One-Stage Parametric Meta-Analysis of time-to-event Outcomes using Individual Patients Data.

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Motivation

The PH structure is the dominating assumption in individual patient data (IPD) meta-analysis of time-to-event endpoints. However:

- The simplicity with which this model is fit, together with the easy interpretation of the results, makes it "too" popular
- The PH could be seen as a rather restrictive assumption, since it is imposed on a number of studies and not just one
- Not many alternatives to the PH model have been suggested for the analysis of IPD
- There are other issues that render time-to-event data different to other types of data used in meta-analyses (potentially informative censoring, competing risks)

Measure of Treatment Efficacy

By considering data structures other than the PH, the log-hazard ratio may no longer be suitable as the main measure of treatment effect.

Therefore, we introduce the ratio of the k^{th} percentiles of the survival distributions of the two groups under investigation

$$q_k = \frac{k^{th} \text{ percentile of treatment group}}{k^{th} \text{ percentile of control group}},$$

as the quantity of interest within the meta-analysis framework $[k \in (0,1)]$.

This quantity is defined for a binary covariate, like the treatment identifier, and provides a relative measure for the treatment effect at each point on the survival probability axes.

Parametric Model

1. Consider a two parameter distribution $f(t; b, \mathbf{u}|\mathbf{x})$, where b is the shape parameter and if x is the treatment covariate then: $\underline{\mathbf{u} = \mu + vx}$.

2. Irrespectively of the choice of $f()$, we can reparameterize it so that

$$v = g(q_k, b, \mu).$$

3. Thus, every distribution $f(t; b, \mathbf{u}|x)$ can be re-expressed as $f(t; b, \mu, q_k|x)$, with q_k now being part of the parameterization of the distribution, for given k.

$\Rightarrow$ Quantity q_k is of interest for meta-analysis purposes. It has: (i) clear interpretation and (ii) its scale does not depend on the choice of distribution $f()$ or indeed any other features of the data being analyzed.

Likelihood Inference

- Assume that $f_i(t; b_i, \mathbf{u}_{ij}|x)$ is the distribution that fits the data in study i $(i = 1 \ldots N,\ j = 1 \ldots n_i)$, where: $\underline{\mathbf{u}_{ij} = \mu_i + v_i x_{ij}}$.

- By reparameterization, the distribution of study i becomes $\underline{f_i(t; b_i, \mu_i, q_k^i|x_{ij})}$.

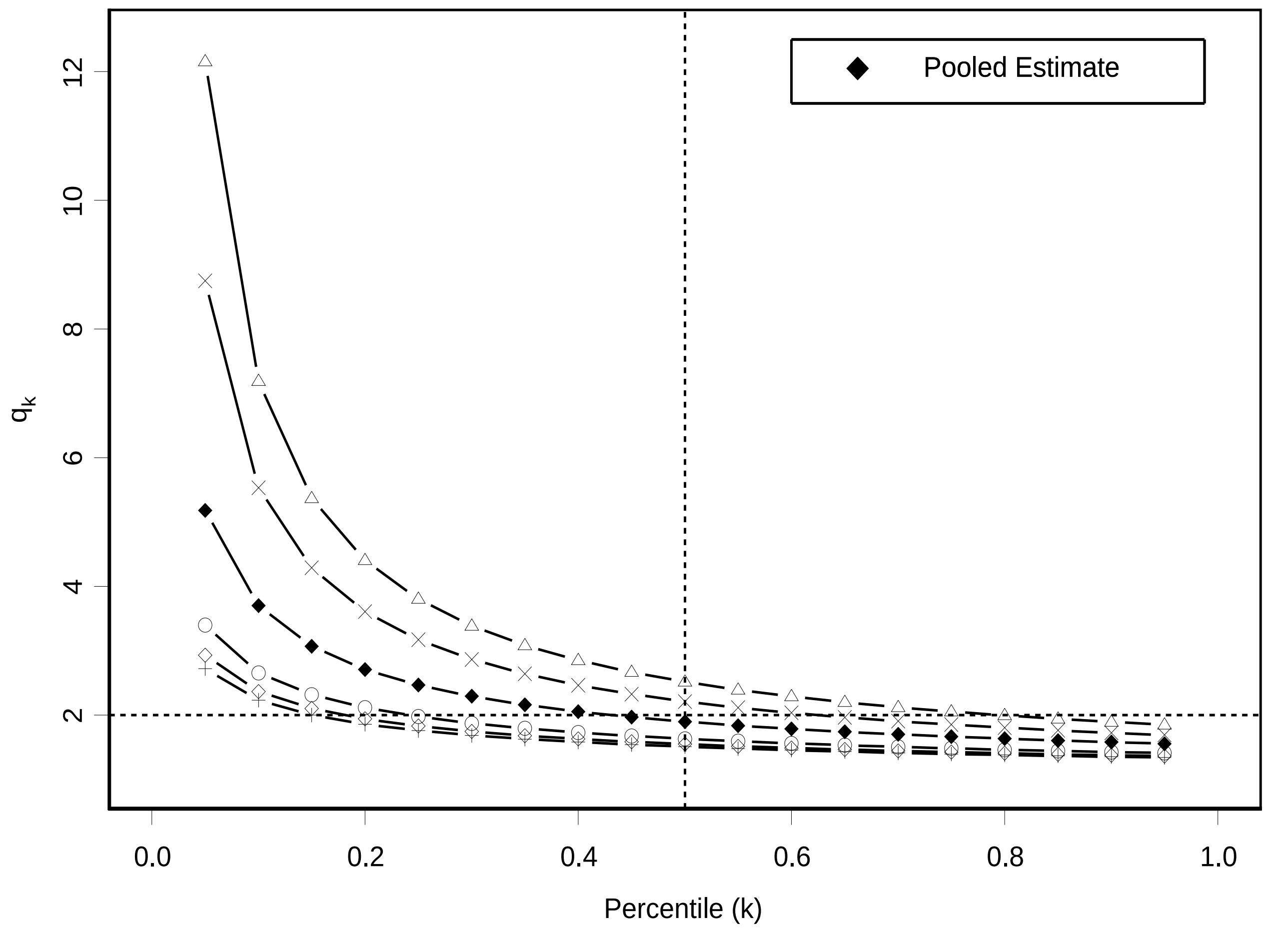
- Allow $\underline{q_k^i = q_k}$, to be the same across studies (common treatment effect).

- The remaining parameters are allowed to be study specific.

- Then, for fixed effects, the likelihood function takes the form

$$L(q_k) = \prod_{i=1}^{N} \prod_{j=1}^{n_i} f_i(t_{ij}; b_i, \mu_i, q_k|x_{ij})^{I_{ij}} S_i(t_{ij}; b_i, \mu_i, q_k|x_{ij})^{1-I_{ij}},$$

where I_{ij} is the usual indicator variable for terminal events.


Pooled Estimate
q_k
12
10
8
6
4
2
0.0
0.2
0.4
0.6
0.8
1.0
Percentile (k)

Log-Location-Scale Models

If $Y = \log T$, we can express the LLS as a regression model

$$Y = \mu + vx + bE$$

where $E \sim$ a suitable pdf. Simple calculations reveal that

$$S_0\left(\frac{\log t_1^k - \mu - v}{b}\right) = k = S_0\left(\frac{\log t_2^k - \mu}{b}\right) \quad \Rightarrow \quad q_k = \frac{t_1^k}{t_2^k} = \exp(v).$$

1. LLS are AFT models, and q_k is equal to the *acceleration factor*.

2. If $f_i(t; b_i, \mathbf{u}_{ij}|x)$ is of a LLS structure, then reparameterization is as simple as $\underline{q_k = \exp(v)}$, which means that we effectively set the treatment regression coefficients to be common across studies.

The Extended Log-Gamma Model

A general case would be the regression model with error p.d.f.

$$\begin{cases} |\gamma|(\gamma^{-2})^{\gamma^{-2}} \exp\{\gamma^{-2}(\gamma w - \exp(\gamma w))\}/\Gamma(\gamma^{-2}) & \gamma \neq 0 \\ (2\pi)^{-\frac{1}{2}} \exp(-\frac{1}{2}w^2) & \gamma = 0 \end{cases},$$

where $w = \frac{Y-\mu-vx}{b}$.

- This distribution is an extension to the log-gamma model by allowing $\gamma < 0$, with the p.d.f. at $-\gamma$ being a reflection about the origin of that at γ [Prentice(1974)].
- Special cases for $T = e^Y$ are (i) Weibull $(\gamma = 1)$, (ii) exponential $(\gamma = b = 1)$, (iii) log-normal $(\gamma = 0)$, (iv) gamma $(b = 1, \gamma > \frac{1}{b})$, (v) generalized gamma $(\gamma > 0)$ and (vi) reciprocal Weibull $(p = -1)$.
- By estimating γ we avoid making assumptions about the distribution of E in each study, allowing the data to influence the choice.

Simulation Study

- Meta-analysis of 5 studies, with $N = 200$, 100 in each arm – 500 replications.
- Censoring is assumed random and exponentially distributed (up to 50%).
- Data are generated based on the extended log-gamma model, where the survival percentile ratio is assumed equal to 2 for every study (reg coef: $\log(2) = 0.6931$).
- The remaining parameters of the error distribution are allowed to take values

	q	μ	b
sim A1	(0.3, 0.6, 0.9, 1.2, 1.5)	(7,7,7,7,7)	(1,1,1,1,1)
sim A2	(0.3, 0.6, 0.9, 1.2, 1.5)	(4,9,7,3,8)	(1,1,1,1,1)
sim A3	(0.3, 0.6, 0.9, 1.2, 1.5)	(4,9,7,3,8)	(1.5,0.6,1.2,0.8,1.1)
sim B1	(-2, -1, 0.3, 1, 2)	(7,7,7,7,7)	(1,1,1,1,1)
sim B2	(-2, -1, 0.3, 1, 2)	(4,9,7,3,8)	(1,1,1,1,1)
sim B3	(-2, -1, 0.3, 1, 2)	(4,9,7,3,8)	(1.5,0.6,1.2,0.8,1.1)

	Stratified Analysis			Single Study Analysis			
	Weib	LN	LL	Weib	LN	LL	ELG
sim A1 (0%)	0.6950 (0.0670)	0.6931 (0.0780)	0.6937 (0.0821)	0.6944 (0.0691)	0.6929 (0.0772)	0.6937 (0.0821)	0.6928 (0.0701)
sim A1 (20%)	0.6971 (0.0739)	0.6968 (0.0811)	0.6997 (0.0906)	0.6960 (0.0749)	0.6966 (0.0803)	0.6994 (0.0913)	0.6966 (0.0723)
sim A1 (40%)	0.6893 (0.0810)	0.6898 (0.0932)	0.6885 (0.1063)	0.6891 (0.0832)	0.6904 (0.0932)	0.6885 (0.1084)	0.6909 (0.0858)
sim A2 (0%)	0.6947 (0.0676)	0.6951 (0.0794)	0.6959 (0.0863)	0.6947 (0.0896)	0.6970 (0.0907)	0.6959 (0.0863)	0.6945 (0.0707)
sim A2 (20%)	0.6936 (0.0699)	0.6957 (0.0798)	0.6953 (0.0868)	0.6947 (0.1075)	0.6948 (0.1221)	0.6955 (0.1143)	0.6950 (0.0710)
sim A2 (40%)	0.6973 (0.0838)	0.6935 (0.0904)	0.6920 (0.1033)	0.6956 (0.1485)	0.6926 (0.1672)	0.6901 (0.1586)	0.6939 (0.0822)
sim A3 (0%)	0.6955 (0.0720)	0.6973 (0.0734)	0.6966 (0.0842)	0.6941 (0.0702)	0.6960 (0.0943)	0.6966 (0.0842)	0.6955 (0.0594)
sim A3 (20%)	0.6925 (0.0763)	0.6948 (0.0846)	0.6965 (0.0966)	0.6984 (0.1030)	0.7016 (0.1327)	0.7012 (0.1216)	0.6919 (0.0660)
sim A3 (40%)	0.6941 (0.0832)	0.6930 (0.0930)	0.6906 (0.1087)	0.6941 (0.1353)	0.6980 (0.1737)	0.6966 (0.1627)	0.6909 (0.0749)

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sim A3 (40%)	0.6941 (0.0832)	0.6930 (0.0930)	0.6906 (0.1087)	0.6941 (0.1353)	0.6980 (0.1737)	0.6966 (0.1627)	0.6909 (0.0749)

	Stratified Analysis			Single Study Analysis			
	Weib	LN	LL	Weib	LN	LL	ELG
sim B1 (0%)	0.6880 (0.3199)	0.6903 (0.0921)	0.6893 (0.1092)	0.6865 (0.4562)	0.6897 (0.0807)	0.6893 (0.1092)	0.6893 (0.0738)
sim B1 (20%)	0.6739 (0.0989)	0.6918 (0.0896)	0.6892 (0.1019)	0.6564 (0.1395)	0.6922 (0.0848)	0.6884 (0.1059)	0.6891 (0.0725)
sim B1 (40%)	0.6965 (0.0926)	0.6945 (0.0911)	0.6948 (0.1061)	0.6940 (0.1132)	0.6935 (0.0938)	0.6932 (0.1169)	0.6944 (0.0755)
sim B2 (0%)	0.6922 (0.3320)	0.6988 (0.0830)	0.6992 (0.1004)	0.6873 (0.2396)	0.7028 (0.1004)	0.6992 (0.1004)	0.6964 (0.0703)
sim B2 (20%)	0.6978 (0.1010)	0.6962 (0.0895)	0.6987 (0.1021)	0.6961 (0.1374)	0.7020 (0.1283)	0.7005 (0.1259)	0.6985 (0.0726)
sim B2 (40%)	0.6913 (0.0958)	0.6910 (0.0963)	0.6921 (0.1101)	0.6814 (0.1613)	0.6893 (0.1681)	0.6867 (0.1657)	0.6939 (0.0750)
sim B3 (0%)	0.7178 (0.5191)	0.6939 (0.0866)	0.6958 (0.1175)	0.7168 (0.5623)	0.6956 (0.1195)	0.6958 (0.1175)	0.6929 (0.0605)
sim B3 (20%)	0.6884 (0.1103)	0.6933 (0.0918)	0.6922 (0.1106)	0.6866 (0.1256)	0.6888 (0.1411)	0.6888 (0.1334)	0.6967 (0.0658)
sim B3 (40%)	0.6987 (0.0937)	0.6994 (0.0946)	0.7027 (0.1127)	0.7041 (0.1370)	0.7043 (0.1632)	0.7047 (0.1577)	0.6977 (0.0667)

	Coverage Probabilities						
	Stratified Analysis			Single Study Analysis			
	Weib	LN	LL	Weib	LN	LL	ELG
sim A1 (0%)	0.952	0.956	0.956	0.94	0.96	0.958	0.96
sim A1 (20%)	0.934	0.954	0.954	0.934	0.958	0.956	0.964
sim A1 (40%)	0.952	0.95	0.946	0.952	0.952	0.948	0.962
sim A2 (0%)	0.93	0.938	0.934	0.998	0.998	0.998	0.946
sim A2 (20%)	0.958	0.952	0.958	1	0.996	0.998	0.964
sim A2 (40%)	0.952	0.956	0.962	0.982	0.988	0.992	0.964
sim A3 (0%)	0.944	0.962	0.958	1	1	1	0.958
sim A3 (20%)	0.944	0.956	0.956	1	0.998	0.998	0.962
sim A3 (40%)	0.954	0.946	0.942	0.998	1	0.998	0.958
sim B1 (0%)	0.95	0.932	0.93	0.502	0.98	0.966	0.952
sim B1 (20%)	0.924	0.956	0.948	0.89	0.974	0.974	0.956
sim B1 (40%)	0.93	0.964	0.95	0.94	0.986	0.978	0.958
sim B2 (0%)	0.51	0.954	0.954	0.87	1	1	0.96
sim B2 (20%)	0.916	0.96	0.952	0.992	1	1	0.954
sim B2 (40%)	0.94	0.954	0.942	0.986	1	1	0.946
sim B3 (0%)	0.416	0.976	0.956	0.57	1	1	0.976
sim B3 (20%)	0.914	0.958	0.948	0.992	0.996	0.992	0.954
sim B3 (40%)	0.946	0.954	0.974	0.996	0.99	0.998	0.954

Summary

- We introduce a new measure for treatment efficacy.

- A parametric approach for meta-analysis is described, where all the studies contribute to the estimation of the common treatment effect (q_k) through likelihood $L(q_k)$.

- The structure of the data in the individual studies is taken into account.

- Covariates are easily incorporated.

- Extension to random treatment effects is possible.

Hierarchical Model

So far we have considered the model

$$Y_{ij} = \mu_i + v_k x_{ij} + b_i E$$

Prior distributions for $\mu_i,\ v_k$ and b_i,

which describes the fixed effects model. An obvious extension is

$$Y_{ij} = \mu_i + v_{ik} x_{ij} + b_i E$$

$$v_{ik} = v_k + g_i$$

$$g_i \sim N(0, \tau^2)$$

Prior distributions for $\mu_i,\ b_i,\ v_k$ and τ,

where $v_k = \log(q_k)$ is the average log-PR for given k.