Fitting smooth-in-time prognostic risk functions via logistic regression

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OUTLINE

CASE I

- Prob[surv. benefit] if man, aged 58, PSA 9.1, $\bar{c}$ 'Gleason 7' prostate cancer, selects radical over conservative Tx?
- RCT: prostate ca. mortality reduced with radical Tx (HR 0.56). 10-y 'cum. incidence, CI' of death: 10% vs. 15%.
- "Benefit of radical therapy ... differed according to age but not according to the PSA level or Gleason score."
- Nonrandomised studies: (1) 'profile-specific' prognoses but limited to conservative Tx (2) few patients took this option (3) n= 45,000 men 65-80: "Using propensity scores to adjust for potential confounders," the authors reported "a statistically significant survival advantage" in those who chose radical treatment (HR, 0.69)". An absolute 10-year survival difference (in percentage points) was provided for each "quintile of the propensity score",
- MD couldn't turn info. into surv. Δ for men with pt's profile.

CASE II

- Physician consults report of a classic randomised trial (Systolic Hypertension in Elderly Program (SHEP) to assess 5-year risk of stroke for a 65-year old white woman with a SBP of 160 mmHg and how much it is lowered if she were to take anti-hypertensive drug treatment.
- Reported risk difference was 8.2% - 5.2% = 3%, and the "favorable effect" of treatment was also found for all age, sex, race, and baseline SBP groups.
- Report did not provide information from which to estimate the risk, and risk difference, for this specific profile.

STATISTICS AND THE AVERAGE PATIENT

- For a patient, $\widehat{HR} = \widehat{IDR} = 0.6$ not very helpful.
- $\widehat{CI_{0-10}} = 15\%$ *if* $Tx = 0; 10\%$ *if* $Tx = 1$, more helpful.
- Not specific to this particular type of patient, if grade & stage {of Pr Ca} or age/race/sex/SPB {SHEP Study} not near the typical of those in trial.

ARE THESE ISOLATED CASES?

- Are survival statistics from clinical trials – and non-randomised studies – limited to the “average” patient?
- Is Cox regression used merely to ensure ‘fairer comparisons’?
- How often is it used to provide profile-specific estimates of survival and survival differences?

SURVEY: SURVIVAL STATISTICS IN RCT REPORTS

- RCT's : Jan - June 2006 : NEJM, JAMA, The Lancet
- 20 studies with statistically significant survival difference between compared treatments w.r.t. primary endpoint.
- Documented whether presented profile-specific t-year and Tx-specific survival, { or complement, t-year risk }.
- Most abstracts contained info. on risk and risk difference for the 'average' patient.
- Some articles provided RD's or HR's for 'univariate' subgroups (e.g. by age or by sex).
- Despite range of risk profiles in each study, and common use of Cox regression, none presented info. that would allow reader to assess Tx-specific risk for a specific profile, e.g., for a specific age-sex combination.

WHY THIS CULTURE?

Predominant use of the semi-parametric 'Cox model.'

- Time is considered as a non-essential element.
- Primary focus is on hazard ratios.
- Form of hazard *per se* as function of time left unspecified.
- Attention deflected from estimates of profile-specific CI.
- Many unaware that software provides profile-specific CI.

DIFFERENT CULTURE

Practice of reporting estimates of profile-specific probability more common when no variable element of time of outcome.

- Estimates can be based on logistic regression.
- Examples
  - ("Framingham-based") estimated 6-year risk for Myocardial Infarction as function of set of prognostic indicators;
  - estimated probability that prostate cancer is organ-confined, as a function of diagnostic indicators.

WHAT WE WISH TO DO

- Model the hazard (h), or incidence density (ID), as a function of
  - set of prognostic indicators
  - choice of intervention
  - prospective time.
- Estimate the parameters of this function.
- Calculate $\widehat{CI_x(t)}$ from this function.

COX MODEL

Hazard modelled, semi-parametrically, as

$$h_x(t) = [\exp(\beta x)]\lambda_0(t),$$

- $T = t$: a point in prognostic time,
- β : vector of parameters with unknown values;
- $X = x$: vector of realizations for variates based on prognostic indicators and interventions;
- $\lambda_0(t)$: hazard as a function – unspecified – of t corresponding to $x = 0$.

FROM $\hat{\beta}$ TO PROFILE-SPECIFIC CI's

- Obtain $\widehat{S_0(t)}$ { the complement of $\widehat{CI_0(t)}$ }.
- Estimate risk (cum. incidence) $CI_x(t)$ for a particular determinant pattern $X = x$ as $\widehat{CI_x(t)} = 1 - \widehat{S_0(t)}^{\exp(\hat{\beta}x)}$.
- Breslow suggested an estimator of $\lambda_0(t)$ that gives a **smooth** estimate of $CI_x(t)$. However, **step function** estimators of $S_x(t)$, **with as many steps as there are distinct failure times in the dataset**, are more easily derived, and the only ones available in most packages.
- Step-function $S_0(t)$ estimators: "Kaplan-Meier" type ("Breslow") and Nelson-Aalen. heuristics: jh, *Epidemiology 2008*
- *Clinical Trials* article (Julien & Hanley, 2008) encourages investigators to make more use of these for 'profiling'.

TOO MUCH OF A GOOD THING? - 1992

the success of Cox regression has perhaps had the unintended side-effect that practitioners too seldomly invest efforts in studying the baseline hazard...

*a **parametric** version, ... if found to be adequate, would lead to more precise estimation of survival probabilities.*

Hjort, 1992, International Statistical Review

TOO MUCH OF A GOOD THING? - 2002

Hjort's statement has been "apparently little heeded"

in the Cox model, the baseline hazard function is treated as a high-dimensional nuisance parameter and is highly erratic.

{we propose to estimate it} informatively (that is, smoothly), by natural cubic splines.

Royston and Parmar, 2002, Statistics in Medicine

TOO MUCH OF A GOOD THING? - 1994

Reid: How do you feel about the cottage industry that's grown up around it [the Cox model]?

Cox: Don't know, really. In the light of some of the further results one knows since, I think I would normally want to tackle problems parametrically, so I would take the underlying hazard to be a Weibull or something. I'm not keen on nonparametric formulations usually.

TOO MUCH OF A GOOD THING? - 1994 ...

Reid: So if you had a set of censored survival data today, you might rather fit a parametric model, even though there was a feeling among the medical statisticians that that wasn't quite right.

Cox: That's right, but since then various people have shown that the answers are very insensitive to the parametric formulation of the underlying distribution [see, e.g., Cox and Oakes, Analysis of Survival Data, Chapter 8.5]. And if you want to do things like predict the outcome for a particular patient, it's much more convenient to do that parametrically.

. . . . Reid N. A Conversation with Sir David Cox.
. . . . Statistical Science, Vol. 9, No. 3 (1994), pp. 439-455

FULLY-PARAMETRIC MODEL: FORM

$$\log\{h(x,t)\} = g(x,t,\beta) \iff h(x,t) = e^{g(x,t,\beta)}$$

- x is a realization of the covariate vector X, representing the patient profile P, and possible intervention I.
- β : a vector of parameters with unknown values,
- $g()$ includes constant 1, variates for P, I;
- $g()$ can have product terms involving $P, I,$ and t.
- $g()$ must be 'linear' in parameters, in '*linear* model' sense.
- 'proportional hazards' if no product terms involving t & I
- If t is represented by a linear term (so that 'time to event' $\sim$ *Gompertz*), then $\widehat{CI_{p,i}(t)}$ has a closed smooth form.
- If t is replaced by $\log t$, then 'time to event' $\sim$ *Weibull*.

FULLY-PARAMETRIC MODEL: FITTING

- Parameters of this loglinear hazard function can be numerically estimated by maximizing the likelihood.
- Unable to find a ready-to-use procedure within the common statistical packages.
- Likelihood becomes quite involved even if no censored observations.
- Albertsen and Hanley(1998), Efron(1988, 2002), and Carstensen(2000-) have circumvented these technical problems of fitting by dividing the observed 'survival time' of each subject into a number of time-slices and treating the number of events in each as a Binomial (1988) or Poisson (2002) variate.

FULLY-PARAMETRIC MODEL: OUR APPROACH

- An extension of the method of Mantel (1973) to binary outcomes with a time dimension.
- Mantel's problem:
  - $(c =)165$ 'cases' of $Y = 1$,
  - 4000 instances of $Y = 0$.
  - Associated regressor vector X for each of the 4165
  - A logistic model for $Prob(Y = 1 \mid X)$
  - A computer with limited capacity.

MANTEL'S SOLUTION

- Form a reduced dataset containing...
  - All c instances (cases) of $Y = 1$
  - Random sample of the $Y = 0$ observations
- Fit the same logistic model to this reduced dataset.

  "Such sampling will tend to leave the dependence of the log odds on the variables unaffected except for an additive constant."

  Anderson (Biometrika, 1972) had noted this too.
- Outcome(Choice)-based sampling common in Epi, Marketing, etc...

DATA TO EXPLAIN OUR APPROACH

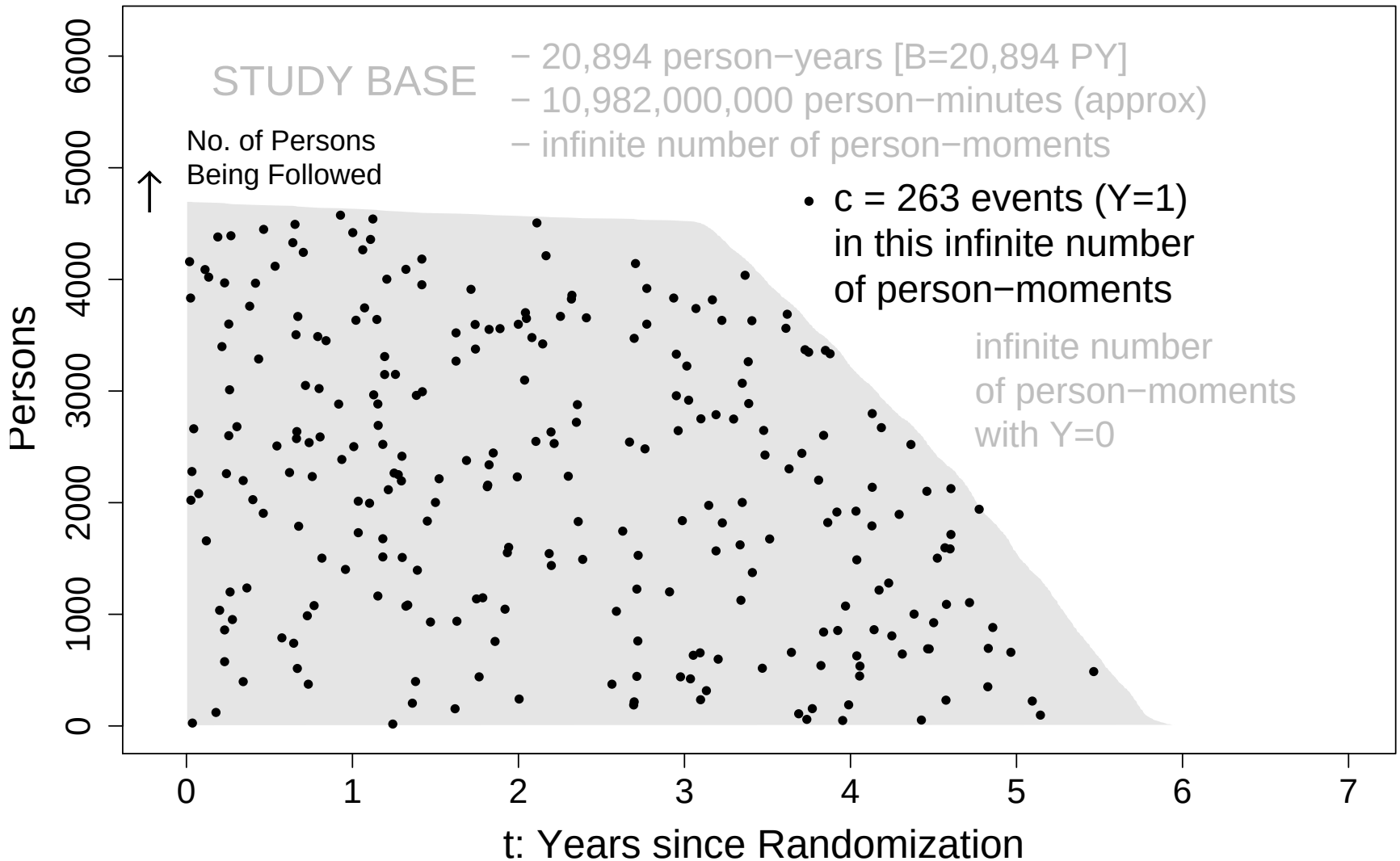
Systolic Hypertension in Elderly Program (SHEP)

..... SHEP Cooperative Research Group (1991).

..... Journal of American Medical Association 265, 3255-3264.

- ??? Effectiveness of antihypertensive drug treatment in preventing ($\downarrow$ risk of) stroke in older persons with isolated systolic hypertension.
- We obtained data, without subject identifications, under program “NHLBI Datasets Available for Research Use”.
- 4,701 persons with complete data on $P = \{$age, sex, race, and systolic blood pressure$\}$ and $I = \{$active, placebo$\}$.
- Study base of $B = 20,894$ person-years of follow-up; $c = 263$ events ("cases") of stroke identified.

STUDY BASE, and the 263 cases



THE ETIOLOGIC STUDY IN EPIDEMIOLOGY

- Aggregate of population-time: 'study base.'
- All instances of event in study base identified $\rightarrow$ study's 'case series' of person-moments, characterized by $Y = 1$.
- Study base – infinite number of person-moments – sampled $\rightarrow$ corresponding 'base series,' characterized by $Y = 0$.
- Document potentially etiologic antecedent, modifiers of incidence-density ratio, & confounders.
- Fit Logistic model

.....

- With our approach . . .
  - $\rightarrow$ Incidence density, $h_x(u)$ in study base.
  - $\rightarrow CI_x(t) = 1 - \exp\{-H_x(t)\} = 1 - \exp\{-\int_0^t h_x(u)du\}$.

WHAT MAKES OUR APPROACH WORK

- Base series: representative (unstratified) sample of base.
- $\longrightarrow$ logistic model, with t having same status as x, and offset, directly yields $\widehat{ID}_{x,t} = \exp\{\widehat{g(x,t)}\}$.
- Using same argument (algebra) as Mantel...

b = size of base series
B = amount of population-time constituting study base.

$$\frac{Prob(Y=1|\{x,t\})}{Prob(Y=0|\{x,t\})} = \lim_{\epsilon \longrightarrow 0} \frac{h(x,t)\epsilon}{1-h(x,t)\epsilon} \times \frac{B/\epsilon}{b} = h(x,t) \times \frac{B}{b}.$$

$$\log\left[\frac{Prob(Y=1|\{x,t\})}{Prob(Y=0|\{x,t\})}\right] = \log[h(x,t)] + \log(B/b).$$

- $\log(B/b)$ is an Offset [a regression term with *known* coefficient of 1].

How large should b be on relation to c?

Mantel (1973)... [our notation, and slight change of wording]

> *By the reasoning that* $cb/(c+b)$ $[= (1/c + 1/b)^{-1}]$ *measures the relative information in a comparison of two averages based on sample sizes of c and b respectively, we might expect by analogy, which would of course not be exact in the present case, that this approach would result in only a moderate loss of information. (The practicing statistician is generally aware of this kind of thing. There is little to be gained by letting the size of one series, b, become arbitrarily large if the size of the other series, c, must remain fixed.)*

- With 2008 computing, we can use a b/c ratio as high as 100.
- $b/c = 100 \rightarrow Var[\hat{\beta}]_{b/c=100} = 1.01 \times Var[\hat{\beta}]_{b/c=\infty}$, i.e. 1% ↑
- $Var[\hat{\beta}] \propto 1/c + 1/100c$ rather than $1/c + 1/\infty$.

OUR HAZARD MODEL FOR SHEP DATA

$\log[h] = \Sigma \beta_k X_k$, where

X_1 = Age (in yrs) - 60
X_2 = Indicator of male gender
X_3 = Indicator of Black race
X_4 = Systolic BP (in mmHg) - 140

.....

X_5 = Indicator of active treatment

.....

$X_6 = T$

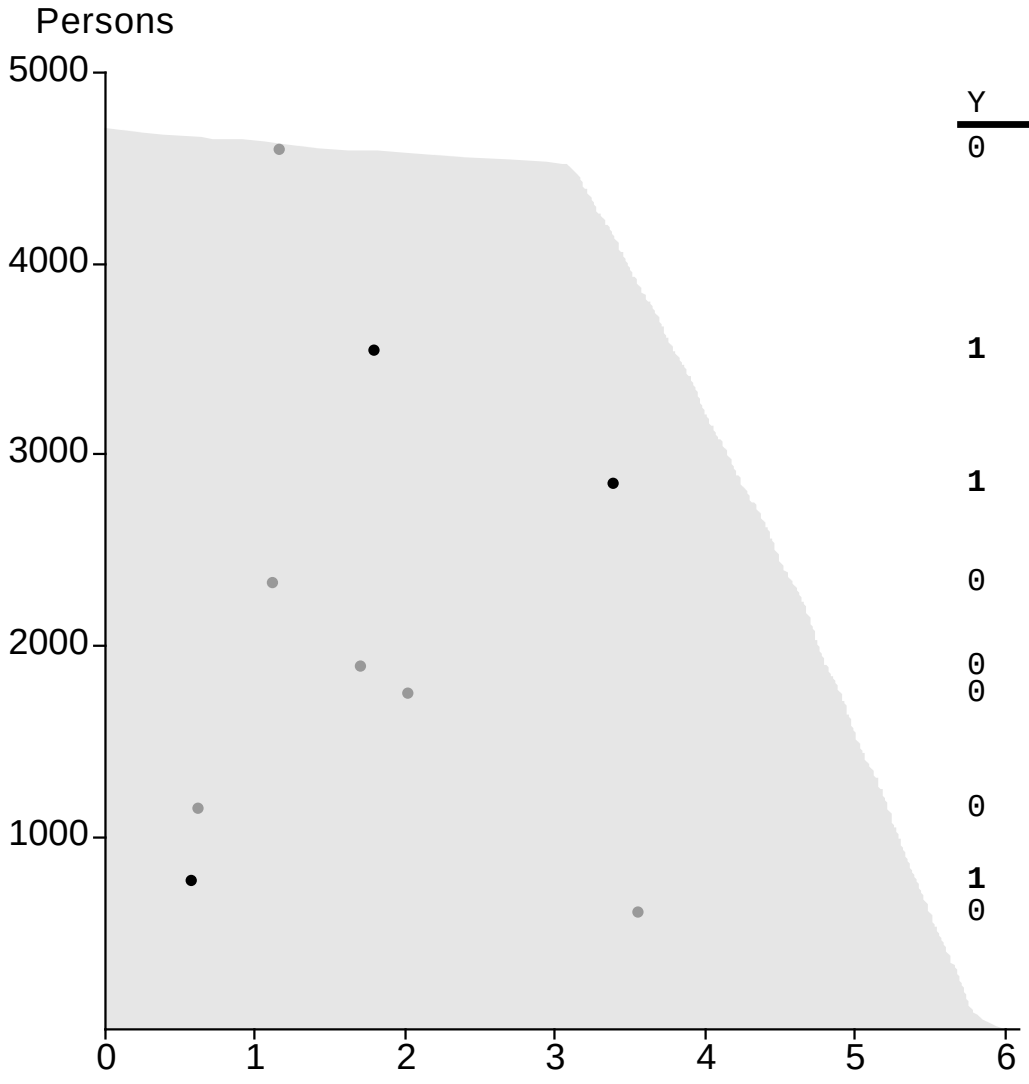
.....

$X_7 = X_5 \times X_6$. (non-proportional hazards)

PARAMETER ESTIMATION

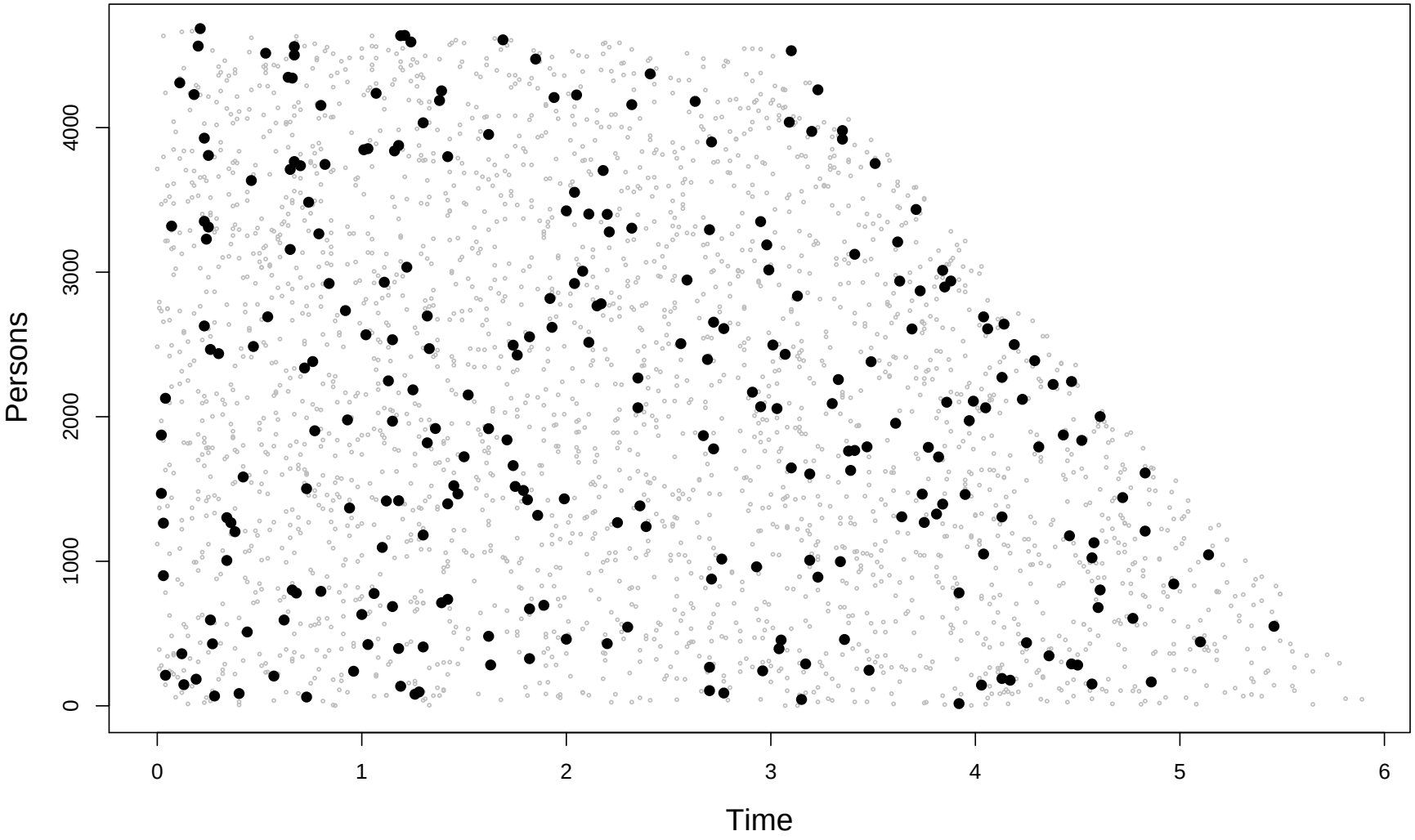
- Formed person-moments dataset pertaining to:
  - case series of size $c = 263$ ($Y = 1$)
    and
  - (randomly-selected) base series of size $b = 26,300$ ($Y = 0$).
- Each of 26,563 rows contained realizations of
  - $X_1, \ldots, X_7$
  - Y
  - offset = $\log(20,894/26,300)$.
- Logistic model fitted to data in the two series.

DATASET FOR LOGISTIC REGRESSION (SCHEMATIC)



Y	Age	B	M	SBP	I	t
0	81	1	0	161	0	1.16
1	**69**	**0**	**1**	**161**	**0**	**1.79**
1	**85**	**0**	**1**	**184**	**0**	**3.39**
0	70	0	1	185	0	1.11
0	69	0	0	182	0	1.70
0	73	0	1	167	1	2.02
0	73	1	0	199	0	0.62
1	**69**	**1**	**0**	**166**	**1**	**0.57**
0	72	0	0	172	1	3.56

DATASET: $c = 263; b = 10 \times 263$



FITTED VALUES

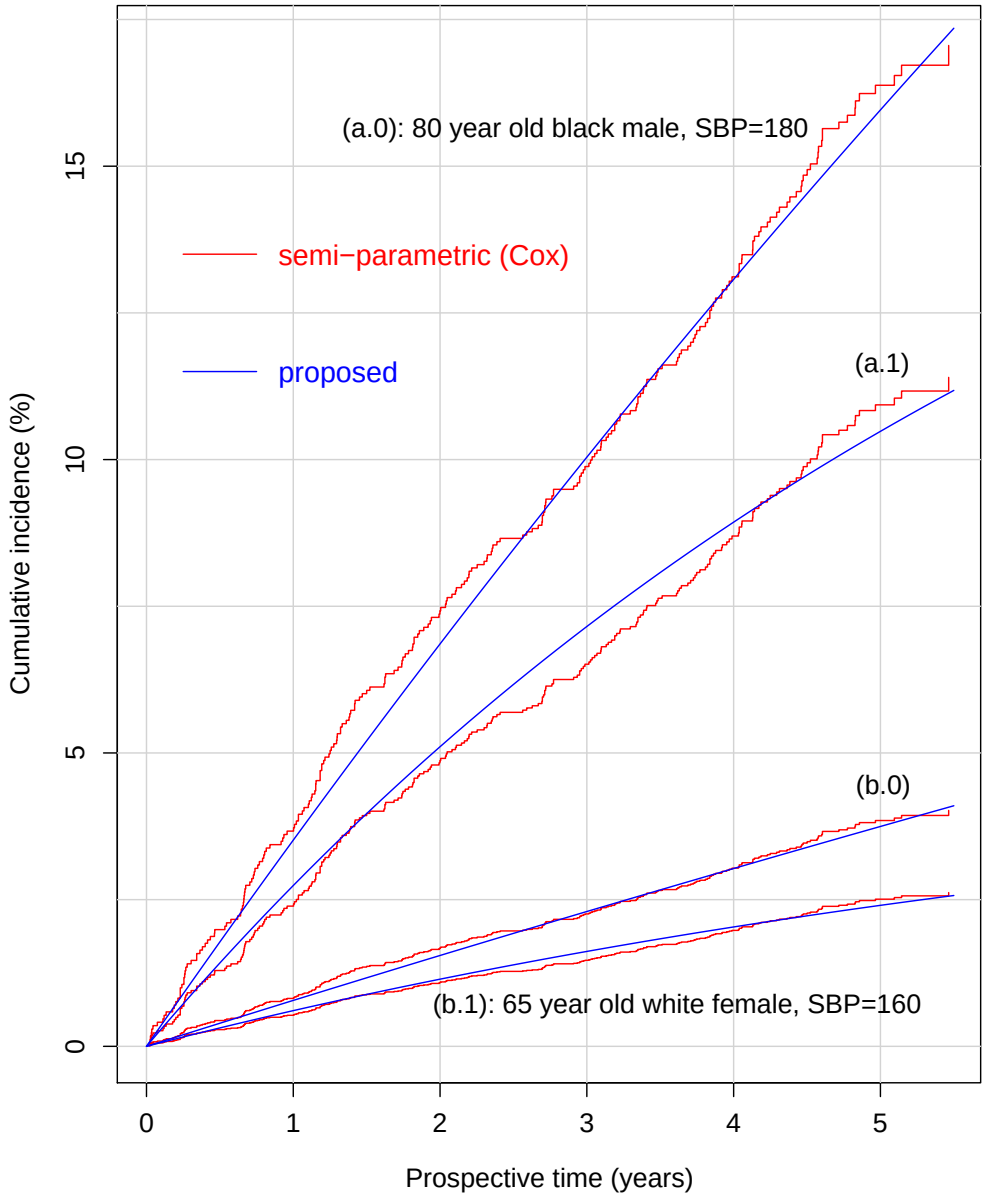
	Proposed logistic regression		Cox regression
β_{age-60}	0.041	0.041	0.041
$\beta_{I_{male}}$	0.257	0.258	0.259
$\beta_{I_{black}}$	0.302	0.301	0.303
$\beta_{SBP-140}$	0.017	0.017	0.017
.....			
$\beta_{I_{Active\ treatment}}$	-0.200	-0.435	-0.435
.....			
β_0	*-5.390*	*-5.295*	
β_t	-0.014	-0.057	
$\beta_{t \times I_{Active\ treatment}}$	-0.107		

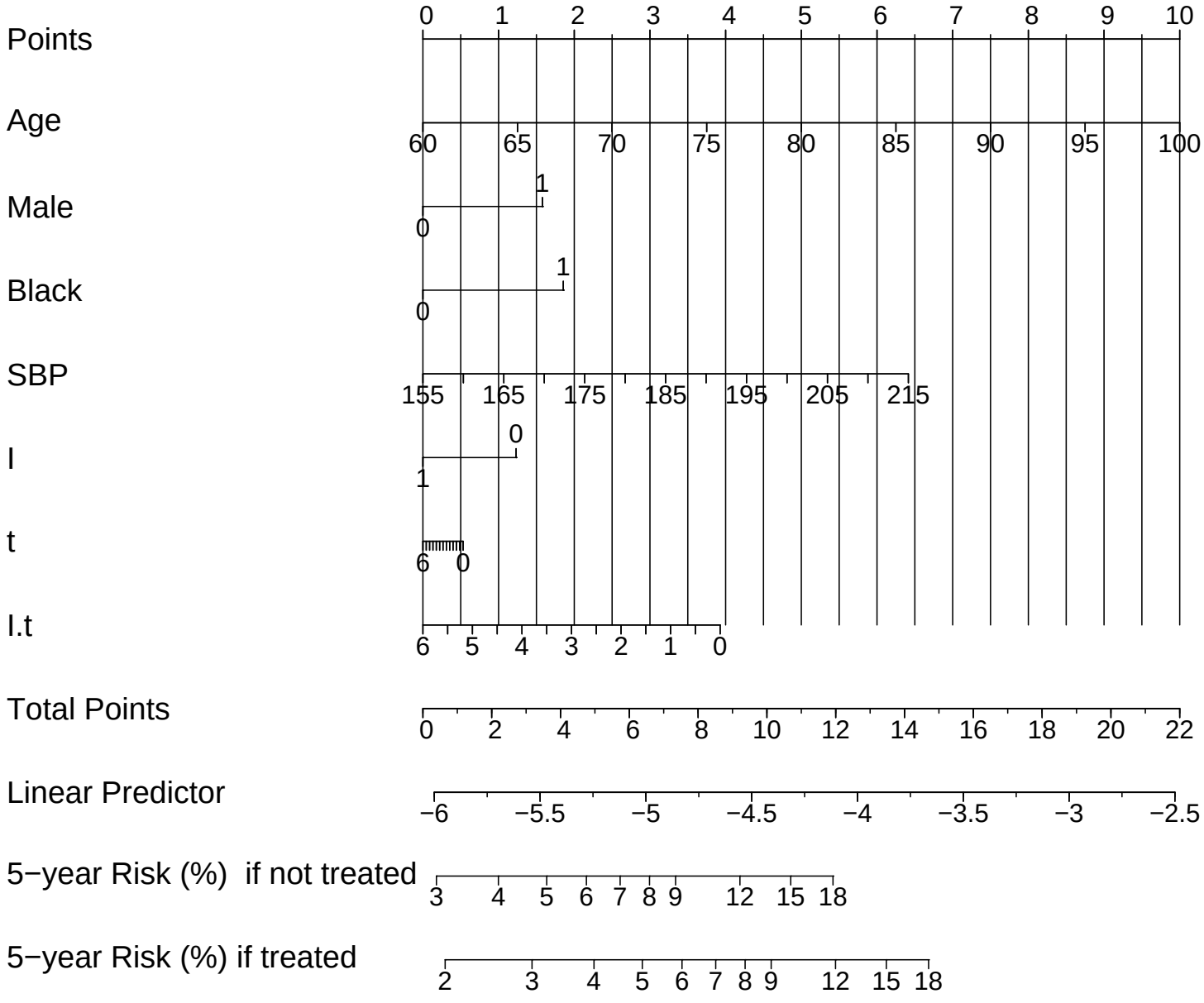
- Fitted logistic function represents $\log[h_x(t)]$
- $\rightarrow$ cumulative hazard $H_X(t)$, and, thus, X-specific risk.

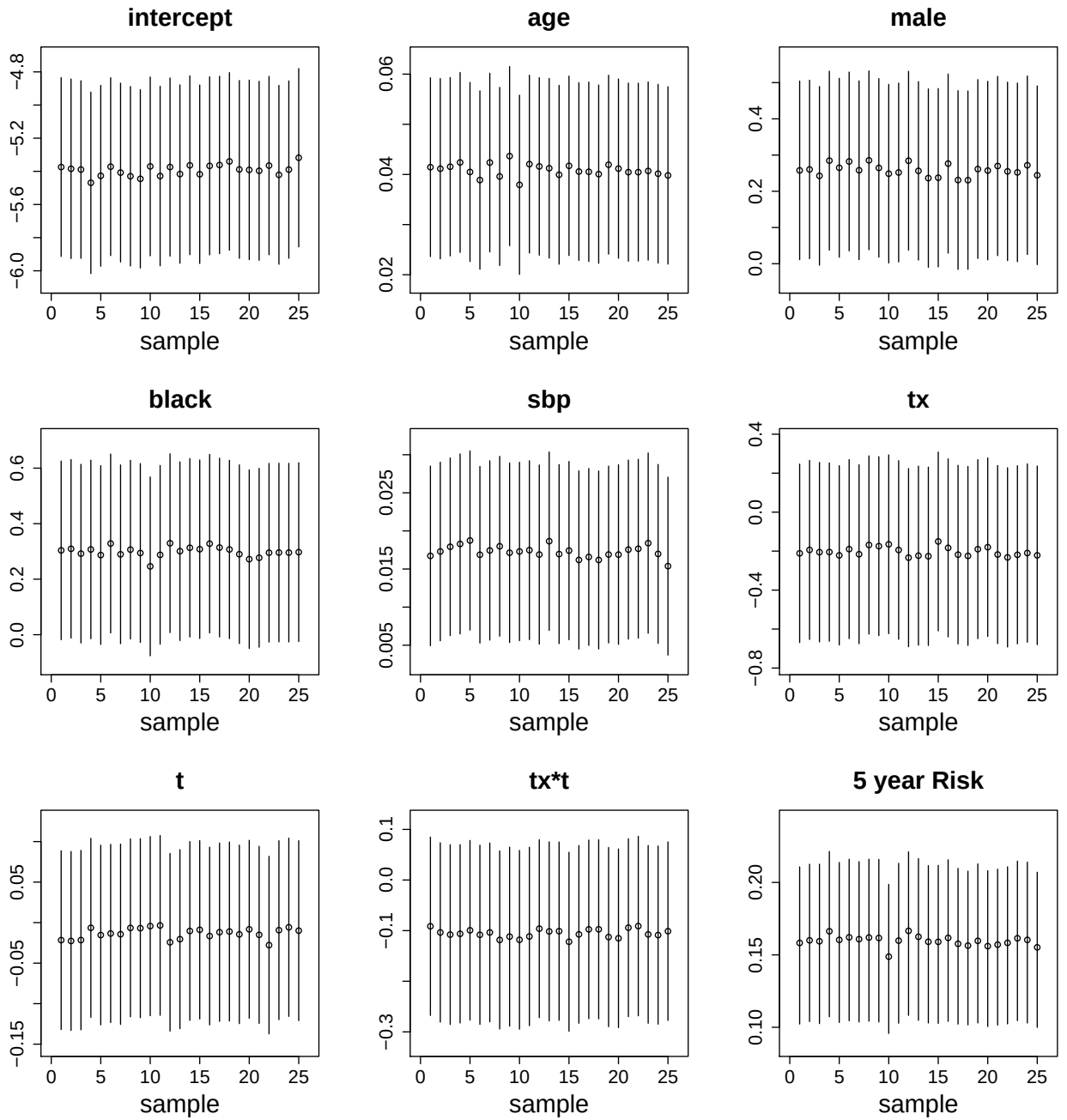
ESTIMATED 5-YEAR RISK OF STROKE

Risk	I	$h(t)$ [ID(t)]	$H(5)$ [$\int_0^5 h_x(t)dt$]	$CI(5)$ [$1 - e^{-H(5)}$]	Δ
Low	0	$e^{-4.86-0.014t}$	0.037	0.036	
	1	$e^{-5.06-0.124t}$	0.024	0.024	1.2%
High	0			0.16	
	1			0.10	6%
Overall	0			0.076	
	1			0.049	2.7%

Low: 65 year old white female with a SBP of 160 mmHg.
High: 80 year old black male with a SBP of 180 mmHg


(a.0): 80 year old black male, SBP=180
semi−parametric (Cox)
proposed
(a.1)
(b.0)
(b.1): 65 year old white female, SBP=160
Cumulative incidence (%)
0
5
10
15
0
1
2
3
4
5
Prospective time (years)


Points
0 1 2 3 4 5 6 7 8 9 10
Age
60 65 70 75 80 85 90 95 100
Male
1
0
Black
1
0
SBP
155 165 175 185 195 205 215
I
0
1
t
6 0
I.t
6 5 4 3 2 1 0
Total Points
0 2 4 6 8 10 12 14 16 18 20 22
Linear Predictor
−6 −5.5 −5 −4.5 −4 −3.5 −3 −2.5
5−year Risk (%) if not treated
3 4 5 6 7 8 9 12 15 18
5−year Risk (%) if treated
2 3 4 5 6 7 8 9 12 15 18



STABILITY ?

Point and (95% confidence) interval estimates of hazard function, and of 5-year risk for a specific (untreated) high-risk profile. Fits are based on 25 different random samples of b =26,300 from the infinite number of person-moments in the study base, and same $c = 263$ cases each run.

KEY POINTS

- Focus on 'individualized' – profile-specific – risk functions.
- Cox model CI's seldom used: dislike 'step-function' form?
- Smooth-in-t $h(t)$—and CI's– not new; fitting procedure is.
- Borrow from *the* etiologic study in epidemiology:
  case series + base series + logistic regression.
- Not just hazard ratio, but hazard per se.
- Keys: 1. representative sampling of the base; 2. offset.
- Information re $h_x(t)$ constrained by c.
- Virtually 100% extracted when b suitably large relative to c.
- b/c =100 feasible and adequate.

MODELLING POSSIBILITIES

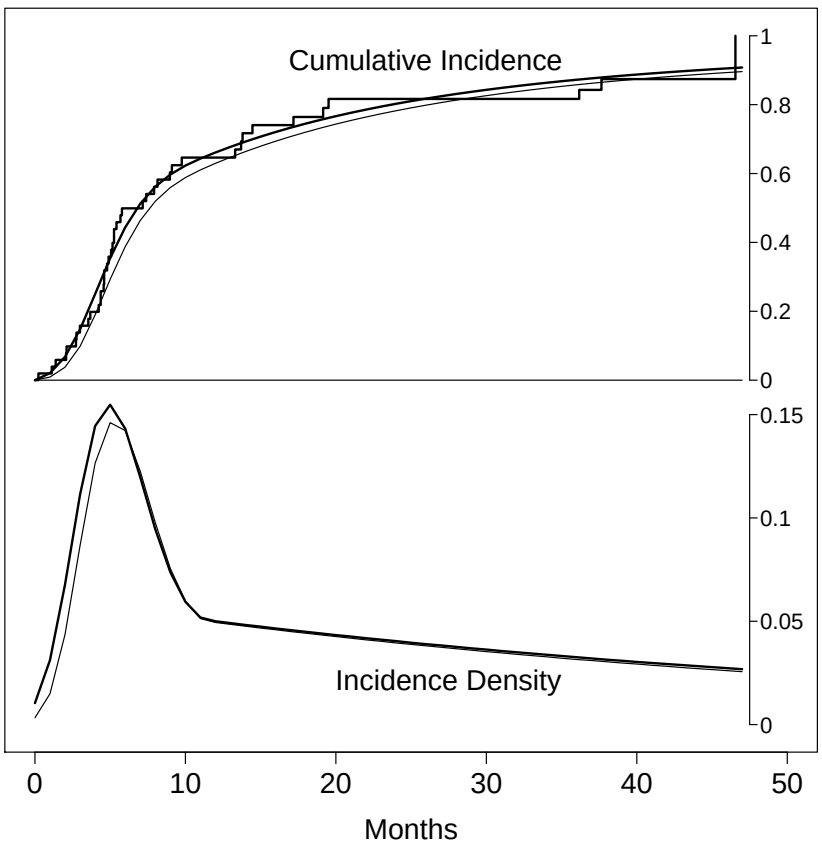
Log-linear modelling for $h_x(t)$ via logistic regression ...

- Standard methods to assess model fit.
- Wide range of functional forms for the t-dimension of $h_x(t)$.
- Effortless handling of censored data.
- Flexibility in modeling non-proportionality over t.
- Splines for $h(t)$ rather than $hr(t)$.

DATA ANALYZED BY EFRON, 1988

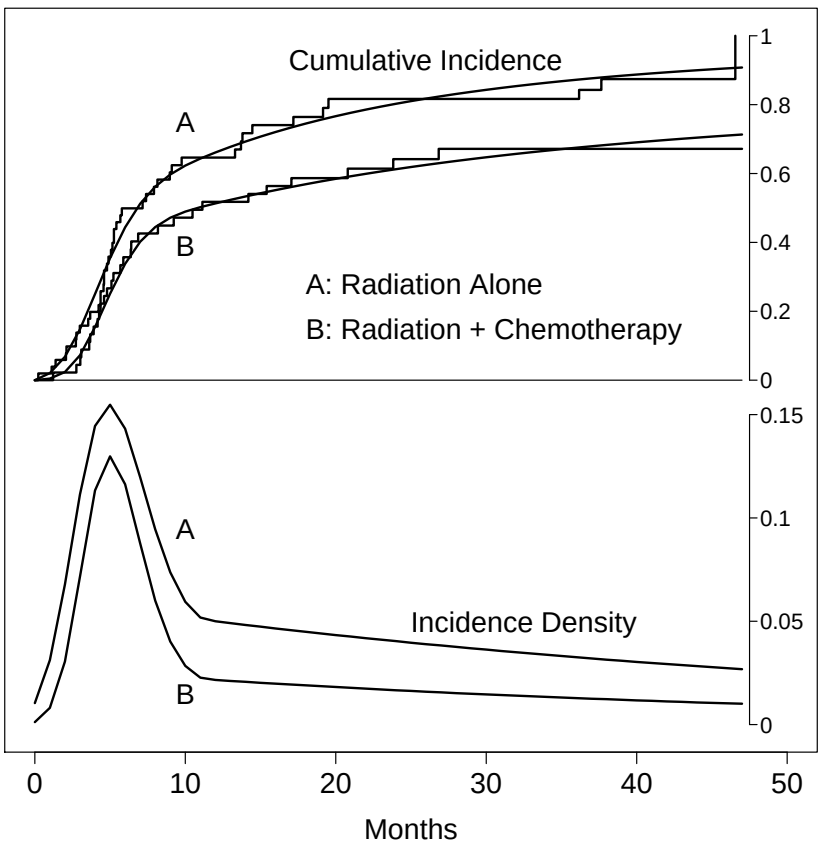
Arm A [time-to-recurrence of head & neck cancer]

Cum. Inc. estimates – K-M, Efron & Proposed



Inc. density estimates – Efron & Proposed

Arm A *vs.* Arm B



CLINICAL POSSIBILITIES / DESIDERATA

- PDAs (personal digital assistants) $\rightarrow$ online information.
- Profile-specific risk estimates for various interventions.
- Already, online calculators: risk of MI, Breast/Lung Cancer; probability of extra-organ spread of cancer.
- RCT reports should contain: suitably designed risk function, fitted parameters of $h_x(t)$, and risk function.
- (Offline:) risk scores $\rightarrow$ risks via nomogram/table.

SUMMARY

- Profile-specific risk (CI) functions are important.
- Two paths to CI, via...
  - Steps-in-time $S_0(t)$
  - Smooth-in-time $ID_x(t)$.
- New simple estimation method for broad class of smooth-in-time ID functions.
- Biostatistics & Epidemiology methods: a little more unified?

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