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Introduction to Survival Analysis

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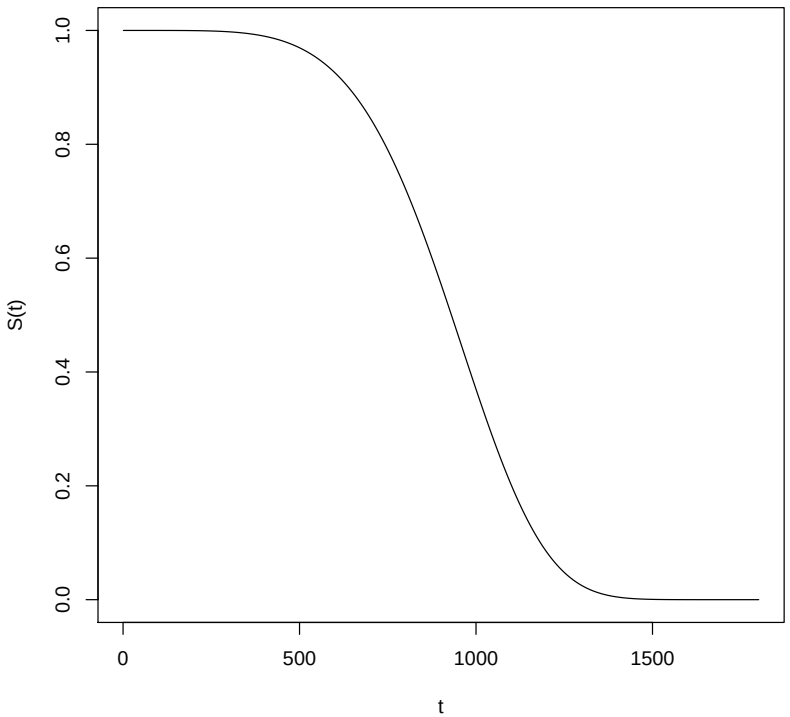
Hazard Function and Cox Regression

dkfz. GERMAN CANCER RESEARCH CENTER IN THE HELMHOLTZ ASSOCIATION

Survival function

Recall:

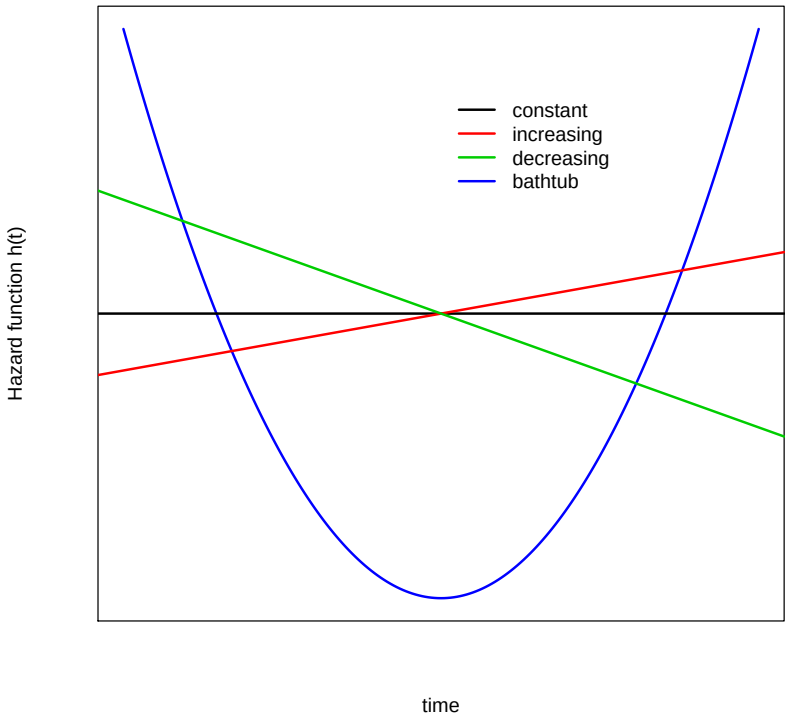
- T denotes the survival time, $T \geq 0$, right-skewed
- $F(t)$: distribution function of the survival times
- Survival function $S(t) = Pr(T > t) = 1 - F(t)$, $t \geq 0$



Hazard function

Hazard function $h(t)$ is the instantaneous rate at which events/failures occur at t, given no event occurred until t.

If t continuous: $h(t) = f(t)/S(t), f = F'$

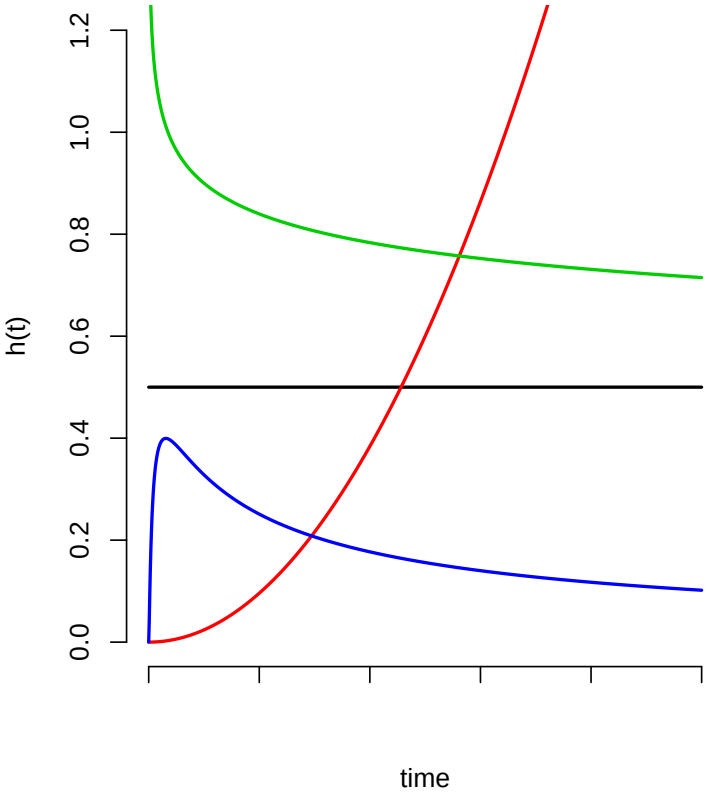


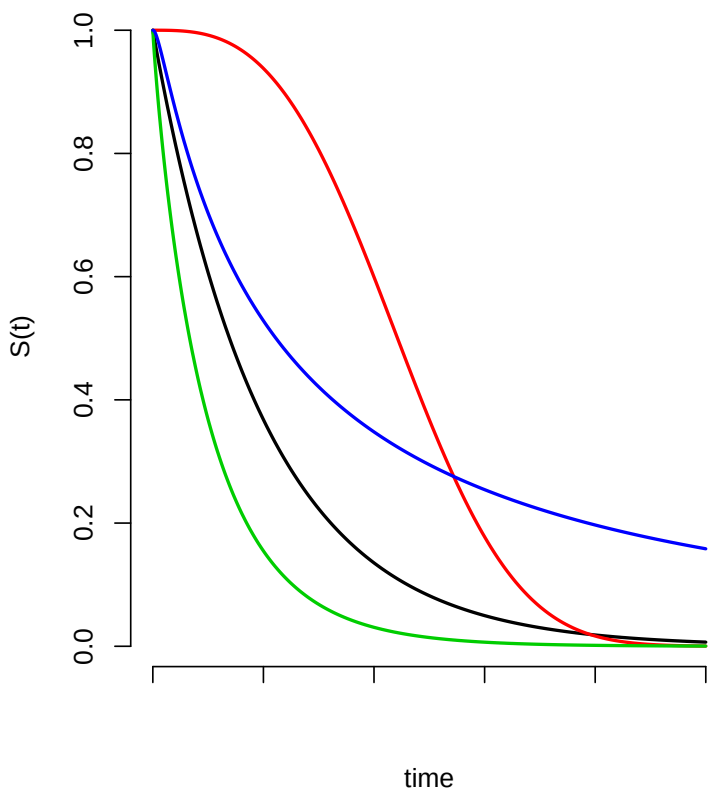
Examples:

- increasing: natural aging
- decreasing: early onset of failure (e.g. transplant)
- bathtub: life span (early risk after birth)

Alias: conditional failure rate, force of mortality, hazard rate

Hazard vs. Survival function





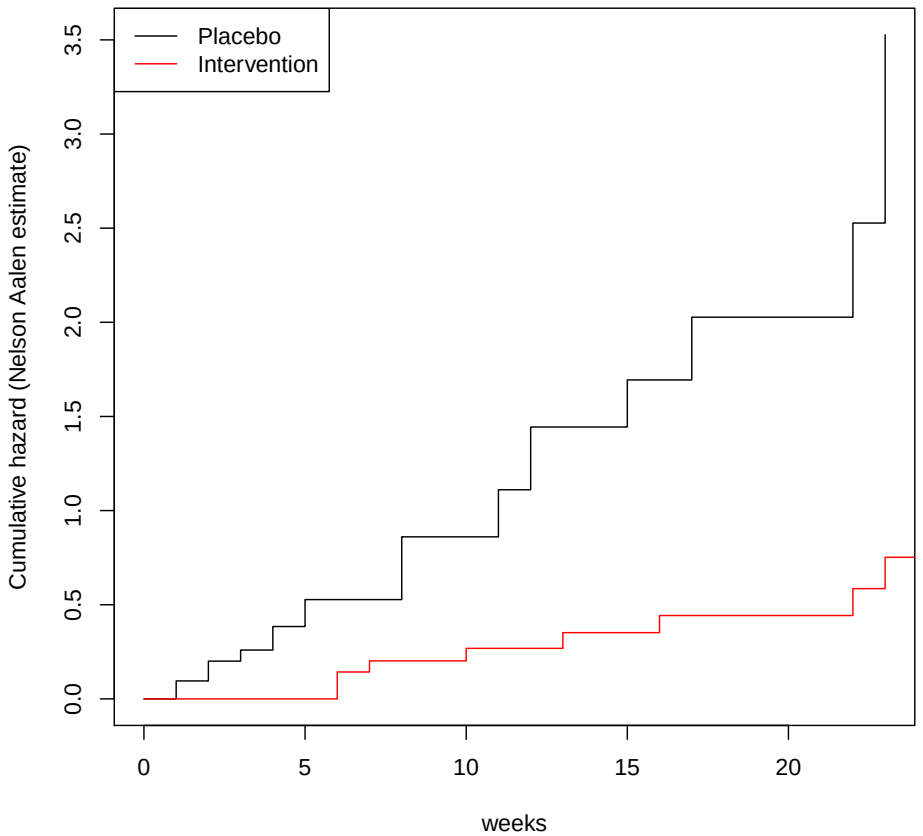
Based on exponential (black), weibull (red/green) and lognormal (blue) distribution

Hazard function

- Is not a probability ($h(t) \geq 0$, but can be larger than 1)
- Can be interpreted as expected number of events per subject per time unit
- Example: $h(t) = 0.5$, time unit is months, on average 0.5 events will occur at t per subject at risk and per month, assuming constant hazard during that month
- If survival times can be described by exponential distribution, hazard is constant:
  $h(t) = \frac{f(t)}{S(t)} = \frac{\lambda e^{-\lambda t}}{e^{-\lambda t}} = \lambda$
- cumulative hazard $H(t) = -log[S(t)]$

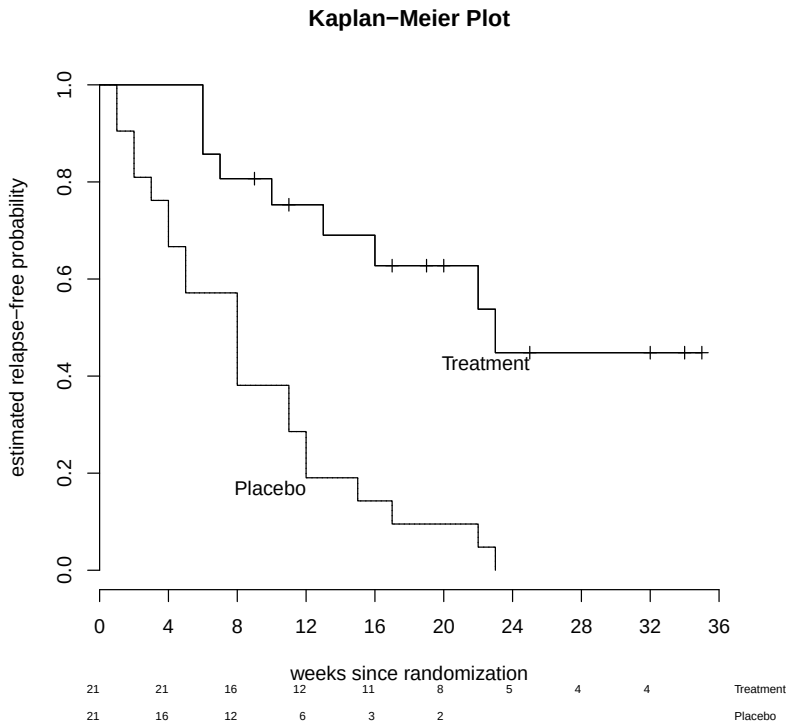
Non-parametric estimation of cumulative hazard function

Nelson Aalen estimator $\widehat{H(t)} = \sum_{t_i \leq t} \frac{d_i}{n_i}$



Example data

Data from Freireich et al.'The effect of 6-mercaptopurine on the duration of steroid-induced remissions in acute leukemia' Blood 21, 699-716, 1963.



- logrank test p-value < 0.001
- Quantify difference in risk of event?
- Adjust for confounders?
- Assess impact of continuous covariates?

Cox Proportional Hazard Regression (1)

Objective:examine the relationship between survival and one or more explanatory variables (covariates)
$X_1, ..., X_k$ are k covariates, measured for all n subjects

- Modeling survival linear-like using (log) hazard function $h(t)$:
  $\log h(t, X) = \alpha(t) + \beta_1 X_1 + ... + \beta_k X_k$
- Equivalent to
  $h(t, X) = h_0(t) \exp\{\beta_1 X_1 + ... + \beta_k X_k\}$, $\alpha(t) = \log h_0(t)$
- $h_0(t)$ is baseline hazard, assumed to be the same for all subjects
- Hazard depends on time and covariates, but effect of covariates time-invariant

Cox Proportional Hazard Regression (2)

- Proportional: hazard rates of two individuals with different covariate values are proportional $\rightarrow$ relative effects
- Use relative hazards or hazard ratio (HR) to compare subjects with covariate values $x_i = (x_{1i}, ..., x_{ki})$:

$$\frac{h(t|X = x_1)}{h(t|X = x_2)} = \frac{h_0(t)\exp\{\beta_1 x_{11} + ...\}}{h_0(t)\exp\{\beta_1 x_{21} + ...\}} \quad (1)$$

$$= \frac{\exp\{\beta_1 x_{11} + ...\}}{\exp\{\beta_1 x_{21} + ...\}} \quad (2)$$

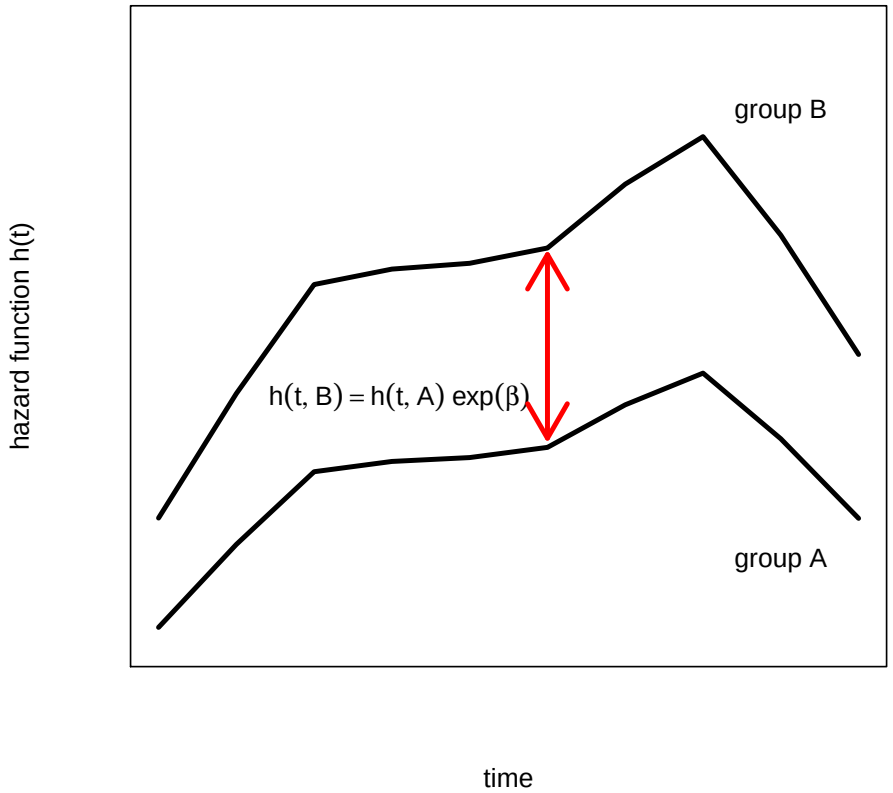
$$= \exp(\beta_1(x_{11} - x_{21}) + ...) \quad (3)$$

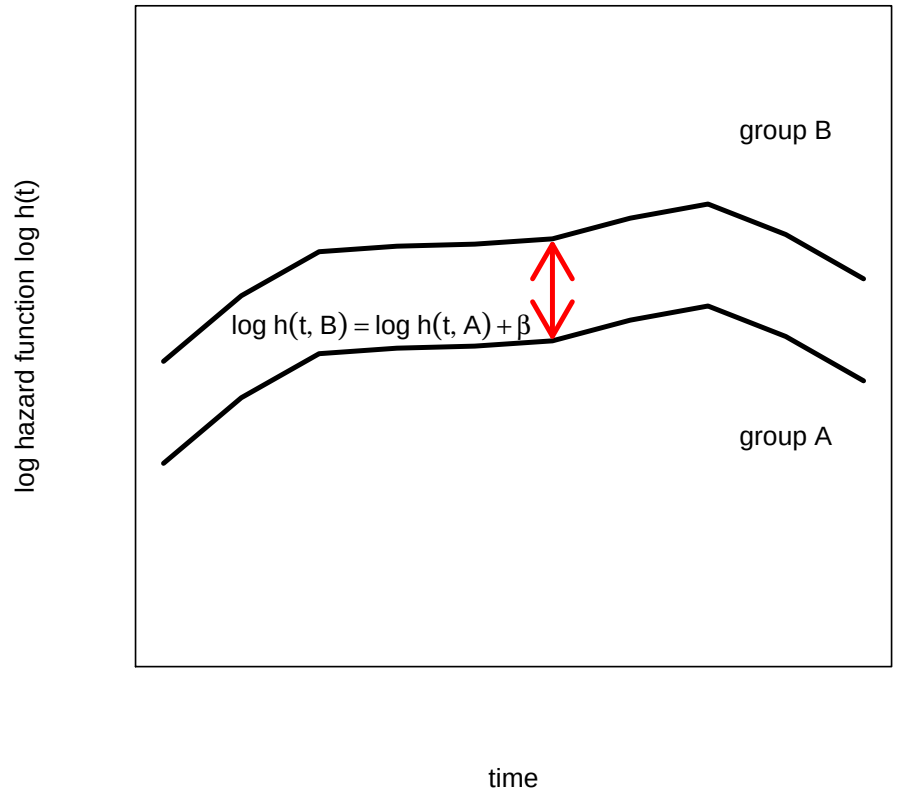
- $h(t|X = x_1) = h(t|X = x_2) \times \exp(\beta_1(x_{11} - x_{21}) + ...)$
- $h_0(t)$ cancels out $\rightarrow$ semiparametric model
- Ratio does not depend on time, i.e. constant over time

Illustration Proportional Hazards

One binary covariate X (k=1), group 1 vs group 0:

relative hazard = $\frac{h(t|group{=}1)}{h(t|group{=}0)} = \exp(\beta(1-0)) = \exp(\beta), \beta > 0$





Interpretation of Hazard Ratio

What does a hazard ratio of 2 in terms of overall survival mean?

- interpretation of relative risks/ risk ratio
- In general: Increasing X_j by one unit multiplies the estimated hazard by $\exp(\beta_j)$
- Binary covariate (group B vs group A): risk of death is 2 times that in group B compared to group A, failure rate is 100% higher at any time point
- Continuous covariate (age per 10 years): risk of death increases by factor 2 for a 50-year old compared to a 40-year old (60 vs 50, etc...)
- If T is exponentially distributed, hazard ratio (B vs A) corresponds to ratio of median survival times (A vs B), i.e. median survival in A is 100% longer

Example data

Covariates X: treatment group placebo (B) vs treatment (A), log-transformed white blood count, sex

		$\hat{\beta}$	$HR = \exp(\hat{\beta})$	se($\hat{\beta}$)	z	p-value
group	B vs A	1.50	4.50	0.46	3.26	0.001
logWBC		1.68	5.38	0.34	5.00	< 0.0001
gender	m vs f	0.31	1.37	0.45	0.69	0.49

- $H_0 : \beta_1 = 0$ (no effect of treatment)
- $z = \hat{\beta}/se(\hat{\beta})$ (Wald test statistic)
- z asymptotically standard-normal distributed
- Hazard ratio: $\exp(\hat{\beta})$=4.5, 4.5-fold increased risk in placebo group
- 95% confidence interval: $\exp(\hat{\beta} + / - 1.96 \times se)$ $\rightarrow$ [1.8 ; 11.1]

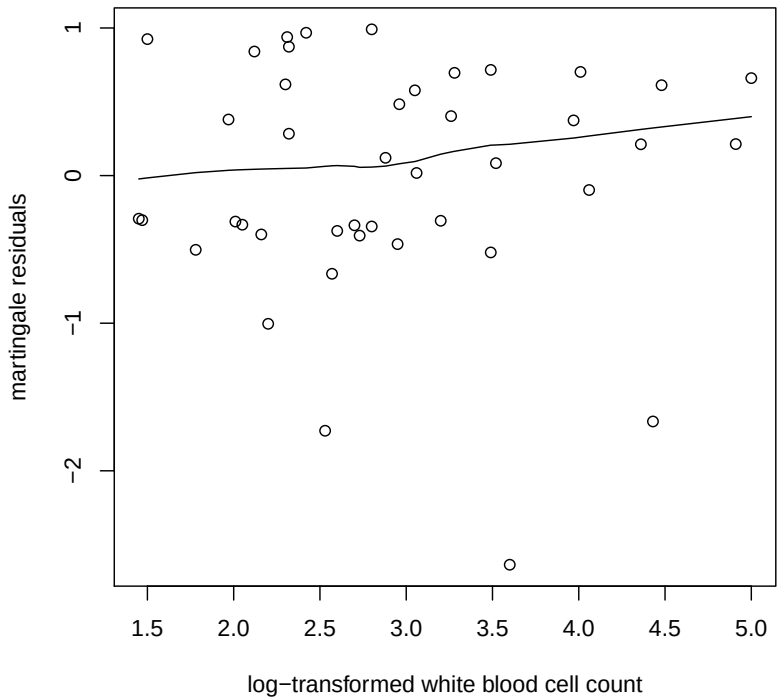
Assumptions to check

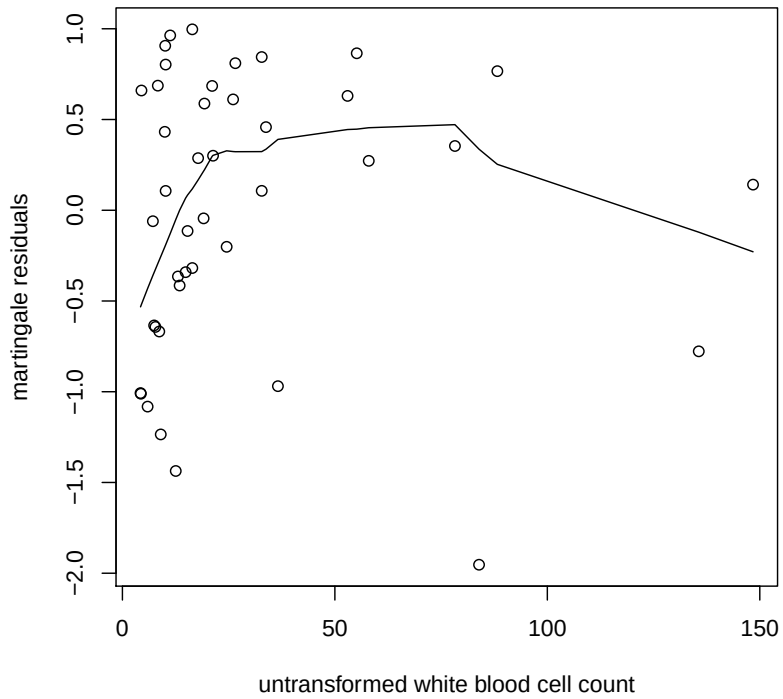
- Proportional hazards
- Linear relationship between (continuous) covariates and log hazard $h(t)$
- Influential observations
- Collinearity of covariates

Note: Nonlinear functional form and interaction of covariates can affect PH assumption

Linearity

Linearity with log hazard.
Martingal residuals for subject i at time t_i: $M_i = \delta_i - H(t_i, x_i, \beta_i)$



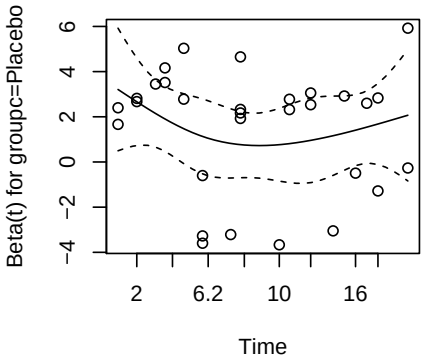


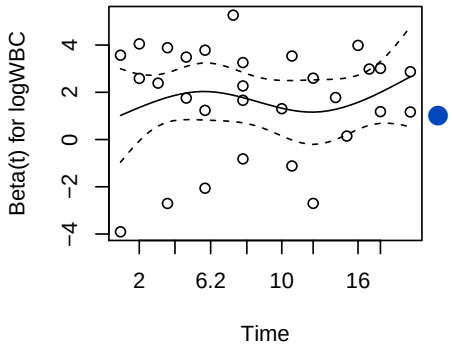
Proportional hazards assumption (1)

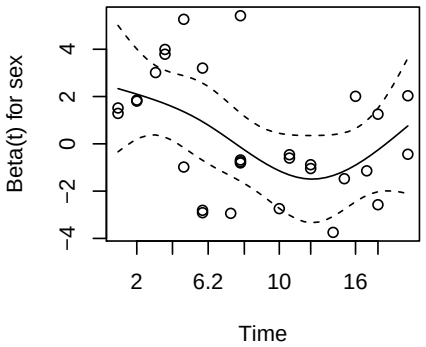
- Assumption is violated, if covariate effect not constant over time
- Graphically: log(-log(S(t)) vs log(time) $\rightarrow$ parallel lines
- Scaled Schoenfeld residuals based on Cox model (Therneau and Grambsch, 2000):
  separate residual for each individual for each covariate
- Plot residuals against time in order to detect non-constant effects
- Test PH assumption based on correlation between scaled Schoenfeld residuals and time

Proportional hazards assumption (2)

Example data







	rho	chisq	p
group	-0.10	0.34	0.56
logWBC	0.06	0.16	0.69
sex	-0.37	4.08	0.04
GLOBAL		4.23	0.24

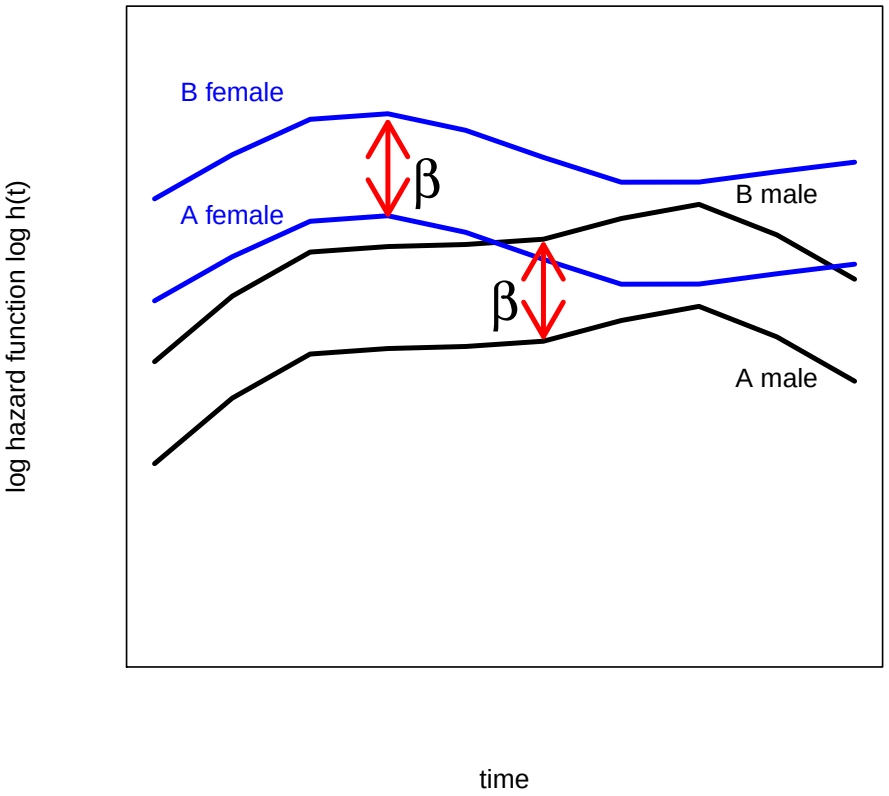
- no correlation, thus no time-varying effect for group
- violation for sex

Proportional hazards assumption (3)

What if PH assumption fails for covariate Z?

- Test/p-value for covariate Z is not needed, but adjustment
  - Stratification (categorical, grouped continuous)
- Test/p-value for covariate Z is needed
  - If p-value is very small: 'principle of conservatism'
  - Include additional time-varying/time-dependent effect $Z \times \log(time)$:
    $h(t, X, Z) = h_0(t) \exp\{\beta_1 Z + \beta_2 Z \times log(t) + ... + \beta_k X_k\}$
  - Local test $H_0 : \beta_1 = 0$ and $\beta_2 = 0$

Stratification



- Divide data into strata based on values of covariate Z (e.g. male vs female)
- Each stratum can have a different baseline hazard
  $h(t, X, Z = j) =$
  $h_{0j}(t) \exp\{\beta_1 X_1 + ... + \beta_k X_k\}$,
  $j = 1, .., k$
- Coefficients are assumed to be equal and constant across strata
- 'Weighted' hazard ratio across strata
- Issue: number of strata

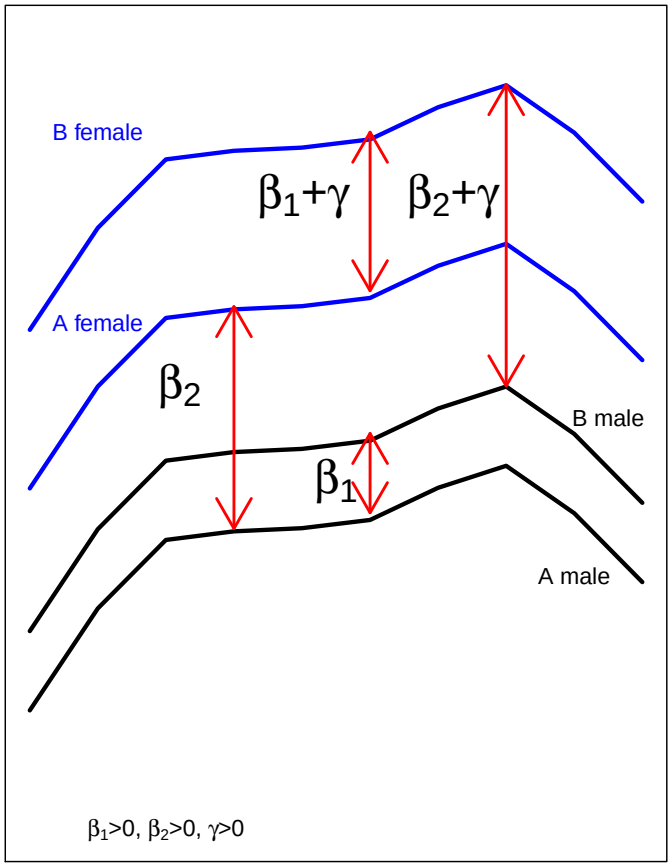
Example data with stratification

Covariates X: treatment group placebo (B) vs treatment (A), log-transformed white blood count
Strata: gender

		$\hat{\beta}$	$\exp(\hat{\beta})$	$\text{se}(\hat{\beta})$	z	p-value
group	B vs A	1.00	2.71	0.47	2.11	0.0351
logWBC		1.45	4.28	0.34	4.22	$<$ 0.0001

- Smaller hazard ratio for treatment: $\exp(\hat{\beta})$=2.7 after adjustment
- No estimate for gender

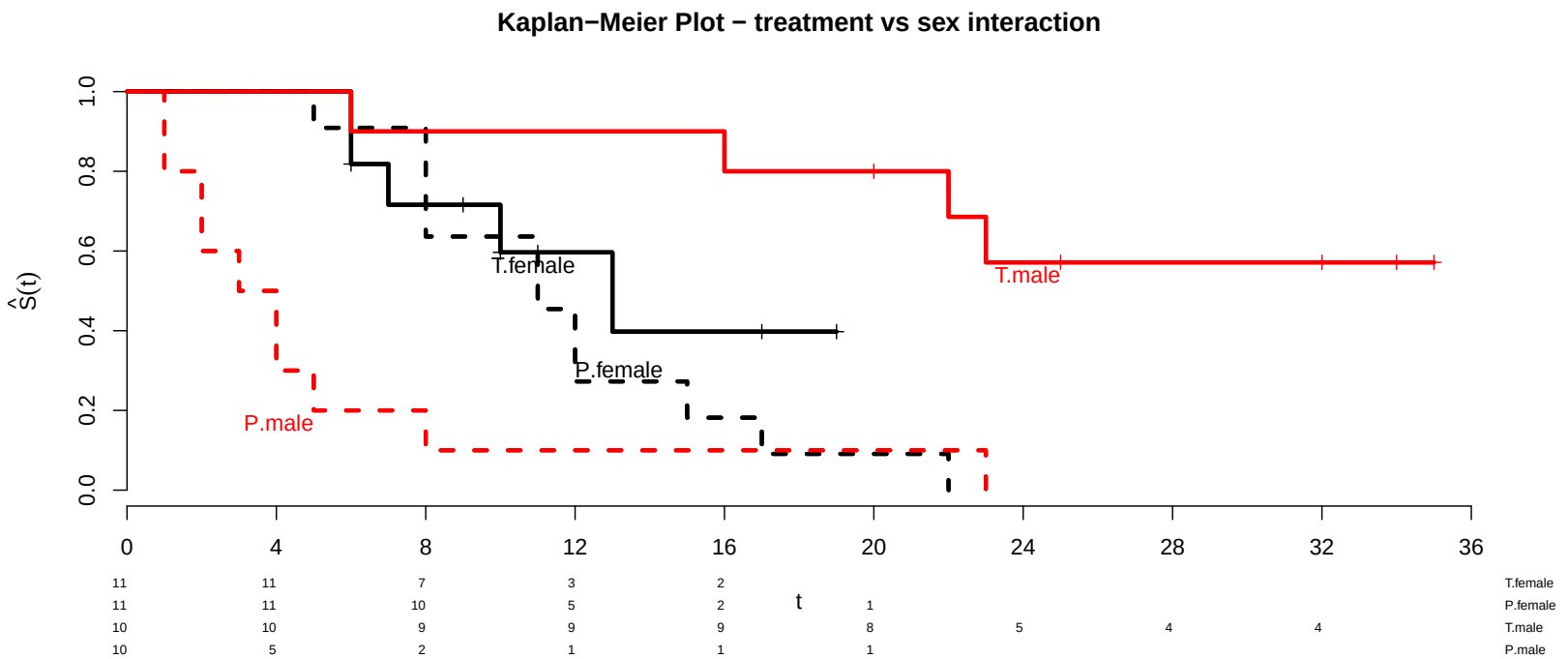
Interaction



- Detection of subgroup effects, predictive factors
- Interaction between two covariates X_1 and X_2 occurs, if effect of X_1 on survival outcome depends on X_2
- $h(t, X) = h_0(t) \exp\{\beta_1 X_1 + \beta_2 X_2 + \gamma Z\}$, $Z = X_1 \times X_2$
- Quantitative interaction: effect of X_1 has same direction, different magnitude for different values of X_2
- Qualitative interaction: effect of X_1 has opposite directions for different values of X_2

Example data with interaction

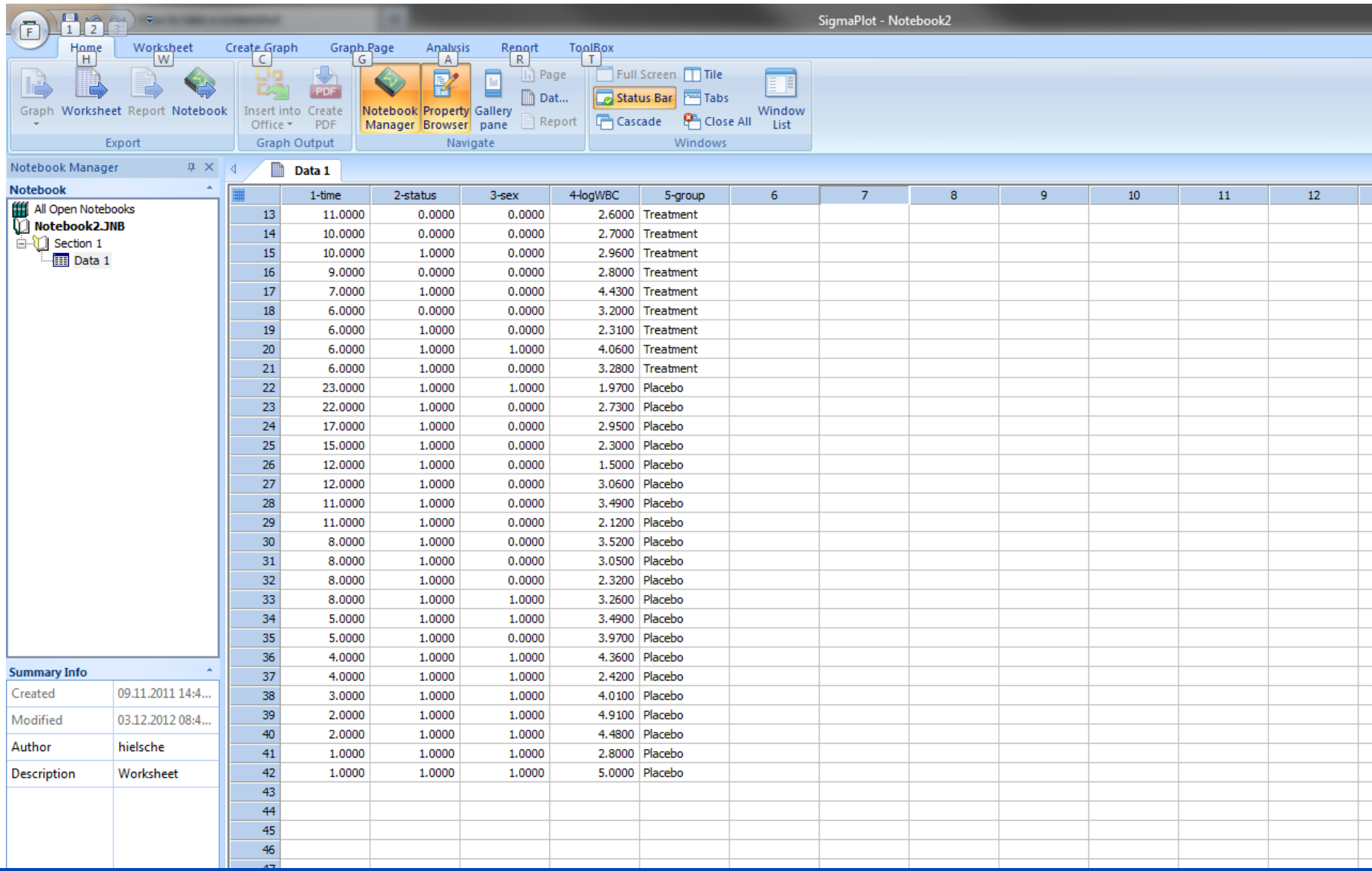
		$\hat{\beta}$	$\exp(\hat{\beta})$	$se(\hat{\beta})$	z	p-value
group	B vs A	0.62	1.87	0.54	1.15	0.25
sex	m vs f	-1.11	0.33	0.71	-1.57	0.12
group * sex		1.96	7.08	0.81	2.40	0.02



Analysis with SigmaPlot

- Cox PH model including local and global tests (Breslow ties method)
- Cox PH model including stratification
- Check PH assumption not possible
- Interaction term inclusion not directly possible, need to be defined in dataset
- More flexible alternatives: R, SAS, SPSS
- Not doable with GraphPad Prism

How to analyze with SigmaPlot?



	1-time	2-status	3-sex	4-logWBC	5-group	6	7	8	9	10	11	12
13	11.0000	0.0000	0.0000	2.6000	Treatment							
14	10.0000	0.0000	0.0000	2.7000	Treatment							
15	10.0000	1.0000	0.0000	2.9600	Treatment							
16	9.0000	0.0000	0.0000	2.8000	Treatment							
17	7.0000	1.0000	0.0000	4.4300	Treatment							
18	6.0000	0.0000	0.0000	3.2000	Treatment							
19	6.0000	1.0000	0.0000	2.3100	Treatment							
20	6.0000	1.0000	1.0000	4.0600	Treatment							
21	6.0000	1.0000	0.0000	3.2800	Treatment							
22	23.0000	1.0000	1.0000	1.9700	Placebo							
23	22.0000	1.0000	0.0000	2.7300	Placebo							
24	17.0000	1.0000	0.0000	2.9500	Placebo							
25	15.0000	1.0000	0.0000	2.3000	Placebo							
26	12.0000	1.0000	0.0000	1.5000	Placebo							
27	12.0000	1.0000	0.0000	3.0600	Placebo							
28	11.0000	1.0000	0.0000	3.4900	Placebo							
29	11.0000	1.0000	0.0000	2.1200	Placebo							
30	8.0000	1.0000	0.0000	3.5200	Placebo							
31	8.0000	1.0000	0.0000	3.0500	Placebo							
32	8.0000	1.0000	0.0000	2.3200	Placebo							
33	8.0000	1.0000	1.0000	3.2600	Placebo							
34	5.0000	1.0000	1.0000	3.4900	Placebo							
35	5.0000	1.0000	0.0000	3.9700	Placebo							
36	4.0000	1.0000	1.0000	4.3600	Placebo							
37	4.0000	1.0000	1.0000	2.4200	Placebo							
38	3.0000	1.0000	1.0000	4.0100	Placebo							
39	2.0000	1.0000	1.0000	4.9100	Placebo							
40	2.0000	1.0000	1.0000	4.4800	Placebo							
41	1.0000	1.0000	1.0000	2.8000	Placebo							
42	1.0000	1.0000	1.0000	5.0000	Placebo							
43												
44												
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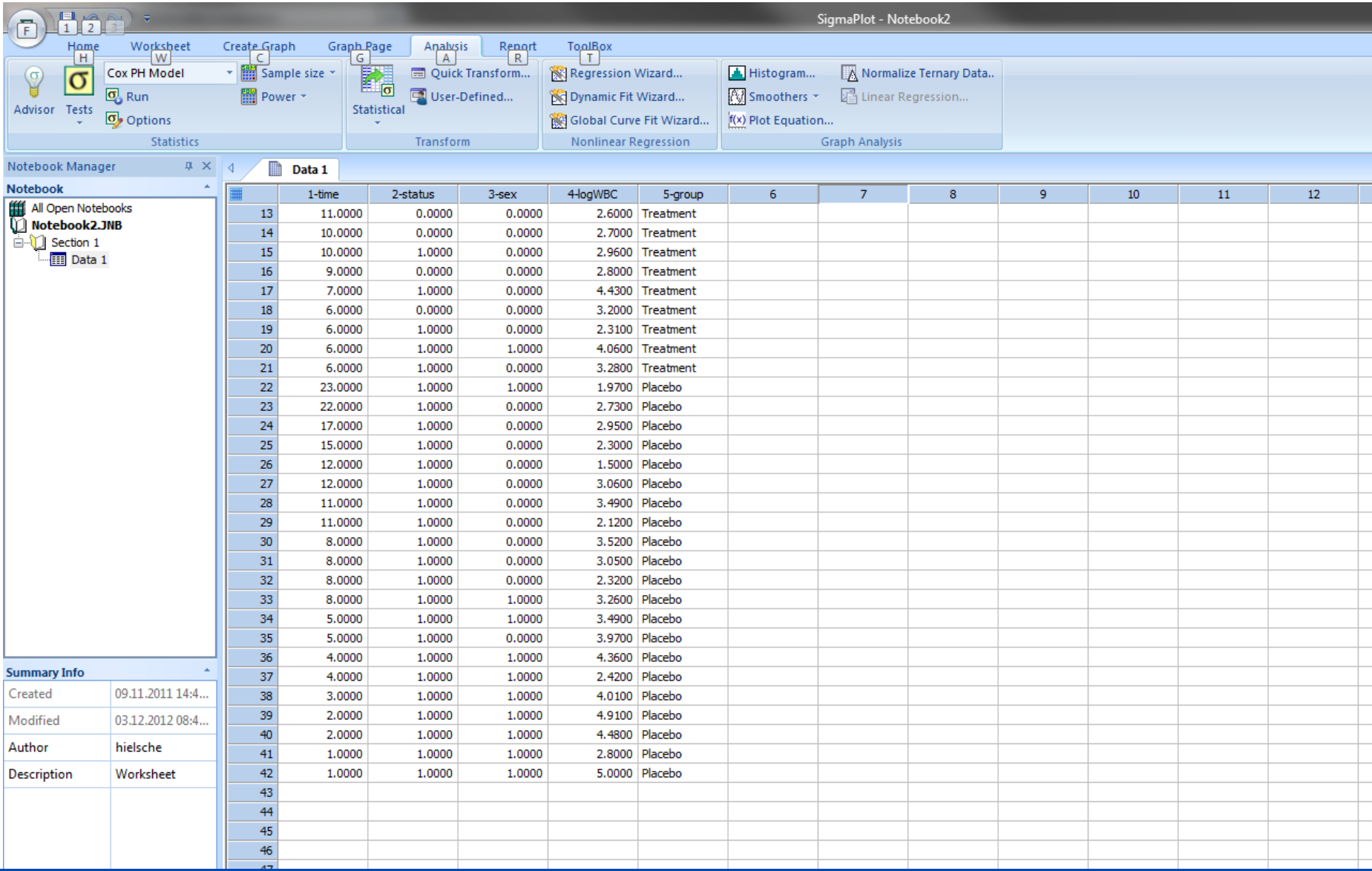
46												

How to analyze with SigmaPlot?



	1-time	2-status	3-sex	4-logWBC	5-group	6	7	8	9	10	11	12
13	11.0000	0.0000	0.0000	2.6000	Treatment							
14	10.0000	0.0000	0.0000	2.7000	Treatment							
15	10.0000	1.0000	0.0000	2.9600	Treatment							
16	9.0000	0.0000	0.0000	2.8000	Treatment							
17	7.0000	1.0000	0.0000	4.4300	Treatment							
18	6.0000	0.0000	0.0000	3.2000	Treatment							
19	6.0000	1.0000	0.0000	2.3100	Treatment							
20	6.0000	1.0000	1.0000	4.0600	Treatment							
21	6.0000	1.0000	0.0000	3.2800	Treatment							
22	23.0000	1.0000	1.0000	1.9700	Placebo							
23	22.0000	1.0000	0.0000	2.7300	Placebo							
24	17.0000	1.0000	0.0000	2.9500	Placebo							
25	15.0000	1.0000	0.0000	2.3000	Placebo							
26	12.0000	1.0000	0.0000	1.5000	Placebo							
27	12.0000	1.0000	0.0000	3.0600	Placebo							
28	11.0000	1.0000	0.0000	3.4900	Placebo							
29	11.0000	1.0000	0.0000	2.1200	Placebo							
30	8.0000	1.0000	0.0000	3.5200	Placebo							
31	8.0000	1.0000	0.0000	3.0500	Placebo							
32	8.0000	1.0000	0.0000	2.3200	Placebo							
33	8.0000	1.0000	1.0000	3.2600	Placebo							
34	5.0000	1.0000	1.0000	3.4900	Placebo							
35	5.0000	1.0000	0.0000	3.9700	Placebo							
36	4.0000	1.0000	1.0000	4.3600	Placebo							
37	4.0000	1.0000	1.0000	2.4200	Placebo							
38	3.0000	1.0000	1.0000	4.0100	Placebo							
39	2.0000	1.0000	1.0000	4.9100	Placebo							
40	2.0000	1.0000	1.0000	4.4800	Placebo							
41	1.0000	1.0000	1.0000	2.8000	Placebo							
42	1.0000	1.0000	1.0000	5.0000	Placebo							
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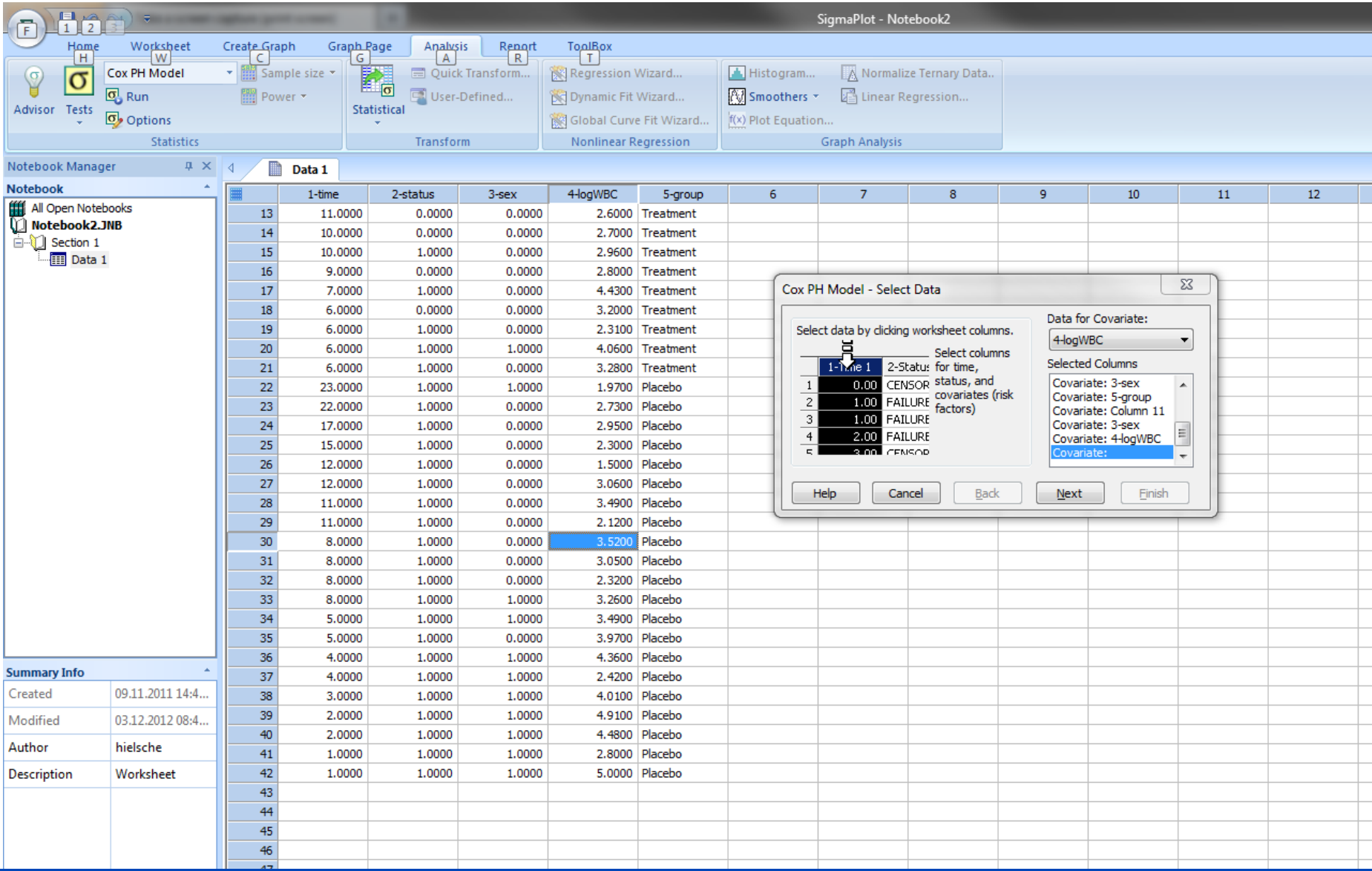

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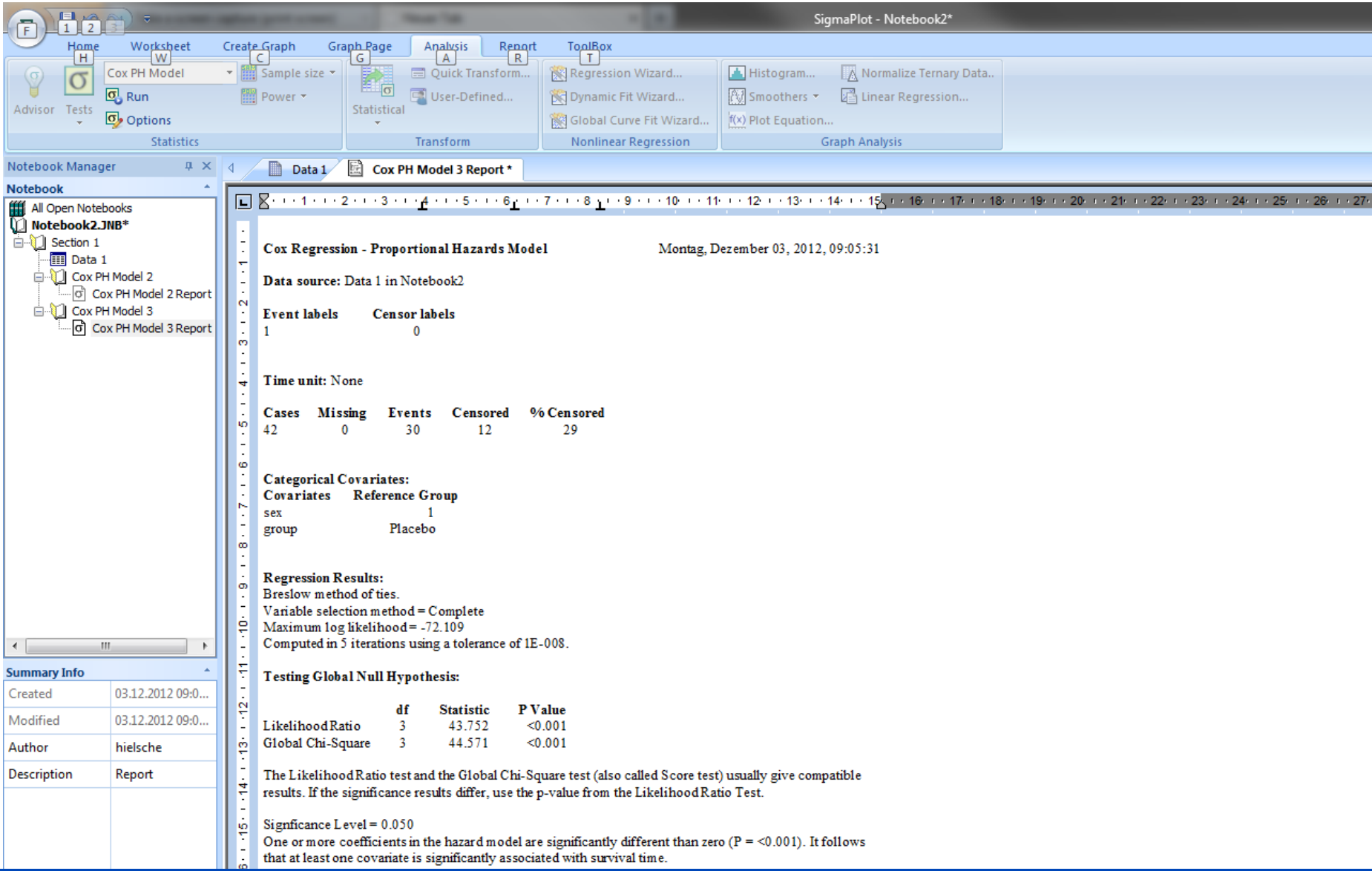

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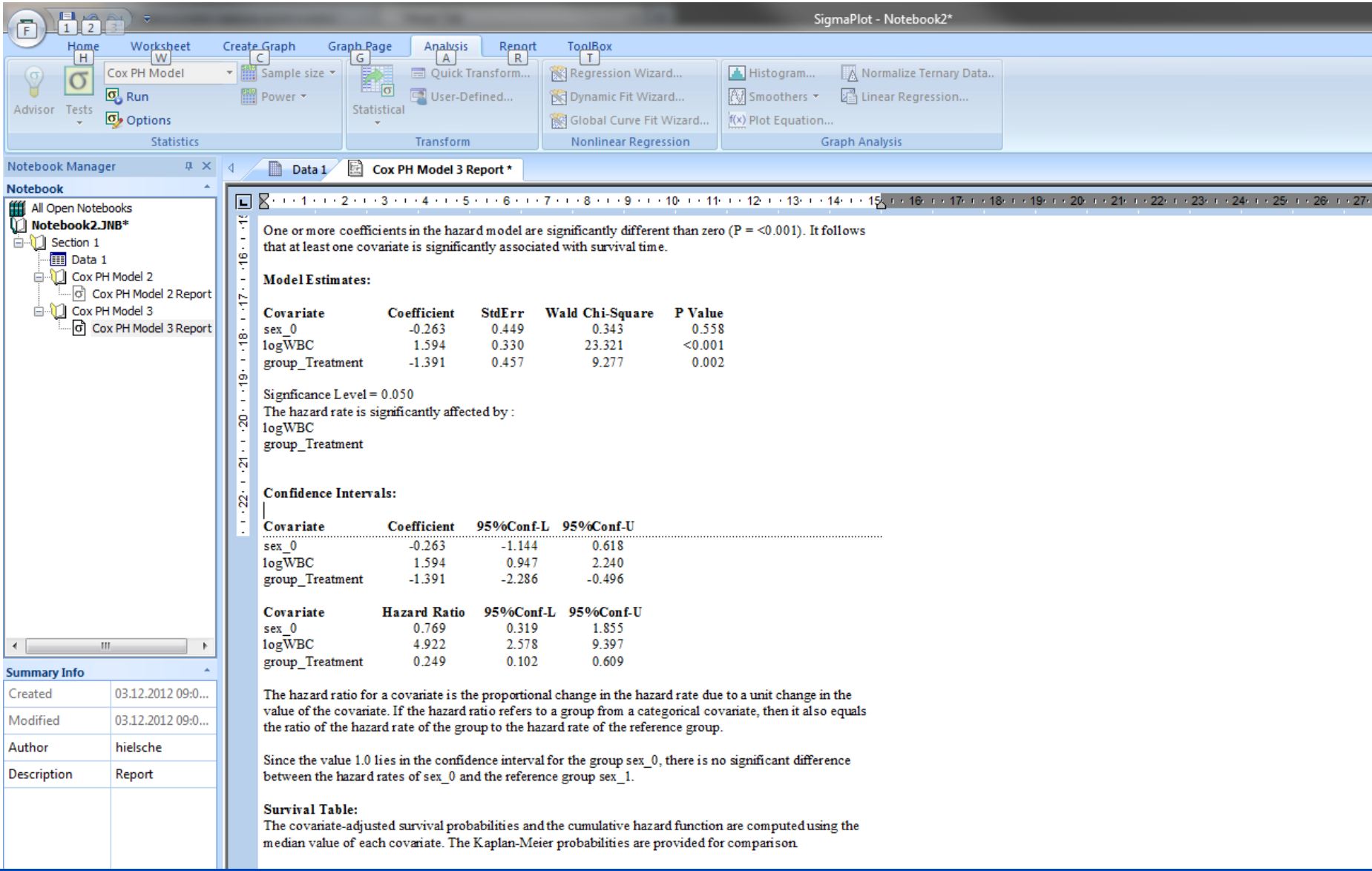


Competing Risk

Recap: Fundamental assumption of independence of event and censoring time distribution:

- Hazard of censored individuals = hazard of individuals remaining at risk
- risk for individual is not to change by censoring
- Violation leads to bias in Kaplan-Meier estimates

Examples

Violations

- loss to follow-up: if more healthy individuals drop out, survival curve will overestimate event rate
- loss to follow-up: toxicity-related drop-out, bias between (treatment-)groups
- competing risk: more than one possible cause of failure, competing risk event precludes occurence of event of interest or fundamentely alters the probability for this event
- Death due to cancer may be of interest, and death due to other causes (surgical mortality, old age) are competing risks.
- One could be interested in time to relapse with death due to any cause being a competing risk.

Approaches

1. Cause-specific hazards (CSH)
2. Cumulative Incidence Function (CIF)/ sub-distribution hazards (SH)

- there is no longer a one-to-one relation between hazard and survival for a certain type of event
- both approaches have pros/cons
- difference in interpretation/generalization

Cause-specific hazard

CSH: instantaneous rate of occurrence of event of cause k amongst the patients still event-free
$h_k(t) = f_k(t)/S(t)$

- cumulative CSHs $H_k(t)$ can be estimated and displayed
- overall hazard $h(t)$ is sum of all CSHs
- the survival function $S(t) = 1 - \sum_{j=1}^{k} F_j(t) = exp(-\sum_{j=1}^{k} H_j(t))$, This survival function is the probability of not having an event of any cause at time t.
- $S_k(t) = exp(-H_k(t))$ can be estimated but is not interpretable as marginal survival function

Cause-Specific Hazard (CSH) - inference

- Failures due to competing event(s) are censored
- non-parametric estimation of cumulative CSH: Nelson-Aalen estimator based on cause k:
  $\widehat{H_k(t)} = \sum_{t_i \leq t} \frac{d_i I(cause=k)}{n_i}$
- non-parametric group comparison: log-rank test
- cause-specific Cox model
- BUT: KM estimator is biased

Cumulative Incidence Function (CIF)

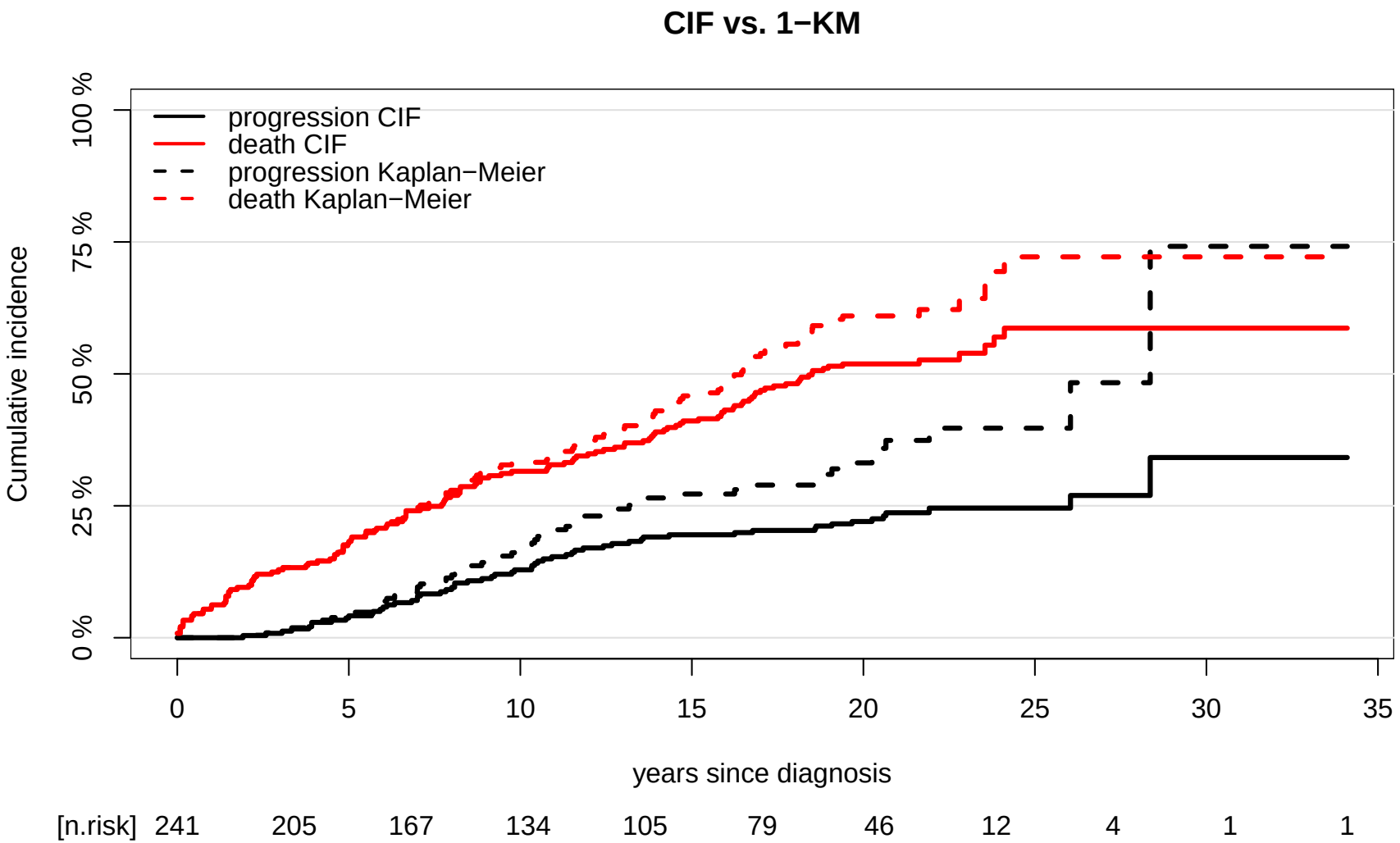
Probability of occurrence of a given event k by time t:
CIF for failure type k: $CIF_k = F_k(t) = P(T \leq t, cause = k)$

- if k=1, CIF = 1 - S(t), i.e. 1 - KM in estimation
- CIF is a crude probability, all risks act on the population, CIF depends on all CSHs
- CIF_k always < 1 if $k > 1$, hence not a proper probability distribution
- $CIF_k(t) \leq 1 - S_k(t)$, KM estimates biased, sum across all causes can exceed 1
- use CIF for graphical display in competing risk data

Cumulative Incidence Function (CIF)

- Aalen-Johansen estimator (non-parametric), like a cause-specific Nelson-Aalen estimator weighted by the overall survival function (KM estimates):
  $\widehat{CIF_k(t)} = \sum_{t_i \leq t} \frac{d_i I(cause=k)}{n_i} * KM_{t-1}$
- non-parametric group comparison: Gray's logrank type test compares CIFs

MGUS Example Data (Kyle et al)



Subdistribution hazards

subdistribution hazard (SH) $i_k(t) = f_k(t)/(1 - F_k(t))$

- SH can be estimated from CIF
- Fine and Gray model with competing events being modelled
- Subjects with competing event are kept in risk set

Interpretation

- CIF is affected by/accounts for hazard of competing event: Gray's test correctly detects whether there is a difference in cumulative incidence between groups for a given event, whether that difference is caused by a difference in hazards between the groups for the event itself or by a difference in hazards for the competing events.
- Gray's test will indicate, for example, that a treatment is beneficial with respect to one event type, when in fact the treatment has simply increased the incidence of a competing event.
- the log-rank test correctly detects differences in cause-specific hazards, and, unless there is strong dependence between failure times, is largely unaffected by between-group differences in hazards for other competing events

References

Clark, Bradburn, Love and Altman, 2003. Survival Analysis Part III: Survival Analysis Part II: Multivariate data analysis – an introduction to concepts and methods. British Journal of Cancer 89, 431-436.

Altman and Royston, 2006, The cost of dichotomizing continuous variables, BMJ, 332(7549): 1080.

SigmaPlot Statistics User Guide (PDF Manuals)

How to get support

- The biostatistics division C060 provides statistical support for all scientific activities of the DKFZ from in vitro and animal studies to human subject.
- Request statistical support via email to biostatistics-consulting@dkfz.de