

# META-REGRESSION OF PAIRS OF SURVIVAL CURVES UNDER HETEROGENEITY: A POISSON CORRELATED GAMMA FRAILTY APPROACH

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# Outline

**Objective**

**Statistical model**

**Random structure**

**Example**

**Meta-regression**

**Summary**

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## Objective

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## Meta-regression

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## Objective

- ▶ Meta-analysis aims to compare and possibly combine estimates of effect across related trials
- ▶ Single outcome (e.g. treatment effect by means of OR)
- ▶ Produce a single pooled result to aid evidence-based clinical decision making
- ▶ Multivariate outcomes (overall DFS, or multiple treatment groups); required multiple pooled outcomes
- ▶ Simple approach: perform separate univariate analysis for each outcome. But: what about the potential correlations between outcomes?
- ▶ Alternative: multivariate model that jointly synthesizes the multiple outcomes from different studies and obtain all the pooled results collectively

# Multivariate analysis

- ▶ A multivariate meta-analysis model improves efficiency over separate univariate synthesis and allows association between endpoints to be modeled
- ▶ Ex: survival proportions reported at multiple times in different studies are correlated
- ▶ Propose a multivariate random effects model for a joint analysis of multiple outcomes reported at multiple times in different studies
- ▶ Another aspect to be considered is the potential heterogeneity between studies

## Investigate possible causes of heterogeneity

- ▶ The random effects model explicitly accounts for the heterogeneity of studies through a statistical parameter representing the inter-study variation
- ▶ One possibility is to incorporate trial-specific covariates in the model that could explain the differences between the studies
- ▶ **Meta-regression** investigates whether particular covariates explain any of the heterogeneity of treatment effects between studies
- ▶ Aggregated information (mean age, percentage males) can describe the differences between studies
- ▶ We will not go into covariates on the individual level. If such information exists, the data should be analyzed on the individual patient level by hierarchical models

## Multiple outcomes

- ▶ Each trial reports multiple outcomes at a series of time points
- ▶ The information per study is a matrix of time intervals and arm specific hazard  $\lambda_{ij}^A, \lambda_{ij}^B$

Interval	Arm A	Arm B
$I_1$	$\lambda_{i1}^A$	$\lambda_{i1}^B$
...	...	...
...	...	...
$I_J$	$\lambda_{iJ}^A$	$\lambda_{iJ}^B$

- ▶  $i$ : trial index;  $i = 1, \dots, N$
- ▶  $j$ : time interval index  $j = 1, \dots, J$

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## Meta-analytic model

- ▶ To make clear that we take the studies to be random we can write the specific hazards

$$\lambda_{ij}^A = Z_{ij}^A \cdot \lambda_j^A, \quad \lambda_{ij}^B = Z_{ij}^B \cdot \lambda_j^B$$

- ▶  $i$ : study index ( $i = 1, \dots, N$ ) and  $j$ : interval index ( $j = 1, \dots, J$ )
- ▶  $\lambda_j^A$ : hazard of arm A;  $\lambda_j^B$ : hazard of arm B
- ▶  $Z_{ij}^A, Z_{ij}^B$ : random frailty for arm A and B
- ▶ Frailties are gamma distributed with mean 1 and variance  $\xi_A$  and  $\xi_B$
- ▶ To handle this situation we need a "doubly-multivariate" analysis

## Meta-analytic "population"

- ▶ Population parameters:  $(\lambda_1^A, \lambda_1^B, \dots, \lambda_J^A, \lambda_J^B)$
- ▶ A log-linear model can be used to model simultaneously the "baseline" hazard  $\lambda_j^A$  and the interval hazard ratio  $\psi_j = \lambda_j^B / \lambda_j^A$
- ▶  $\psi_j \equiv \psi$ : proportional hazards meta-model
- ▶ Study specific hazard ratio

$$HR_{ij} = \frac{\lambda_{ij}^B}{\lambda_{ij}^A} = \frac{Z_{ij}^B}{Z_{ij}^A} \cdot \psi_j$$

- ▶ Between studies variation:  $Z_{ij}^B / Z_{ij}^A$  (random effects component for each study and each time point)

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## Bivariate gamma-process

- ▶ Model the distribution of the frailty vector by a bivariate gamma-process with mean 1 and (co)variances given by

$$\text{var}(Z_j^A) = \xi_A, \quad \text{var}(Z_j^B) = \xi_B,$$

$$\text{corr}(Z_j^A, Z_{j'}^A) = \rho_{time}^{|j-j'|}, \quad \text{corr}(Z_j^B, Z_{j'}^B) = \rho_{time}^{|j-j'|}$$

$$\text{corr}(Z_j^A, Z_{j'}^B) = \rho_{arm} \cdot \rho_{time}^{|j-j'|}$$

- ▶ These frailties are all time-dependent
- ▶ The variance of the gamma distribution models the heterogeneity between studies

## Piece-wise constant likelihood

- ▶ Assume a piecewise constant hazards model on the intervals, i.e. the hazards  $\lambda_j^A$  and  $\lambda_j^B$  are piecewise constant on the intervals
- ▶ piece-wise constant likelihood

$$\ell = \prod_{intervals_j} \exp(-Z_j \cdot \lambda_j \cdot PY_j) (Z_j \lambda_j)^{D_j}$$

- ▶  $D_j$ : number of events;  $PY_j$ : person-year
- ▶ looks like a  $Poisson(\lambda_j PY_j)$

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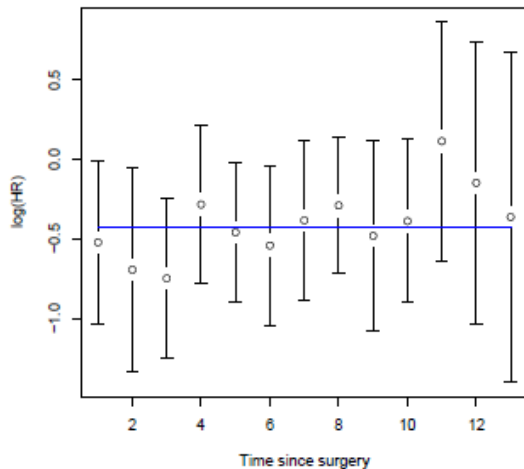
## Application: Breast cancer follow-up

- ▶ N=9 studies with published survival curves
- ▶ Comparison between arms based on the patients without symptoms versus patients with symptoms
- ▶ The purpose was to establish the impact on survival of early detection of a local recurrence of breast cancer as compared to late detection
- ▶ Estimate two random effects models:
  - ▶ time varying treatment effects
  - ▶ constant treatment effects

## Parameter Estimates and SE for time-varying and proportional hazards random effects model

Time	$\lambda_j^A$	$\lambda_j^B$	$\lambda_j^A$	$\lambda_j^B$
1	0.092(0.030)	0.054(0.018)	0.088(0.025)	0.057(0.016)
2	0.130(0.036)	0.065(0.022)	0.116(0.031)	0.076(0.021)
3	0.190(0.057)	0.090(0.028)	0.165(0.046)	0.108(0.029)
.				
12	0.119(0.066)	0.102(0.168)	0.138(0.055)	0.090(0.036)
13	0.103(0.058)	0.071(0.037)	0.107(0.042)	0.070(0.027)
	$\rho_{time} : 0.644(0.170)$		$\rho_{time} : 0.637(0.147)$	
	$\rho_{arm} : 0.983(0.039)$		$\rho_{arm} : 0.983(0.013)$	
	$\xi : 0.652(0.160)$		$\xi : 0.662(0.156)$	
	—		HR: 0.653(0.014)	

# Random effects time-varying and proportional hazards model



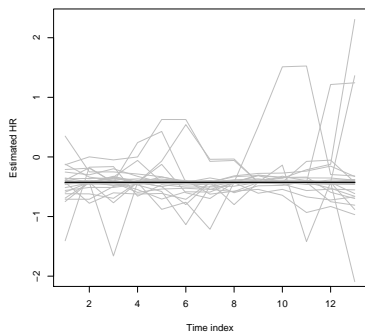
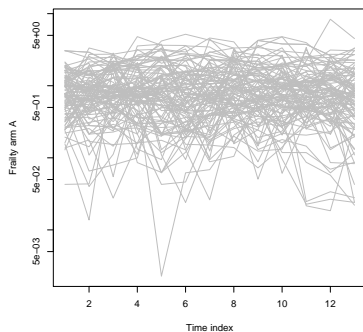
## General model for study specific log hazard ratio

- ▶ log hazard ratio for for each study  $i$  and each point  $j$

$$\log HR_{ij} = \log\left(\frac{Z_{ij}^B}{Z_{ij}^A}\right) + \log(\psi_j)$$

- ▶  $\psi_j = \lambda_j^B / \lambda_j^A$ 
  - ▶ proportional hazard model:  $\psi_j$  is constant over time
  - ▶ time-varying hazard model:  $\psi_j$  is allow to vary over time
- ▶  $Z_{ij}^B / Z_{ij}^A$ : random effect component
  - ▶  $\rho_{time} = 1$ : correlated time-fixed gamma frailties
  - ▶  $\rho_{arm} = 1$  implies  $Z_j^B \equiv Z_j^A$ : there is no random variation in the study specific hazard ratios
  - ▶ More generally the between studies variation in the  $\log(\text{hazard ratio})$  given by  $\log(Z_{ij}^B / Z_{ij}^A)$  will increase with the variance of the frailty; the distribution is complicated but it is possible to simulate

# Random structure implied by the model



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## Random effects meta-regression model

- ▶ Meta-regression aims to investigate whether heterogeneity among results of multiple studies is related to specific characteristics of the studies
- ▶ The random effects meta-regression model allows the inclusion of trial-specific covariates which may explain a part of the heterogeneity

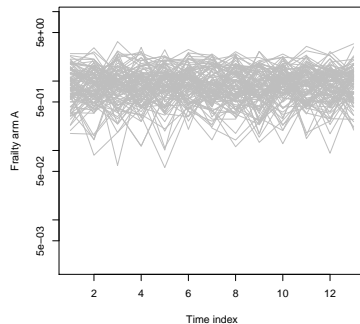
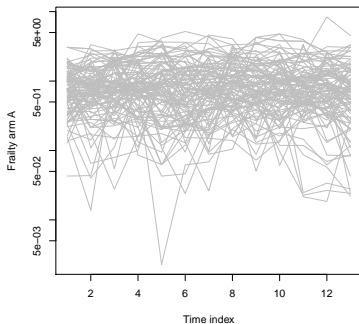
# Random effects proportional hazard models

Fit a meta-regression model that includes year of publication (a proxy for time of conduct of a trial)

- ▶ random effects model:  $\xi = 0.662(0.160)$ ;  
 $\rho_{time} = 0.637(0.147)$ ;  $\rho_{arm} = 0.983(0.013)$
- ▶ meta-regression:  $\xi = 0.336(0.070)$ ;  $\rho_{time} = 0.285(0.840)$ ;  
 $\rho_{arm} = 0.962(0.099)$

Standard errors estimated with sandwich methodology

# Random structure implied by the two models



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## Discussion

- ▶ Standard analysis: apply Cox PH model to obtain an estimate of the ln(hazard ratio)  $\hat{\theta}_i$  and its standard error  $s_i$
- ▶ Apply random effects meta-analysis on the pair  $(\hat{\theta}_i, s_i)$
- ▶ Standard analysis is of course correct, but would miss some important pieces of information
- ▶ Traditional random effects meta-analysis for time-to-event outcomes does not consider the relation between effect and time
- ▶ Model introduced deals with all these aspects

## Discussion

- ▶ This approach allows for heterogeneity between studies and over time and leads to heterogeneity in the (log) hazard ratio which may depend on time
- ▶ It has clearly the advantage of being linked to the popular gamma frailty models
- ▶ Sensitivity analysis (not discussed)
- ▶ Still some work can be done....
- ▶ Develop a test for homogeneity
- ▶ Apply this methodology to model spatial variation between data

# References



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R software used for fitting the correlated gamma-frailty model:  
<http://www.msbi.nl/metaanalysis>