Competing risks.

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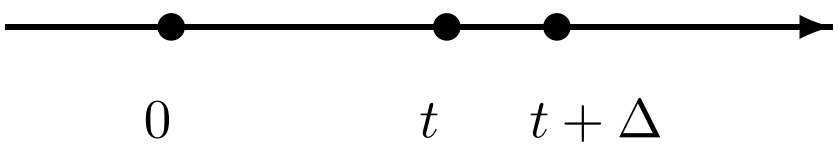
Summary:

- Introduction: survival analysis and competing risks as multi-state models
- Competing risks examples
- Mathematical formulations
- Inference for cause-specific hazards, examples
- Cumulative incidences, examples
- Regression analysis, examples
- Conclusions, references

Survival data

- X: time from "zero" to event (death)
- right-censoring at C: observe $\widetilde{X} = \min(X, C), D = I(\widetilde{X} = X)$
- (delayed entry)
- basic quantity:
  - hazard function (= death intensity = mortality rate)
  - $= \alpha(t) \approx \text{Prob}(\text{die before } t + \Delta \mid \text{alive } t)/\Delta$



Survival data

Survival function:
$S(t) = \text{Prob}(\text{alive time } t) = \exp(-\int_0^t \alpha(u)\mathrm{d}u) = \exp(-A(t))$.

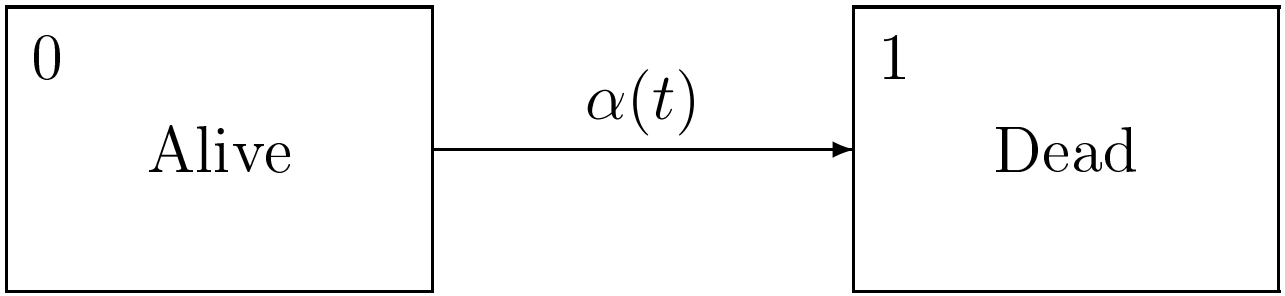
Likelihood based on independent $(\widetilde{X}_i, D_i, i = 1, \ldots, n)$:
$\prod_i S(\widetilde{X}_i)\alpha(\widetilde{X}_i)^{D_i}$.

Models for $\alpha(t)$:

- non-parametric: estimate $A(t)$ by Nelson-Aalen estimator
- parametric models: Weibull, piecewise exponential, ...
- regression: Cox, Poisson (piecewise exponential), ...
- ...

Simple one-to-one correspondance between the "local" parameter, the hazard, $\alpha(t)$, and the "global" parameter, the survival probability, $S(t)$.

Survival data as a two-state model.



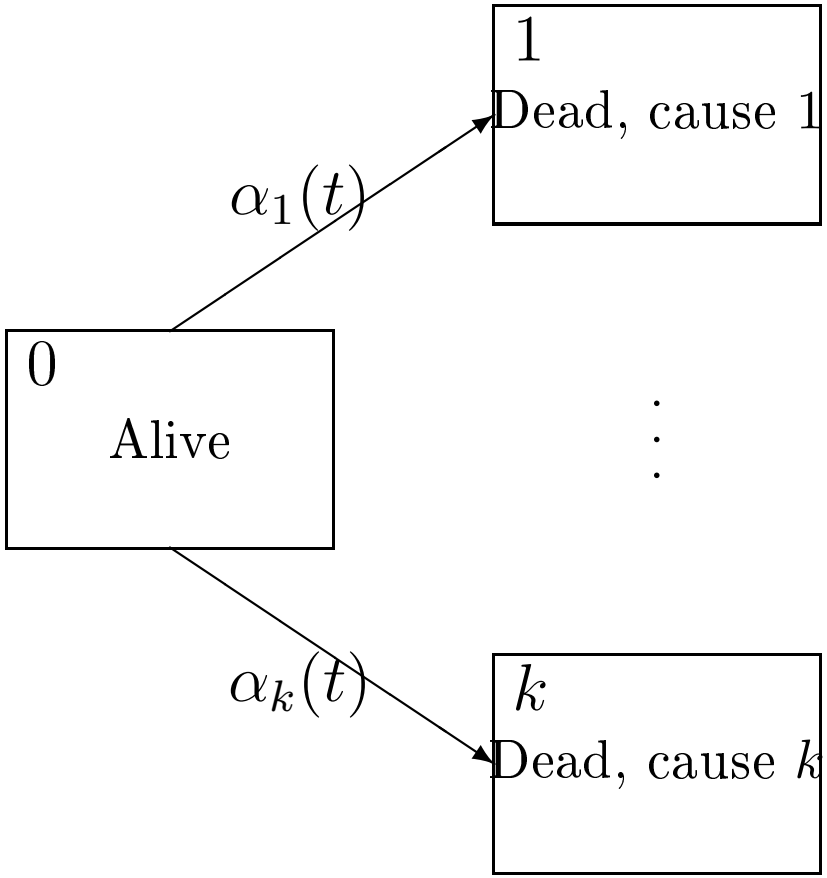
Transition intensity

$\alpha(t) \approx \text{Prob}(\text{state } 1 \text{ time } t+\Delta \mid \text{state } 0 \text{ time } t)/\Delta$

State occupation probabilities

$S(t) = \text{Prob}(\text{state } 0 \text{ time } t), \quad F(t) = 1 - S(t).$

Competing risks as a multi-state model.



Parameters.

Transition intensities: Cause-specific hazards, $j = 1, \ldots, k$:

$$\alpha_j(t) \approx \text{Prob}(\text{state } \ j \ \text{ time } \ t + \Delta \mid \text{state } \ 0 \ \text{ time } \ t)/\Delta,$$

State occupation probabilities:

$$S(t) = \text{Prob}(\text{state } 0 \text{ time } t),$$

$$F_j(t) = \text{Prob}(\text{state } j \text{ time } t), j = 1, \ldots, k.$$

$$S(t) + \sum_{j=1}^{k} F_j(t) = 1.$$

Radiation-exposed male mice, Hoel and Walburg (1972).

- 95 male mice in conventional lab. environment
- and 82 in germ-free lab. environment
- were exposed to 300 rad. at age 5-6 weeks
- and followed to death (NB: no censoring), classified (by necropsy) as
  - thymic lymphoma (cancer, solid line on figure, later)
  - reticulum cell sarcoma (also cancer, dashed line on figure, later)
  - other causes (dotted-dashed line on figure, later)
- Purpose: study temporal patterns of failure causes and compare between environments.

Bone marrow transplantation.

1715 leukemia patients with BMT: (Szydlo et al., 1997)

- 537 ALL, 340 AML, 838 CML
- 1026 early stage, 410 intermediate stage, 279 advanced stage
- 1224 HLA-identical sibling, 383 HLA-matched unrelated donor, 108 HLA-mismatched unrelated donor
- 311 patients relapsed, 557 died in remission.

Purpose:

- Study risk factors for relapse and death in remission

Register-based studies in psychiatric epidemiology.

References:

[1] Kessing, Nilsson, Siersma, Andersen, *Diabetes Research and General Practice*, 2003.

[2] Thomsen, Kvist, Andersen, Kessing, *Thyroid*, 2005

[3] Thomsen, Kvist, Andersen, Kessing, *European Journal of Endocrinology*, 2005

[4] Kessing, Harhoff, Andersen, *International Psychogeriatrics*, 2007.

Data extracted from Danish registers: *National Hospital Register, Psychiatric Central Research Register, Cause of Death Register, Medicinal Product Statistics Register.*

Data.

Study	[1]:		[2-3]:			[4]:	
Outcome	depression		affective disorders			antidepressants	
	Index	Control	Index	Control1	Control2	Index	Control
Diagnosis	Diabetes	Osteo.	Hyper-thyr.	Non-toxic goitre	Osteo.	Dementia	Osteo.
Number	91507	108487	28190	32687	122770	24137	100378
Median age	63.1	68.5	57.7	45.2	68.0	81.0	65.0
% females	48.1	59.7	84.2	85.3	58.8	60.6	58.8
Event (%)	0.38	0.46	1.2	0.8	0.6	43.2	16.0
Death (%)	50.7	32.8	27.7	11.3	34.4	30.7	6.7

Osteo.=osteoarthritis, Hyper-thyr.=hyper-thyroidism

Common features for psychiatric studies.

Purpose: compare risk of outcome between index and control groups.

- Large samples
- Death competing event
- Death rates high
- Death rates may differ between index and control groups

Mathematical formulation (1).

X, survival time, D cause of failure, joint distribution:

$$P(X \leq t, D = j).$$

Cause-specific hazards:

$$\alpha_j(t) = \lim_{\Delta \to 0} \frac{P(X \leq t + \Delta, D = j \mid X \geq t)}{\Delta}.$$

Marginal distribution of X: survival function

$$S(t) = P(X > t) = \exp(-\sum_j \int_0^t \alpha_j(u) \mathrm{d}u).$$

Total hazard is $\alpha(t) = \sum_{j=1}^k \alpha_j(t)$.

Mathematical formulation (2).

Latent failure times

$$X_1^L, \ldots, X_k^L,$$

observe $\min\{X_1^L, \ldots, X_k^L\}$ and corresponding D.

Joint survival distribution:

$$Q(t_1, \ldots, t_k) = P(X_1^L > t_1, \ldots, X_k^L > t_k).$$

Relations between the two formulations:

$$S(t) = Q(t, \ldots, t),$$

$$\alpha_j(t) = -\frac{\partial \log Q(t_1, \ldots, t_k)}{\partial t_j} \rfloor_{t_1 = \cdots = t_k = t}.$$

Parameter identification.

Which parameters may be identified from the competing risks data $(X_i, D_i), i = 1, \ldots, n$?

(or from similar right-censored data $(\widetilde{X}_i, D_i), i = 1, \ldots, n$ where either $X_i = \widetilde{X}_i$ and $D_i \in \{1, \ldots, k\}$ or $X_i > \widetilde{X}_i$ and $D_i = 0$.)

Likelihood: $\prod_i S(\widetilde{X}_i) \prod_j (\alpha_j(\widetilde{X}_i))^{I(D_i=j)}$.

From this we may identify the cause specific hazards $\alpha_j(t)$ but not the whole joint distribution $Q(\cdot)$ of the "latent failure times" $X_1^L, \ldots, X_k^L$.

For instance NOT the "marginal distribution" of X_j^L:
$P(X_j > t_j) = Q(0, \ldots, 0, t_j, 0, \ldots, 0) = S_j(t_j)$

with ("net") hazard function $h_j(t) = -\partial \log S_j(t)/\partial t$.

"Independent" competing risks.

Definition: $X_1^L, \ldots, X_k^L$ are independent, i.e.
$Q(t_1, \ldots, t_k) = \prod_j S_j(t_j)$

or (weaker): marginal (or "net") and cause-specific ("crude") hazards are identical: $\alpha_j(t) = h_j(t)$.

Since $S_j(t)$ and $h_j(t)$ cannot be identified from the data (without further, unidentifiable conditions) these assumptions are unverifiable.

Likewise: the question of "what would happen if certain causes were removed" ("partial crude hazards") is quite hypothetical in most biological settings.

(Sensitivity analysis?)

Possible exception: failure of technical systems due to components in "unrelated parts" of the system.

"Counterexample".

Kalbfleisch and Prentice (2002). Let $k = 2$ and:

$$Q(t_1, t_2) = \exp(1 - \alpha_1 t_1 - \alpha_2 t_2 - \exp(\alpha_{12}(\alpha_1 t_1 + \alpha_2 t_2))).$$

Cause-specific hazards: $\alpha_j(t) = \alpha_j(1 + \alpha_{12} \exp(\alpha_{12}(\alpha_1 + \alpha_2)t))$.

If $\alpha_{12} = 0$ then risks 1 and 2 are "independent". However, likelihood would be the same if the model was

$$Q^*(t_1, t_2) = \exp(1 - \alpha_1 t_1 - \alpha_2 t_2)$$
$$\times \exp(-\frac{\alpha_1 e^{\alpha_{12}(\alpha_1+\alpha_2)t_1} + \alpha_2 e^{\alpha_{12}(\alpha_1+\alpha_2)t_2}}{\alpha_1 + \alpha_2})$$

risks are independent (also for $\alpha_{12} \neq 0$); cause-specific hazards are the same (but marginal hazards are different).

Identifiable probabilities.

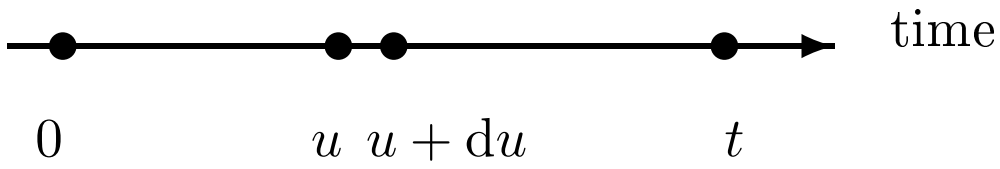
These are the state occupation probabilities in the competing risks multi-state model. That is,

the overall survival function:

$$S(t) = \exp(-\sum_j \int_0^t \alpha_j(u)\mathrm{d}u),$$

and the *cumulative incidences*:

$$F_j(t) = \int_0^t S(u-)\alpha_j(u)\mathrm{d}u, j = 1, \ldots, k.$$



Inference for cause-specific hazards.

Likelihood:

$$\prod_{i=1}^{n} S(\widetilde{X}_i) \prod_{j=1}^{k} (\alpha_j(\widetilde{X}_i))^{I(D_i=j)}$$

$$= \prod_{i=1}^{n} \big(\exp(-\sum_{j=1}^{k} A_j(\widetilde{X}_i))\big) \prod_{j=1}^{k} (\alpha_j(\widetilde{X}_i))^{I(D_i=j)}$$

$$= \prod_{j=1}^{k} \big(\prod_{i=1}^{n} \exp(-A_j(\widetilde{X}_i))(\alpha_j(\widetilde{X}_i))^{I(D_i=j)}\big).$$

Note:

- Product over causes, j,
- The jth factor is what we would get if only that cause was studied *and all other causes were right-censorings*

Inference for cause-specific hazards.

- This has nothing to do with "independence" of causes - it is solely a consequence of the definition of cause-specific hazards as hazards of exclusive events.
- It means that all standard hazard-based models for survival data apply when analyzing cause-specific hazards
  - non-parametric: estimate $A_j(t) = \int_0^t \alpha_j(u)\mathrm{d}u, j = 1, \ldots, k$ by Nelson-Aalen estimator, compare using, e.g. logrank tests
  - parametric models
  - Cox regression, Poisson regression
  - ...

Radiation-exposed male mice, Hoel and Walburg (1972).

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- and 82 in germ-free lab. environment
- were exposed to 300 rad. at age 5-6 weeks
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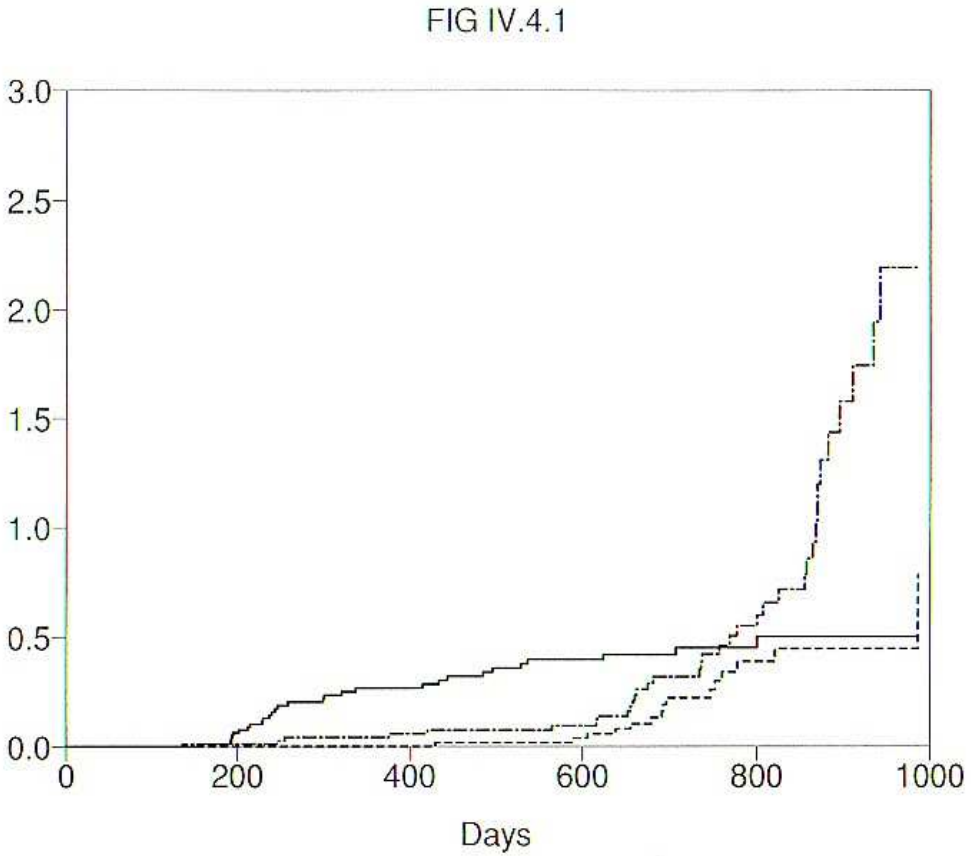
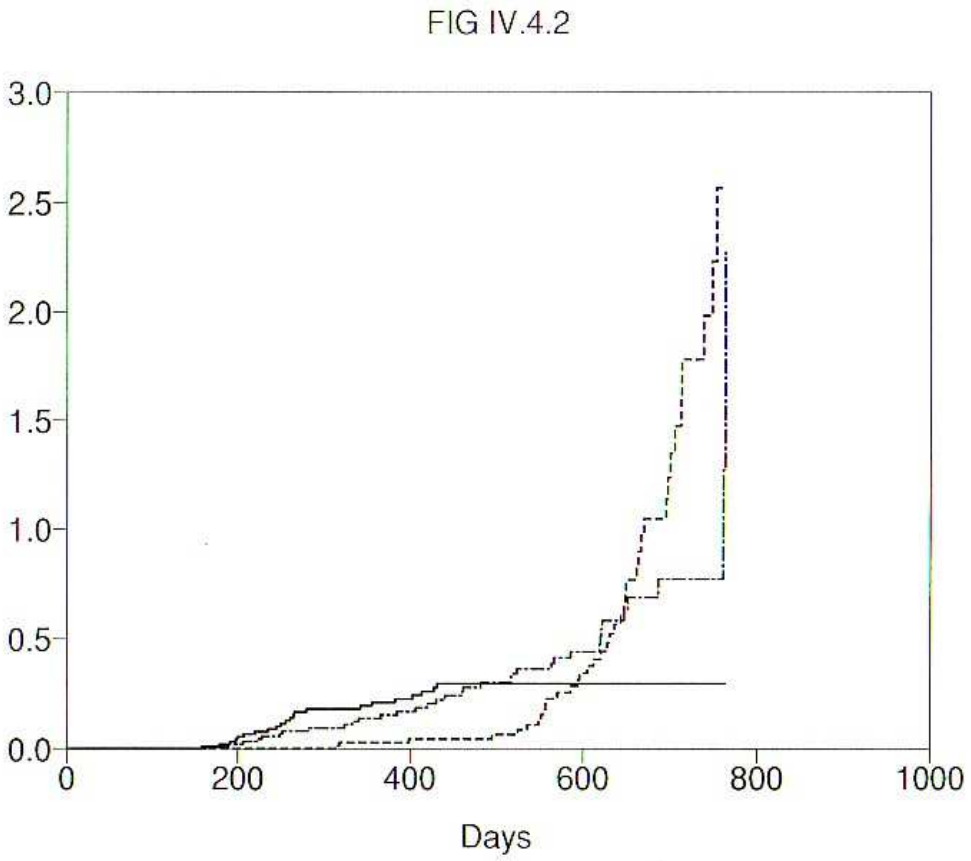
- Purpose: study temporal patterns of failure causes and compare between environments.

Nelson-Aalen estimates, germ-free mice.



Nelson-Aalen estimates, conventional mice.



Radiation-exposed male mice, Hoel and Walburg (1972).

Cox models for cause-specific hazards: conventional vs. germ-free

- TL $\widehat{\beta}$ =-0.323 (0.286) (solid)
- RCS $\widehat{\beta}$ =2.004 (0.345) (dashed)
- OC $\widehat{\beta}$ =1.080 (0.304) (dotted-dashed)

Bone marrow transplantation.

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Analysis:

- Cox regression models for cause-specific hazards of "relapse" and "death in remission"

Cox regression models for cause-specific hazards

	Relapse		Death	
Covariate	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)
HLA-id. sibling	0	-	0	-
HLA-matched donor	0.011	0.15	0.811	0.097
HLA-mismatched donor	-0.944	0.36	1.118	0.14
ALL	0	-	0	-
AML	-0.271	0.15	-0.195	0.14
CML	-0.721	0.16	0.291	0.117
Early stage	0	-	0	-
Intermed. stage	0.640	0.15	0.474	0.10
Advanced stage	1.848	0.15	0.781	0.13
Karnofsky$>$ 90	-0.118	0.14	-0.504	0.11

Register-based studies in psychiatric epidemiology.

Study	[1]		[2-3]:			[4]:	
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Osteo.=osteoarthritis, Hyper-thyr.=hyper-thyroidism

Models for cause-specific hazards.

Due to the large sample sizes *Poisson* regression models are natural choices for hazard models. This is because tables of events and person-years according to (categorical) explanatory variables are sufficient for the parameters in the model.

Models used:

$$\alpha_j(t \mid Z) = \alpha_{j0}(t) \exp(\beta_j' Z(t)), j = 1, 2$$

where t =age, $\alpha_{j0}(t) = \alpha_{j\ell}$ when $t \in (a_\ell, a_{\ell+1})$, and $Z(t)$ includes diagnosis, gender, time since diagnosis, calendar time, ... as categorical variables (and possible interactions).

Some results: rate ratios.

[2]: Hyperthyroidism and affective disorders:

	0-0.5 years	0.5-1 years	1 year+
Hyperthyroidism	3.60 (2.58,5.04)	2.47 (1.57,3.90)	1.34 (1.14,1.56)
Non-toxic goitre	1.46 (0.92,2.30)	1.27 (0.71,2.27)	1.00 (0.84,1.18)
Osteoarthritis	1 (ref)	1 (ref)	1 (ref)

[4]: Dementia and purchase of anti-depressants

	Overall	Women	Men
Dementia	4.17 (4.05,4.29)	3.67 (3.55,3.80)	5.49 (5.24,5.75)
Osteoarthritis	1 (ref)	1 (ref)	1 (ref)

Cumulative incidences.

Recall:

$$F_j(t) = \int_0^t S(u-)\alpha_j(u)\mathrm{d}u, j = 1, \ldots, k$$

$$= \int_0^t \exp(-\sum_{h=1}^{k} A_h(u-))\alpha_j(u)\mathrm{d}u, j = 1, \ldots, k.$$

Note that $F_j(t)$, via $S(u) = \exp(-\sum_{h=1}^{k} A_h(u-))$, depends on the cause-specific hazards for *all causes*: think of cancer and cardio-vascular mortality in smokers.

That is, the simple one-to-one correspondance between the "rate", $\alpha_j(t)$, and the "risk", $F_j(t)$, which we are used to from simple survival analysis does no longer hold when competing risks are operating.

This is the key to understanding competing risks!

Rates and risks.

Comparison of rates (cause-specific hazards) and risks (cumulative incidences differ):

$\alpha_j^{(1)}$	$\alpha_j^{(2)}$	$\alpha_h^{(1)}$	$\alpha_h^{(2)}$	$\frac{\alpha_j^{(2)}}{\alpha_j^{(1)}}$	$\frac{F_j^{(2)}(t_1)}{F_j^{(1)}(t_1)}$	$\frac{F_j^{(2)}(t_2)}{F_j^{(1)}(t_2)}$
0.1	0.2	1.0	2.0	2	1.33287^{*}	1.11080^{*}
0.1	0.2	2.0	1.0	2	2.78712	3.23094
0.1	0.1	1.0	2.0	1	0.68902	0.58025
0.1	0.1	2.0	1.0	1	1.45134	1.72340
0.1	0.2	1.0	1.0	2	1.92038	1.87474
0.1	0.1	1.0	1.0	1	1.00000	1.00000
0.1	0.2	0.1	0.2	2	1.81873^{**}	1.67032^{**}
0.1	0.2	0.2	0.1	2	2.00000	2.00000
0.1	0.1	0.1	0.2	1	0.95321	0.91238
0.1	0.1	0.2	0.1	1	1.04909	1.09604
0.1	0.2	0.1	0.1	2	1.90642	1.82475
0.1	0.1	0.1	0.1	1	1.00000	1.00000

Inference for cumulative incidences.

Estimate for $F_j(t)$: plug-in.

For simple non-parametric inference, plugging the Nelson-Aalen estimator into $F_j(t)$ gives the estimator

$$\widehat{F}_j(t) = \int_0^t \widehat{S}(u-)\mathrm{d}\widehat{A}_j(u),$$

where $\widehat{S}$ is the Kaplan-Meier estimator for the overall survival function, S.

This is a simple special case of the general *Aalen-Johansen estimator* for non-homogeneous Markov processes.

A variance estimator is also available.

Sidetrack.

In the competing risks model, what is the interpretation of

$$\bar{F}_j(t) = 1 - \exp(-\int_0^t \alpha_j(u)\mathrm{d}u)?$$

It is: Prob(Dead from cause j before t) **IF** all other $\alpha_h(t) = 0$, i.e. if the competing risks did not exist!

It can, therefore, only be interpreted in a hypothetical population where mortality from causes other than cause j have been eliminated (and where the mortality from cause j is still given by the same $\alpha_j(t)$ - "independent competing riks").

This is an untestable assumption and the estimator $\widehat{\bar{F}}_j(t)$ should not be used.

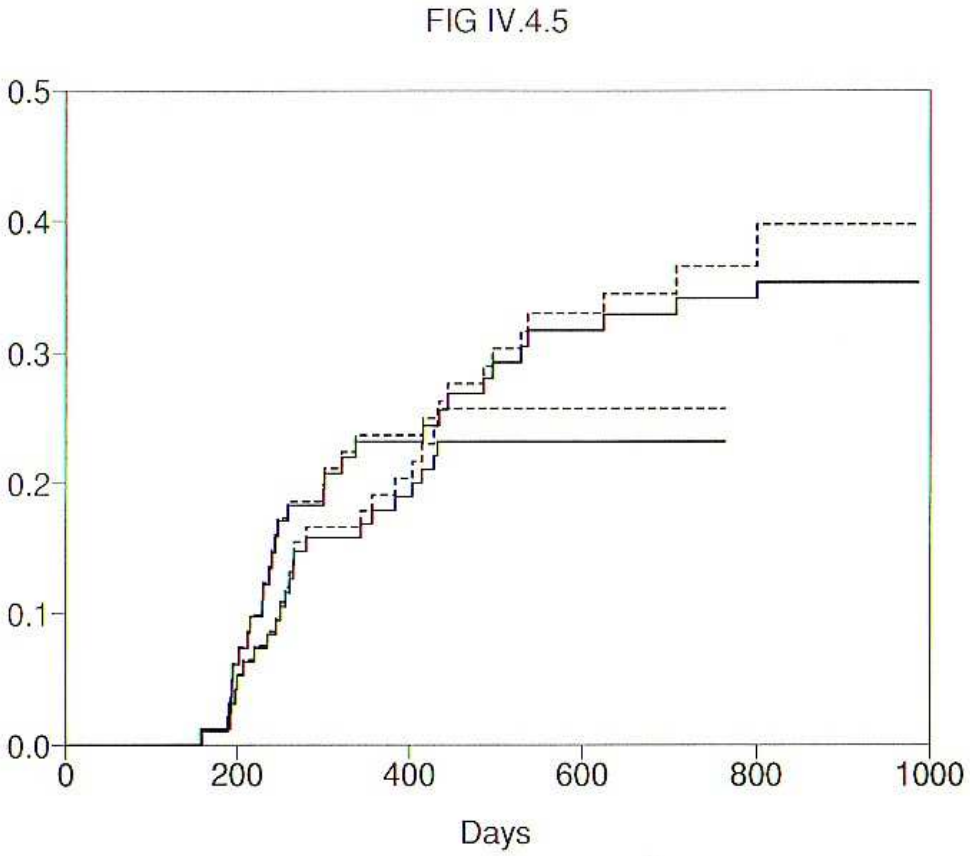
It has, in fact, been used extensively in, e.g. clinical cancer studies: "Relapse survival curve".

The paradox is that $\widehat{A}_j(t)$, the cumulative cause-specific hazard, **is not** problematic (except for the fact that a cumulative hazard is hard to interpret), but presenting this as a "Kaplan-Meier-type" estimator **is** problematic since this does not have a probability interpretation.

The magnitude of this problem, obviously, depends on the magnitude of the competing risk; but note that we always have: $\bar{F}_j(t) \geq F_j(t)$.

The quantity $\bar{F}_j(t)$ corresponds to the *partial* Markov process where all transition intensities other than $\alpha_j(t)$ are set to 0.

Radiation-exposed male mice, thymic lymphoma.



Censoring in survival studies

When, in survival studies, we draw the Kaplan-Meier estimator only the death intensity is taken into account - NOT the censoring intensity. This makes sense if **BOTH**: (I), the population without censoring makes sense **AND**: (II), censoring is *"independent"*.

Example: event = death due to cancer, consider censoring due to:

- end of study
- emigration
- loss to follow-up
- death due to traffic accidents
- death due to cardiovascular diseases

The magnitude of the first problem (I) depends on the magnitude of the competing risk.

BMT study: Cox regression models for cause-specific hazards

	Relapse		Death	
Covariate	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)
HLA-id. sibling	0	-	0	-
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Karnofsky$>$ 90	-0.118	0.14	-0.504	0.11

BMT study: cumulative incidences for relapse.

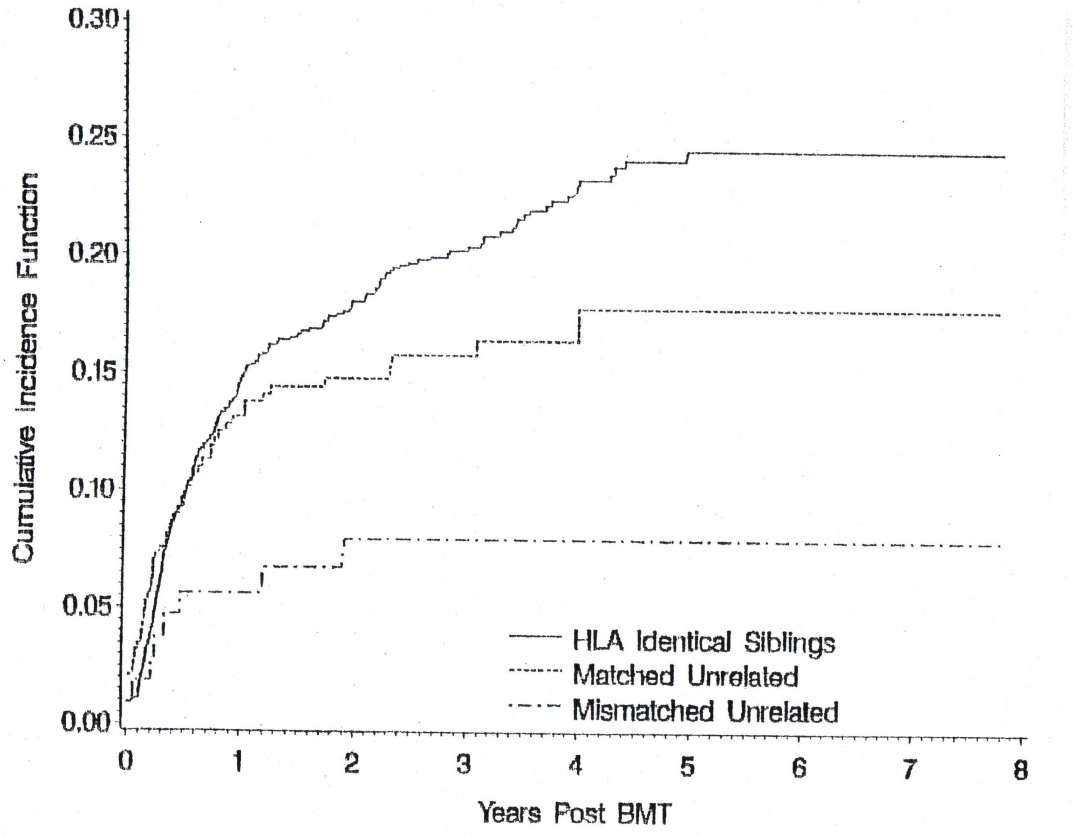

Figure 1. Cumulative incidence of relapse.

Time-dependent covariates.

As in many standard hazard-based models for survival data, time-dependent covariates are easily accomodated in models for cause-specific hazards.

However, as in standard survival models, the one-to-one relation between hazard and probability only holds when time-dependent covariates are exogenous or deterministic. If covariates are endogeneous ("truly random") then the survival probability depends on the possible future development of the time-dependent covariate.

Models used in psychiatric epidemiology studies:

$$\alpha_j(t \mid Z) = \alpha_{j0}(t) \exp(\beta' Z(t)), j = 1, 2$$

where t =age, $\alpha_{j0}(t) = \alpha_{j\ell}$ when $t \in (a_\ell, a_{\ell+1})$, and $Z(t)$ includes diagnosis, gender, time since diagnosis, calendar time, ... as categorical variables (and possible interactions).

Some results.

[2]: Hyperthyroidism and affective disorders - rate ratios (**).

	0-0.5 years	0.5-1 years	1 year+
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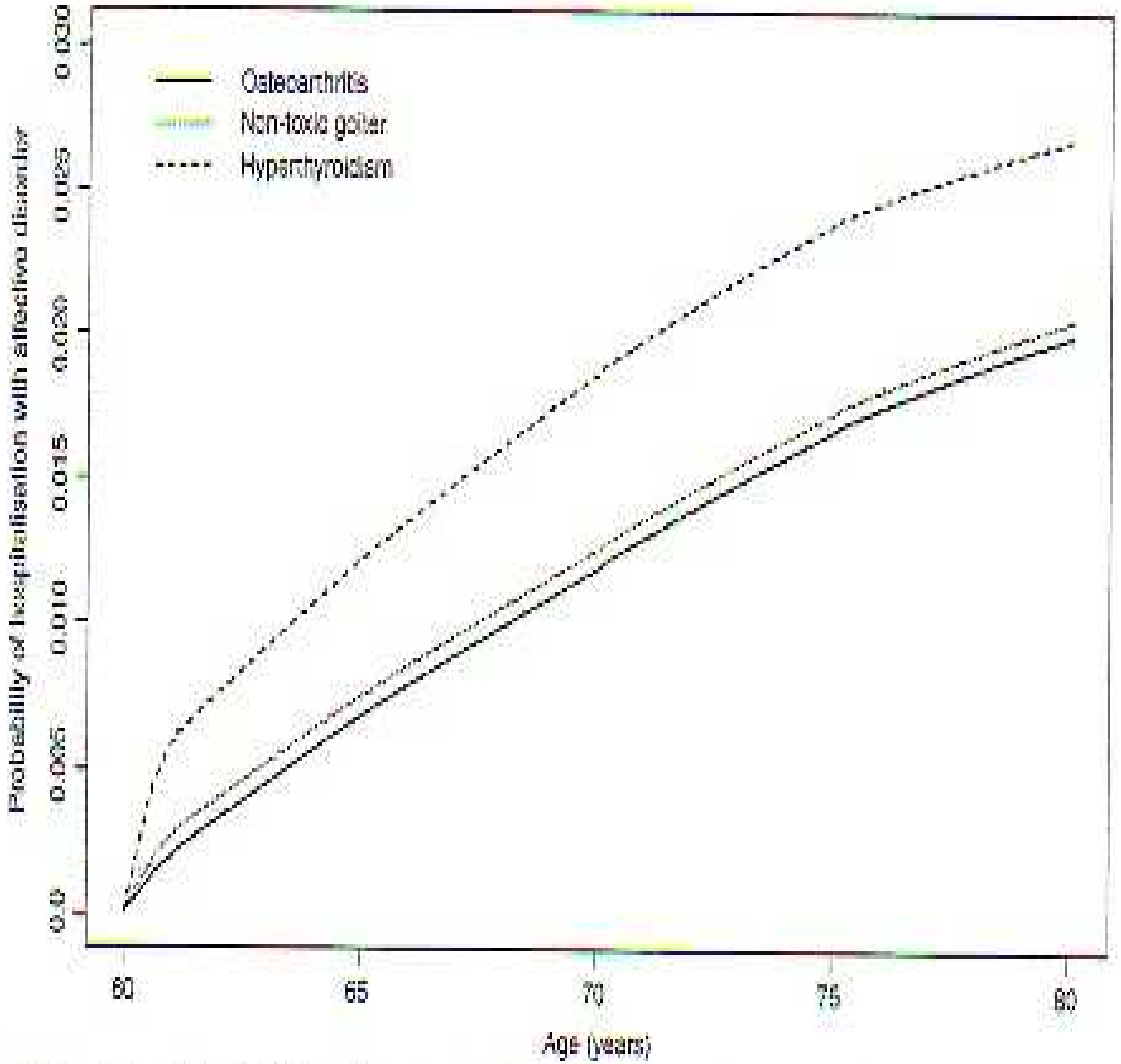


Figure 1 Estimated probability of admission with a resulting discharge diagnosis of affective disorder for women from each of the study cohorts (osteoarthritis, non-toxic goitre, hyperthyroidism), hospitalised with an index episode at 50 years of age. The estimated probabilities relate to the calendar period 1 January 1994 to 31 December 1999.

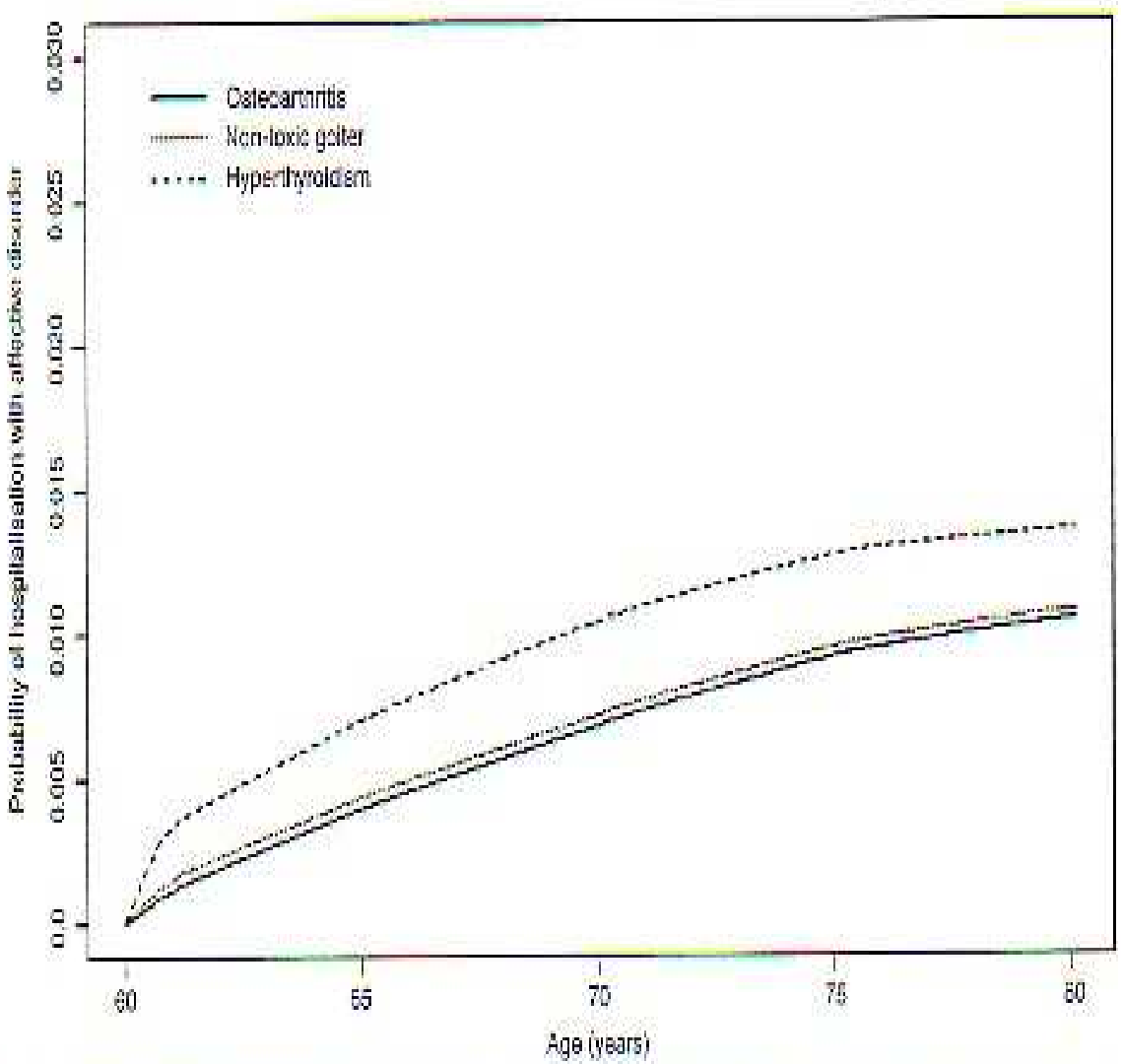
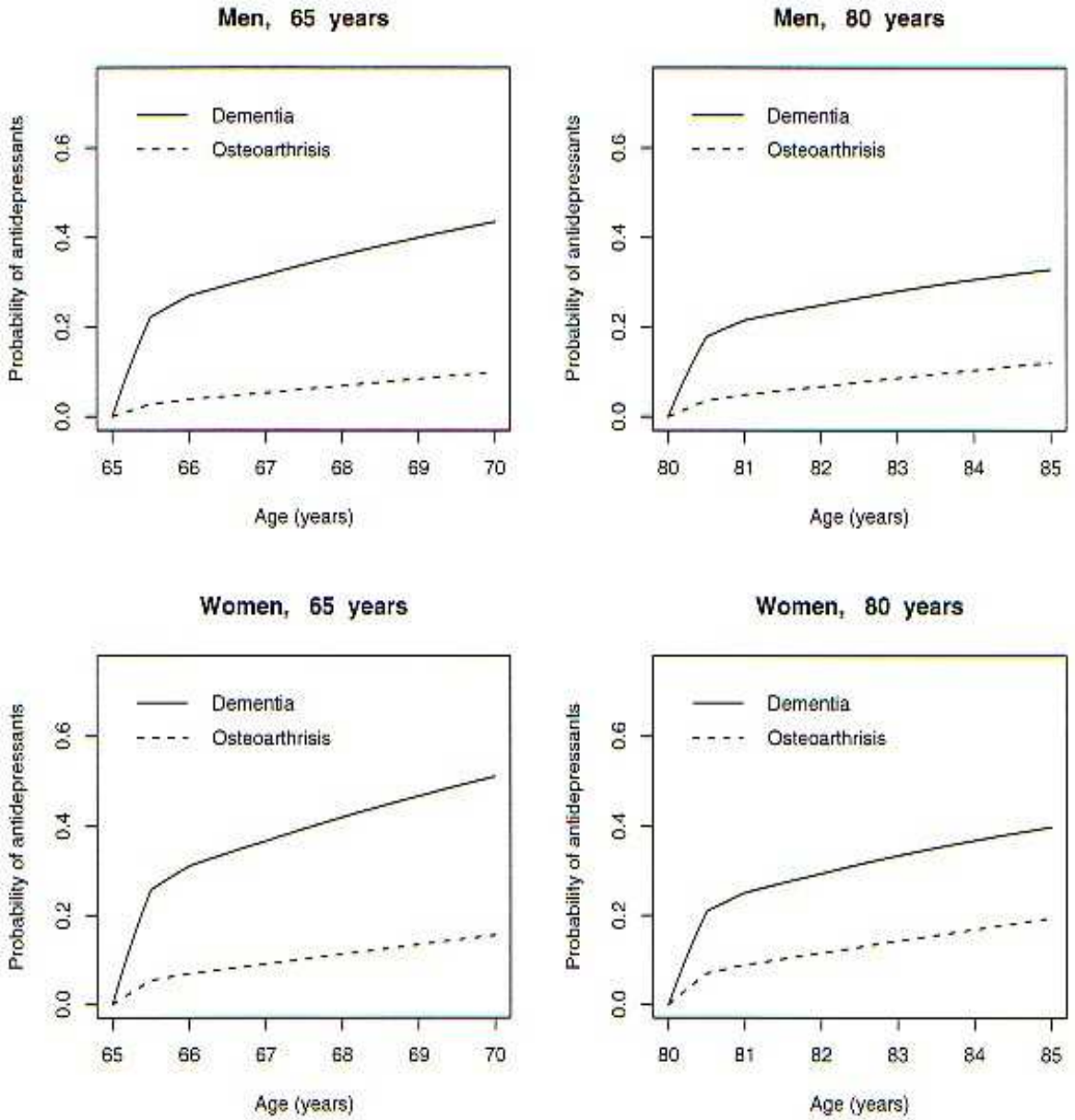


Figure 2 Estimated probability of admission with a resulting discharge diagnosis of affective disorder for men from each of the study cohorts (osteoarthritis, non-toxic goitre, hyperthyroidism), hospitalised with an index episode at 60 years of age. The estimated probabilities relate to the calendar period 1 January 1994 to 31 December 1999.

Some results.

[4]: Dementia and purchase of antidepressants - rate ratios (∗).

	Overall	Women	Men
Dementia	4.17 (4.05,4.29)	3.67 (3.55,3.80)	5.49 (5.24,5.75)
Osteoarthritis	1 (ref)	1 (ref)	1 (ref)


Men, 65 years
Men, 80 years
Women, 65 years
Women, 80 years
Dementia
Osteoarthrisis
Probability of antidepressants
Age (years)
0.0
0.2
0.4
0.6
65
66
67
68
69
70
80
81
82
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Regression models for competing risks

- Models for rates (cause-specific hazards):
  - all well-known hazard regression models from survival analysis
- Models for risks (cumulative incidences):
  - plug in models for rates: no simple covariate effects, but prediction of cumulative incidence for given covariates is possible (e.g., psychatric studies). Standard errors available via the delta-method (Cox model: Andersen, Hansen and Keiding (1992, *SJS*), Cheng, Fine and Wei (1998, *Biometrics*); additive hazard model: Shen and Cheng (1999, *Biometrics*); flexible "Cox-Aalen" model: Scheike and Zhang (2003, *Biometrics*)).

- Direct regression models
  - Fine & Gray (1999, *JASA*), cloglog model: (Sub-distribution) hazard for $X_j^* = X \cdot I(D = j) + \infty \cdot I(D \neq j)$ is $\tilde{\alpha}_j(t) = -\frac{\mathrm{d}}{\mathrm{d}t} \log(1 - F_j(t))$, model: $\log(\tilde{\alpha}_j(t \mid Z)) = \log(\tilde{\alpha}_{j0}(t)) + \beta^{\mathsf{T}} Z$ where β is estimated by partial likelihood with no or known censoring and by an IPCW score equation with general censoring. Related to the Gray (1988, *Ann. Statist.*) test for comparison of cumulative incidences.
  - Fine (1999, *JRSS B*, 2001, *Biostatistics*), general links
  - pseudo-observations (Andersen, Klein et al., *Biometrika*, 2003; *Biometrics*, 2005; *SJS*, 2007),
  - Direct binomial regression using inverse probability of censoring weights (Scheike & Zhang, 2007, *SJS*, Scheike, Zhang & Gerds *Biometrika*)
  - (The latter two work for more general multi-state models.)

Direct models for probabilities:

Without censoring, the counting process $N_{ij}(t) = I(X_i \leq t, D_i = j)$ is observed and its values can be used as outcome variables in a regression model.

1. Pseudo-observations:

$\hat{\theta}(t) = \widehat{F}_j(t)$ estimator based on entire sample,

$\hat{\theta}_{-i}(t)$ estimator based on data obtained by deleting i.

Pseudo-observation no. i is then given by

$$\hat{\theta}_i(t) = n \cdot \hat{\theta}(t) - (n-1) \cdot \hat{\theta}_{-i}(t).$$

For selected (all?) time points, $t_1, \ldots, t_m$, these are used as outcome variables in standard regression models using GEE with some choice of link function, e.g. cloglog, and sandwich estimator for variances.

Note that censoring must be independent of covariates.

2: Direct binomial regression:

Let

$$V_{ji} = X_i I(C_i > X_i, D_i = j) + \infty(I(D_i \neq j) + I(C_i < X_i)).$$

Then

$$\mathrm{E}\left(\frac{I(V_{ji} \leq t)}{S_C(V_{ji})}\right) = F_j(t),$$

and inverse probability of censoring weights (IPCW) can be used in the regression.

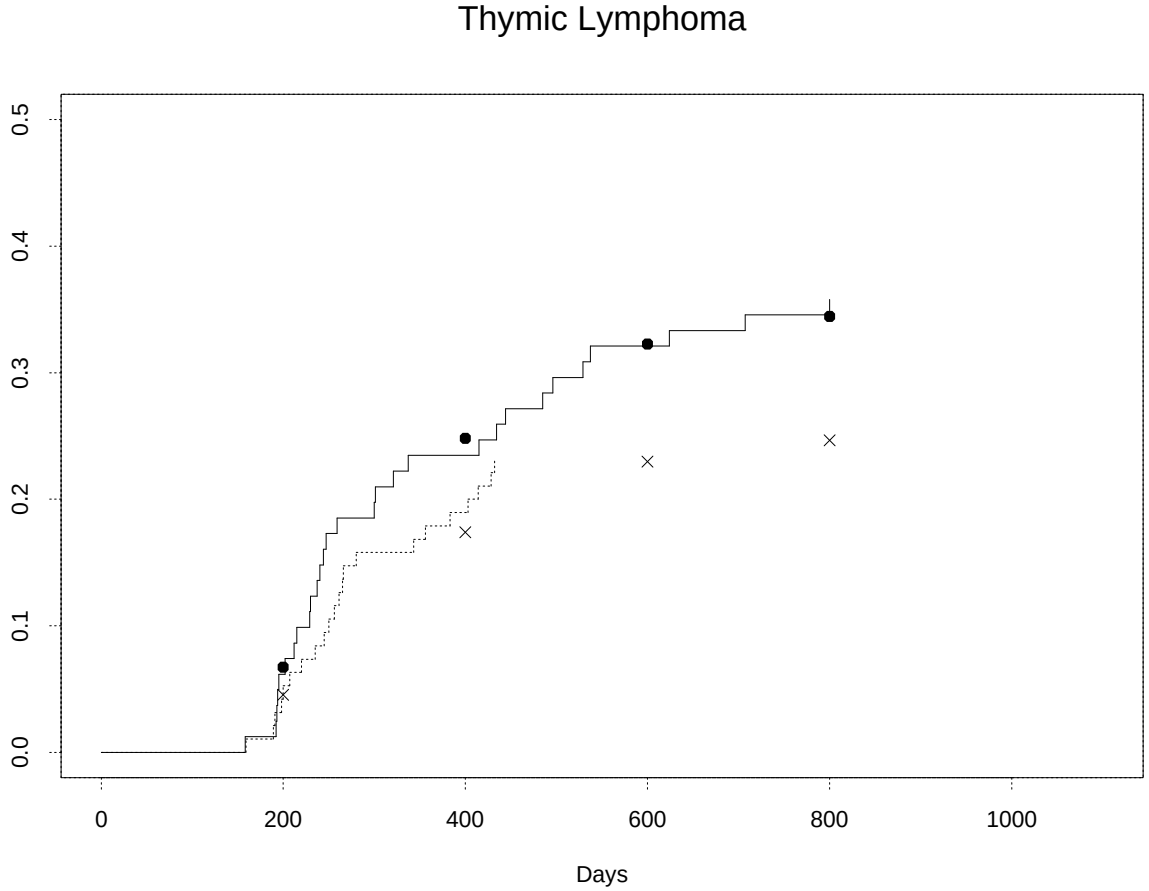
1. and 2. shown by Graw, Gerds & Schumacher (2007) to be equivalent:

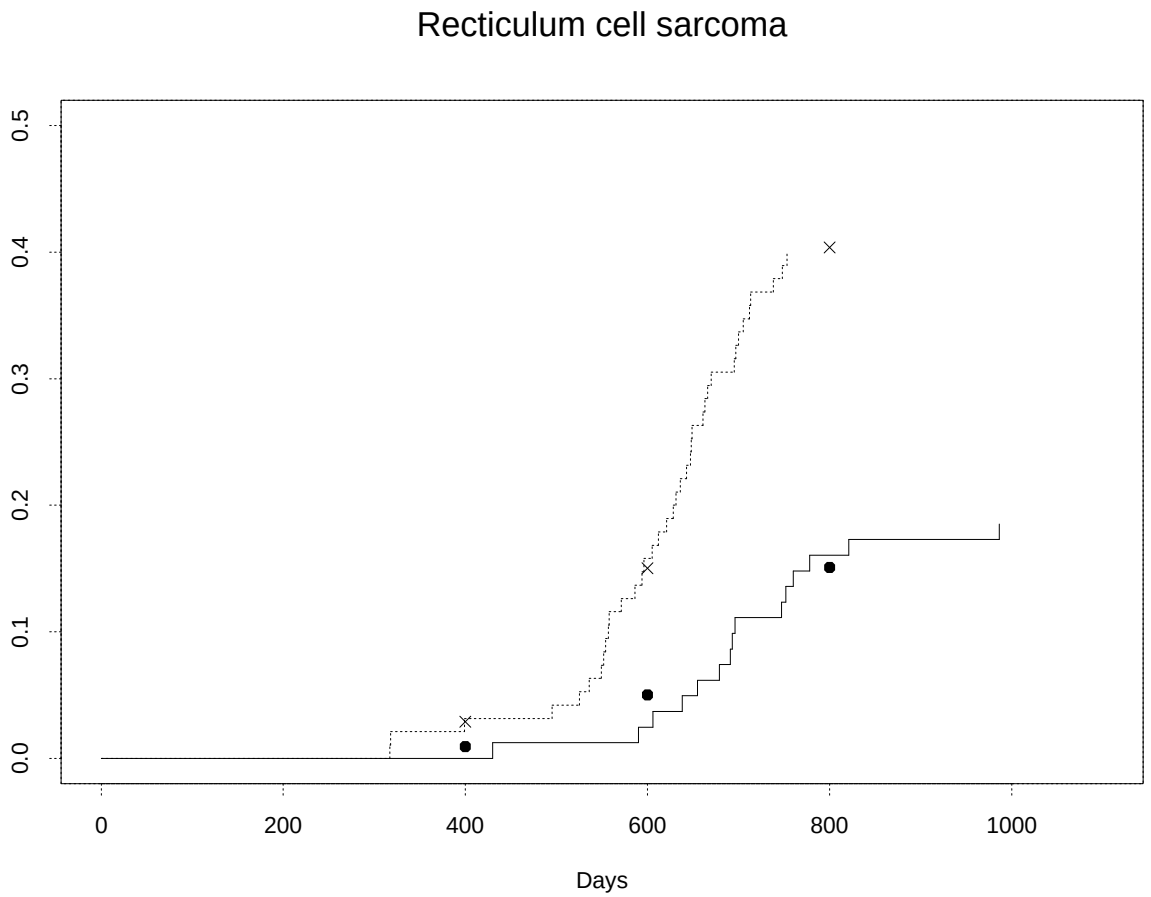
$$\hat{\theta}_i(t) = \frac{I(X_i \leq t, D_i = j, X_i \leq C_i)}{S_C(X_i)} + o_P(1).$$

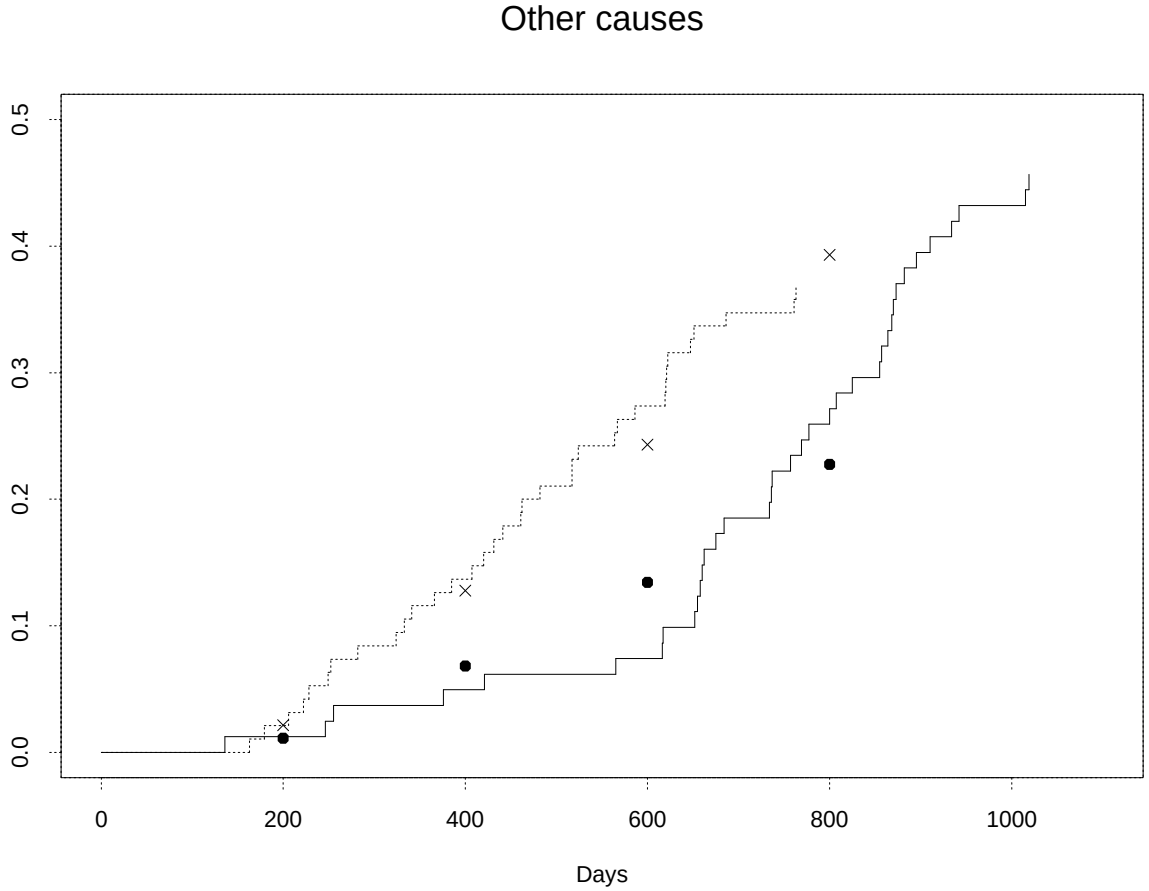
Radiation-exposed male mice, Hoel and Walburg (1972).

- Fine-Gray (1999) regression analysis of cumulative incidences.
- Pseudo-observations computed at $t = 200, 400, 600, 800$ days.
- $\widehat{\beta}$: conventional vs. germ-free

Cause of death	TL	RCS	OC
Fine and Gray $\hat{\beta}$	-0.487	0.975	-0.090
Fine and Gray (SE)	(0.283)	(0.305)	(0.236)
Pseudo-obs. $\hat{\beta}$	-0.401	1.151	0.659
Pseudo-obs. (SE)	(0.286)	(0.321)	(0.276)


Thymic Lymphoma
0.0
0.1
0.2
0.3
0.4
0.5
0
200
400
600
800
1000
Days


Recticulum cell sarcoma
0.0
0.1
0.2
0.3
0.4
0.5
0
200
400
600
800
1000
Days


Other causes
0.0
0.1
0.2
0.3
0.4
0.5
0
200
400
600
800
1000
Days

Bone marrow transplantation.

Regression models for cumulative incidences (adjusted for disease, stage, Karnofsky) at 10 time points.

Relapse	Fine-Gray		Pseudo: cloglog		Pseudo: logit	
Covariate	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)
HLA-id. sibling	0	-	0	-	0	-
HLA-matched donor	-0.32	0.16	-0.37	0.16	-0.45	0.19
HLA-mismatched donor	-1.37	0.38	-1.61	0.45	-1.88	0.51

Death in remission	Fine-Gray		Pseudo: cloglog		Pseudo: logit	
Covariate	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)	$\hat{\beta}$	(SE)
HLA-id. sibling	0	-	0	-	0	-
HLA-matched donor	0.76	0.10	0.75	0.10	0.95	0.12
HLA-mismatched donor	1.15	0.13	1.23	0.14	1.64	0.21

Further topics.

- Missing failure type information, e.g. Goetghebeur and Ryan (*Biometrika*, 1995).
- Relative survival: $\alpha_i(t) = \alpha_i^*(t) + \alpha(t)$.
- Pattern mixture regression model, e.g. Larson and Dinse (*Appl. Stat.*, 1985):

  $\text{logit}P(D = j \mid Z) = a_j + b_j^\mathsf{T} Z, \text{cloglog}P(X > t \mid Z, D = j) = \log(\alpha_{0j}(t)) + \beta_j^\mathsf{T} Z.$
- Parameters in common for several cause-specific hazards, e.g.

  $$\alpha_h(t \mid Z) = \alpha_{0h}(t) \exp(\beta_{h1} Z_1 + \beta Z_2), h = 1, 2$$

  (Andersen, Borgan, Gill and Keiding, 1993, Springer).
- Random effects (frailty) models

More on identifiability.

We saw previously that the joint survival function for the latent failure times was not identifiable from the competing risks data.

Two remarks to that effect:

1. Heckman and Honoré (*Biometrika*, 1989) showed that, with quantitative covariates and marginal proportional hazards models, the joint distribution *is* identifiable under suitable regularity conditions.

2. Zheng and Klein (*Biometrika*, 1995) showed that, with an assumed form of the joint distribution (an assumed "copula"), the marginal distribution of an X_j^L is identifiable. They used this to estimate in the presence of dependent censoring.

Software.

- Models for cause-specific hazards: `coxph` in `R`, `PHREG` in `SAS`, ...
- Fine-Gray model, Gray's test: `cmprsk` package in `R`
- Plug-in estimation of cumulative incidence based on Cox models for cause-specific hazards: `SAS MACRO` by Rosthøj, Andersen and Abildstrom (*Comp. Progr. Meth. Biomed.*, 2004).
- Computation of pseudo-values: `SAS MACRO` and `R` function by Klein, Gerster, Andersen, Tarima, Pohar Perme (*Comp. Progr. Meth. Biomed.*, in press).
- ...

Conclusions.

- Competing risks are frequently seen in biomedical (and other) applications of survival analysis.
- The identifiable parameters are cause-specific hazards and cumulative incidences (and overall survival function).
- In standard survival analysis, rates (hazards) and risks (failure probabilities) are equivalent
- In the competing risks model, this is no longer the case: for each failure type, the failure risk depends on all failure rates

- Modelling cause-specific hazards using techniques from standard survival analysis is quite straightforward
- The cause-specific hazards, however, only provide a *local* (in time) description of the operation of the causes
- To obtain a *global* description (cumulated over time), the competing risks must be specified (and accounted for) unless they are small
- Questions like independence of risks and what would happen if certain causes were removed may be important and interesting but their answers rely on unverifiable assumptions. However, sensitivity analysis may give useful insight.

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