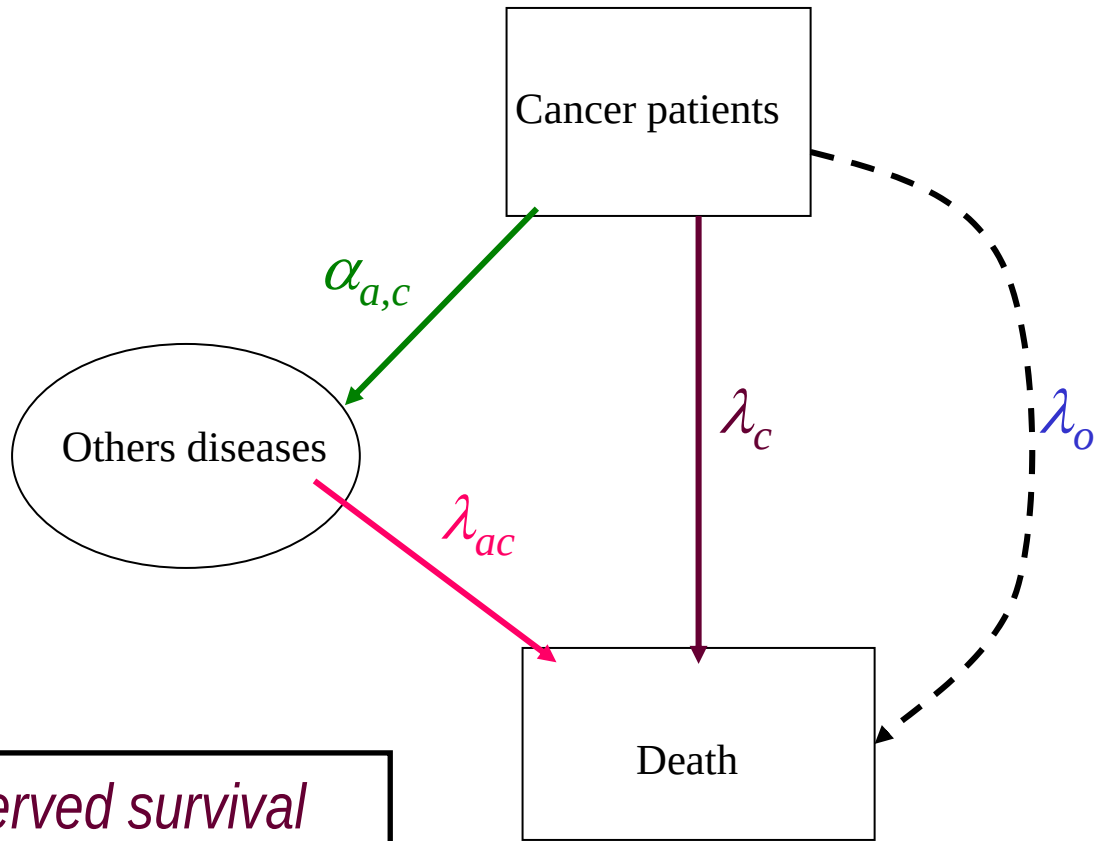
Relative survival vs Net survival definition of concepts and current methods of estimation

PARIS, March 2009

The concept of net survival

α=incidence

λ=lethality



Total Lethality $\Leftrightarrow$ *observed survival*

$$\lambda_o = \lambda_c + \alpha_{ac} \otimes \lambda_{ac}$$

Net survival $= \exp[-\int_0^t \lambda_c(u)du]$

= survival which would be observed in absence of other causes of death

- The net survival may be *estimated* from survival data of a given cohort, if the cause of death of each deceased subject is known i.e cause-specific survival :
  - An observation is censored at the time of death if the death is not caused by the cancer under study.

→ This estimation may be biased due to the subjective determination of the cause of death

The concept of Relative survival

- Relative survival was initially defined as the ratio :

  observed survival / expected survival

where expected survival is the survival of a group of the general population with similar characteristics z (sex, age, ….) than the studied cohort (obtained from the life table)

➔ Relative survival coincide in *some* situations with Net survival as

$S_c = S_O / S_e \Leftrightarrow \lambda_c = \lambda_O - \lambda_e$

How to estimate relative survival

The "ratio estimate"

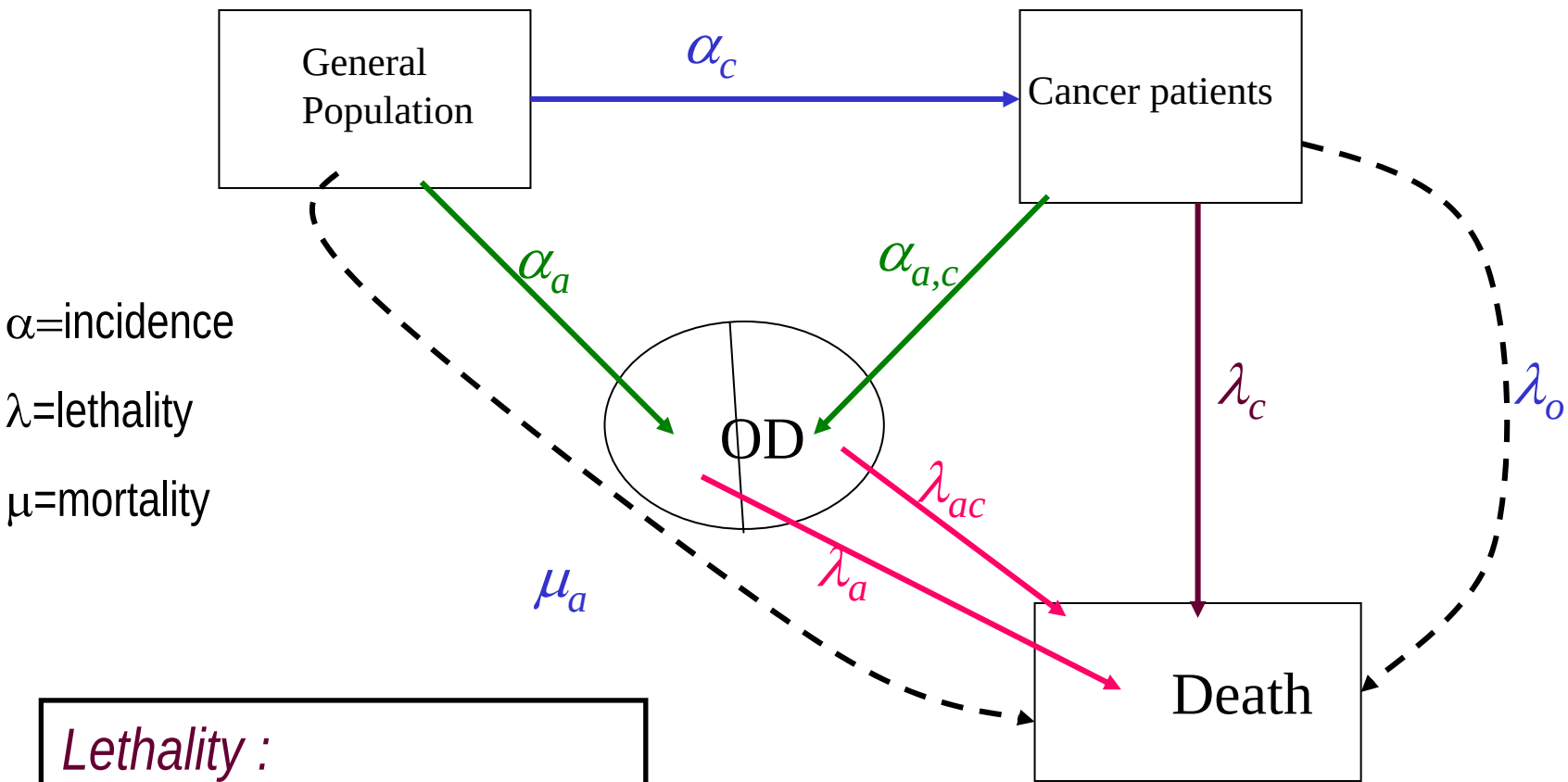
$$S_c(t) = S_o(t) / S_e(t) \rightarrow \hat{S}_c(t) = \hat{S}_o(t) / \hat{S}_e(t)$$

The relative survival probability is estimated from the observed survival estimate divided by the "known" probability of surviving as obtained from the life table= Plug-in estimate

- Initially the estimation methods relied on the simple calculation of the expected survival from *ad-hoc* life table.
  - The relative survival was then calculated by dividing the "actuarial" or the "KM" survival estimate by this expected survival

- The methods (Ederer I, Ederer II, Hakulinen) differed only in the way the expected survival was computed

How to estimate net survival from excess rate model (1)



α=incidence

λ=lethality

μ=mortality

Lethality :

$$\lambda_o = \lambda_c + \alpha_{ac} \otimes \lambda_{ac}$$

Hypothesis of excess rate model

$$\lambda_o = \lambda_c + \mu_a$$

How to estimate Net survival (2)

The excess death rate model

- The idea is to estimate the *death rate in excess of the background mortality rate* to obtain the Net relative survival from it (instead of working in survival level)

$$\lambda_o(t) = \lambda_c(t) + \mu_e(x+t, z)$$

Where $\lambda_c(t)$ is a function to be estimated from survival data and μ_e is obtained from vital statistics or life table

- An initial choice for λ_c was the step function:

$$\lambda_c(t) = f(t) = \sum_{k=1}^{K} \tau_k I_k(t)$$

where the follow-up time has been split in K intervals.

Alternatives for *f* have been developed.

Problems with relative survival/Net survival (1)

- If the whole group is a heterogeneous group relative to variables (age) affecting
  - the cancer death and/or
  - the death for others causes and/or
  - the probability of being censored,

  $\Rightarrow$ RS and NS don't necessarily coincide

  $\Rightarrow$ RS gives biais estimates of NS

  Ex: SR from Ederer 1 coincide to NS (and is an estimator of…) only if cancer death and censoring are independent of age

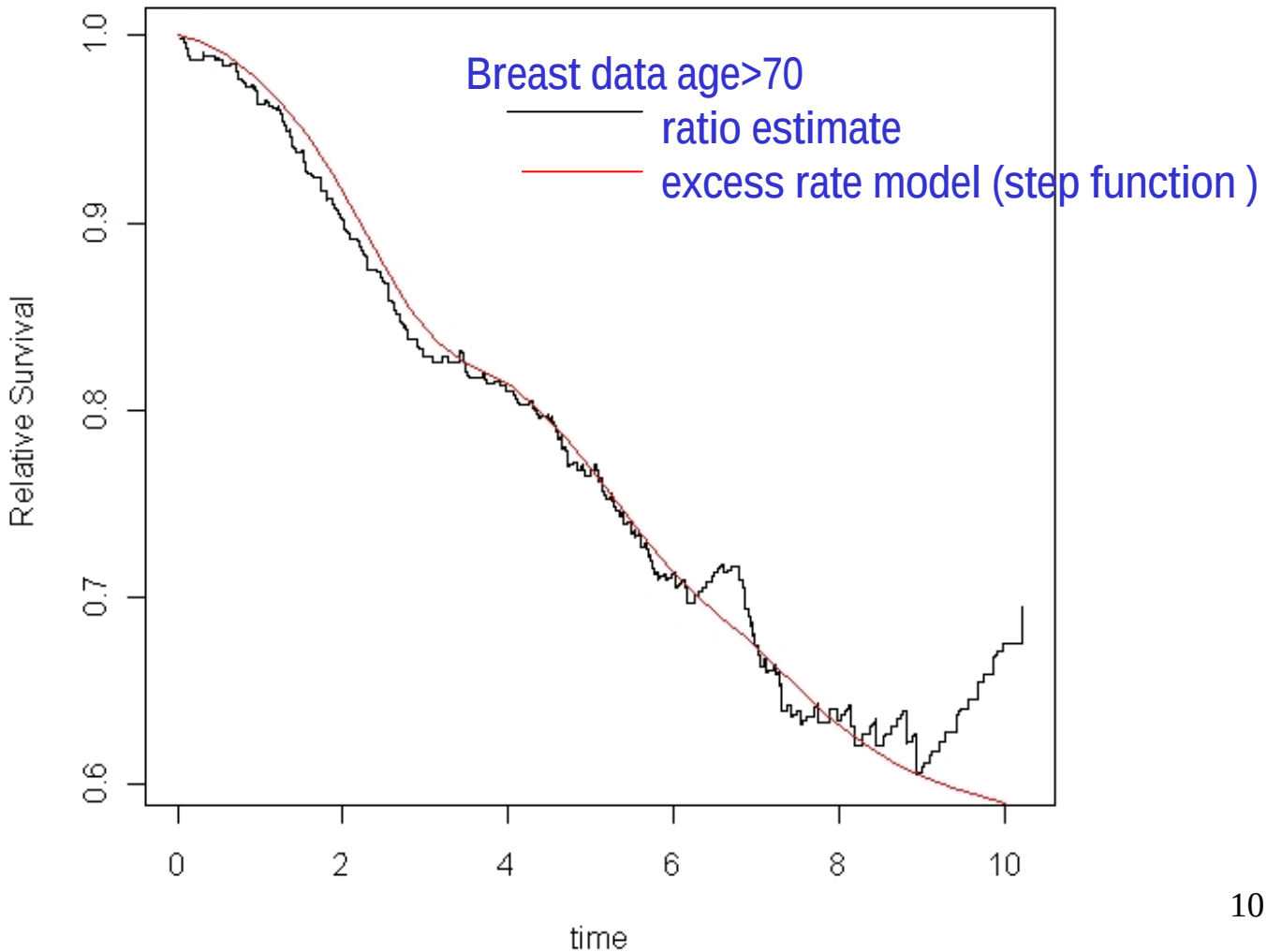
Problems with relative survival/Net survival (2)

- We need estimate of $S_c(t, age)$ to calculate age standardised relative survival (for worldwide comparisons)

  - The ratio estimate in each strata may be subject to a lack of “robustness” and may show rising relative survival

Example : breast cancer age >70 years

Relative survival estimates by the "ratio estimate" *vs* Net survival estimates by "excess rate model“ in a strata



Estimating Net survival from a (excess rate) model may be more robust by

1) Modelling f(t) with a smooth continuous function instead of a step function, in a given strata, or

2) An appropriate modelling for age (non linear, non proportional..)…on the whole dataset.

→ Illustrations …

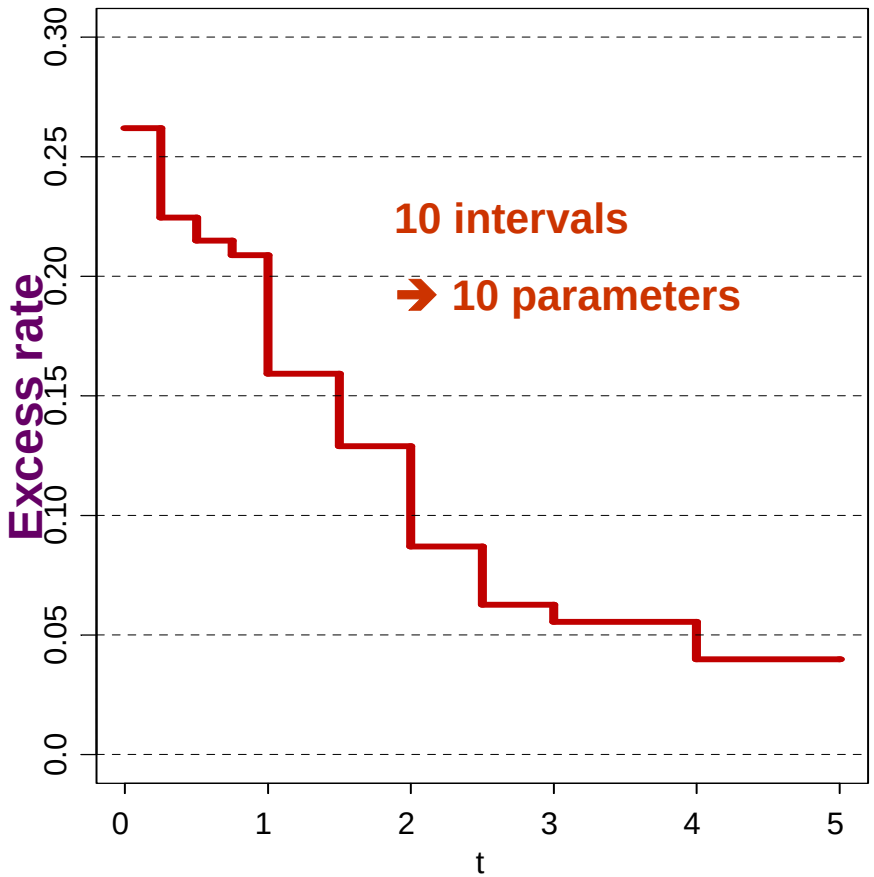
Step versus Smooth function

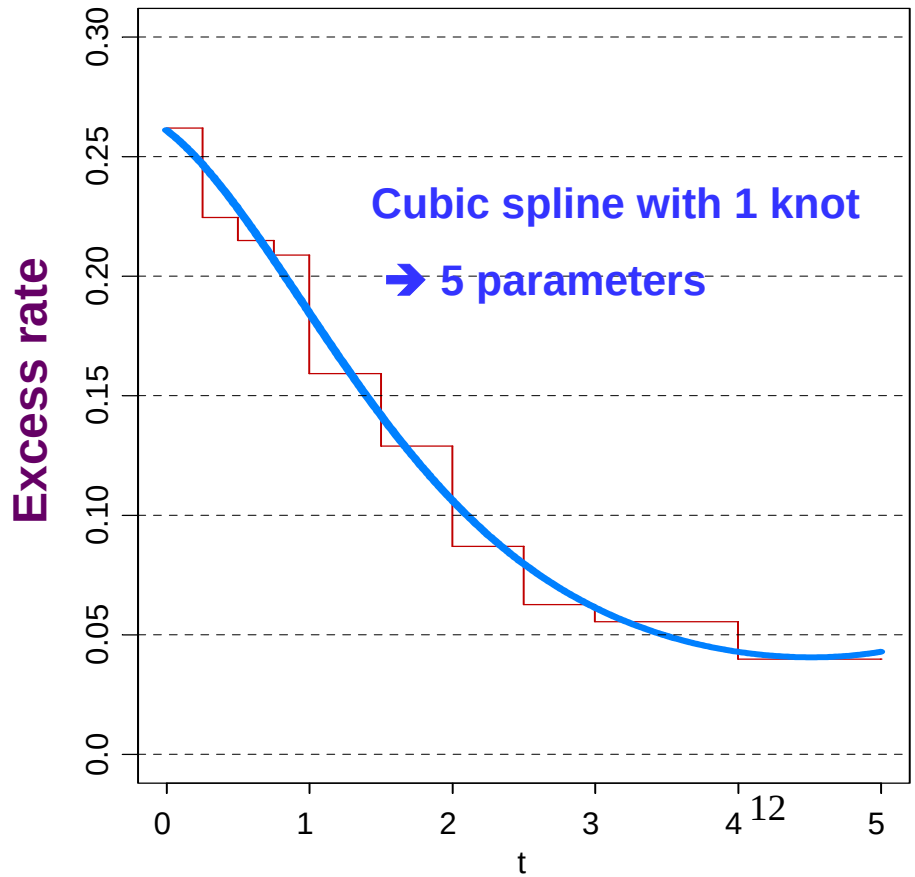
$$\lambda_c(t,z) = \exp(\beta z)\, f(t)$$

with $f(t)$ being

constant within intervals defined a priori

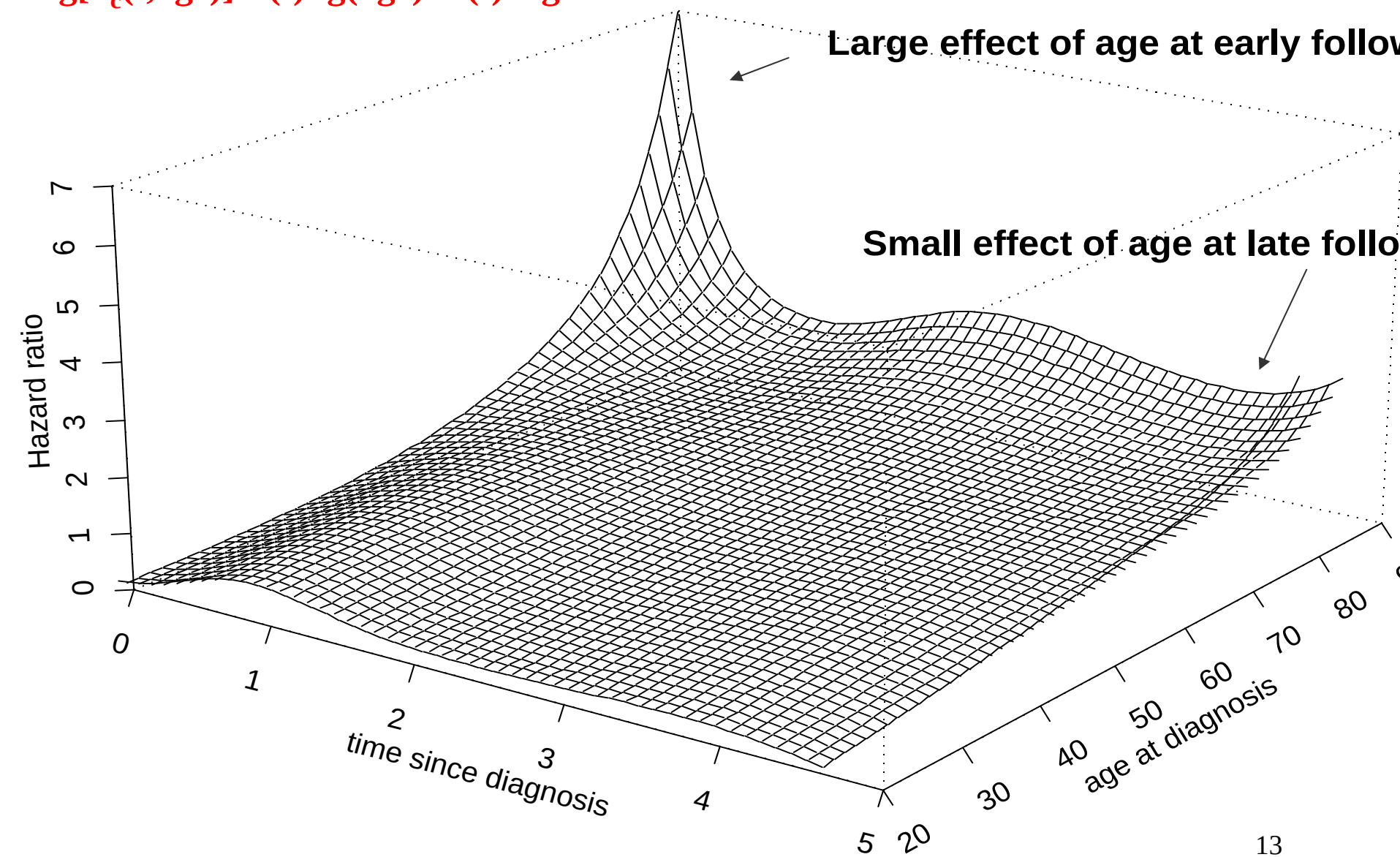
A smoothed parametric function





Time varying age effect (Kidney cancer)

$$\text{Log}[\lambda_c(t,age)]=f(t)+g(age)+h(t)*age$$



Review of methods of estimation of

Relative survival / Net survival

and

their availability in usual statistical sofware (SAS, Stata, S+/R)

- Ederer I et II , Hakulinen &al, Biometrics 1982

Methods for relative survival

- Hakulinen &al, Applies Stat, 1987
  - λ_c=step function
  - Grouped data:
    - GLM implementation (Bin, log-log)
    - Categorical explanatory variable

- Esteve &al, SIM, 1990
  - λ_c=step function
  - Full ML on Individual data
  - Available in command strel (Stata)
  - Available in function relsurv (R-package, Pohar &al)

- Dickman, SIM 2004
  - λ_c=step function
  - Likelihood(survival model)= Likelihood(Poisson model) : GLM (P, log) on splitted data
  - Available in function relsurv (R-package, Pohar &al)

Methods for Net survival (1)

$$\lambda_c(t) = \lambda_0(t)\exp(\beta X)$$

Methods for Net survival (2)

- Bolard&al, JCEP 2002
  - λ_c=quadratic regression splines
  - Non proportionnal hazard
- Giorgi &al, SIM 2003
  - λ_c=quadratic regression splines
  - NPH
  - Available in RSurv (R-package, Giorgi)
- Lambert, SIM 2005
  - λ_c= fractionnal polynomial
- Remontet &al, SIM 2007
  - λ_c= regression splines
  - NPH & NLIN
  - Specific strategy for survival estimate

Flexible parametric of modelling of $\lambda_0(t)$

$$\lambda_c(t) = \lambda_0(t)\exp(\beta X)$$

$$\lambda_c(t) = \lambda_0(t)\exp(\beta X)$$

Non parametric modelling of $\lambda_0(t)$

- Pohar-Perme &al, Biostatisctics 2009
  - λ_c= not specified = Partial Likelihood
  - Estimation procedure by EM algorithm (cause of death treated as missing data)
  - Available in R-package relsurv (Pohar &al)

Others approaches that are NOT:

- $\lambda_{obs}=\lambda_c+\lambda_E$
- $\lambda_c=\lambda_0 \exp(\beta X)$

-Additive model for $\lambda_c(t)$ [Zahl LDA 1998, Cortese SIM 2008]: $\lambda_c(t)=\lambda_0(t) + \beta X$

- Multiplicative model for $\lambda_{obs}(t)$ [Andersen, Biometrics 1985]: $\lambda_{obs}(t)=\lambda_c \times \lambda_e$

Project : part 1
theoretical comparison of methods

Several methods of estimation of relative survival/ Net survival have been developed in the last decades

→ There is a need for a collaborative work aiming at

- Understanding when the concepts SR/NS coincide
- Understanding what the concepts and the methods of estimation are supposed to do
- Identifying their underlying hypothesis, their robustness
- Evaluating their respective performances in terms of biais and precision using simulation

The MESURE project is an opportunity for achieving this goal

Project : part 2
Empirical comparison of methods: Simulations

- Comparison of Net survival estimates (or β) from the different methods with the 'true' simulated net survival using several scenarii:

1) Different patterns of the excess death rate with time elapsed since the diagnosis
2) Effect of covariates (age) on the excess death rate : null, linear, non linear, non proportional…
3) Effect of covariates (age) on expected survival and censoring
4) sample size scenarii leading to sparse data

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