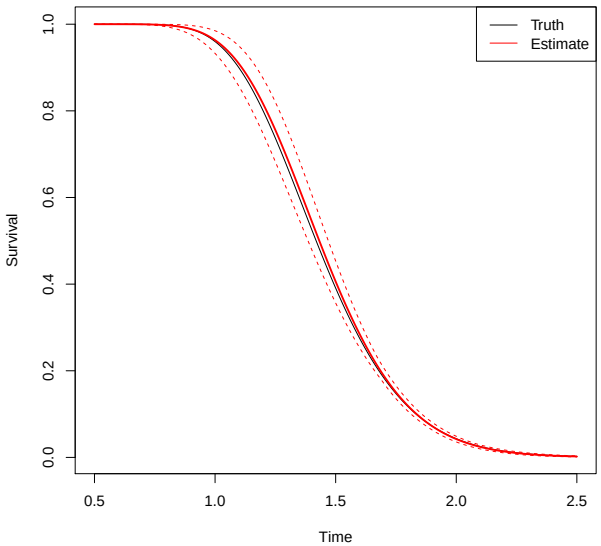
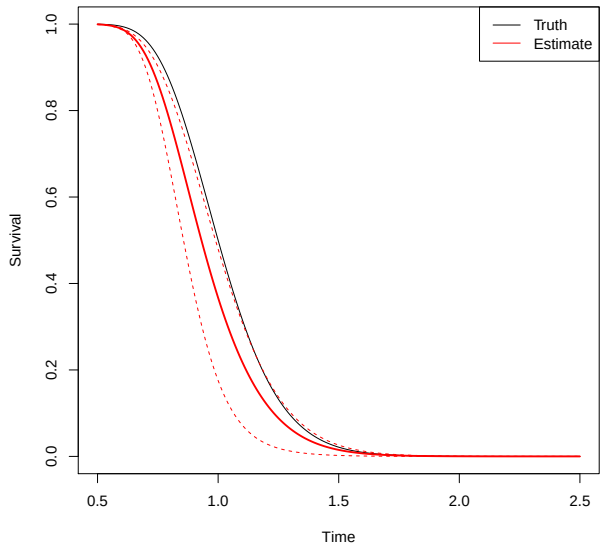
BNP survival regression with variable dimension covariate vector

Peter Müller, UT Austin





BC, BRAF

TT (left),
S (right)

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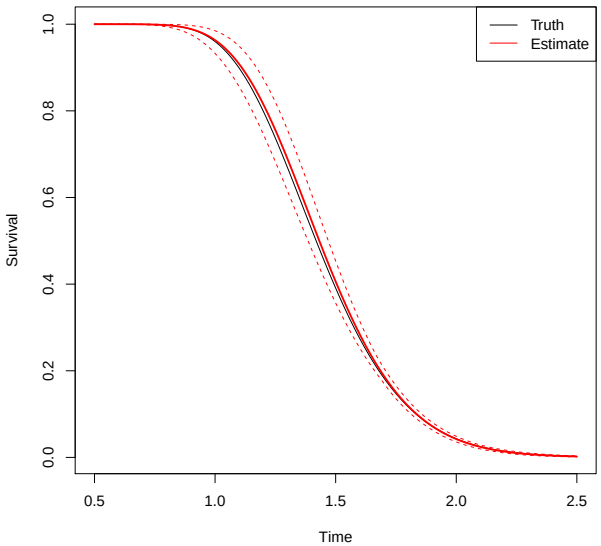

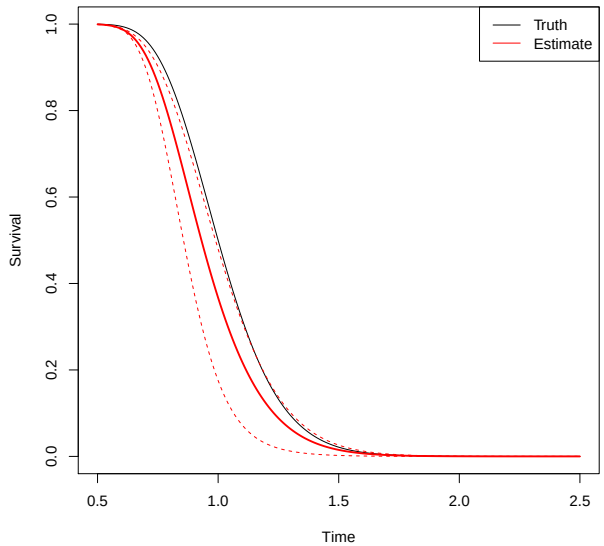

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TRT	TUMOR	PFS	CENS	MUTATIONS								
				m1	m2	m3	m4	m5	m6	m7	m8	. . .
TT	THYROID	2.6	0	NA	NA	NA	NA	NA	NA	NA	NA	
TT	THYROID	3.6	0	NA	0	0	0	NA	0	NA	NA	
S	OVARIAN	4.2	1	0	NA	0	0	0	0	0	0	
S	MELANOMA	5.8	1	NA	0	0	0	NA	0	0	0	
. . .	. . .	. . .	. . .									

1. Clinical Trial of Targeted Therapies

w. Don Berry & Lia Tsimbouridou, M.D. Anderson, Riten Mitra, U. Louisville, Yanxun Xu, JHU,

Clinical trial: study of targeted therapy (TT) vs. standard care (S) in metastatic cancers.
patients with metastatic cancers (thyroid, ovarian, melano, lung, breast, CRC and other)

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heterogeneous pat population different mutations; different cancers; basline covs ...

Treatment might be effective in a sub-population

2. BNP survival regression for variable dim **x**

with F. Quintana, PUCC, Chile and Gary Rosner, JHU.

Variables: for each patient $i = 1, \ldots, n$

- Outcome y_i PFS;
- Covariates $\mathbf{x}_i = (c_i, m_i, b_i)$
  - tumor type $c_i \in \{1, \ldots, C\}$ (categorical)
  - molecular aberrations $\mathbf{m}_i = (m_{i1}, \ldots, m_{iM})$ with $m_{is} = 1$ for observed aberration, $m_{is} = -1$ for not observed (and 0 for n/a).
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Random Partition

$\mathbf{s} = (s_1, \ldots, s_n) =$ cluster membership indicators $s_i \in \{1, \ldots, J\}$.
Let $\mathbf{y}_j^\star$ and $\mathbf{x}_j^\star$ variables by cluster and $S_j = \{i : \ s_i = j\}$.

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Sampling model: exchangeable within clusters

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Prediction: future patient $i = n + 1$ is

- matched with one of the earlier clusters, on the basis of similar covariates $\mathbf{x}_i = (c_i, \mathbf{m}_i, b_i)$.
- predict similar PFS. That's all!

Covariate dependent partition

Random partition:

$$p(\mathbf{s} \mid \mathbf{x}) \propto \prod_{j=1}^{J} c(S_j)\, g(\mathbf{x}_j^{\star})$$

favor clusters homogeneous in $\mathbf{x}_i$;

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Similarity function: over observed covariates only.

Assume only 1 covariate:

$$g(\mathbf{x}_j^{\star}) = g\left(\{x_i,\ i \in S_j\right.$$

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$S_j^\star = S_j \cap \{i : x_i \text{ observed }\}$

Default construction – single covariate $x_{i\ell}$: with auxiliary model $\prod_{i \in S_j^\star} q(x_i \mid \xi_j)$ and aux prior $q(\xi_j) \Rightarrow$

$$g(\mathbf{x}_j^\star) = \int \left\{ \prod_{i \in S_j^\star} q(x_i \mid \xi_j) \right\} q(\xi_j)\, d\xi_j$$

analytical evaluation with conjugate pairs $q(x \mid \xi), q(\xi)$ for continuous, binary, count etc.

Easy extension to mv continous vector etc.

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Multiple covariates: for mix of multiple data types

$$g(\mathbf{x}_j^\star) = \prod_{\ell=1}^{L} g_\ell(\mathbf{x}_{j\ell}^\star)$$

with product over covariates (covariate subvectors)

Computation

Scaled $g(\mathbf{x}_j^\star)$: scale with $q(x_{i\ell} \mid \bar{\xi}_\ell)$ for any choice of $\bar{\xi}$

$$\tilde{g}_\ell(x_{j\ell}^*) = \frac{g_\ell(x_{j\ell}^*)}{\prod_{i \in S_j} q(x_{i\ell} \mid \bar{\xi}_\ell)},$$

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Evaluation: simplifies to

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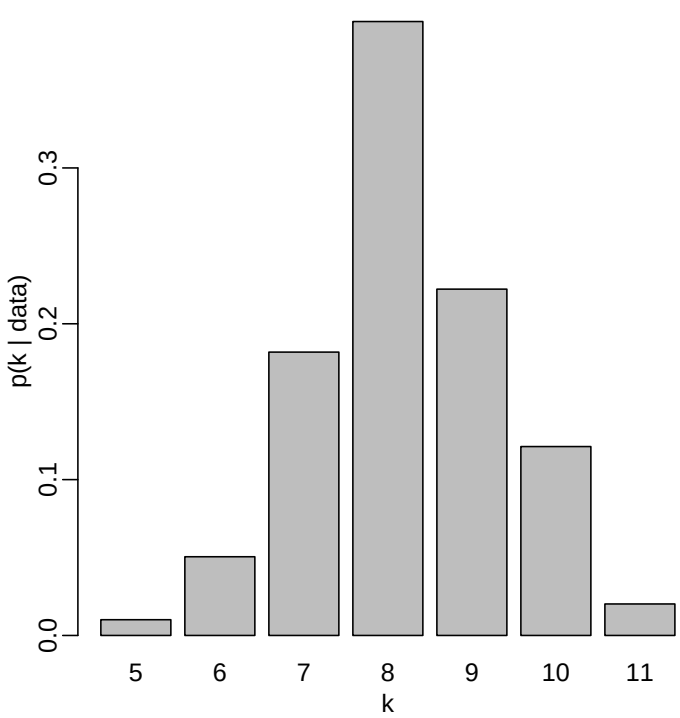
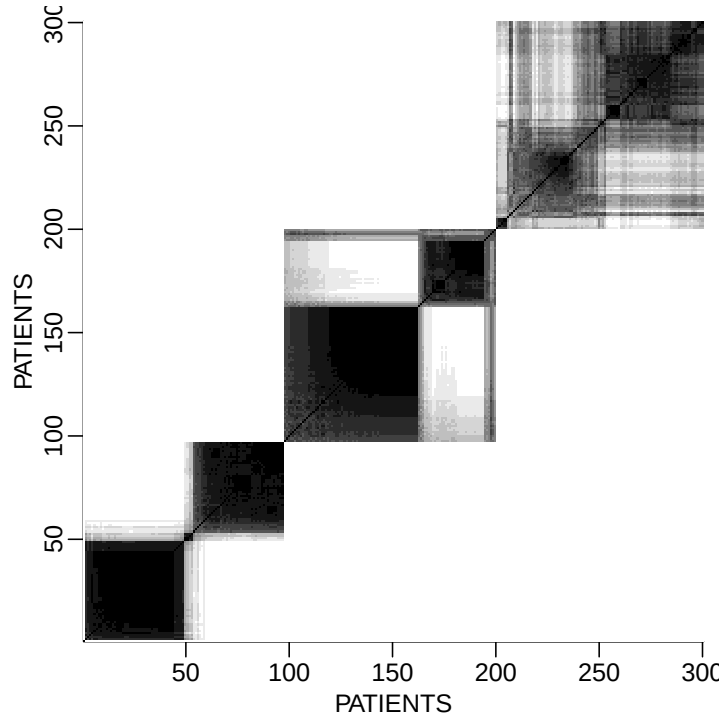
Variable selection: could add variable selection with $\gamma_{j\ell} \in \{0, 1\}$ (Quintana, M & Papoila, ScanJ, 2015).

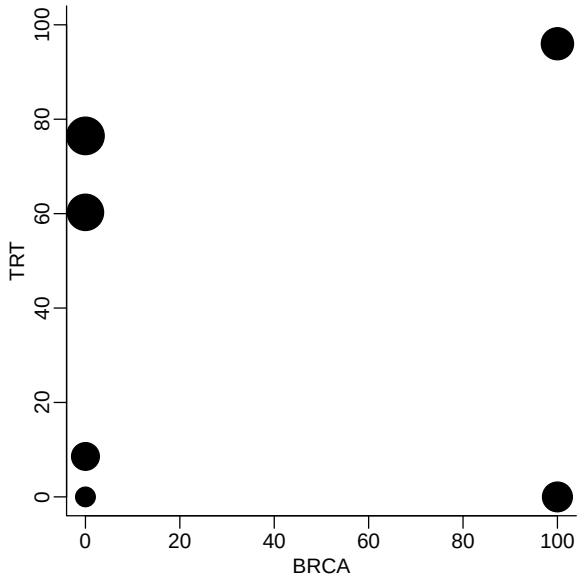
3. Results

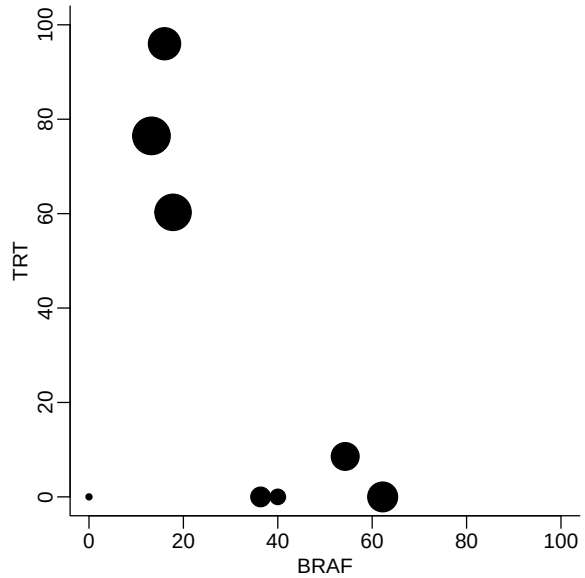


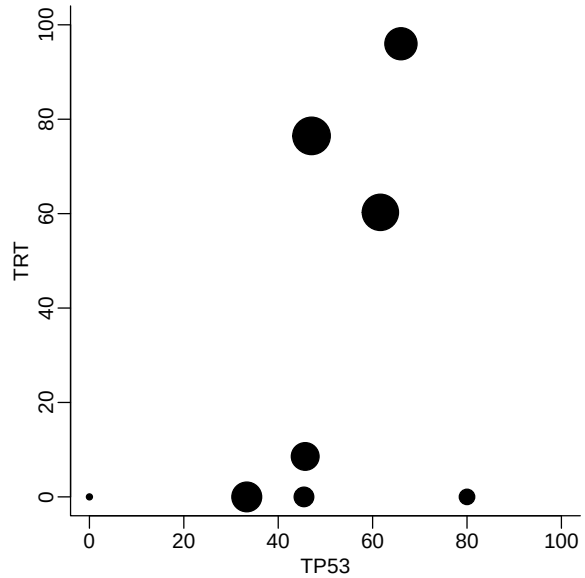
(a) $p(k \mid y)$



(b) co-clustering probs







clusters by . . .

(a) %BRCA and %TT (b) %BRAF and %TT (b) %P53 & TT

4. Bayesian Subgroup analysis

- Treatment/cov interaction: Dixon and Simon (1991, Bmcs), Simon (2002, StatMed), Jones et al. (2011, ClinTrials)
- Tree based methods: Foster, Taylor & Ruberg (2011, StatMed)
- Model selection: Berger, Wang and Shen (2014, JBiophStat), Sivaganesan et al. (2011, StatMed)
- Decision problem: next slides...

Decision Problem

Data: response y_i (PFS), covariates $\mathbf{x}_i = (x_{i1}, \ldots, x_{ip})$.

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Actions: Report a (i.e., *one*) subgroup of patients who might most benefit from the experimental therapy:

$$\mathbf{a} = (I, \mathbf{x^o}),$$

Covariates: $I \subset \{1, \ldots, p\}$
Levels: $\mathbf{x^o} = (x_\ell^o,\ \ell \in I)$.
Population finding: recommend subpop $\{x_{i\ell} = x_\ell^o,\ \ell \in I\}$

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- no need for multiplicity control
- arbitrary prob model, e.g. BNP survival regression

Utility: we favor a subpopulation with difference (relative to the overall population) in log hazards ratio (LR), large size and parsimonious description with few covariates

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$$u(a, \theta) = (\mathrm{LR}(a, \theta) - \beta) \cdot \frac{n(\mathbf{a})^{\alpha}}{(|I| + 1)^{\gamma}}$$

with $\beta > 0$ a fixed clinically decided threshold and $n(\mathbf{a})$ is the size of the subpopulation.
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Model: Decicsion problem and solution meaningful for any model. We compute the expectations w.r.t. the BNP survival regression.

Operating Characteristics: Error Rates

TIE $= p(H_0^c \mid H_0)$ type-I error

TPR $= p(H_1 \mid H_1)$ true positive r.

TSR $= p(H_{\mathbf{a}} \mid H_{\mathbf{a}})$ true subgroup r.

FNR $= p(H_0 \mid H_0^c)$ false negative rate

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$p(A \mid B)$ = frequentist probability of A over repeat simulation under truth B.

	Truth		
	Subgroup Effect		
Decision	H_0	H_a	H_1
H_0	1-TIE		FNR
H_a		TSR_a	FSR
H_1		FPR_a	TPR

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- Choose c_0 to control TIE, and c_1 to control (average) FSR.

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H_a		TSR_a	FSR
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- Choose c_0 to control TIE, and c_1 to control (average) FSR.
- All but the TIE require additional specification:
  - effect size for FNR, TPR and FSR.
  - TSR and FPR depend on specific subgroup a.

Simulation results

Scenario	TIE	TSR	TPR	FSR	FNR	FPR
1	-	.74	-	.02	.00	.00
2	0.05	-	-	-	-	-
3	-	.98	-	.00	.01	.00
4	-	.93	-	.00	.00	.00
5	-	.81	-	.02	.01	.00
6	-	.91	-	.00	.01	.00
7	-	.77	-	.00	.00	.03
8	-	.62	-	.00	.01	.00
9	-	-	.89	-	-	-
10	-	.66	-	.00	.00	.00

TIE $= \Pr(H_0^c \mid H_0)$; TSR $= \Pr(a \mid a)$; TPR $= \Pr(H_1 \mid H_1)$; FSR $= \Pr(a \mid a^c)$; FNR $= \Pr(H_0 \mid H_0^c)$; and FPR $= \Pr(H_1 \mid H_1^c)$.

Simulation results

Scenario	TIE	TSR	TPR	FSR	FNR	FPR
1	-	.74	-	.02	.00	.00
2	0.05	-	-	-	-	-
3	-	.98	-	.00	.01	.00
4	-	.93	-	.00	.00	.00
5	-	.81	-	.02	.01	.00
6	-	.91	-	.00	.01	.00
7	-	.77	-	.00	.00	.03
8	-	.62	-	.00	.01	.00
9	-	-	.89	-	-	-
10	-	.66	-	.00	.00	.00

TIE $= \Pr(H_0^c \mid H_0)$; TSR $= \Pr(a \mid a)$; TPR $= \Pr(H_1 \mid H_1)$; FSR $= \Pr(a \mid a^c)$; FNR $= \Pr(H_0 \mid H_0^c)$; and FPR $= \Pr(H_1 \mid H_1^c)$.

* scenario 2 is true H_0 – others are true subgroup & overall effects

Summary

- BNP survival regression, with arbitrary interactions (clusters), variable dim cov vectors, no extrapolation
- useful for prediction, not for interpretation of parameters
- Example: subgroup analysis; implements multiplicity control
  - choice of priors,
  - by controlling frequentist error rate.
- Extension: variable selection within each cluster