\gamma = 0$	**Clayton 1978**
inverse Gaussian	$\gamma = 0.5$	
PVF	$0 \le \gamma \le 1$	**Hougaard 1992**
compound Poisson	$-\infty \le \gamma \le 1$	

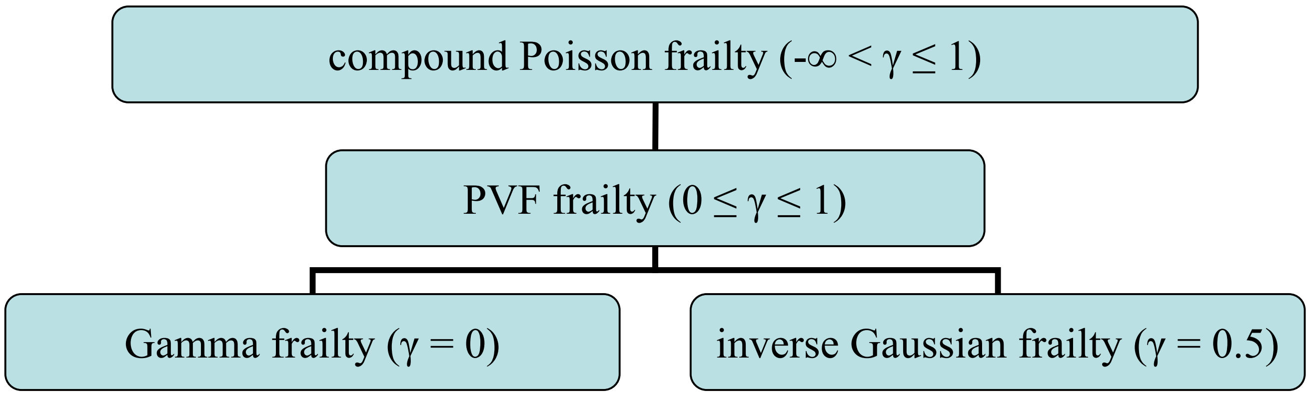
Correlated compound Poisson frailty model

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

$0 \leq \rho \leq 1$ (correlated frailty model)

frailty distribution		
gamma	$\gamma = 0$	Yashin et al. 1993
inverse Gaussian	$\gamma = 0.5$	Zahl 1994
PVF	$0 \leq \gamma \leq 1$	Yashin et al. 1999
compound Poisson	$-\infty \leq \gamma \leq 1$	Wienke et al. 2006

Compound Poisson frailty model



Swedish Twin Registry

The 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

Results

breast cancer in Swedish female twins (n=5857 pairs)

715 cases of breast cancer

	gamma frailty	inverse Gaussian frailty	compound Poisson frailty
γ	0	0.5	-0.05 (0.10)
σ	7.61 (0.47)	7.41 (1.08)	7.03 (0.99)
ρ_{MZ}	0.12 (0.04)	0.20 (0.06)	0.12 (0.04)
ρ_{DZ}	0.10 (0.03)	0.16 (0.05)	0.10 (0.03)
φ	**1.00**	**1.00**	**0.34** (-)
log-L	-5218.64	-5265.76	-5218.46

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

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Univariate fit