Generic solution of the heterogeneity-induced competing risk problem in survival analysis

Ton Coolen

Institute for Mathematical and Molecular Biomedicine, King's College London
London Institute for Mathematical Sciences

- Survival analysis and competing risks
- Individual versus cohort level risk analysis
- Modelling heterogeneity-induced competing risks
- Applications: synthetic data and prostate cancer data

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Survival analysis and competing risks

- N individuals, subject to R 'hazards' or 'risks'
  e.g. cancer recurrence, other death, end of trial ...
- If one event happens, others can no longer be observed
- Data, $i = 1 \ldots N$:

$$\begin{aligned} \mathbf{z}_i = (z_1^i, \ldots, z_p^i) : &\qquad \textit{values of } p \textit{ covariates} \\ t_i \geq 0 : &\qquad \textit{time of first event} \\ r_i \in \{1, \ldots, R\} : &\qquad \textit{type of first event} \end{aligned}$$

Question:

- Extract regularities that connect covariates to risks

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competing risk problem

- If event times of risks correlated: informative censoring
  primary hazard rate contaminated by non-primary risks

$$\mathcal{P}(t_1,\ldots,t_R|\mathbf{z}) \neq \mathcal{P}(t_1|\mathbf{z})\mathcal{P}(t_2,\ldots,t_R|\mathbf{z})$$

- What would be primary risk survival function
  if all other risks were disabled?

  nontrivial ...

  – disabling non-primary risks affects also primary hazard rate
  – Tsiatis: without further assumptions one cannot infer
  risk correlations from survival data

- Most methods assume risk independence
  so non-primary risks don't affect primary hazard rate
  (Cox, KM, fraily models ...)

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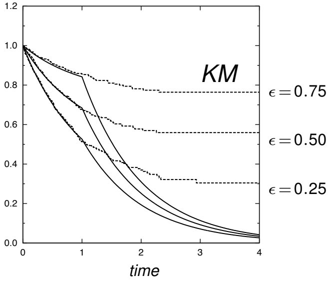
a serious problem?

some illustrations ...

$$\mathcal{P}(t_1,t_2) = \epsilon\, e^{-t_2}\delta(t_1-t_2-1) + (1-\epsilon)e^{-t_1-t_2}$$



KM & Cox-Breslow estimators

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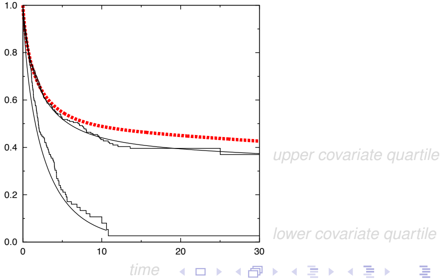

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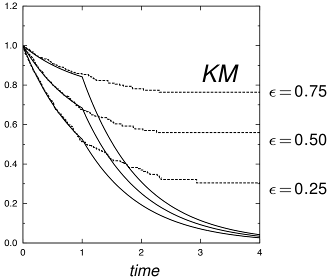

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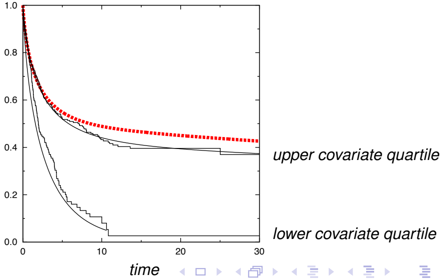

Possible causes of informative censoring

Say we have 1000 people in a cohort
two risks, hazard rates h_A and h_B

- homogeneous cohort:
  all *individuals* have (h_A, h_B)

- heterogeneous cohort,
  four subgroups:

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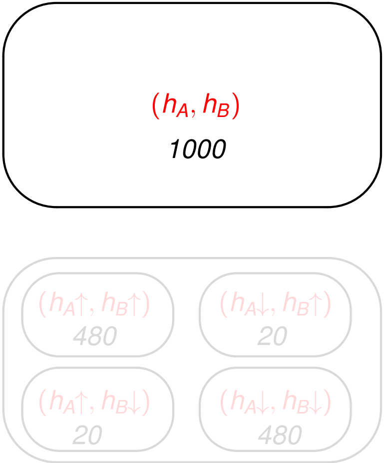

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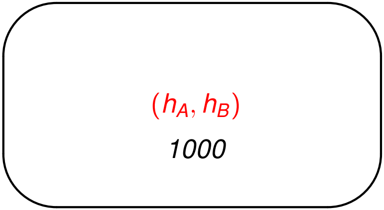

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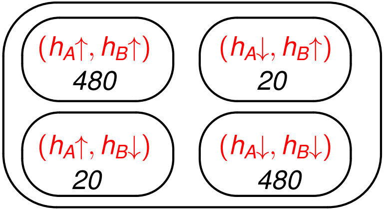

to make progress:

model all risks and their relations

at individual and cohort level

individual versus cohort level risk description

	cohort:	individual i:
event time statistics:	$\mathcal{P}(t_1,\ldots,t_R)$	$\mathcal{P}_i(t_1,\ldots,t_R)$
cause-specific hazard rates:	$h_r(t)$	$h_r^i(t)$
cause-specific survival functions:	$S_r(t)$	$S_r^i(t)$

links:

$$\mathcal{P}(t_1,\ldots,t_R)=\frac{1}{N}\sum_{i=1}^N \mathcal{P}_i(t_1,\ldots,t_R) \qquad S_r(t)=\frac{1}{N}\sum_{i=1}^N S_r^i(t)$$

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Complexity levels of cohorts

level 1 : homogeneous cohort, no competing risks

$$\mathcal{P}_i(t_1,\ldots,t_R) = \prod_r \overline{\mathcal{P}}(t_r|\mathbf{z}_i)$$
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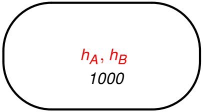

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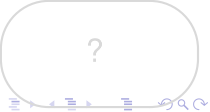

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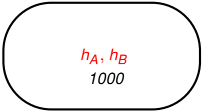

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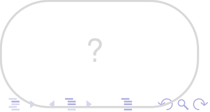

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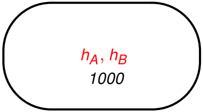

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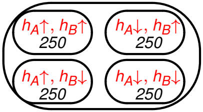

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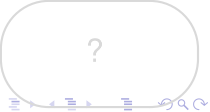

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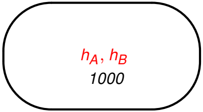

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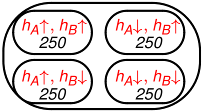

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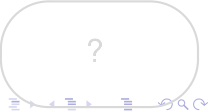

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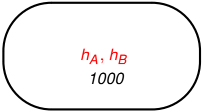

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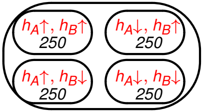

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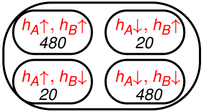

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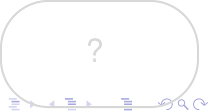

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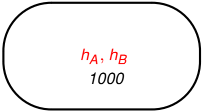

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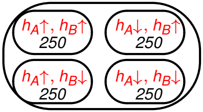

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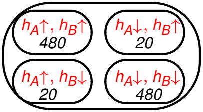

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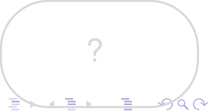

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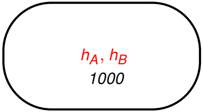

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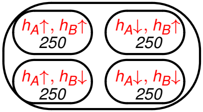
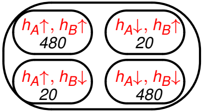


level 3 : heterogeneity-induced competing risks

$$\mathcal{P}_i(t_1,\ldots,t_R) = \prod_r \mathcal{P}_i(t_r)$$
$$\mathcal{P}(t_1,\ldots,t_R|\mathbf{z}) \neq \prod_r \mathcal{P}(t_r|\mathbf{z})$$



level 4 : individual *and* cohort level competing risks

$$\mathcal{P}_i(t_1,\ldots,t_R) \neq \prod_{r=1} \mathcal{P}_i(t_r)$$
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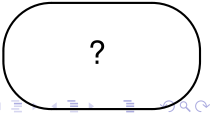

Heterogeneity-induced competing risks

Natural description

covariate-conditioned joint *distribution*
of all cause-specific hazard rates:

$$\mathcal{W}[h_1,\ldots,h_R|\mathbf{z}] = \frac{\sum_{i,\mathbf{z}_i=\mathbf{z}} \prod_r \delta_{\rm F}[h_r - h_r^i]}{\sum_{i,\mathbf{z}_i=\mathbf{z}} 1}$$

$h_r^i = \{h_r^i(t)\}$
risk r hazard rate
of individual i

Disabling non-primary risks:

$h_r^i \to 0$ *for all $r > 1$*

$$\mathcal{W}[h_1,\ldots,h_R|\mathbf{z}] \to \mathcal{W}[h_1|\mathbf{z}] \prod_{r>1} \delta_{\rm F}[h_r] \qquad \mathcal{W}[h_1|\mathbf{z}] = \frac{\sum_{i,\mathbf{z}_i=\mathbf{z}} \delta_{\rm F}[h_1 - h_1^i]}{\sum_{i,\mathbf{z}_i=\mathbf{z}} 1}$$

Data log-likelihood:

$$\mathcal{L}(D|\mathcal{W}) = \sum_{i=1}^{N} \log \int \{{\rm d}h_1 \ldots {\rm d}h_R\}\, \mathcal{W}[h_1,\ldots,h_R|\mathbf{z}_i]\, h_{r_i}(t_i) {\rm e}^{-\sum_{r=1}^{R} \int_0^{t_i} {\rm d}s\, h_r(s)}$$

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Decontamination formulae

'crude' cause-specific quantities:

$$S_r(t|\mathbf{z}) = \mathrm{e}^{-\int_0^t \mathrm{d}s\ h_r(s|\mathbf{z})}$$

$$h_r(t|\mathbf{z}) = \frac{\int\{\mathrm{d}h_1 \ldots \mathrm{d}h_R\}\ \mathcal{W}[h_1, \ldots, h_R|\mathbf{z}]\ h_r(t)\mathrm{e}^{-\sum_{r'}\int_0^t \mathrm{d}s\ h_{r'}(s)}}{\int\{\mathrm{d}h_1 \ldots \mathrm{d}h_R\}\ \mathcal{W}[h_1, \ldots, h_R|\mathbf{z}]\ \mathrm{e}^{-\sum_{r'}\int_0^t \mathrm{d}s\ h_{r'}(s)}}$$

decontaminated:

$$\tilde{S}_r(t|\mathbf{z}) = \int\{\mathrm{d}h_1 \ldots \mathrm{d}h_R\}\ \mathcal{W}[h_1, \ldots, h_R|\mathbf{z}]\ \mathrm{e}^{-\int_0^t \mathrm{d}s\ h_r(s)}$$

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Parametrisations of $\mathcal{W}[h_1,\ldots,h_R|\mathbf{z}]$

proportional hazards at level of individuals

$$\mathcal{W}[h_1,\ldots,h_R|\mathbf{z}] = \int \mathrm{d}\boldsymbol{\beta}_1\ldots\mathrm{d}\boldsymbol{\beta}_R \int \{\mathrm{d}\lambda_1\ldots\mathrm{d}\lambda_R\}\, \mathcal{M}(\boldsymbol{\beta}_1,\ldots,\boldsymbol{\beta}_R;\lambda_1,\ldots\lambda_R) \times \prod_r \delta_{\mathrm{F}}\Big[h_r - \lambda_r \mathrm{e}^{\beta_r^0+\sum_{\mu=1}^p \beta_r^\mu z_\mu}\Big]$$

includes as special cases:
Cox regression, frailty models, random effect models, ...

- e.g. latent class heterogeneity:

$$\mathcal{M}(\boldsymbol{\beta}_1,\ldots,\boldsymbol{\beta}_R;\lambda_1,\ldots,\lambda_R) = \mathcal{M}(\boldsymbol{\beta}_1,\ldots,\boldsymbol{\beta}_R)\prod_{r=1}^R \delta_{\mathrm{F}}[\lambda_r - \hat{\lambda}_r]$$

$$\mathcal{M}(\boldsymbol{\beta}_1,\ldots,\boldsymbol{\beta}_R) = \sum_{\ell=1}^L w_\ell \prod_{r=1}^R \delta(\boldsymbol{\beta}_r - \hat{\boldsymbol{\beta}}_r^\ell)$$

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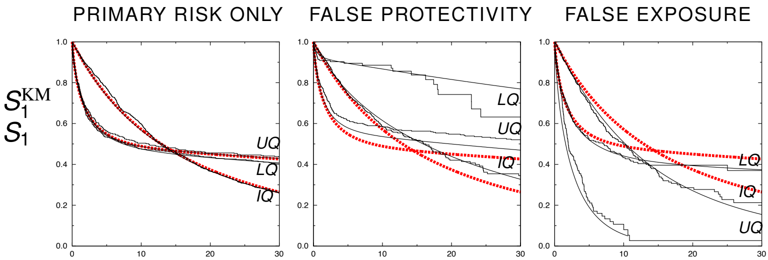
Applications – synthetic data



S_1^{KM} : *Kaplan-Meier*

S_1 : *crude survival curve*

red dashed: true survival curves

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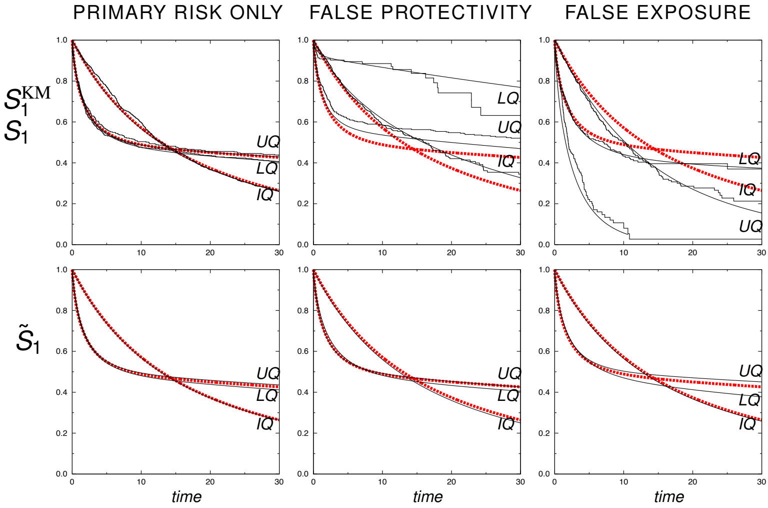

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retrospective class identification

$$P(\ell|t,r,\mathbf{z}) = \frac{w_\ell\, e^{\hat{\boldsymbol{\beta}}_r^\ell\cdot\mathbf{z}-\sum_{r'=1}^R \exp(\hat{\boldsymbol{\beta}}_{r'}^\ell\cdot\mathbf{z})\int_0^t ds\;\hat{\lambda}_{r'}(s)}}{\sum_{\ell'=1}^L w_{\ell'}\, e^{\hat{\boldsymbol{\beta}}_r^{\ell'}\cdot\mathbf{z}-\sum_{r'=1}^R \exp(\hat{\boldsymbol{\beta}}_{r'}^{\ell'}\cdot\mathbf{z})\int_0^t ds\;\hat{\lambda}_{r'}(s)}}$$

Data:

3 classes,
$w_1 = w_2 = w_3 = \frac{1}{3}$
2 competing risks

$\beta_1^1 = (0.5, 0.5, 0.5) + (2, 0, 2)$
$\beta_1^2 = (0.5, 0.5, 0.5) + (-2, -2, 0)$
$\beta_1^3 = (0.5, 0.5, 0.5) + (0, 2, -2)$

each individual i:
point (p_1^i, p_2^i, p_3^i) in $\mathbb{R}^3$
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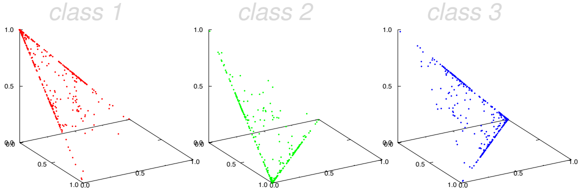

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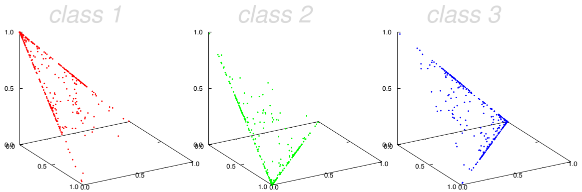

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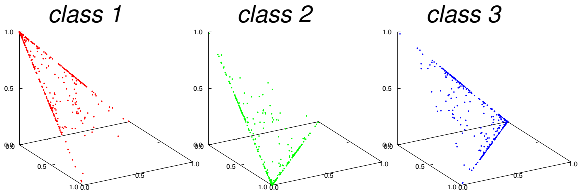

Applications – ULSAM prostate cancer data set

$N = 2047$,
primary events: 208
death (non-PC): 910
end of trial: 929

covariates:		
	body mass index	(real-valued)
	serum selenium level	(integer)
	physical activity, leisure time	(0/1/2)
	physical activity, work	(0/1/2)
	smoking	(0/1/2)

Cox regression:

BMI	*selenium*	*phys1*	*phys2*	*smoking*
$\beta_1 = 0.14$	$\beta_2 = -0.15$	$\beta_3 = 0.20$	$\beta_4 = -0.09$	$\beta_5 = -0.08$

$$\mathrm{HR}_\mu = \exp(2\beta_\mu)$$

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	CLASSES	PRIMARY RISK					SECONDARY RISK				
		208 events					910 events				
		BMI	*selen*	*phys1*	*phys2*	*smok*	*BMI*	*selen*	*phys1*	*phys2*	*smok*
Cox		0.14	-0.15	0.20	-0.09	-0.08					
new	$w_1 = 0.51$	1.22	-0.41	0.73	-0.01	1.43	0.82	-0.42	-0.31	-0.14	1.35
	$w_2 = 0.49$	-0.07	-0.16	0.19	-0.10	-0.27	0.10	-0.07	-0.07	0.04	0.18
	frailties:	$\beta^1_{10} - \beta^2_{10} = -4.61$ (HR 0.010)					$\beta^1_{20} - \beta^2_{20} = -4.06$ (HR 0.017)				

healthy class: strong effects of covariates,
BMI and smoking important risk factors

frail class: weak effects of covariates,
BMI and smoking weakly protective
(reverse causal effects?)

phys1? (leisure time physical activity)

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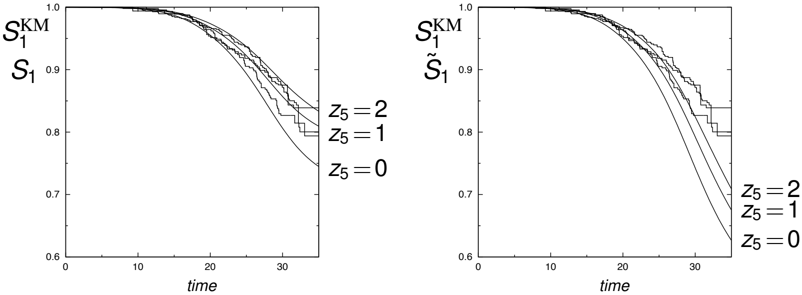

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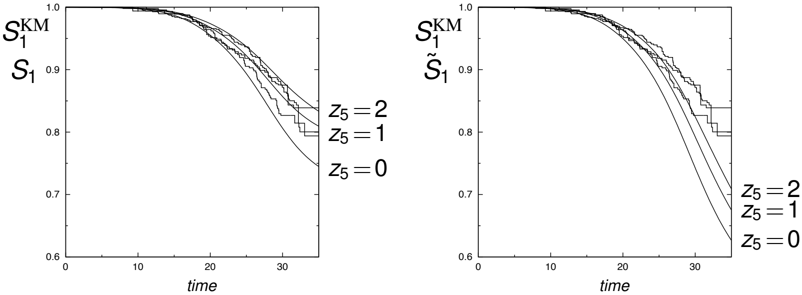
S_1 : crude survival curves,
$\tilde{S}_1$: decontaminated curves

$z_5 = 0$: non-smokers
$z_5 = 1$: ex-smokers
$z_5 = 2$: smokers

false protectivity due to competing risks

Cox/KM underestimate PC risk

BMI & smoking important risk factors in *healthy class*, *frail class* dominate Cox regression and survival curves (due to larger nr of events)



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Summary

- competing risk problem can be solved if we assume risk correlations are caused by *residual heterogeneity* (heterogeneity not captured by covariates)
- formulae for decontaminated survival curves, expressed in terms of $\mathcal{W}[h_1, \ldots, h_R|\mathbf{z}]$ *covariate-conditioned joint distribution of hazard rates for all risks*
- Natural parametrisation of $\mathcal{W}[h_1, \ldots, h_R|\mathbf{z}]$, includes standard methods as special cases (Cox, frailty models, random effects models, ...)
- Application to synthetic data with competing risks: method detects structure, parameters, and survival curves correctly
- Application to ULSAM cancer data: new intuitive explanations for previously unexplained results

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Katherine Lawler

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SEVENTH FRAMEWORK PROGRAMME

Prostate Action