A CLASS OF NON PARAMETRIC ONE SAMPLE TESTS FOR THE ANALYSIS OF RECURRENT EVENTS

P. Rebora, S. Galimberti, M.G. Valsecchi

UNIVERSITÀ DEGLI STUDI DI MILANO BICOCCA

Center of Biostatistics for Clinical Epidemiology.
Department of Clinical Medicine and Prevention.
University of Milan-Bicocca. Monza. Italy

30th Annual Conference of the International Society for Clinical Biostatistics

August 23rd-27th, 2009 - Prague

Motivating clinical context

Clinical trial on Adenosine deaminase deficiency

Very rare disease (1 case/million live birth/year)

+

Fragile population

+

Innovative gene therapy

↓

a non randomized study is planned

to assess the efficacy and safety of gene therapy as treatment for ADA-SCID

End-points:

- hazard of death

$$H_0 : \lambda(s) = \lambda_0(s)$$

$$H_1 : \lambda(s) \neq \lambda_0(s)$$

-> One-sample Log-rank test (Breslow 1975)

$$T_B = \frac{\left\{ \int_0^{\tau} \hat{Y}(s)\{\hat{\lambda}(s) - \lambda_0(s)\} ds \right\}^2}{\int_0^{\tau} \hat{Y}(s)\lambda_0(s) ds}$$

- rate of severe recurrent infections

(defined as infections requiring hospitalization)

$$H_0 : \mu(s) = \mu_0(s)$$

$$H_1 : \mu(s) \neq \mu_0(s)$$

?

Reference values from historical data: λ_0 μ_0

Counting process notation

- $N_i(s)$ = # of events observed for subject i up to time s
- $dN_i(s)$ = # of events observed for subject i over [s, s+ds)
- $Y_i(s)$ = at risk indicator for subject i at time s
- $Y.(s)$ = number of person at risk at time s
- τ = largest of the observed follow-up times τ_i (i=1...n)
- $\mu(s) = E(N_i(s))$ mean function of events

Assuming that end of observation times are independent of the event processes

One sample non-parametric test
for recurrent events

$$H_0 : \mu(s) = \mu_0(s)$$
$$H_1 : \mu(s) \neq \mu_0(s)$$

One sample log-rank test

Two-sample test in recurrent event setting

(Lawless and Nadeau, 1995)

$$U(\tau) = \int_0^{\tau} w(s)\{d\hat{\mu}(s) - d\mu_0(s)\}$$

Weigth function:
a non negative predictable function such that w(s)=0 whenever Y.(s)=0

Mean rate function in the sample according Aalen-Nelson

Reference mean rate function

Variance for "Memory less" process

$$H_0 : \mu(s) = \mu_0(s)$$
$$H_1 : \mu(s) \neq \mu_0(s)$$

- **Under H_0**
- **Cov(N_i(t,u),N_i(v,z))=0 with t<u<v<z**

$$U(\tau) = \int_0^{\tau} w(s)\{d\hat{\mu}(s) - d\mu_0(s)\}$$ is a Mean Zero Martingale

with variance estimated by:

$$\mathrm{var}(U(\tau)) = \int_0^{\tau} \frac{w^2(s)}{Y_\bullet(s)} d\mu_0(s)$$

Robust Variance

$$H_0 : \mu(s) = \mu_0(s)$$
$$H_1 : \mu(s) \neq \mu_0(s)$$

No assumption of independent increments

$$\Rightarrow \quad U(\tau) = \int_0^{\tau} w(s)\{d\hat{\mu}(s) - d\mu_0(s)\}$$

Variance estimate:

$$\text{var}_R(U(\tau)) = \sum_{i=1}^{n} \left\{ \int_0^{\tau} \frac{w(s)Y_i(s)}{Y_{\bullet}(s)} [dN_i(s) - \text{d}\hat{\mu}(\text{s})] \right\}^2$$

Weight functions

Weight w(s)	**H_1**
(1) $Y_{\cdot}(s)$	Powerful under proportional mean rate functions $\mu(t) = e^{\beta}\mu_0(t)$
(2) $Y_{\cdot}^2(s)$	Emphasise period with more subjects at risk
(3) $Y_{\cdot}(s)(\tau - s)$	For decaying effect in time
(4) $Y_{\bullet}(s)\hat{\mu}(s)$	Increasing effect in time/ Emphasise periods with more information collected

Simulations

DIFFERENT SCENARIOS EXPLORED:

- event generating process (Mixed and not) :
  1. homogeneous Poisson
  2. non-homogeneous Poisson (Piecewise and Weibull)
  3. Renewal
  4. Autoregressive
- sample size ;
- magnitude of effect (10-30% reduction of the mean number of events at τ);
- censoring mechanisms .

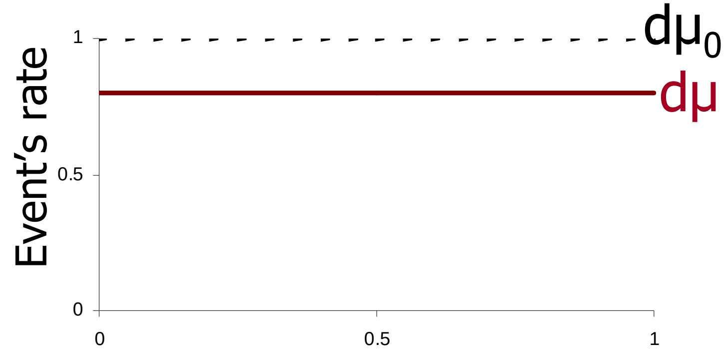
Homogenous Poisson

Maximum follow-up τ=1 year

Rate of censoring = 0.1/year

$d\mu_0$=1/year

w_i~Gamma $E(w_i)=1$ $Var(w_i)=\theta$



		H_0: $d\mu(s)=d\mu_0$					H_1: $d\mu(s)=0.8d\mu_0$				
		TYPE I ERROR RATE					POWER				
n	**θ**	$T_{(1)}$	$T_{(1)R}$	$T_{(2)R}$	$T_{(3)R}$	$T_{(4)R}$	$T_{(1)}$	$T_{(1)R}$	$T_{(2)R}$	$T_{(3)R}$	$T_{(4)R}$
w(s)=Y.(s)		**1**	**1**	**Y.(s)**	**(τ-s)**	$\hat{\mu}(s)$	**1**	**1**	**Y.(s)**	**(τ-s)**	$\hat{\mu}(s)$
25	**0**	0.053	0.074	0.077	0.081	0.083	0.146	0.268	0.268	0.253	0.278
50	**0**	0.049	0.060	0.062	0.062	0.065	0.275	0.386	0.384	0.328	0.353
100	**0**	0.041	0.048	0.048	0.053	0.049	0.507	0.599	0.598	0.485	0.509
25	**0.25**	0.080	0.077	0.075	0.080	0.096	0.148	0.249	0.249	0.240	0.254
50	**0.25**	0.079	0.068	0.067	0.073	0.069	0.284	0.340	0.343	0.324	0.326
100	**0.25**	0.074	0.047	0.048	0.047	0.059	0.498	0.518	0.518	0.447	0.464

Non-homogeneous Poisson

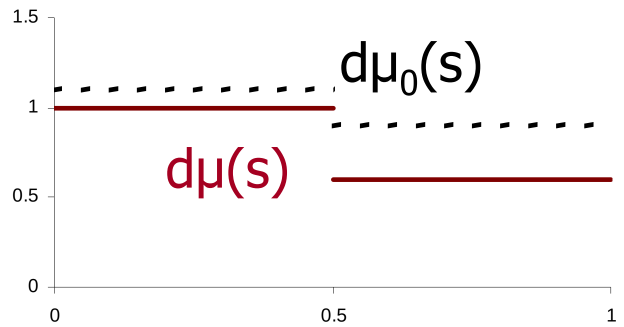
(No proportional means)

τ=1 year

Rate of censoring = 0.1/year

$d\mu_{01}$=1.1/year $d\mu_{02}$=0.9/year

w_i~Gamma $E(w_i)=1$ $Var(w_i)=\theta$



		H_0: $d\mu(s)=d\mu_{01}I(0<s\leq 0.5)+d\mu_{02}I(0.5<s\leq 1)$					***H_1: $d\mu(s)=1.1d\mu_{01}I(0<s\leq 0.5)+0.6d\mu_{02}I(0.5<s\leq 1)$***				
		TYPE I ERROR RATE					**POWER**				
n	**θ**	**$T_{(1)}$**	**$T_{(1)R}$**	**$T_{(2)R}$**	**$T_{(3)R}$**	**$T_{(4)R}$**	**$T_{(1)}$**	**$T_{(1)R}$**	**$T_{(2)R}$**	**$T_{(3)R}$**	**$T_{(4)R}$**
w(s)=	**Y(s)·**	**1**	**1**	**Y(s)**	**(τ-s)**	$\hat{\mu}(s)$	**1**	**1**	**Y(s)**	**(τ-s)**	$\hat{\mu}(s)$
25	**0**	0.051	0.076	0.076	0.082	0.096	0.118	0.237	0.232	0.161	0.339
50	**0**	0.050	0.064	0.063	0.061	0.064	0.251	0.369	0.359	0.203	0.499
100	**0**	0.040	0.043	0.043	0.055	0.051	0.492	0.578	0.561	0.287	0.725
25	**0.25**	0.085	0.076	0.076	0.084	0.098	0.147	0.244	0.240	0.170	0.334
50	**0.25**	0.063	0.053	0.053	0.060	0.064	0.278	0.344	0.337	0.198	0.464
100	**0.25**	0.081	0.053	0.053	0.057	0.060	0.472	0.497	0.482	0.244	0.658

Renewal Process

τ=1 year

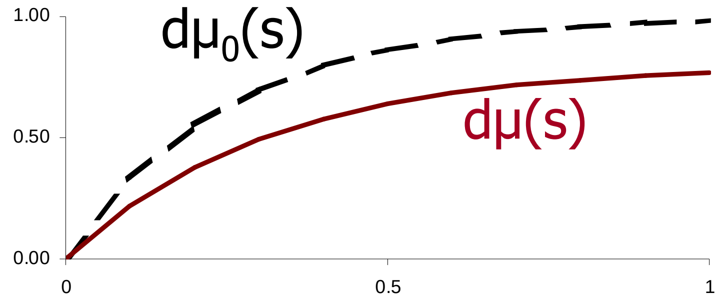
Rate of censoring = 0.1/year

X_{ij}~ Gamma(2,π)

-> inter-event time $X_{ij} \cdot w_i$

π_0=0.5

w_i~Gamma $E(w_i)=1$ $Var(w_i)=\theta$



$H_0: d\mu(s)=(1-e^{-2s/\pi 0})\ /2\pi_0$

$H_1: d\mu(s)=(1-e^{-2s/1.25\pi 0})\ /(2 \cdot 1.25\pi_0)$

		TYPE I ERROR RATE					POWER				
n	**θ**	$T_{(1)}$	$T_{(1)R}$	$T_{(2)R}$	$T_{(3)R}$	$T_{(4)R}$	$T_{(1)}$	$T_{(1)R}$	$T_{(2)R}$	$T_{(3)R}$	$T_{(4)R}$
w(s)=Y.(s)		**1**	**1**	**Y.(s)**	**(τ-s)**	$\hat{\mu}(s)$	**1**	**1**	**Y.(s)**	**(τ-s)**	$\hat{\mu}(s)$
25	**0**	0.022	0.070	0.072	0.084	0.060	0.127	0.383	0.394	0.349	0.180
50	**0**	0.018	0.050	0.052	0.061	0.040	0.304	0.556	0.567	0.498	0.296
100	**0**	0.020	0.060	0.059	0.056	0.054	0.655	0.834	0.839	0.743	0.551
25	**0.25**	0.086	0.083	0.085	0.093	0.050	0.256	0.378	0.385	0.375	0.210
50	**0.25**	0.081	0.070	0.072	0.071	0.060	0.441	0.495	0.500	0.449	0.349
100	**0.25**	0.104	0.065	0.068	0.063	0.058	0.711	0.696	0.700	0.637	0.551

Conclusions

- Versions T suitable for not mixed Poisson process
- Robust versions T_R suitable for wide variety of event generating processes (mixed, in particular) but less efficient for small sample size
- Weighting suitable for gaining power in different alternatives

In progress

- Adjustment for covariates
- Sample size formula

Motivating example

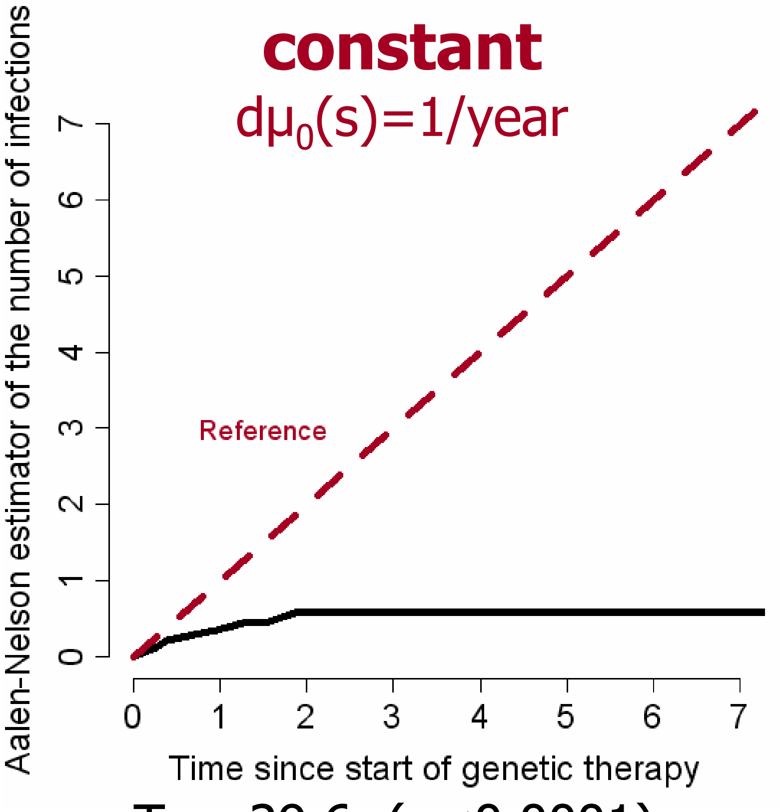
•n=9 ADA-SCID children

-max observation time τ=7.6 years
-total person-years of observation≅39

Reference rate of infections :

constant

$d\mu_0(s)$=1/year

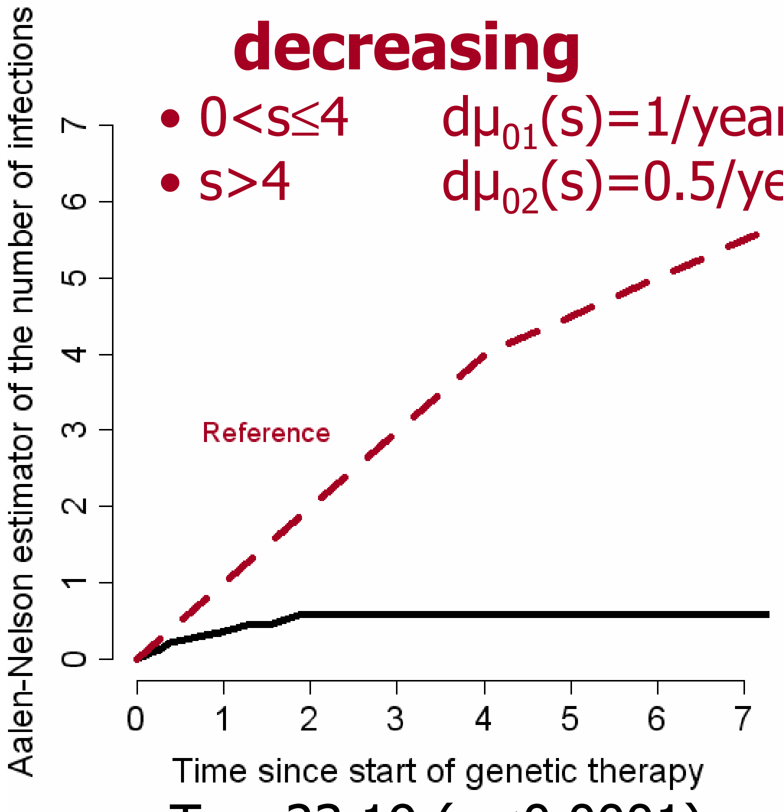


$T_{(1)}$=29.6 (p<0.0001)

$T_{(1)R}$=177.31(p<0.0001)

decreasing

- 0<s≤4 $d\mu_{01}(s)$=1/year
- s>4 $d\mu_{02}(s)$=0.5/year



$T_{(1)}$=23.19 (p<0.0001)

$T_{(1)R}$=115.5 (p<0.0001)

References

- N. E. Breslow "Analysis of Survival Data under the Proportional Hazards Model. International Statistical Review, 43: 45-57; 1975.
- J. F. Lawless and C. Nadeau. Some simple robust methods for the analysis of recurrent events. Technometrics, 37(2), 1995.
- R. J. Cook, J. F. Lawless, and C. Nadeau. Robust tests for treatment comparisons based on recurrent event responses. Biometrics, 52:557 – 571, 1996.

Class of non-parametric one-sample tests

$$U(\tau) = \int_0^{\tau} w(s)\{d\hat{\mu}(s) - d\mu_0(s)\}$$

	w(s)	$T = U^2/var(U)$	$T_R = U^2/var_R(U)$
1	$Y_{\cdot}(s)$	$T_{(1)}$	$T_{(1)R}$
2	$Y_{\cdot}^2(s)$	$T_{(2)}$	$T_{(2)R}$
3	$Y_{\cdot}(s)(\tau-s)$	$T_{(3)}$	$T_{(3)R}$
4	$Y_{\bullet}(s)\hat{\mu}(s)$	$T_{(4)}$	$T_{(4)R}$

Under H_0: $T \sim \chi^2_1$ $T_R \sim \chi^2_1$