Failure-Time Mixture Models for Analyzing Time to Response

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Time to onset of benefit/response

Motivation for topic arises from depression

- Current antidepressants take several weeks to obtain a meaningful response
- Fast onset is important unmet need in MDD
  - Patients in the throes of severe symptomatic exacerbation are at risk for days to weeks before experiencing resolution
  - faster onset of action would improve compliance
- This has compelled one to develop drugs with potential for early onset
- How does one assess time to onset and compare 2 treatments
- In depression, there has been much discussion on this topic and no strong consensus on the best analytical approach

In studies of many indications, one collects information longitudinally according to a planned schedule (i.e., weekly, hourly), and if the visits are frequent enough

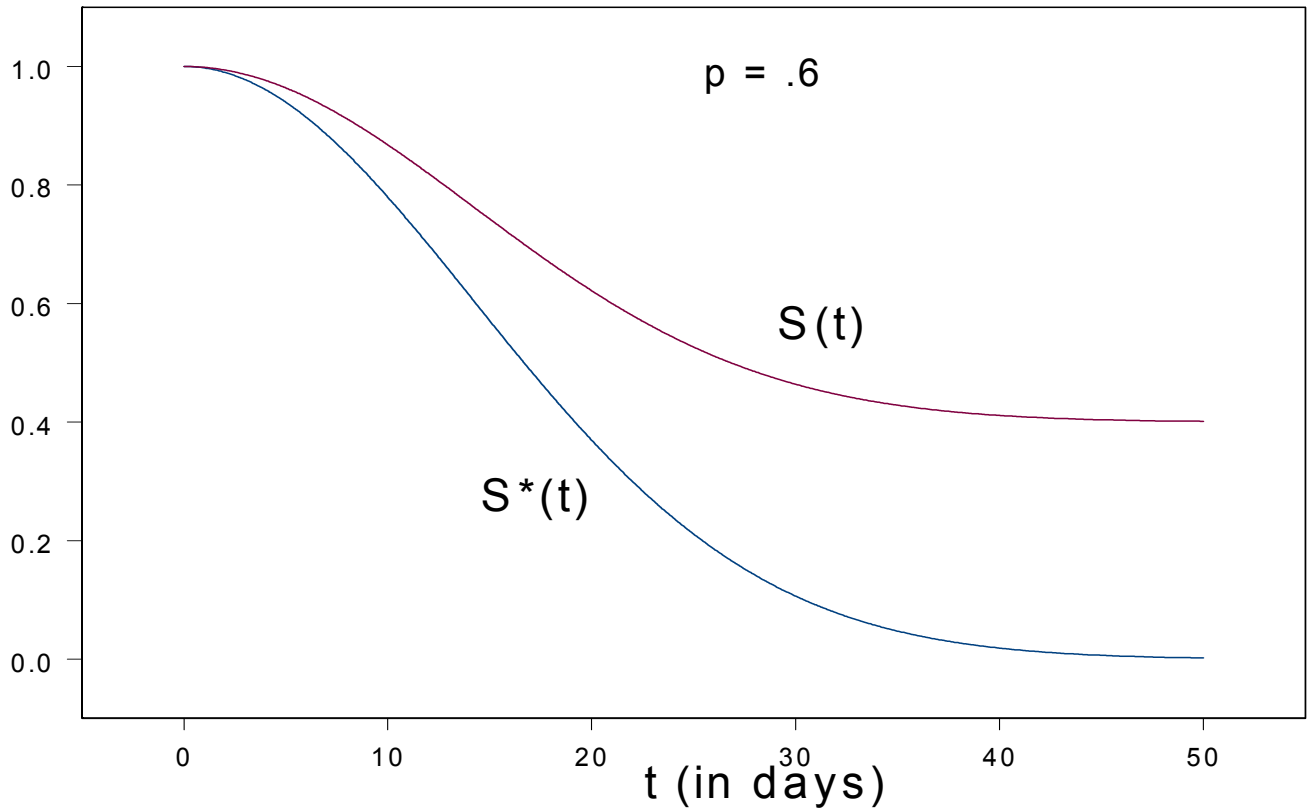
- the onset of action can be assessed by an analysis of the data at early visits
  - i.e., time of onset or response might be considered the time of the first visit when one rejects $\mu_A = \mu_{PBO}$ or $\pi_A = \pi_{PBO}$
  - But difference from pbo need to be sustained at all subsequent visits?
- Many statisticians (Leon, 2001, Mallinckrodt) have recommended the approach above using MMRM (at least in depression)

- Early/Earlier response means **LESS TIME** to response
  - if response can be defined (in terms of a binary variable)
- This compels one to compare the distribution of time to response between/among treatments; i.e. SURVIVAL ANALYSIS METHODS
- But "ordinary" survival analysis is sensitive to both time to response and proportion that respond over a sufficiently long-time period
- If we reject $H_0 : S_2(t) = S_1(t)$ it is either because proportion that respond are different and/or time to response conditional on response is different. Example from Tamura (2000):
- Trt 1: 80% respond all at week 3. Trt 2: 60% respond all at week 3
- For large sufficiently large N, log-rank would be statistically significant
- But misleading to state trt 1 works faster than trt 2

Mixture survival models for the analysis of time to response in depression - Laska & Siegel (Psychopharmacology Bulletin,1995)

- Paradigm: population is a mixture of responders & nonresponders.
- Two properties needed to characterize response to a treatment:
  1. p - the proportion that respond ($\geq$50% decrease in B.L HAMD)
  2. S^* - the distribution of time to response conditional on response
- Try to estimate 1 & 2 for two or more treatments by conducting a RCT
- Moreover for 2 treatments say, want to test: $p_1 = p_2$ and $S_1^* = S_2^*$
- In the presence of dropouts, even testing of $p_1 = p_2$ is not trivial
- Focus of this talk will be on testing $S_1^* = S_2^*$
  - Need to incorporate data from dropouts as this provides information

- For some trt, in a mixed population of responders and nonresponders, denote $S(t) = \Pr\{T>t\}$
- Denote $S^*(t) = \Pr\{T>t\}$ among those that will respond to this treatment
- Let p be the probability of response (i.e., the proportion that respond). It is assumed that those that respond will respond by at least time u
- $S^*(t)=\Pr\{T>t|T\le u\}=\frac{P(t<T\le u)}{P(T\le u)}=\frac{P(T\le u)-P(T\le t)}{P(T\le u)}=\frac{p-\{1-S(t)\}}{p}=\frac{S(t)-(1-p)}{p}$

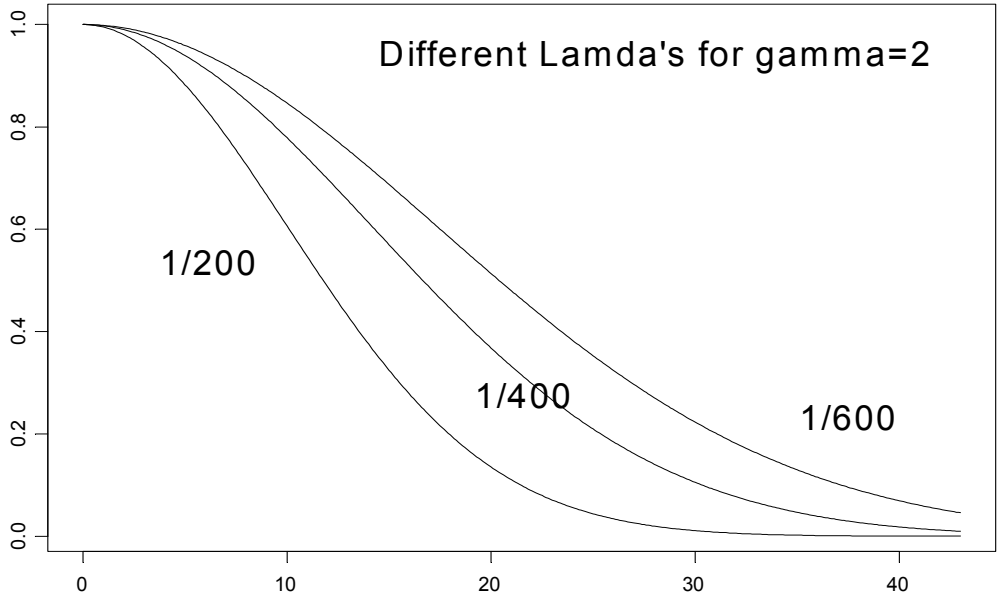


Estimating S_1^* and S_2^*, and then testing $S_1^* = S_2^*$

- Nonparametric methods (no strong distributional assumptions)
  - use product limit or Kaplan–Meier (KM) methods for estimation
  - to test $S_1^* = S_2^*$
    - weighted log-rank statistic
    - Cramer-von Mises statistic
- Parametric mixture methods models
  - Use logistic regression to estimate p_1 and p_2 or a common p
  - Use “time to event" distributions to estimate S_1^* and S_2^*
  - fit a model with a common $\widehat{S}^*$, then fit a model resulting in $\widehat{S}_1^*$ and $\widehat{S}_2^*$–statistically evaluate the change in the likelihood
- Semiparametric mixture models
  - Extension of the Cox P.H. model (Sy and Taylor 2000, Peng and Dear 2000, Li 2010). Will not be covering in this presentation.

Parametric Mixture Model Approach Using Common Event Time Distributions such as the Weibull or Loglogistic

- Weibull distribution is as central to parametric survival analysis as the normal distribution is to linear models. Some details about the Weibull; for $t, \lambda, \gamma > 0$
- $S(t) = e^{-\lambda t^{\gamma}} \qquad f(t) = \lambda\gamma t^{\gamma-1} e^{-\lambda t^{\gamma}} \qquad h(t) = \lambda\gamma t^{\gamma-1}$
- γ is the shape parameter and λ is the scale parameter; as $\lambda \uparrow, S^{*}(t) \downarrow \forall\ t$



Consider a Weibull mixture model in the case of two treatments

- Model the probability of response with a logistic regression model
  - $\log \frac{p_i}{1-p_i} = \beta_0 + \beta_1 X_i$ where $p_i = \Pr(Y_i = R)$

$$\Pr(Y = R) = f(y) = \frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)} \text{ where } X = \begin{cases} 1 \text{ if trt=1} \\ 0 \text{ if trt=2} \end{cases}$$

- For responders, model the time to response with a Weibull

$$f(t|Y = R) = \psi^X \lambda \gamma t^{\gamma-1} e^{-\psi^X \lambda t^\gamma} \text{ where } X = \begin{cases} 1 \text{ if trt=1} \\ 0 \text{ if trt=2} \end{cases}$$

Note that the scale parameter for trt 1 is $\psi\lambda$, for trt 2 it is $\lambda \Rightarrow$ if ψ>1, $S_1^*(t)<S_2^*(t)\ \forall\ t$

And $S_1^*(t) = e^{-\psi\lambda t^\gamma} = (e^{-\lambda t^\gamma})^\psi = \{S_2^*(t)\}^\psi \Rightarrow \frac{h_1^*(t)}{h_2^*(t)} = \psi$

- Interpretation: among the responders that have yet to respond, the chance of responding at any particular time, is ψ times greater in trt 1 than trt 2
- This Weibull model is not only a (conditional) proportional hazards model but it is also a conditional accelerated failure time model
- This means the response time for one treatment is a multiple of the response time for another treatment
- Specifically $S_1^*(t) = S_2^*(\phi t)$ where ϕ is the acceleration factor

  $\Rightarrow$ Proportion of responders that respond by t in trt 1 is equal to the proportion of responders that respond by ϕt in trt 2

  $\Rightarrow$ Among responders, the time in which the proportion π respond is ϕ times greater in trt 2 than trt 1
- To show that the mixture Weibull model is also an accelerated failure time model, note that
- $S_1^*(t) = S_2^*(\phi t) = e^{-\lambda(\phi t)^\gamma} = e^{-\phi^\gamma \lambda t^\gamma}$
- Recall, $S_1^*(t) = e^{-\psi \lambda t^\gamma} \Rightarrow \psi = \phi^\gamma$, or $\phi = \psi^{1/\gamma}$

- Maximum Likelihood procedures to estimate S_1^*, S_2^* and to test $S_1^* = S_2^*$

First fit a null model assuming a common S^* i.e., $\theta_{null} = [\beta_0, \beta_1, \gamma, \lambda]'$

Then fit an expanded alternative model allowing a different S^* for each treatment, i.e., $\theta_{alt} = [\beta_0, \beta_1, \gamma, \lambda, \psi]'$.

Specifically, the construction of the likelihood for estimating θ_{alt}

- A completing nonresponder's contribution to the likelihood is:

$$\frac{1}{1 + \exp(\beta_0 + \beta_1 X)}$$

- A responder's (who responded at time t) contribution to the likelihood is:

$$\frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)} * \psi^X \lambda \gamma t^{\gamma - 1} e^{-\psi^X \lambda t^\gamma}$$

- A nonresponding dropout (at time t) contributes this to the likelihood:

$$\frac{1}{1 + \exp(\beta_0 + \beta_1 X)} + \frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)} * e^{-\psi^X \lambda t^\gamma}$$

- Maximize the log of the joint likelihood with respect to $\boldsymbol{\theta}_{alt}$ given the data
- No closed form solution: need interative procedure
- Implement Newton-Ralphson with PROC NLP
- Similarly fit the null model, i.e., maximize log of the joint likelihood with respect to $\boldsymbol{\theta}_{null}$ given the data
- A test of $S_1^* = S_2^*$ vs $S_1^* \neq S_2^*$ is based on two times the difference in the maximized log likelihoods which is asymtotically chi-square with 1 d.f.

$$2\{logf(\hat{\boldsymbol{\theta}}_{alt}|\mathbf{t},\mathbf{x}) - logf(\hat{\boldsymbol{\theta}}_{null}|\mathbf{t},\mathbf{x})\} \sim \boldsymbol{\chi}_1$$

Mixture Model Using the Loglogistic Distribution

- Model using the Weibull assumes PH, and the hazard is monotonic
- A loglogistic distribution allows for departures from PH
  - Instead, a proportional odds assumption will be imparted
- Loglogistic permits a unimodel hazard
- $S(t) = \frac{1}{1+(t\rho)^{\kappa}}$ $f(t) = \frac{\kappa t^{\kappa-1}\rho^{\kappa}}{[1+(t\rho)^{\kappa}]^2}$ $h(t) = \frac{\kappa t^{\kappa-1}\rho^{\kappa}}{1+(t\rho)^{\kappa}}$ for $t, \rho, \kappa > 0$
- note that as $\rho \uparrow, S^*(t) \downarrow \forall\ t$

Consider a loglogistic mixture model in the case of two treatments

- As before, model the probability of response with a logistic regression model
  - $\log \frac{p_i}{1-p_i} = \beta_0 + \beta_1 X_i$ where $p_i = \Pr(Y_i = R)$

$$\Pr(Y = R) = f(y) = \frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)} \text{ where } X = \begin{cases} 1 \text{ if trt=1} \\ 0 \text{ if trt=2} \end{cases}$$

- For responders, model the time to response with a loglogistic distribution

$$f(t|Y = R) = \frac{\kappa t^{\kappa-1}(\phi^X \rho)^\kappa}{[1 + (t\phi^X \rho)^\kappa]^2} \text{ where } X = \begin{cases} 1 \text{ if trt=1} \\ 0 \text{ if trt=2} \end{cases}$$

Note that “scale" parameter for trt 1 is $\phi\rho$, for trt 2 it is $\rho \Rightarrow$ if ϕ>1, $S_1^*(t) < S_2^*(t) \ \forall \ t$

- Maximum Likelihood procedures to estimate S_1^*, S_2^* and to test $S_1^* = S_2^*$

First fit a null model assuming a common S^* i.e., $\theta_{null} = [\beta_0, \beta_1, \kappa, \rho]'$

Then fit an expanded alternative model allowing a different S^* for each treatment, i.e., $\theta_{alt} = [\beta_0, \beta_1, \kappa, \rho, \phi]'$.

Specifically, the construction of the likelihood for estimating θ_{alt}

- A completing nonresponder's contribution to the likelihood is:

$$\frac{1}{1 + \exp(\beta_0 + \beta_1 X)}$$

- A responder's (who responded at time t) contribution to the likelihood is:

$$\frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)} * \frac{\kappa t^{\kappa-1} (\phi^X \rho)^\kappa}{[1 + (t\phi^X \rho)^\kappa]^2}$$

- A nonresponding dropout (at time t) contributes this to the likelihood:

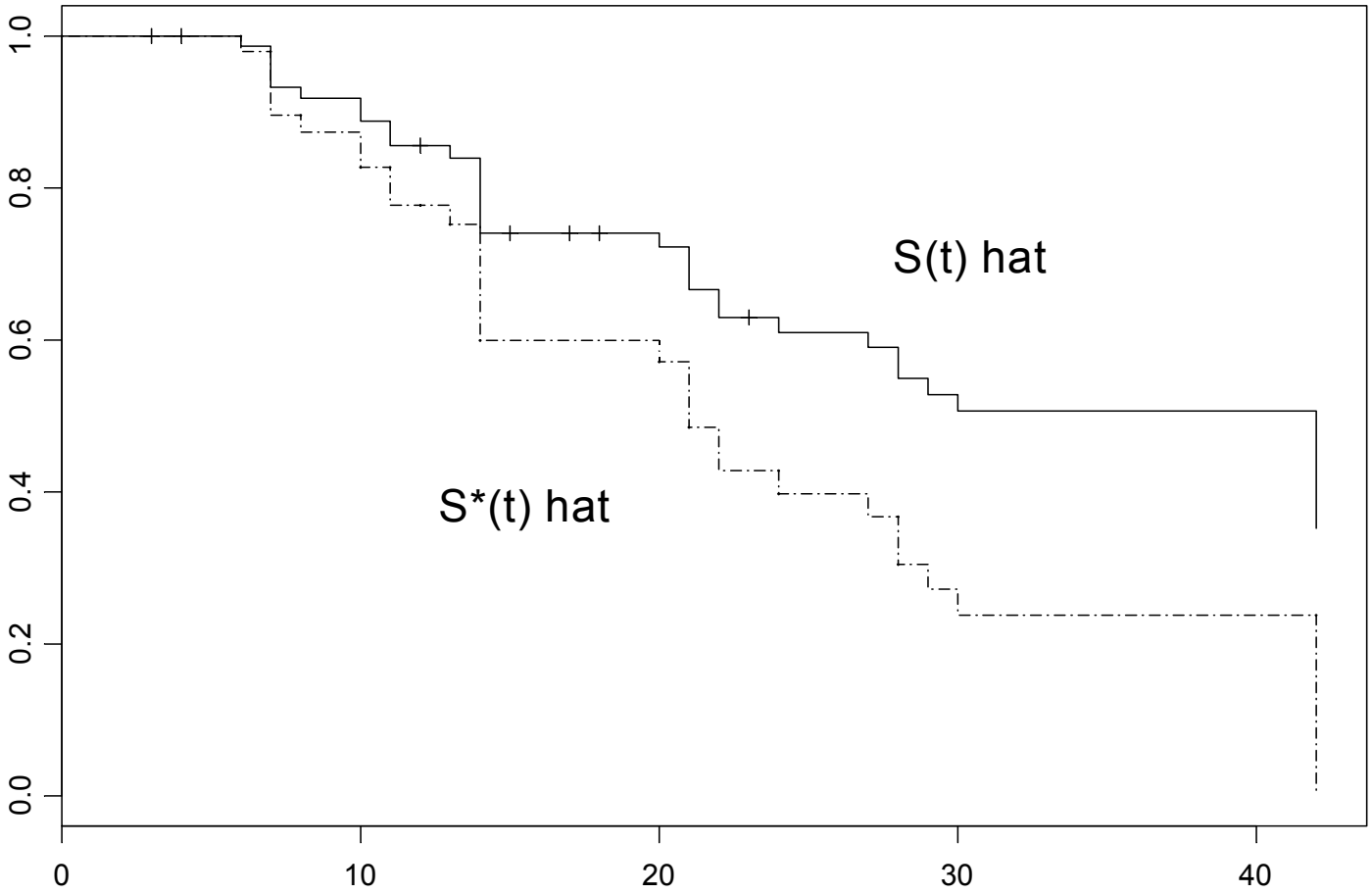
$$\frac{1}{1 + \exp(\beta_0 + \beta_1 X)} + \frac{\exp(\beta_0 + \beta_1 X)}{1 + \exp(\beta_0 + \beta_1 X)} * \frac{1}{1 + (t\phi^X \rho)^\kappa}$$

- Since $S_1^*(t) = \frac{1}{1+(t\phi\rho)^\kappa} = S_2^*(\phi t)$, this loglogistic model is a conditional accelerated failure time model
  - Interpretation: Among responders, the time in which proportion π response in trt 2 is ϕ times greater than that of trt 1
- To show that the mixture loglogistic model is also a proportional odds model, note that
- $1 - S_1^*(t) = \frac{(t\phi\rho)^\kappa}{1+(t\phi\rho)^\kappa}$ and that $\frac{1-S_1^*(t)}{S_1^*(t)} = (t\phi\rho)^\kappa$
- Likewise, $\frac{1-S_2^*(t)}{S_2^*(t)} = (t\rho)^\kappa \Rightarrow$ odds ratio is ϕ^κ
- Interpretation: among responders, the odds of responding prior to time t, is ϕ^κ times greater for trt 1 than for trt 2

Nonparametric estimation of $\widehat{S^*}$(t)

$\widehat{S_1^*}(t) = \frac{\hat{S}_1(t)-(1-\hat{p}_1)}{\hat{p}_1}$ where $\hat{S}_1$, $\hat{p}_1$ are obtained from KM methods

KM Estimates of S(t) and S*(t) for one Treatment



Nonparametric tests for $S_1^* = S_2^*$

- If $p_1 = p_2$, then a test of $S_1 = S_2$ is a test of $S_1^* = S_2^*$
  - since $S_1^* = S_2^*$ if and only if $S_1 = S_2$
- If assume $p_1 = p_2$ (perhaps, after testing) test $S_1 = S_2$ with logrank test
- But logrank test of $S_1^* = S_2^*$ (when $p_1 = p_2$) it will be highly inefficient (e.g., power of .2 when more appropriate methods will have a power of .9)
- Why? Log-rank test is most powerful in the case of "proportional hazards". But in a mixture of responders and nonresponders in which $p_1 = p_2$, this condition is violated big time
- When $p_1 = p_2$ Orazem (Ph.D. Thesis, Columbia University, 1991) proposed a weighted log-rank test under the assumption of proportional conditional hazards

- When $p_1 = p_2$, the Orazem's weighted log-rank test is

$$\mathsf{T}_{WLR} = \frac{\sum w(t_k)\{d_{1k} - E_{1k}\}}{\sqrt{\sum w^2(t_k) Var(d_{1k})}} \quad \text{where } w(t_k) = 1 - \Lambda_1^*(t)\frac{S_1(u)}{S_1(t)}$$

- $w(t_k)'s$ are optimal weights when $\frac{h_2^*(t)}{h_1^*(t)} = \psi$ for all $t \in (0, u)$
- under the null, an estimator of $w(t_k)$ is $\widehat{w}_{t_k} = 1 - \frac{\widehat{S}(u)}{\widehat{S}(t_k)} \sum_{i=1}^{k} (d_i / n^*(t_i))$
- $n^*(t_i) = \sum_{t_k \geq t_i} \{c_k + (1 - c_k)(1 - \frac{\widehat{S}(u)}{\widehat{S}(t_k)})$ is the est # of responders at "risk" at t_i
- numerator in T_{WLR} can be shown to be equal $\sum_k \{d_{1k} - d_k \frac{n_1^*(t_k)}{n^*(t_k)}\}$
- Under the null, with no ties, T_{WLR} converges in distrib. to N(0,1)

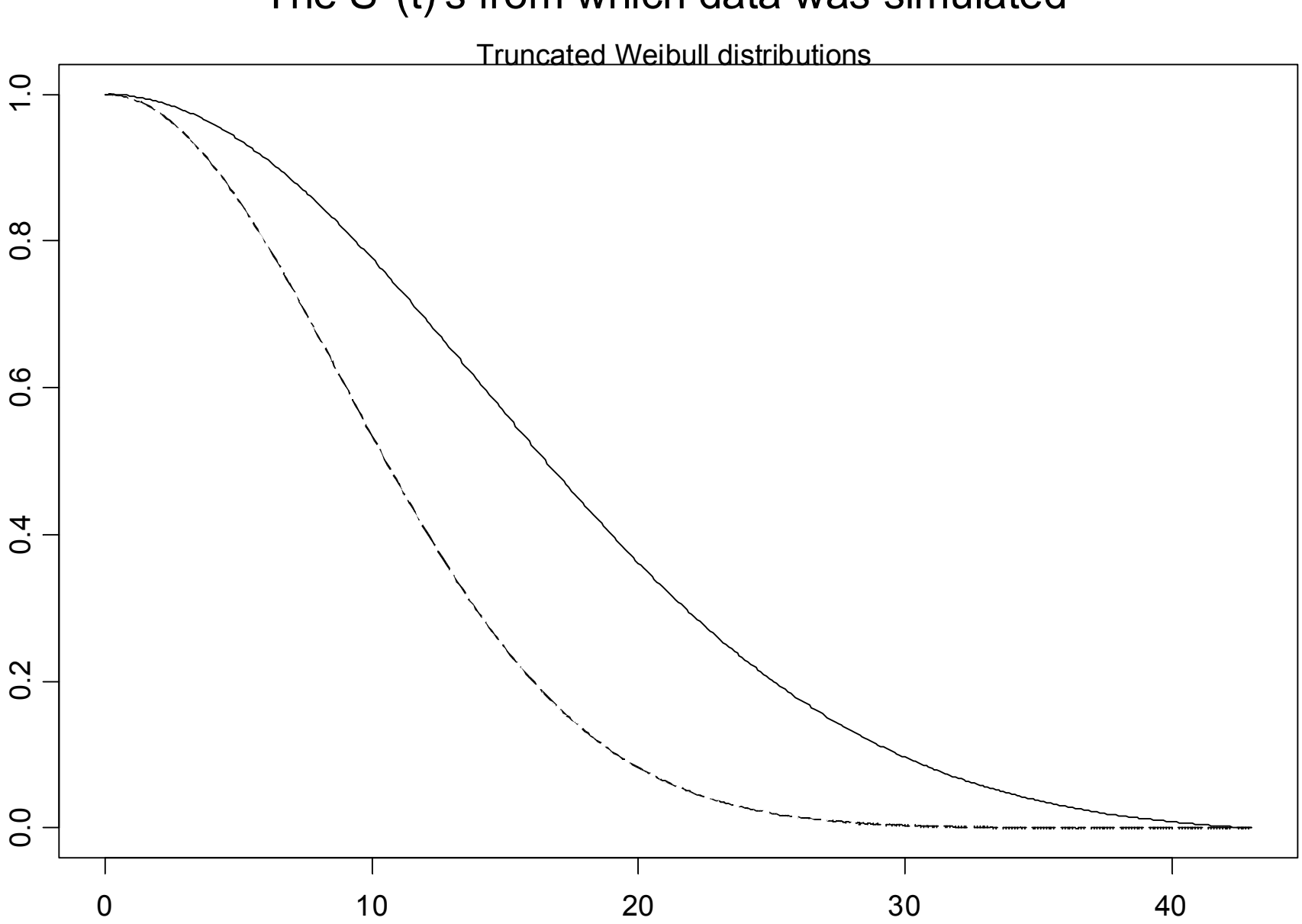
Tamura, et.al (Statistics in Medicine, 2000)

- Use a Cramer-von Mises test statistic to test $S_1^* = S_2^*$
- $W^2 = -(n_1\hat{p}_1)(n_2\hat{p}_2)/(n_1\hat{p}_1 + n_2\hat{p}_2)\int[\widehat{S^*}_1(t) - \widehat{S^*}_2(t)]^2 d\widehat{S^*}(t)$
- where $\widehat{S^*}(t) = \sum n_i\hat{p}_i\widehat{S^*}_i(t)/\sum n_i\hat{p}_i$ is the est. of the common S*(t)
- Tamura, et. al derived the asymptotic distribution - holds with ties
- Hard to tabulate percentiles
- So they proposed a Bootstrap procedure in order to obtain an empirical distribution of W^2 under the null.
- For group 1, for example, resample from $B(\hat{p}_1)$, $\widehat{G}_1$, $\widehat{S^*}$
- If the W^2 equals the qth percentile of the empirical distribution, then the p-value = $\frac{100-q}{100}$

- Tamura et. al conducted simulations to evaluate their procedure. I simulated data from the exact same distributions as Tamura.

The simulation specifications are:

- Interval censoring case: visits at days 5,10,15,22,29,36,43
- Set $p_1 = p_2 = .6$
- For group 1, T~Weibull ($\lambda = 1/400, \gamma = 2$) truncated at day 43 ⇒median=16.6 and 90% respond within 30 days
- Group 2: $S_2^*(t) = \{S_1^*(t)\}^{\beta}$ β=1 or 2.5; when β=2.5, median=10.4
- Censoring distribution (i.e., time to dropout), also truncated Weibull
  - $U \sim W_{tr}(\lambda = 1/40^4, \gamma = 4) \Rightarrow \approx$ 35% censored prior to day 43
- Take min(t,u) and round up to nearest scheduled visit day
- Used a sample size of 75 per group, and 1000 iterations


The S*(t)'s from which data was simulated
Truncated Weibull distributions
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40

Time to onset data ~W$_{tr}$ $med_1 = 16.6,$ in alternative $med_2 = 10.4$

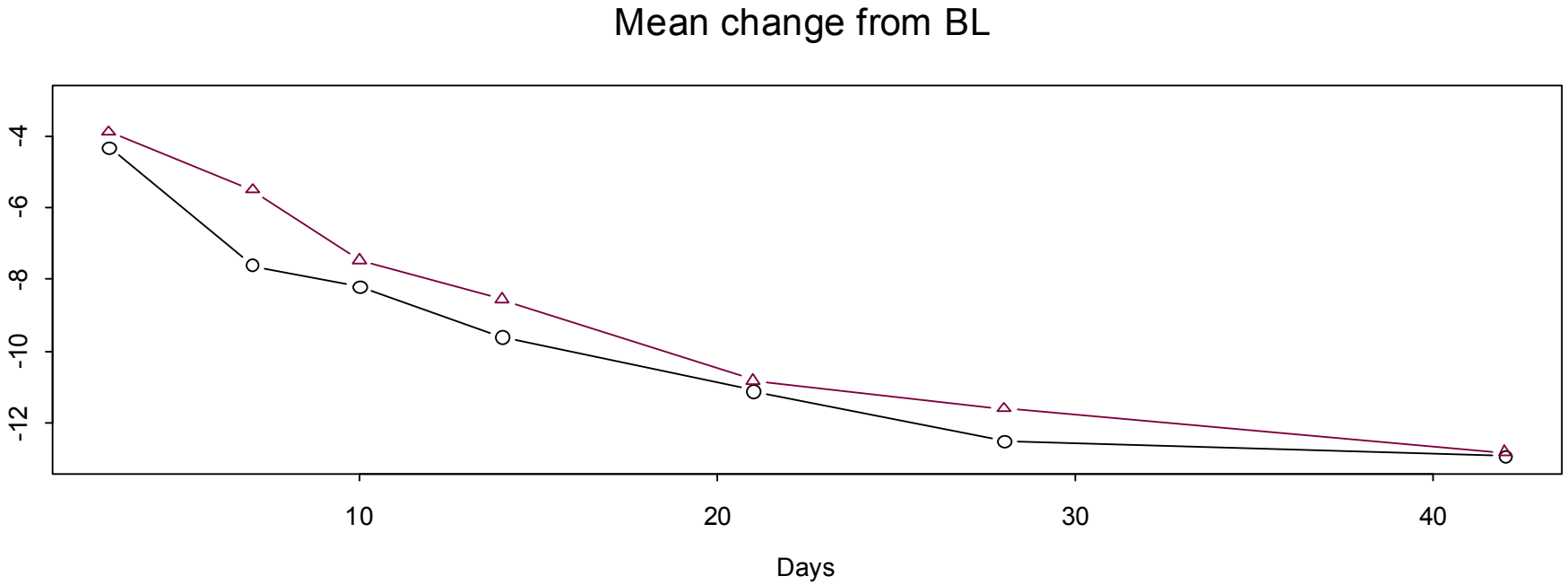
Time to censoring ~W$_{tr}$ ≈ 35% dropout rate

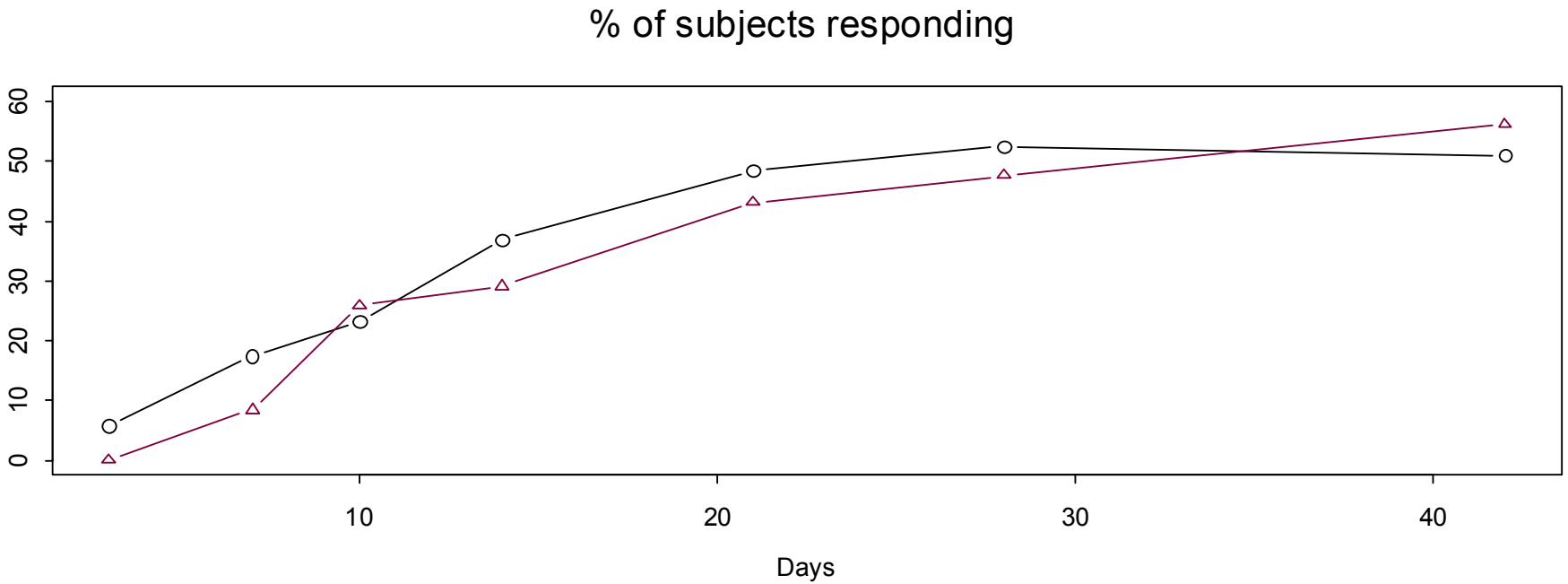
$p_1 = .6, p_2 = .6,$ n = 75/group, 1000 iterations

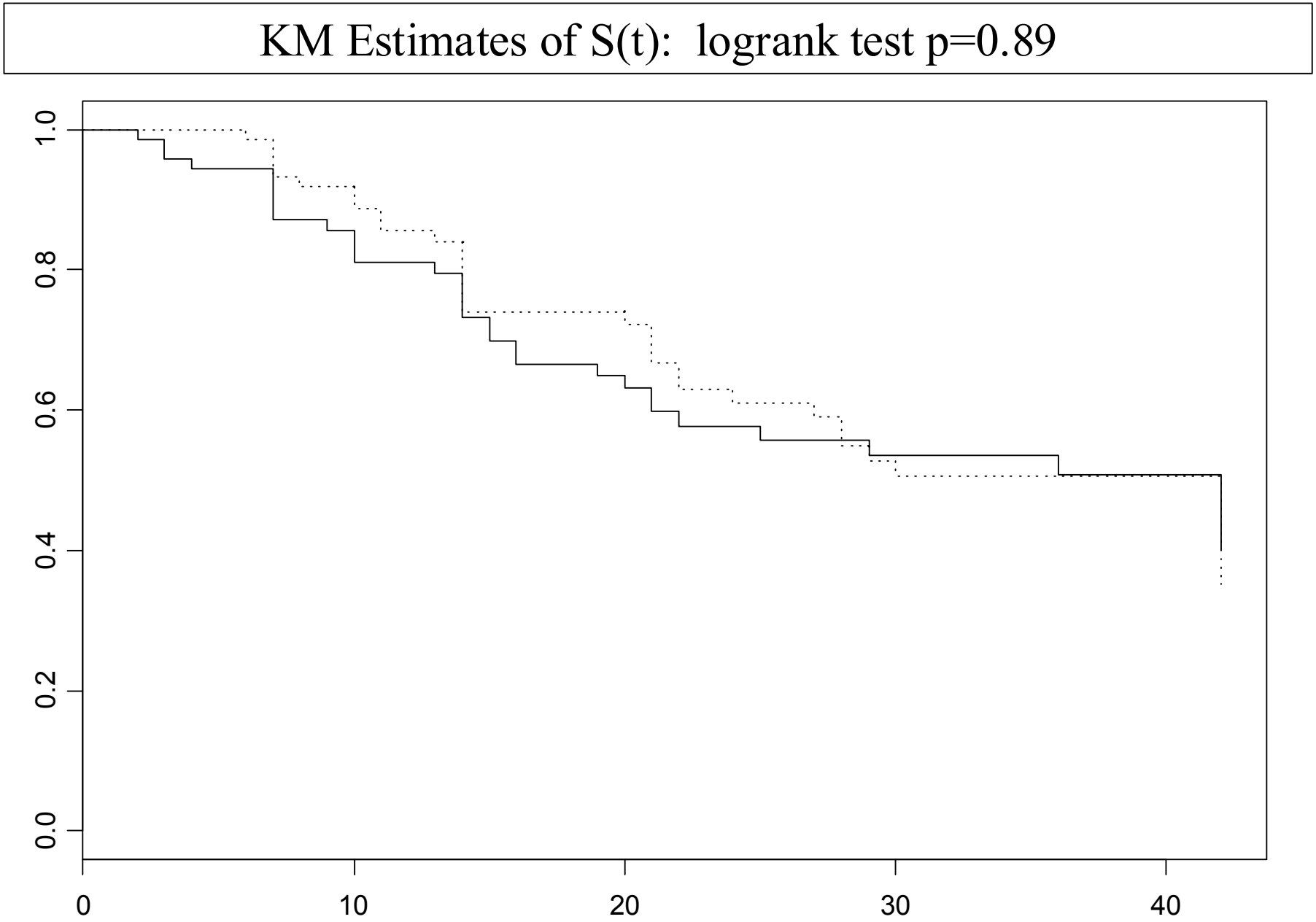
	Rejection rate	
Method	Null	Alternative
Cramer-von Mises	.048	.904
T_{WLR}	.052	.911
M-M Weibull	.056	.929
M-M Log logistic	.059	.875
log-rank test	.045	.256

Exploratory analysis of a real dataset

- 6 week MDD study with 5 groups, 3 doses of test drug, PBO, and a positive control
- comparison in this illustration is between the positive control (N=76, 51 completers) and one dose of the test drug (N=79, 56 completers)
- Time to ≥50 reduction from baseline in HAM-D total
  - partially sustained (≥35 reduction from baseline) at all subsequent visits
  - early terminators were classified as responders if they had a ≥50 reduction from baseline at last two visits
  - Visits beyond 2 days of last day of medication were not considered
  - Visits > 38 days were set equal to 42 days


Mean change from BL
-4
-6
-8
-10
-12
10
20
30
40
Days


% of subjects responding
0
10
20
30
40
50
60
10
20
30
40
Days


KM Estimates of S(t): logrank test p=0.89
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40

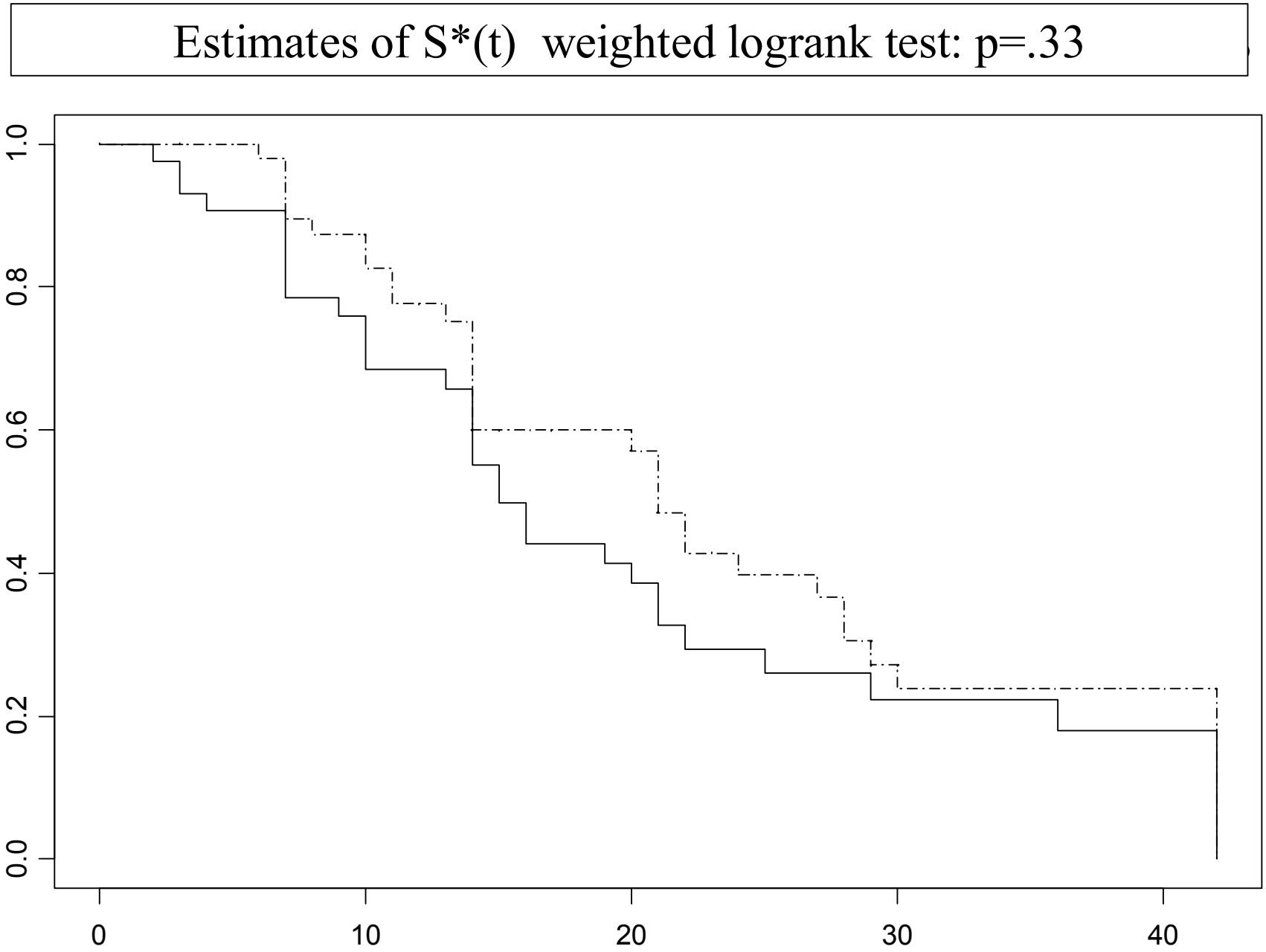

Estimates of S*(t) weighted logrank test: p=.33
1.0
0.8
0.6
0.4
0.2
0.0
0
10
20
30
40

Fig. 4 KM estimates of S*(t)'s along with fitted Weibull models

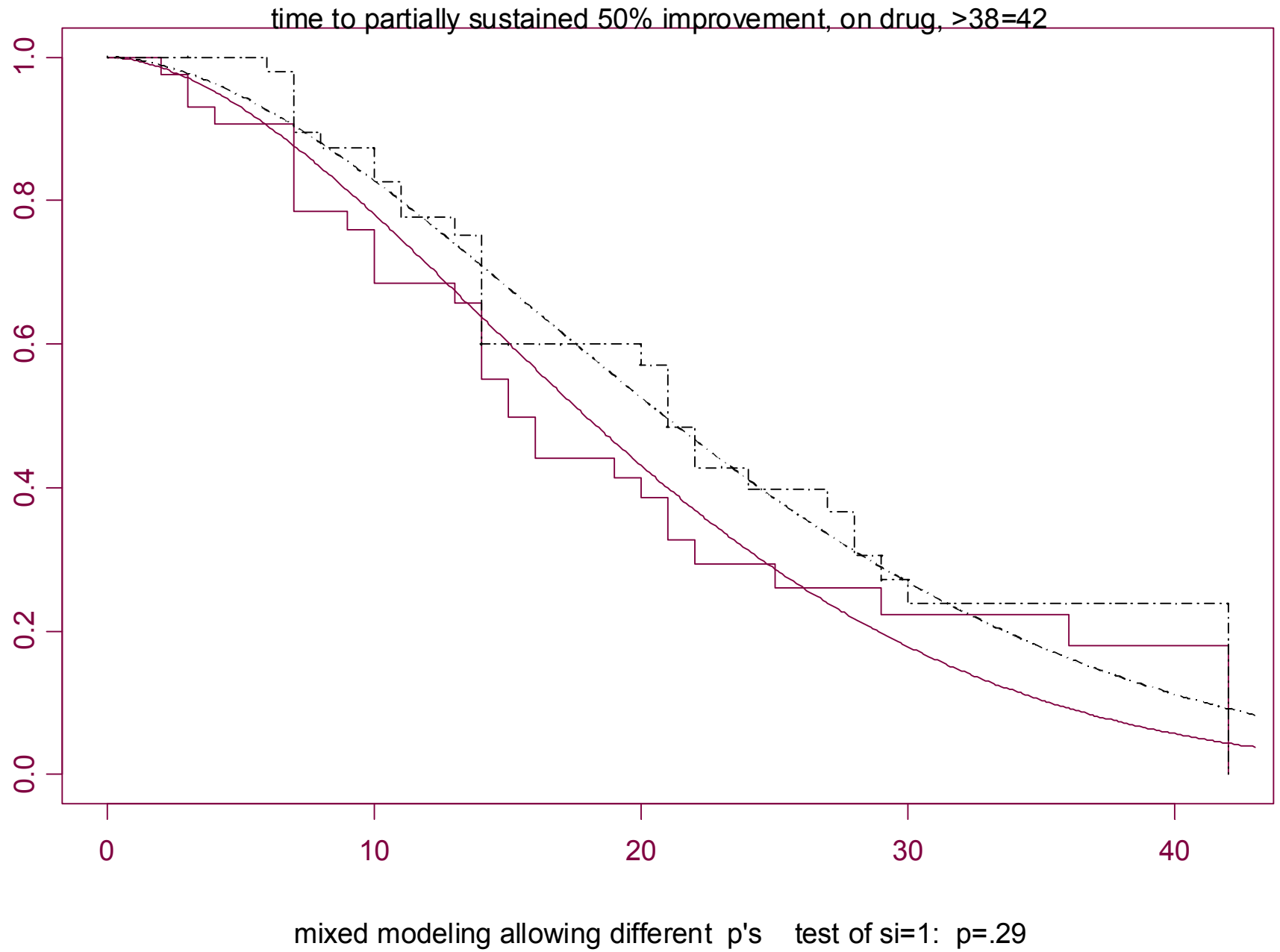
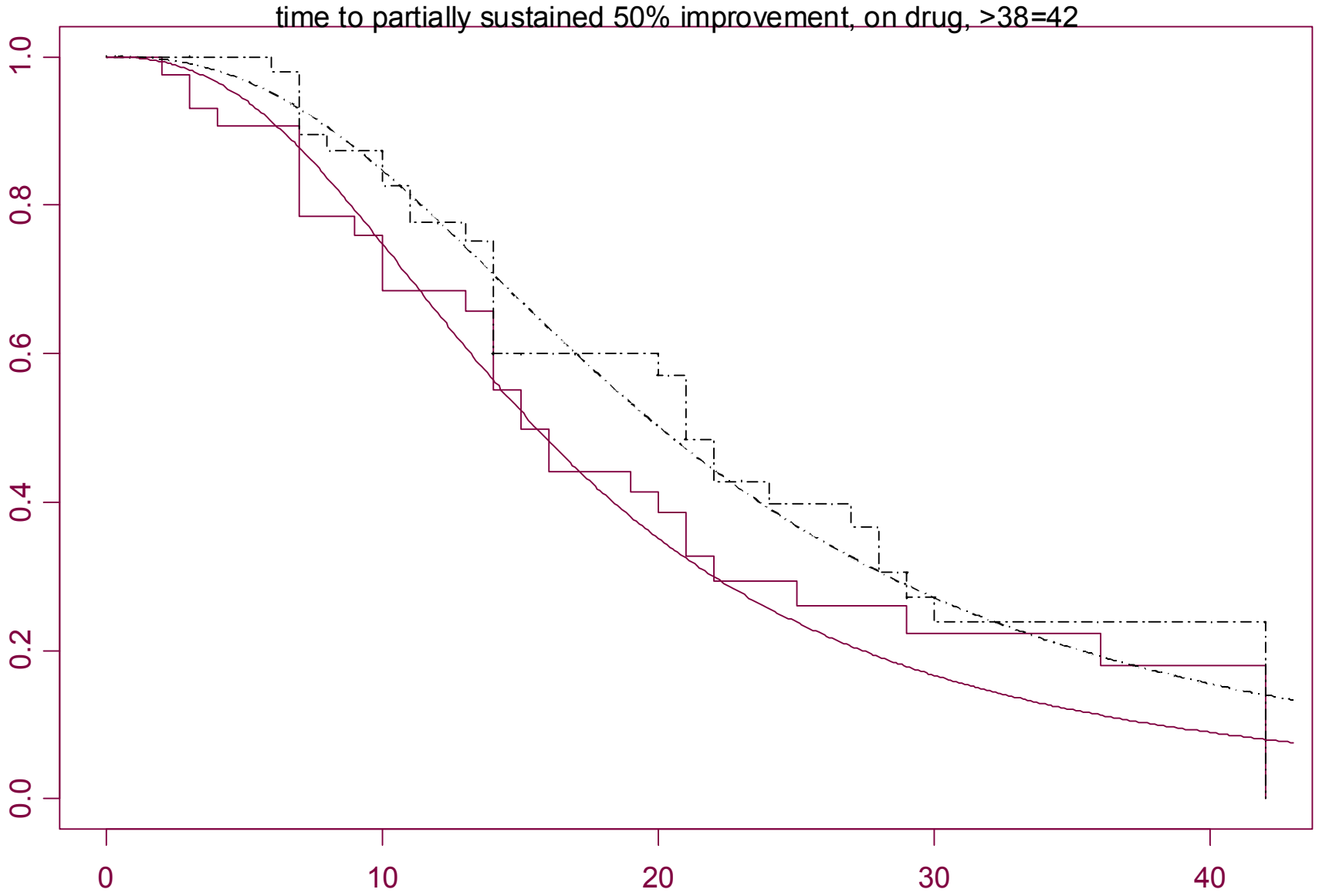


Fig. 5 KM estimates of S*(t)'s along with fitted log logistic models



Assessing Model Fit

Specifically, assess the appropriate of the chosen time to event distribution

- Plot log of the KM estimated conditional cumulative hazard vs log time
- Plot KM estimated log-odds of response beyond t vs. log time
- Likelihood ratio test of the PH or PO assumption
- Comparing the KM-type estimates of the conditional hazard to those estimated from the parametric models
- Assess whether the Cox-Snell residuals behave as if they are a censored sample from unit exponential distribution

- Recall that for the Weibull model, $S_2^*(t) = e^{-\lambda t^\gamma}$

  $\Rightarrow \log\{-\log S_2^*(t)\} = \log\lambda + \gamma \log t$

- Substitute the KM estimate $\widehat{S}_2^*(t)$ for $S_2^*(t)$ in the above equation
- If a Weibull distribution is tenable, then $\widehat{S}_2^*(t)$ should be "close" to $S_2^*(t)$ and
- a plot of $\log\{-\log \widehat{S}_2^*(t)\}$ of $\log t$ should yield an approximately straight line
- As shown earlier, for the loglogistic model, $\frac{1-S_2^*(t)}{S_2^*(t)} = (t\rho)^\kappa$

  $\Rightarrow \log \frac{S_2^*(t)}{1-S_2^*(t)} = -\kappa \log\rho - \kappa \log t$

- a plot of $\log \frac{\widehat{S}_2^*(t)}{1-\widehat{S}_2^*(t)}$ of $\log t$ should yield an approximately straight line

- In the Weibull model, the assumption of PH corresponds to the assumption of a common shape parameter γ
- Let each the conditional survivor function for each treatment group have a separate scale **and** shape parameter, i.e., $S_i^*(t) = e^{-\lambda_i t^{\gamma_i}}$
- compare the loglikelihood of this model with the PH model which imposes the contraint of a common shape parameter γ
- Analogously, the assumption of PO in the loglogistic model corresponds to the assumption of a common shape parameter κ
- Likelihood ratio test results:
  - Test of PH in Weibull PH model: p=.18
  - Test of PO in loglogistic PO model: p=.23

- For a particular group or sample of survival data, the KM type estimator of the hazard in the interval t_k to t_{k+1} is $\frac{d_k}{n_k \Delta_k}$ where d_k is the number of "deaths" at the k^{th} death time, n_k is the number at "risk" at time t_k, and $\Delta_k = t_{k+1} - t_k$

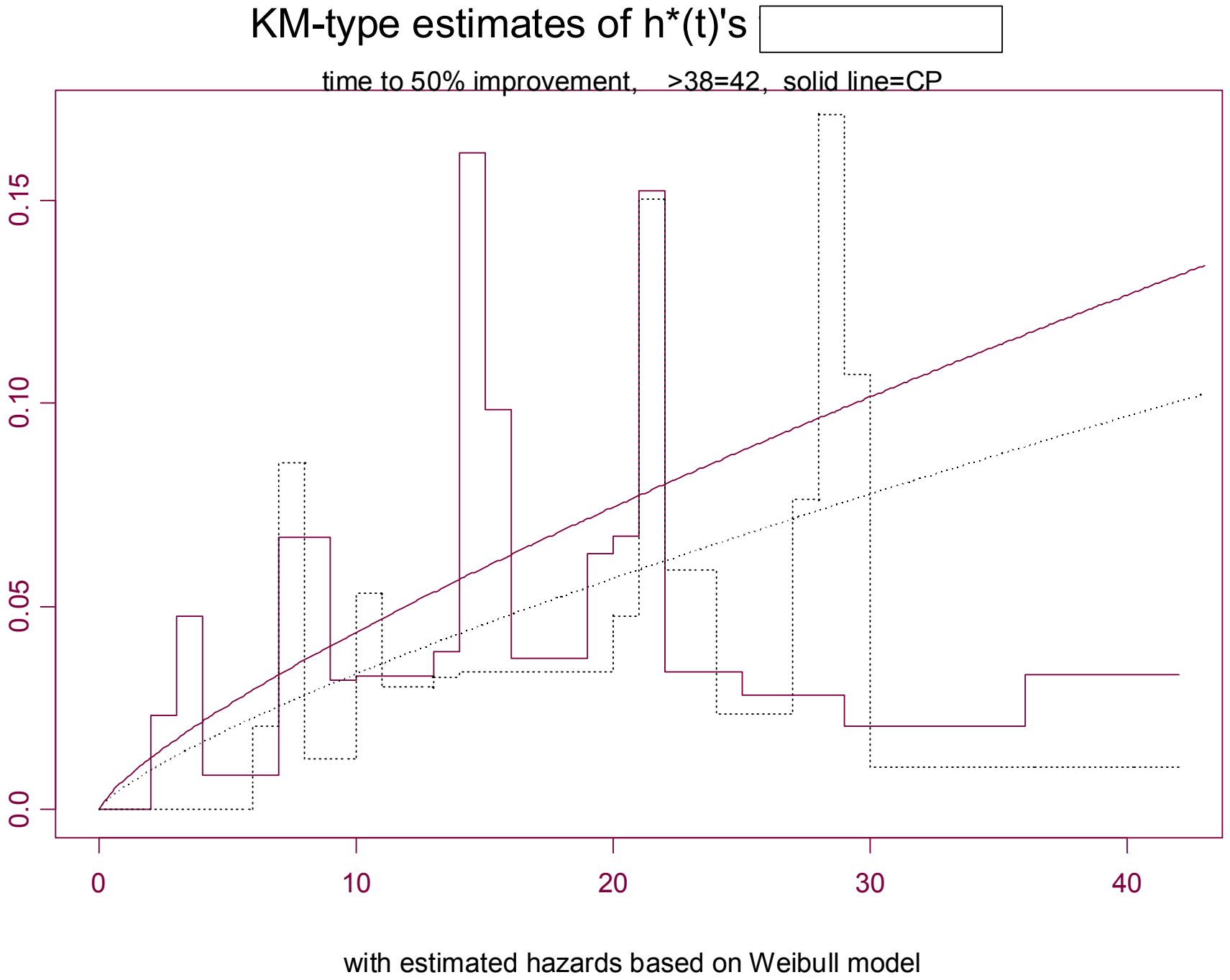
- Let's denote the KM estimator of $S(t)$ in the interval $[t_k, t_{k+1})$ as $\widehat{S}(t_{\Delta_k}) = \Pi_{j=1}^{k}(1 - \frac{d_j}{n_j})$

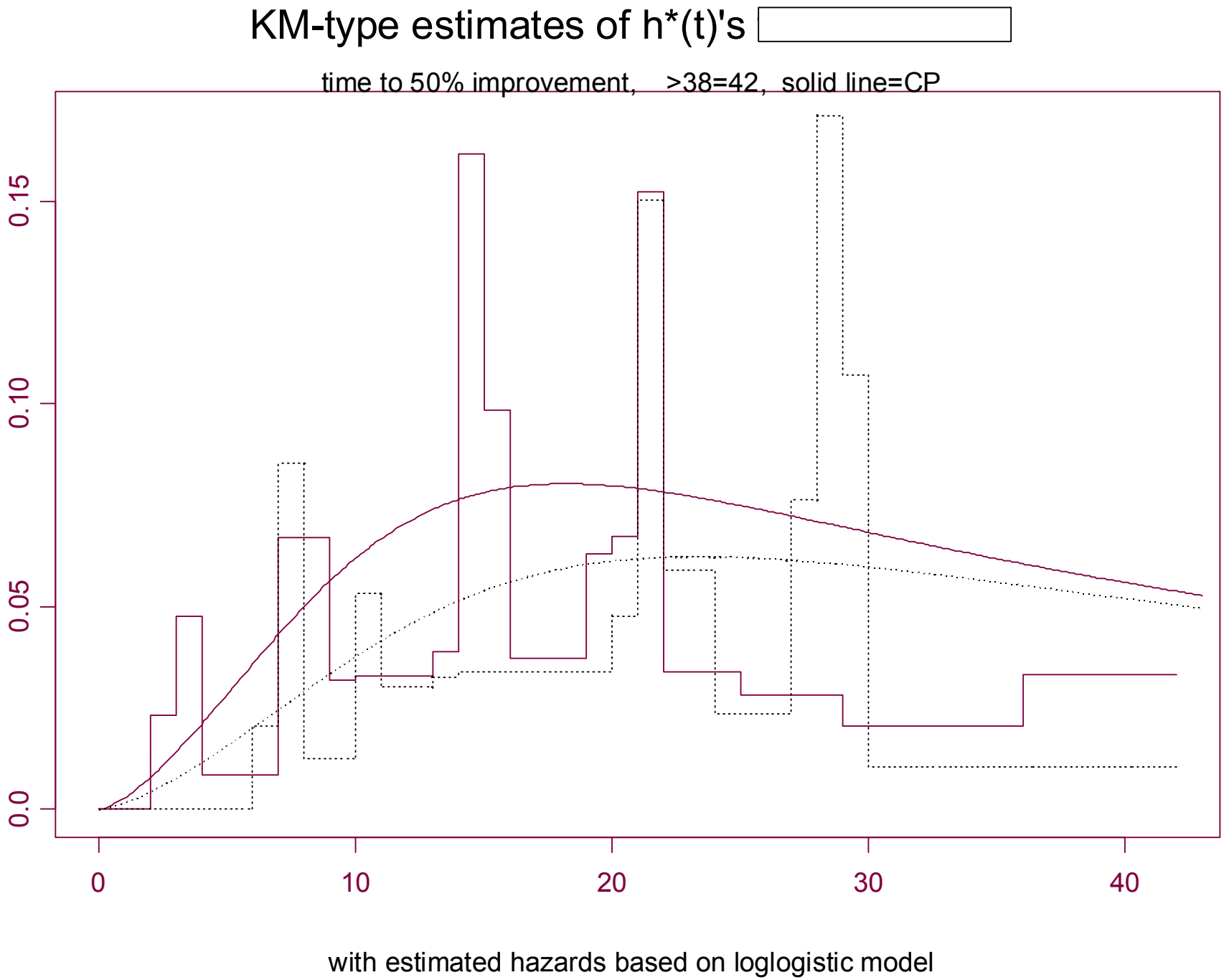
  $\Rightarrow \widehat{S}(t_{\Delta_k}) = \widehat{S}(t_{\Delta_{k-1}})(1 - \frac{d_k}{n_k}) \Rightarrow \frac{d_k}{n_k} = \frac{\widehat{S}(t_{\Delta_{k-1}}) - \widehat{S}(t_{\Delta_k})}{\widehat{S}(t_{\Delta_{k-1}})}$

- It then follows that a corresponding estimator of the conditional hazard in the interval t_k to t_{k+1} is

$$\frac{\widehat{S^*}(t_{\Delta_{k-1}}) - \widehat{S^*}(t_{\Delta_k})}{\widehat{S^*}(t_{\Delta_{k-1}})\Delta_k}$$

- Compare these KM type conditional hazard estimates to those estimates obtained from the Weibull and loglogistic models


KM-type estimates of h*(t)'s
time to 50% improvement, >38=42, solid line=CP
0.0
0.05
0.10
0.15
0
10
20
30
40
with estimated hazards based on Weibull model


KM-type estimates of h*(t)'s
time to 50% improvement, >38=42, solid line=CP
0.0
0.05
0.10
0.15
0
10
20
30
40
with estimated hazards based on loglogistic model

Cox-Snell residuals: $r_{\mathrm{Ci}} = -\log \widehat{S}_i(t_i)$

t_i is the observed survival time for subject i

In general if $T \sim S(t)$, then $Y = -\log S(T) \sim \exp(1)$

proof: $f_Y(y) = f_T(t) / \left| \frac{dy}{dt} \right| = f_T(t) / \frac{f_T(t)}{S(t)} = S[S^{-1}(e^{-y})] = e^{-y}$

$\Rightarrow$ if model fits well, r_{Ci} will represent a censored sample ~$\exp(1)$

Obtain r_{Ci}, treat as survival times and compute KM estimates $\widehat{S}(r_{\mathrm{Ci}})$; residuals for censored times are considered censored observations

If $\log\{-\log \widehat{S}(r_{\mathrm{Ci}})\}$ vs $\log r_{\mathrm{Ci}}$ yields a reasonably straight line with unit slope and zero intercept model fits well

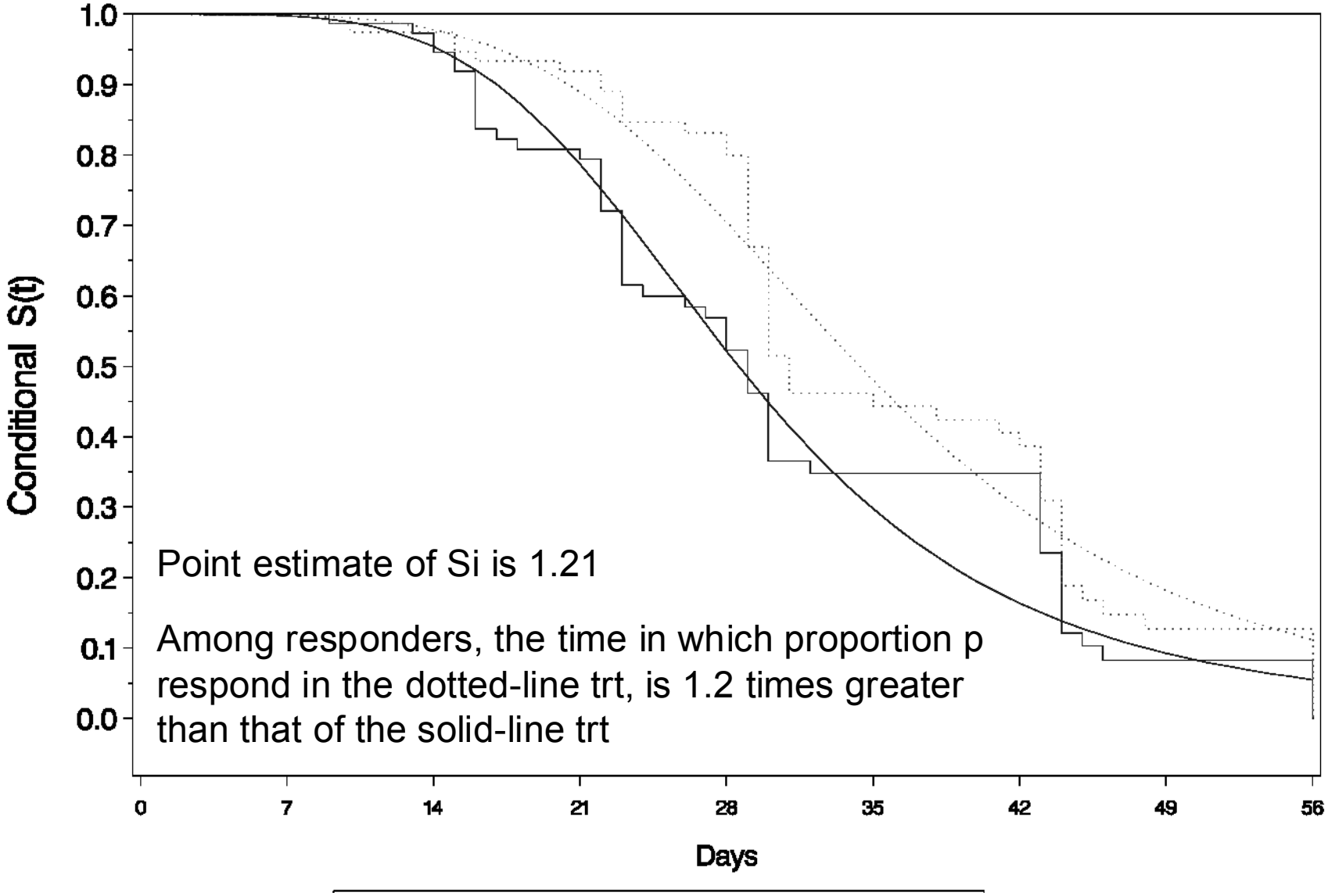
Can one apply this residual analysis in this mixture model setting?

In the case of 2 treatments, the Cox-Snell residual for the i^{th} subject in the g^{th} group is: $r_{\mathrm{Ci}} = -\log\{\widehat{S_g^*}(t_i)\hat{p}_g + (1 - \hat{p}_g)\}$

A follow-up example in which the loglogistic parametric model as specified apriori

- 8 week MDD study with 3 groups, combo of test drug + positive control (PC), PC alone, and PBO
- comparison is between combo (N=103, 72 completers) and PC (N=101, 74 completers)
- Time to ≥50 reduction from baseline in MADRS total
  - must be sustained at all subsequent visits
  - early terminators were classified as responders if they had a ≥50 reduction from baseline at last two visits
  - Visits between 52 and 59 days were set equal to 56 days

Test of Si=0, yielded a p = 0.015; logrank test, p=0.28



Issues, concerns and criticisms of this mixture method/paradigm

- discard information by dichotomizing a nice “continuous" variable
- how does one dichotomize (onset, response, etc.)?
- sustained response or partially sustained, and for how long?
- interval censoring (i.e., unlike many applications of survival analysis, don’t know precise time of response–only that it was between visits
- time to response and time to censoring may not be independent
- $S_1^* < S_2^*$ only meaningful if $p_1 \geq p_2$ (perhaps requiring $\hat{p}_1 \geq \hat{p}_2$)?
- most applicable for comparing 2 efficacious treatments
- estimates of p and hence of S^* can be unstable
- parametric models may not be robust to departures from assumptions
- no standard ready-to-use software procedures
- analyze time to response among responders to obtain $\hat{S}_i^*$ and for testing
  - works reasonably well, but
  - 1) subgroup analysis; not ITT, 2) consored subjects provide info