January 23, 2018, 2 - 3:00 p.m.

Speaker:
Bingshu Chen, PhD, Queen's University

Title:
Bayesian methods for biomarker threshold models with binary and survival data

Abstract:
In biomedical studies, it is often of interest to estimate how the outcome variables (either the efficacy outcome such as survival or risk profile of an adverse event) are related to an intervention and other related biomarker variable. For example, in randomized controlled clinical trials of bivalent human papillomavirus (HPV) vaccine, investigators are interested to know how miscarriage rate relates to the timing of HPV vaccination. We developed hierarchical Bayesian Biomarker Threshold Models to make simultaneous inference on both the cut-points of the biomarker variable and the magnitude of the biomarker-treatment interaction. Hierarchical priors are proposed and used in Markov Chain Monte Carlo for statistical inference. We further implement the proposed method in an R package for Biomarker Threshold Models ('bhm'). Several clinical trials examples will be demonstrated how to use the 'bhm' package to analyze outcome from linear models, generalized linear models and survival models.

Reading material:
- A hierarchical Bayes model for biomarker subset effects in clinical trials
- A Bayesian method for risk window estimation with application to HPV vaccine trial

Bayesian methods for Biomarker Threshold Models with binary and survival data

Bingshu E. Chen, Ph. D.

OICR, Toronto, Canada, January 23rd , 2018

Outline

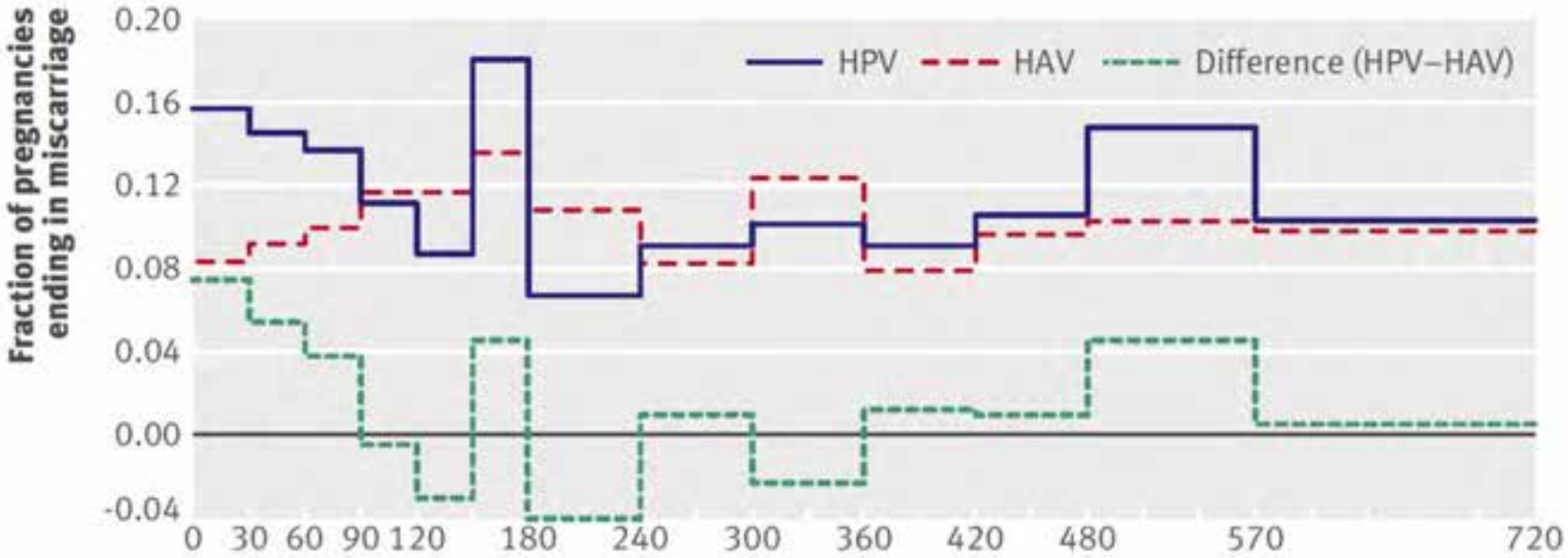
- Background examples and objectives
- Methods
  - Bayes model
  - Markov Chain Monte Carlo (MCMC)
  - Biomarker Threshold Models R package
- Simulation Studies
- Applications:
  - Costa Rica Vaccine Trial (CVT)
  - Prostate Cancer data with AP biomarker
  - Breast Cancer data with ki67 biomarker
- Summary

Background

- Example 1: Vaccine for Cervical Cancer
  - The 3rd most common mortality in women worldwide
  - The 5th most deadliest cancer in women
  - 529 000 new cases and 275 000 deaths in 2008, about 90% occurred in developing countries
  - 527 000 new cases and 265 000 deaths in 2016, about 84% occurred in developing countries

Background

- Example 1: Vaccine for Cervical Cancer
  - HPV (Human Papilloma Virus) is a cause of cervical cancer
  - The vaccine is effective but safety have to be assessed
  - Pervious study showed a numerically higher (but not statistically significant) miscarriage risk when vaccination was near to pregnancy date.
  - Knowledge on the potential "risk window" may have important public health implications. Define by $I\{c_1<W<c_2\}$



Count of miscarriages

HPV	24	18	16	12	9	14	11	11	13	13	11	20	12
HAV	11	10	13	14	12	13	19	11	20	11	12	11	9

Pregnancies at risk

HPV	153	124	117	108	104.5	77.5	165.5	121.5	129	144	104.5	136	117
HAV	133	109.5	131	120.5	103	96	176.5	134.5	161.5	139.5	124.5	107.5	92

Background

- Example 2: Treatment Prostate Cancer
  - A clinical trial with 506 prostate cancer patients
  - Treatment (Z): Control and diethylstilbestrol (DES)
  - Biomarker (W): Serum prostatic acid phosphatase (AP) level affects treatment outcome (More on this late)

$$h(t) = h_0(t)\exp\{\beta(W) * Z\}$$

  - Interested in finding biomarker cut-point to make clinical decision

$$\beta(W) \approx I(W > c\}$$

Background

- Biomarker for clinical studies
  - Binary/Continuous/Counts/Survival outcome
  - Prognostic biomarker: A measurement that is associated with clinical outcome in the absence of therapy or with standard therapy.
  - Predictive biomarker: Biological characteristics of patients measured at baseline, that helps identify patients who are likely or not likely to benefit from a therapy.

Prognostic and predictive biomarker

In biological term

	Is the biomarker predictive?	
Is the biomarker prognostic	No	Yes
No	Neither prognostic nor predictive	Predictive but not prognostic
Yes	Prognostic but not predictive	Both prognostic and predictive

Prognostic and predictive biomarker

- In statistical term: Interaction effect between treatment Z and a biomarker W

$$g(Y|Z,W) \sim \beta_0 + \beta_1 Z + \beta_2 W + \beta_3 ZW$$

- Neither prognostic nor predictive: $\beta_2 = 0,\ \beta_3 = 0$
- Prognostic but not predictive: $\beta_2 \neq 0,\ \beta_3 = 0$
- Predictive but not prognostic: $\beta_2 = 0,\ \beta_3 \neq 0$
- Both predictive and prognostic: $\beta_2 \neq 0,\ \beta_3 \neq 0$

Background

- Generalized Linear models (GLM)
  - Random variable Y that takes continuous or discrete values
  - Interest in conditional expectation of E(Y|X) = $p(\beta, W, Z)$
  - Linear Regression

$$g(Y|Z,W) = E(Y|Z,W) = \beta_0 + \beta_1 Z + \beta_2 W + \beta_3 ZW$$

  - Logistic Regression (Y = 0, or 1)

$$g(Y|Z,W) = \log\left(\frac{p}{1-p}\right) = \beta_0 + \beta_1 Z + \beta_2 W + \beta_3 ZW$$

  - Poisson Regression (Y = 0, 1, 2, 3, …), E(Y|X) = $\lambda(\beta, W, Z)$

$$g(Y|Z,W) = \log(\lambda) = \beta_0 + \beta_1 Z + \beta_2 W + \beta_3 ZW$$

Background

- Survival Analysis
  - Time to failure (death) is a random variable Y > 0
  - Interest in survival function S(t|W, Z) = 1 – F(t|W, Z) = P(Y>t|W, Z)
  - Hazard function is define by

$$g(t|W,Z) = \lim_{\Delta t \to 0} \frac{\Pr\{t \le Y < t+\Delta t | W,Z\}}{\Pr\{\, Y \ge t | W,Z \,\}} = \frac{f(t|W,Z)}{S(t|W,Z)}$$

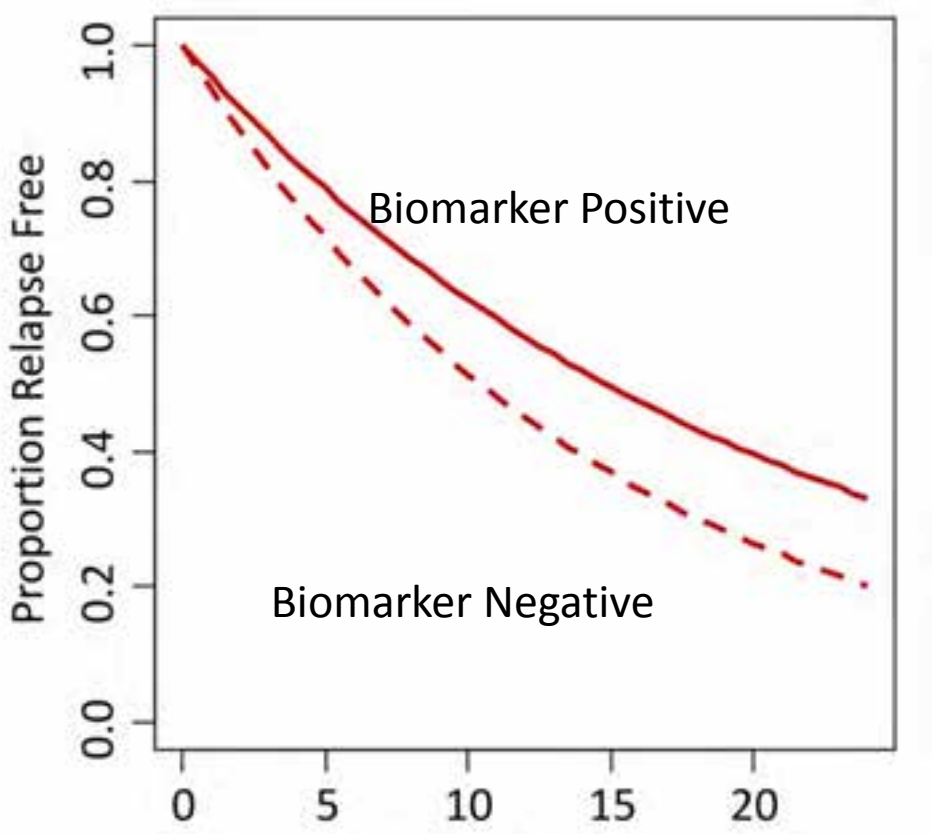
$$S(t|W,Z) = \exp\{-\int_0^t g(s|W,Z)ds\}$$

  - Cox Proportional Hazards Model (Cox 1972)

$$g(t|W,Z) = g_0(t)\exp\{\beta_1 Z + \beta_2 W + \beta_3 ZW\}$$

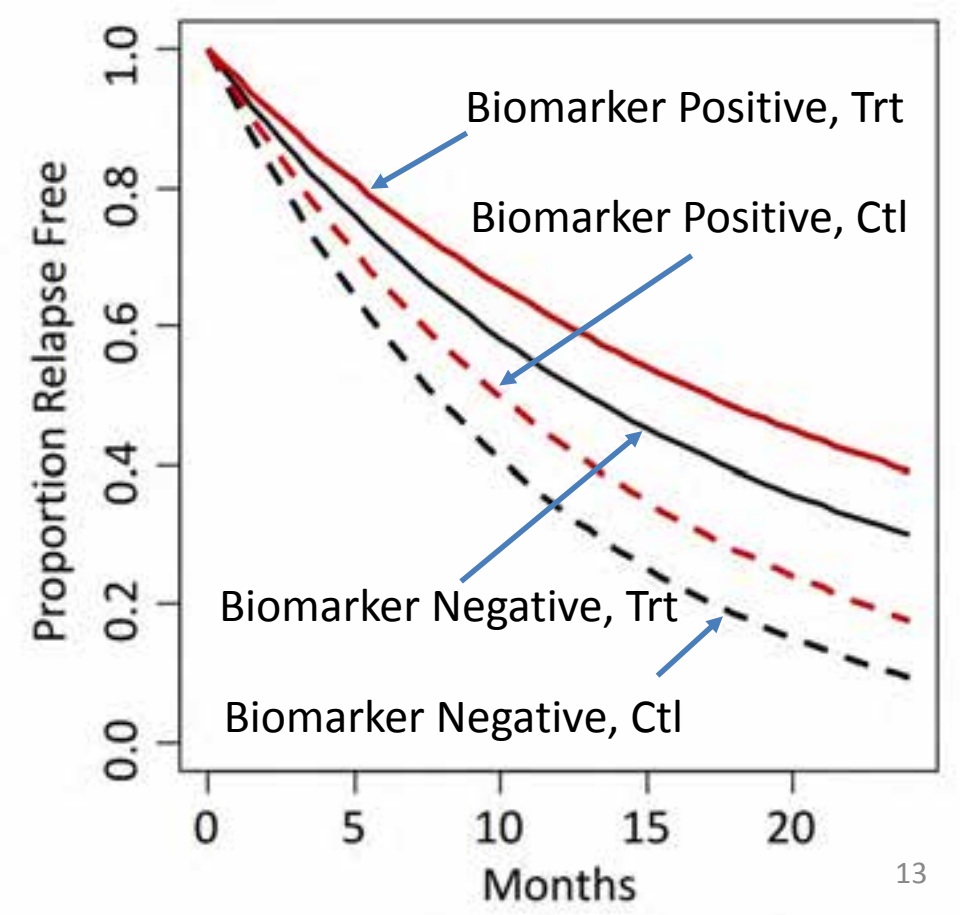
Background

- Examples of biomarker (Survival outcome)
  - Prognostic
  - But no predictive
  - No treatment effect

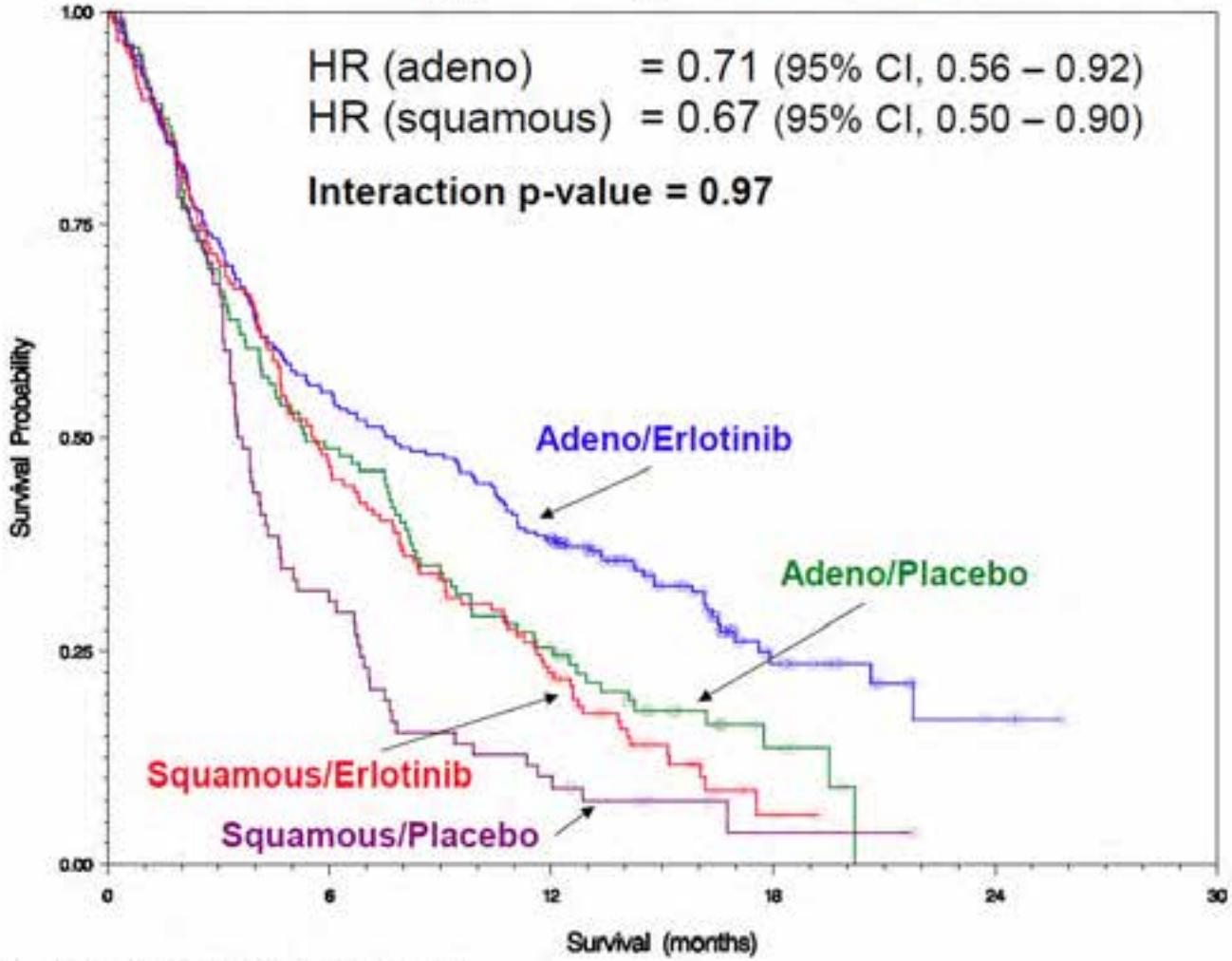


Background

- Examples of biomarker (Survival outcome)
  - Prognostic
  - But no predictive
  - Trt benefit equally
    - Trt: Treatment
    - Ctl: Control



BR.21: Histology is Prognostic but not Predictive

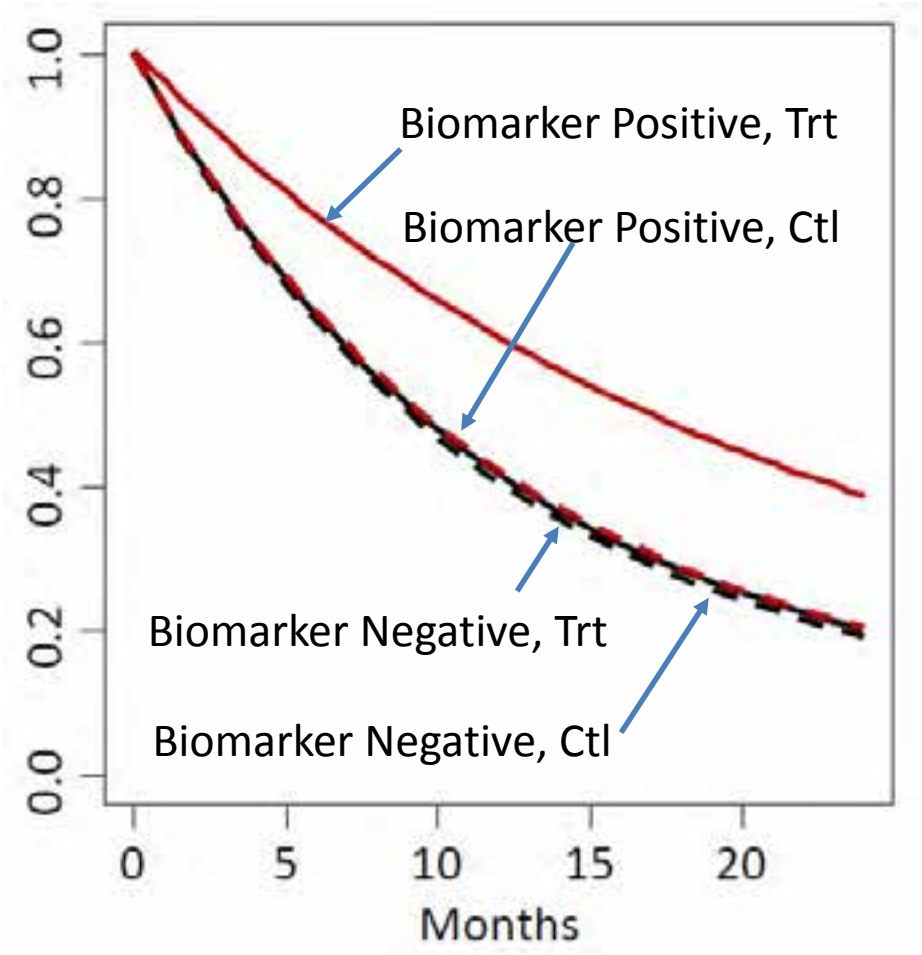


Clark GM. Mol Oncol 2008; 1:406-12

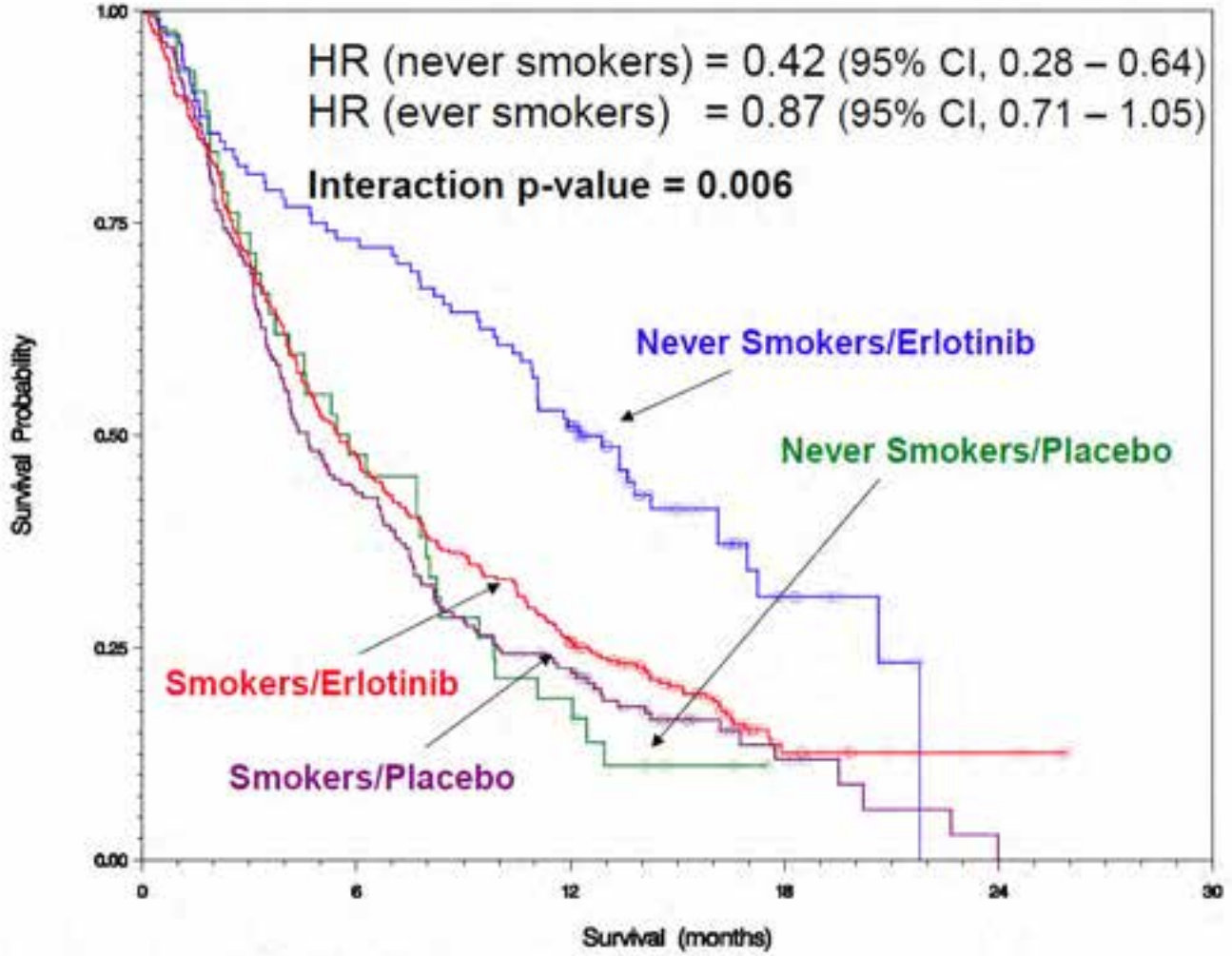
Background

- Examples of biomarker (Survival outcome)
  - Predictive
  - But no prognostic
  - Treatment benefit only the biomarker positive group but not the biomarker negative group

Background


Biomarker Positive, Trt
Biomarker Positive, Ctl
Biomarker Negative, Trt
Biomarker Negative, Ctl
0.0
0.2
0.4
0.6
0.8
1.0
0
5
10
15
20
Months

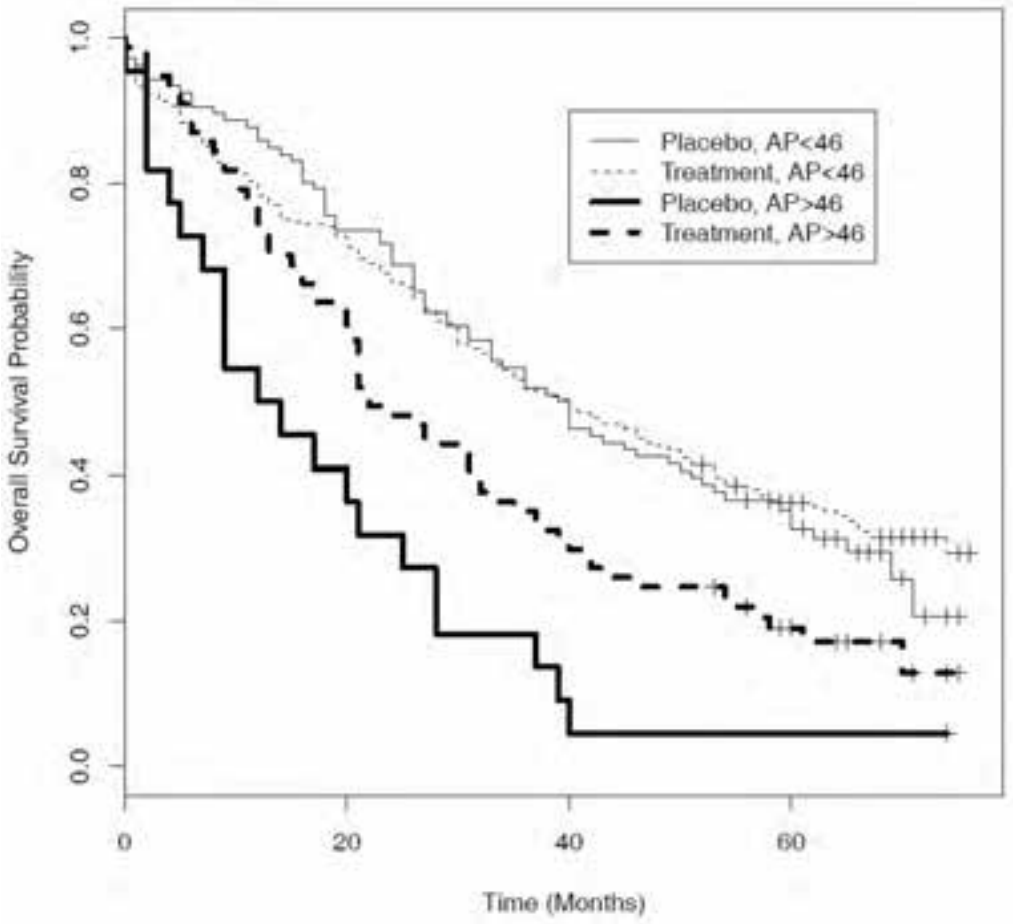
BR.21: Smoking is Predictive but not Prognostic



Clark GM. Mol Oncol 2008; 1:406-12

Background

One more example: Prostate Cancer



AP $\leq$ 46
HR = 1.1, p = 0.32

AP > 46
HR = 1.7, p = 0.01

Background

- Target: Study the interaction between treatment and a biomarker
- Why?
  - Advances in biotechnology: e.g. Molecularly targeted drugs
  - Patients with different biomarker values may benefit differently from a treatment
- Application: Personalized Medicine

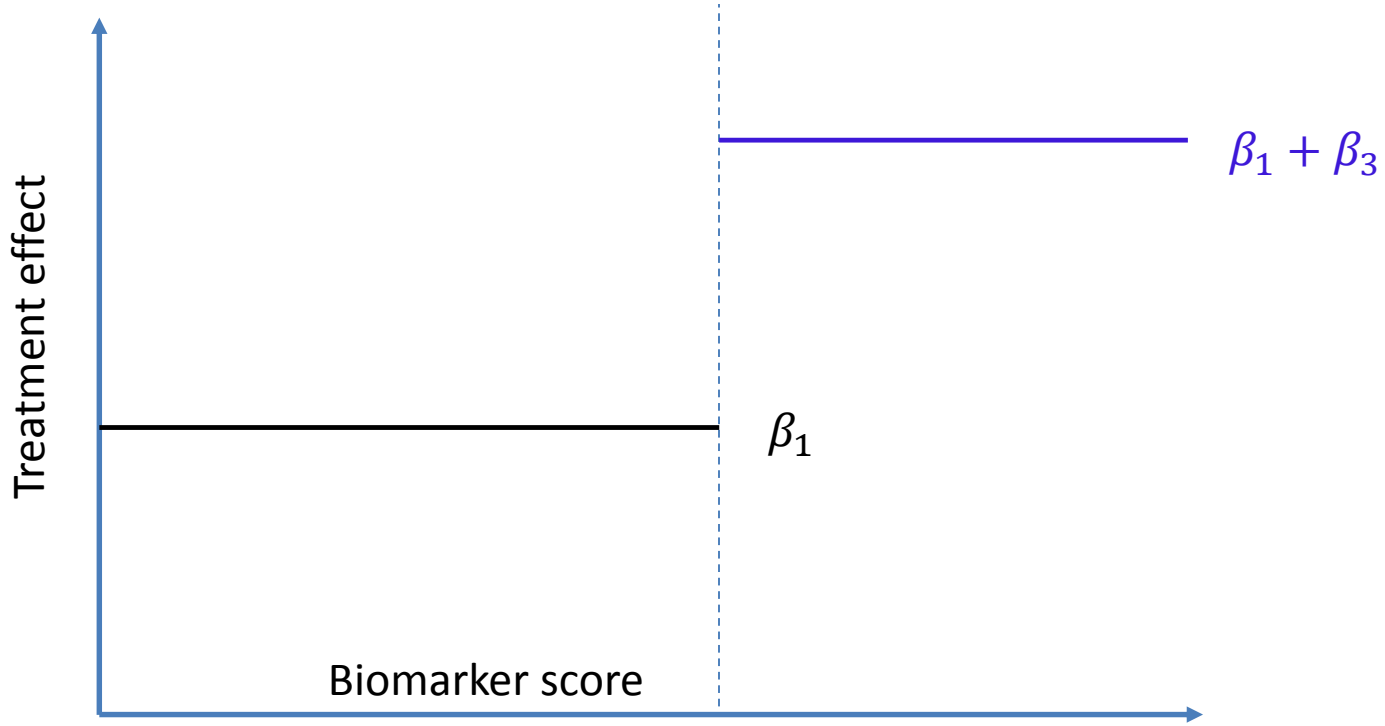
Background

- Actionable predictive biomarker? Clinically useful vs Statistically significance
  - Idea situation: exists an obvious threshold (or a cut point)
  - Clinically useful situation: exists a potential threshold
  - Clinically not useful situation: a moderate but statistically significant linear relationship

Background

- Idea

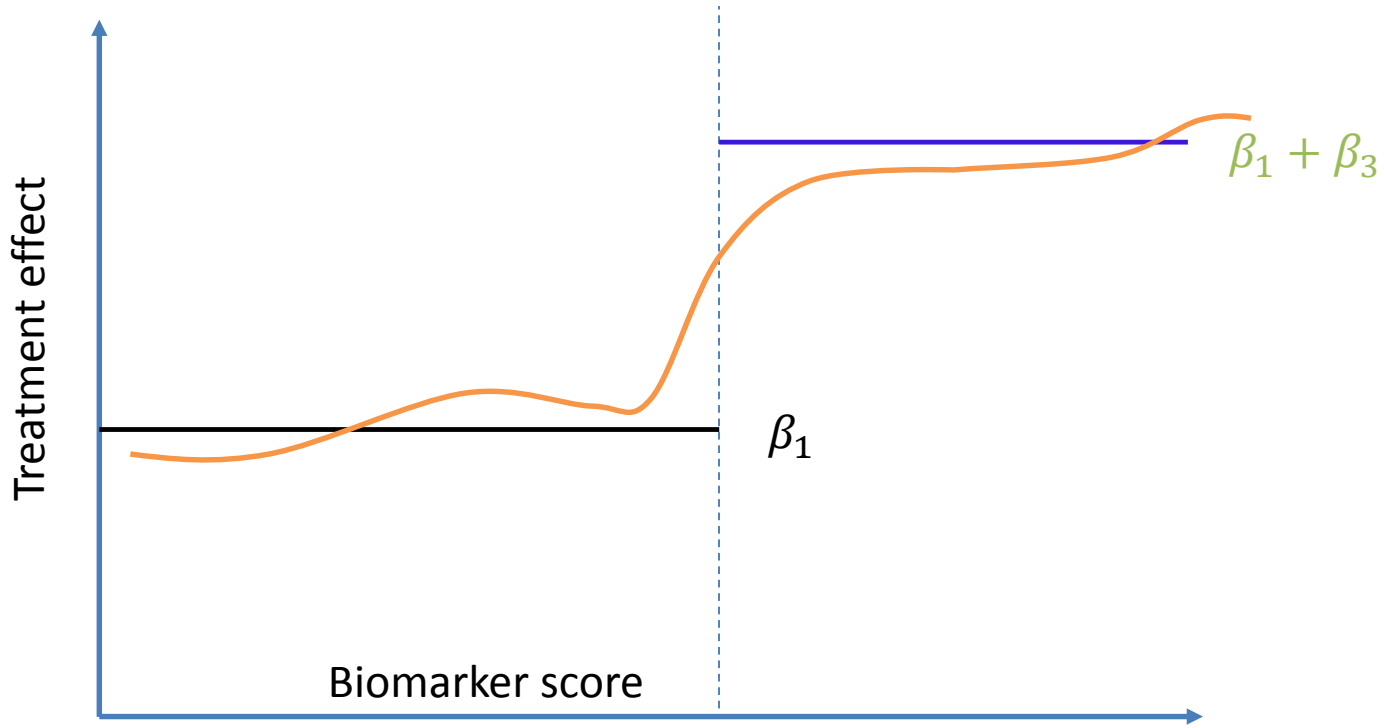
$$\beta_0 + \{\beta_1 + \beta_3 I(W \geq c)\}Z$$



Background

- Clinically useful

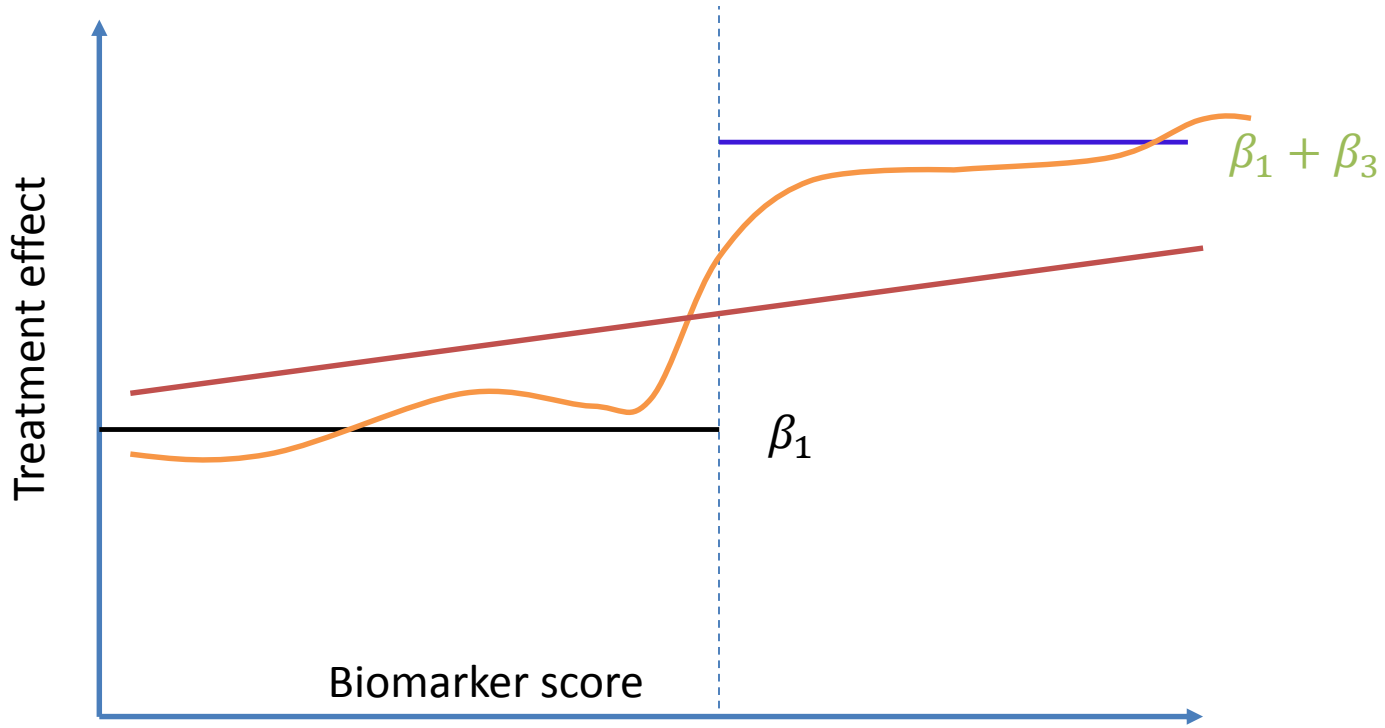
$$\beta_0 + \beta(W)\, Z$$



Background

- Clinically not useful

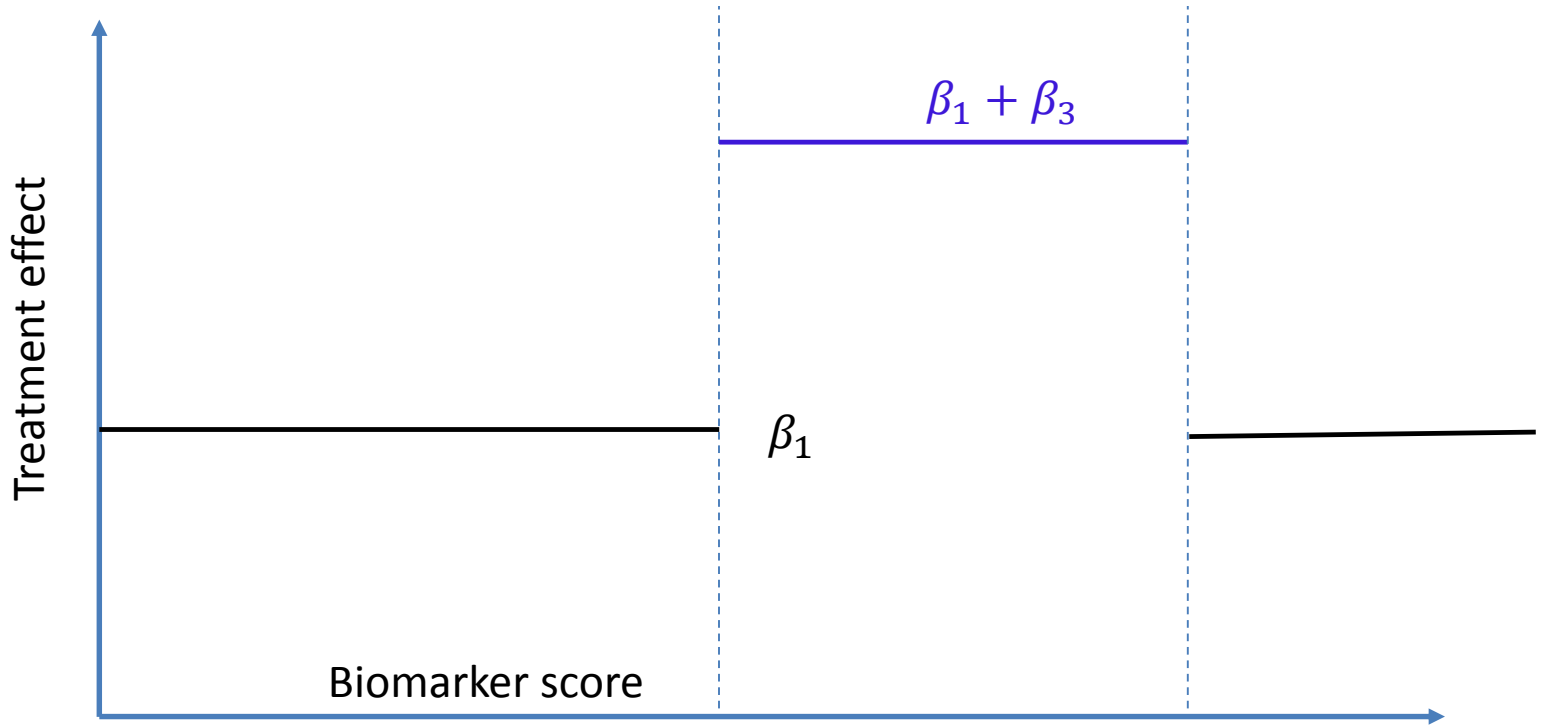
$$\beta_0 + (\beta_1 + \beta_3 W)\, Z$$



Background

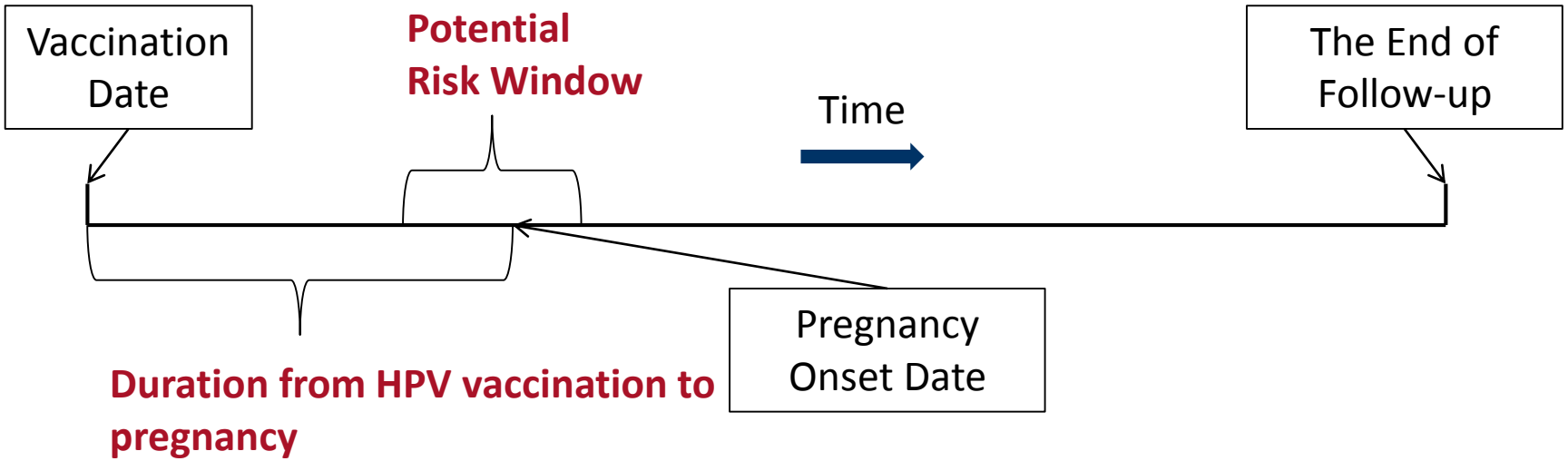
- General: multiple cut points

$$\beta_0 + \{\beta_1 + \beta_3 I(c_1 \leq W \leq c_2)\}Z$$



Rationale

Whether or not there is a risk window that is associated with increased miscarriage risk in pregnancies following the HPV vaccination?



- *Interested in estimation of the risk window! HOW?*

Objective

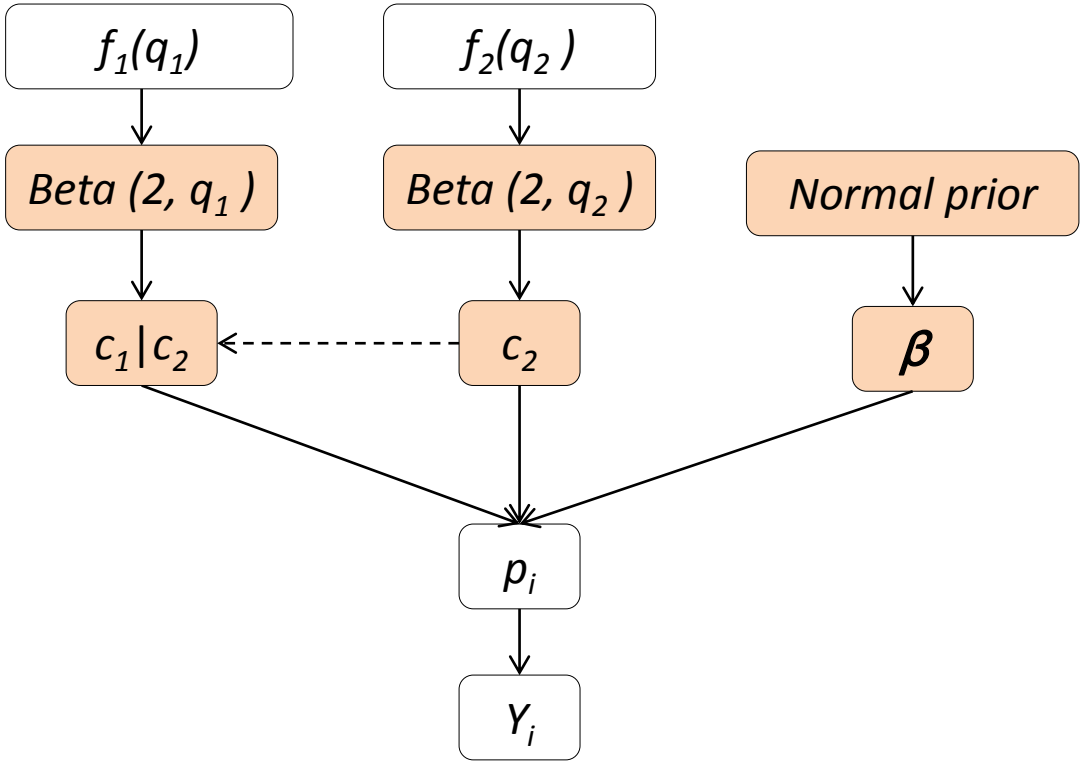
- To develop a Bayes model for the estimation of a risk window of adverse events
  - Construct an algorithm for parameter estimation
  - Evaluate the finite sample properties of the proposed method
  - Compare with existing methods
  - Apply the proposed Bayes model to the HPV trial

Methods

- Estimation
  - Select prior distributions for c1, c2, and β
    - We also introduce hyper prior (q1, q2) for c1 and c2
  - Find the joint posterior distributions of all parameters
  - Obtain the marginal distribution of each parameter based on the joint posterior
  - Compute point estimate and 95% credible interval for each parameter based on their respective marginal distribution

Methods

The Hierarchical Bayes Model:



MCMC

- Gibbs sampling method can be used to generate random samples representing the marginal distribution of each model parameter
  - c_1 and c_2: Metropolis-Hasting algorithm
  - **β**'s: Metropolis-Hasting algorithm
  - q_1 *and* q_2 : Exponential distribution

Simulations

- Generate data for
  - Sample size: n=2000, 4000
  - Different combination of c1, c2 and β
- Simulated data were analyzed by
  - Gibbs Sampling: 500 burn-in samples + 5000 random samples
  - Replications: 500
  - Examine: bias, coverage probability, and power

Results: Bias

Table 1

Empirical bias of the estimation for risk window $(\hat{c}_1, \hat{c}_2)$ and the relative risk $(\hat{\beta}_3)$ using the Bayesian method. The true values for $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ in all simulations. Results are based on $B = 5000$ MCMC iterations and $R = 500$ simulation replications.

(c_1, c_2)	Δc	$\beta_3 = \log(1.5)$			$\beta_3 = \log(2.5)$			$\beta_3 = \log(3.5)$		
		$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$
$n = 2000$										
(0.1, 0.2)	0.1	0.002	0.001	0.085	0.001	0.003	0.021	0.001	0.002	0.041
(0.2, 0.4)	0.2	0.001	0.003	0.083	0.001	0.003	0.028	0.002	0.005	−0.031
(0.2, 0.5)	0.3	0.002	0.004	−0.004	0.002	0.004	−0.002	0.003	0.003	−0.011
(0.3, 0.7)	0.4	0.004	0.002	0.008	0.001	−0.001	0.006	0.003	0.001	−0.030
(0.2, 0.7)	0.5	0.002	−0.001	0.006	0.003	−0.001	−0.007	0.007	−0.001	−0.048
(0.3, 0.9)	0.6	0.001	−0.001	−0.011	−0.001	−0.003	−0.019	−0.001	−0.002	−0.023
$n = 4000$										
(0.1, 0.2)	0.1	0.001	0.003	−0.002	0.001	0.006	−0.010	0.001	0.008	−0.009
(0.2, 0.4)	0.2	0.001	0.001	0.010	0.001	0.001	−0.010	−0.001	0.001	0.006
(0.2, 0.5)	0.3	−0.001	−0.001	−0.012	0.002	0.002	−0.020	−0.003	0.001	0.003
(0.3, 0.7)	0.4	0.001	−0.001	0.008	−0.001	−0.006	−0.032	0.002	0.001	−0.010
(0.2, 0.7)	0.5	0.002	−0.001	−0.009	0.002	−0.001	−0.020	0.001	−0.002	−0.006
(0.3, 0.9)	0.6	−0.001	−0.001	−0.002	−0.001	−0.002	−0.012	0.001	−0.001	−0.011

Results: Coverage Probability

Table 2
Coverage probabilities (C.P. in percentage) for 95% credible intervals using the Bayesian method. The true values for $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ in all simulations. Results are based on $B = 5000$ MCMC iterations and $R = 500$ simulation replications.

(c_1, c_2)	Δc	$\beta_3 = \log(1.5)$			$\beta_3 = \log(2.5)$			$\beta_3 = \log(3.5)$		
		$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$	$\hat{c}_1$	$\hat{c}_2$	$\hat{\beta}_3$
$n = 2000$										
(0.1, 0.2)	0.1	95.0	92.6	90.4	91.4	93.0	94.0	92.6	93.0	93.4
(0.2, 0.4)	0.2	93.6	95.8	92.6	93.0	94.2	91.2	91.6	90.4	94.0
(0.2, 0.5)	0.3	91.6	93.6	96.2	93.2	93.4	94.2	92.2	93.2	92.2
(0.3, 0.7)	0.4	93.4	94.0	93.8	92.8	94.6	92.4	92.8	92.4	92.8
(0.2, 0.7)	0.5	93.6	94.8	92.4	93.4	93.6	93.2	92.0	91.4	92.0
(0.3, 0.9)	0.6	93.6	94.6	93.0	94.0	92.4	92.0	93.2	92.8	94.8
$n = 4000$										
(0.1, 0.2)	0.1	93.8	95.0	93.8	92.4	91.8	93.4	93.4	92.2	92.8
(0.2, 0.4)	0.2	93.6	93.8	94.0	94.8	92.0	93.2	93.4	93.6	93.0
(0.2, 0.5)	0.3	94.8	92.4	94.0	93.4	91.4	91.2	90.2	91.8	94.4
(0.3, 0.7)	0.4	93.2	94.6	95.8	92.0	90.6	92.0	94.0	90.8	93.6
(0.2, 0.7)	0.5	95.0	91.8	94.4	93.4	94.2	93.6	91.2	92.6	94.6
(0.3, 0.9)	0.6	94.6	93.8	91.6	94.0	93.0	94.2	94.0	92.2	94.8

Results: Power

Table 3
Empirical test size and power (in percentage) of the Bayesian method in testing the null hypothesis $H_0 : \beta_3 = 0$. The true values for $\beta_0 = \log(0.1)$, $\beta_1 = \log(1.5)$ and $\beta_2 = \log(2.5)$ in all simulations. Results are based on $B = 5000$ MCMC iterations and $R = 500$ simulation replications.

(c_1, c_2)	Δc	$\beta_3 = 0$	$\beta_3 = \log(1.5)$	$\beta_3 = \log(2.5)$	$\beta_3 = \log(3.5)$
$n = 2000$					
(0.1, 0.2)	0.1	7.0	20.0	74.6	92.6
(0.2, 0.4)	0.2	6.8	32.6	87.6	96.4
(0.2, 0.5)	0.3	4.8	32.6	94.0	98.2
(0.3, 0.7)	0.4	5.4	37.2	95.4	98.2
(0.2, 0.7)	0.5	4.0	35.0	93.4	97.4
(0.3, 0.9)	0.6	5.8	33.4	91.6	98.8
$n = 4000$					
(0.1, 0.2)	0.1	7.2	33.4	95.0	98.0
(0.2, 0.4)	0.2	6.2	55.8	98.4	100.0
(0.2, 0.5)	0.3	4.8	83.0	98.0	100.0
(0.3, 0.7)	0.4	5.6	65.0	97.0	99.6
(0.2, 0.7)	0.5	4.4	62.2	99.0	99.4
(0.3, 0.9)	0.6	4.4	53.0	99.2	100.0

Biomarker Threshold Models

- R source code are now available: We implemented the proposed method as a part of R software package for biomarker threshold models (the *bhm* package).
- Source code from the Comprehensive R Archive Network (https://CRAN.Rproject.org/package=bhm). To install the package:

>install.packages("*bhm*")

The most recent version of *bhm* package for R can be installed in two simple steps.

1. Load the devtools package.

```
library(devtools)
```

This package allows users to install other R packages from a wide range of repositories. If you do not have 'devtools' in your R system, invoke R and then type install.packages(''devtools'') to install it.

2. Install *bhm* package using the R command

```
install_github(''statapps/bhm'')
```

bhm package tutorial

Bingshu Chen

September 29, 2017

A tutorial of 'bhm' package for biomarker threshold models

This is an R Markdown tutorial of 'bhm' package. For more details on using the 'bhm' https://cran.r-project.org/web/packages/bhm/index.html.

To install the *bhm* package

```
install.packages('bhm')
```

To load *bhm* into R

```
library(bhm)
```

Get help on *bhm*

```
?bhm
```

Biomarker Threshold Models

bhm {bhm} R Documentation

Fitting Biomarker Threshold Models

Description

{bhm} is a R package for Biomarker Threshold Models. It uses either Hierarchical Bayes method or proflie likehood method (Chen, et al, 2014 and Tian, et al, 2016) to identify a cut-point (thershold parameter) for the biomarker in either generalized linear models or Cox proportional hazards model. The model is specified by giving a symbolic description of the linear predictor and a description of the distribution family.

Usage

```
bhm(x, ...)

## S3 method for class 'formula'
bhm(formula, family, data, control = list(...),...)

# use
#          bhm(y ~ biomarker)
#
# to fit a prognostic model with biomarker term only
#
# use
#
#          bhm(y ~ biomarker+treatment)
```

Biomarker Threshold Models

Bayesian Model for binary data can be fitted with

$$fit = bhm(y \sim x_1 + x_2 + x_3 \ldots, family = \text{'binomial'}, data = data, c.n = 2),$$

where family specifies the distribution of response variable Y and $c.n$ specifies number of cut points to be used in the model.

- Both $summary(fit)$ and $print(fit)$ can be used to summary and display the results.
- More details can be found from R command $help(bhm)$.

Load breast cancer data big-I98 with ki-67 biomarker

```
library(stepp)
```

```
## Loading required package: car
```

```
## Loading required package: survival
```

```
## Loading required package: splines
```

```
data(big)
print(big[1:5, ])
```

```
##    id rxgroup time event ki67
## 1  44       2   18     2 1.33
## 2  55       1    7     0 5.98
## 3  99       2   20     1 6.16
## 4 121       2   38     1 2.24
## 5  22       1    5     0 6.17
```

Fit a prognostic model with biomarker term only with control arm data

```
big$event = ifelse(big$event > 0, 1, 0)
big1 = big[big$rxgroup == 1, ]
set.seed(101)
print(big1[1:5, ])
```

```
##    id rxgroup time event ki67
## 2  55       1    7     0 5.98
## 5  22       1    5     0 6.17
## 8  44       1   18     0 6.00
## 9  22       1   24     0 6.10
## 12 88       1   30     1 2.57
```

```
fit1 = bhm(Surv(time, event)~ki67, data = big1, B=100, R = 200)
```

```
## bhm: Biomarker thershold models
```

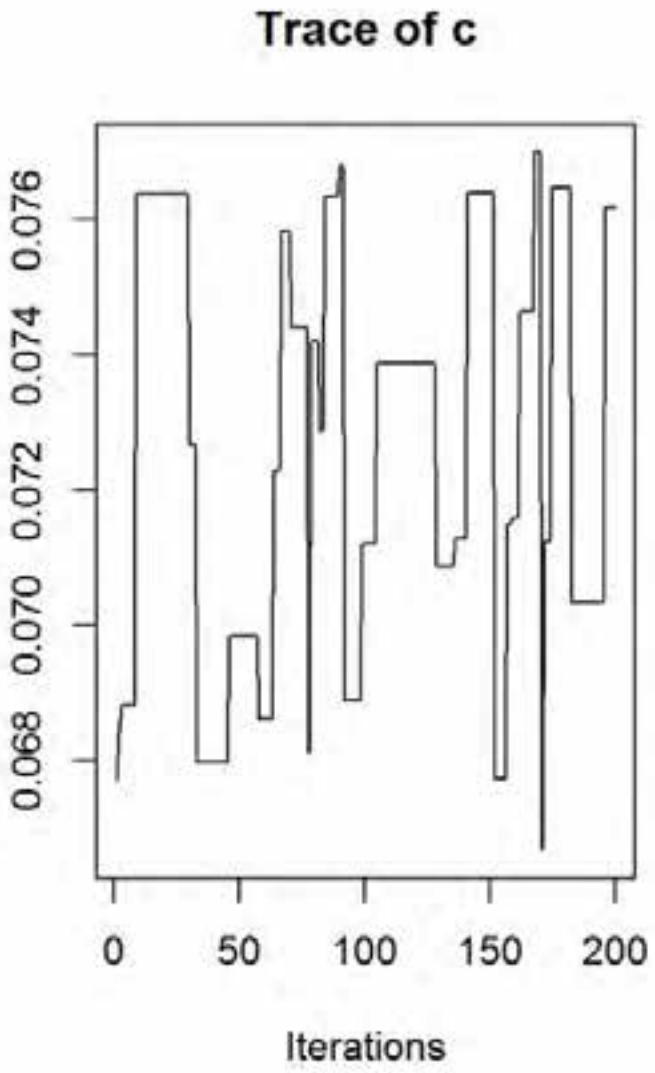
```
print(summary(fit1))
```

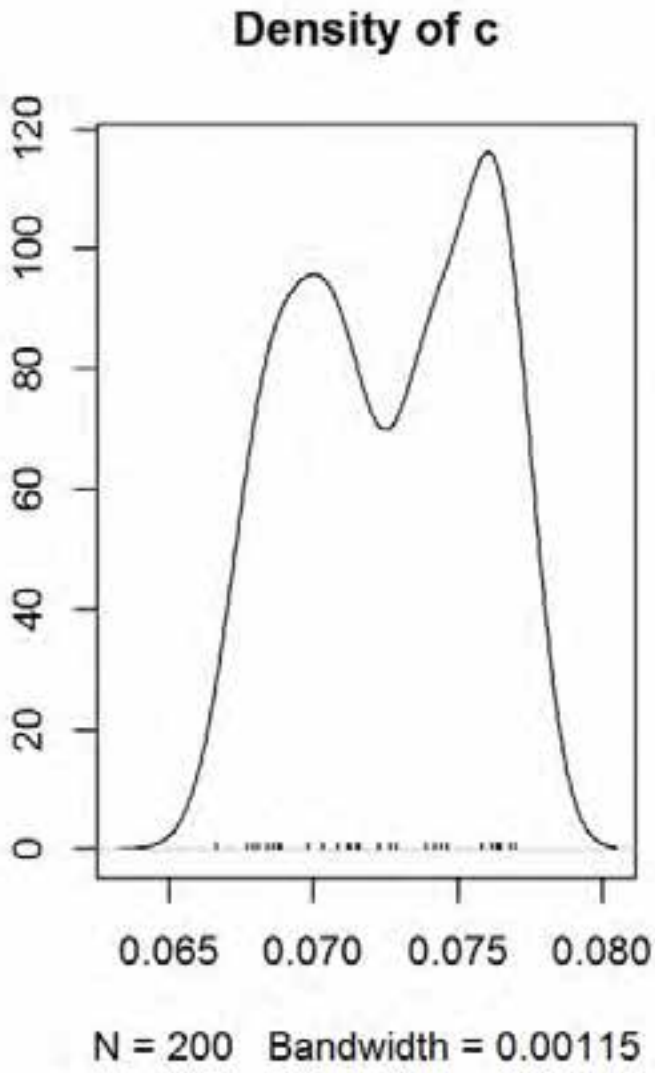
```
print(summary(fit1))
```

```
## Call:
## bhm.formula(formula = Surv(time, event) ~ ki67, data = big, B = 100,
##     R = 200)
##
## Regression coefficients:
##      Estimate StdErr  lower upper
## ki67   -2.106  0.112 -2.291 -1.89
##
##  ki67 biomarker threshold:
##           Estimate  2.5% 97.5%
## 7.266145%    2.380 2.354   2.4
##
```

```
## Conditional regression coefficients given ki67 biomarker =  2.38
## Call:
## coxph(formula = y ~ x.c_)
##
##   n= 2684, number of events= 303
##
##         coef exp(coef) se(coef)      z Pr(>|z|)
## x.c_ -2.1022    0.1222   0.1162 -18.09   <2e-16 ***
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
##      exp(coef) exp(-coef) lower .95 upper .95
## x.c_    0.1222      8.184    0.0973    0.1535
```

```
plot(fit1$cg)
```


Trace of c
0.068
0.070
0.072
0.074
0.076
0
50
100
150
200
Iterations


Density of c
0
20
40
60
80
100
120
0.065
0.070
0.075
0.080
N = 200 Bandwidth = 0.00115

Fit a ki67 prognostic biomarker model adjusted for treatment and age

```
Call:
bhm.formula(formula = Surv(time, event) ~ ki67 + rxgroup + age,
    data = big, B = 100, R = 200)

Coefficients:
[1] -3.330795462 -0.408588754  0.804952116 -0.002729243

 ki67 Thresholds:
6.947197%
     2.37

Conditional regression coefficient given  ki67 biomarker =  2.37
Call:
coxph(formula = y ~ x.c_)

                     coef exp(coef) se(coef)     z       p
x.c_ki67         -3.20882   0.04040  0.39818 -8.06 7.8e-16
x.c_rxgroup      -0.33310   0.71670  0.17850 -1.87  0.0620
x.c_ki67:rxgroup  0.69050   1.99472  0.23895  2.89  0.0039
x.c_age          -0.00339   0.99662  0.00388 -0.87  0.3825
```

Fit a ki67 prognostic biomarker model adjust for treatment and age

```
bhm: Biomarker thershold models
Call:
bhm.formula(formula = Surv(time, event) ~ ki67 + rxgroup + age,
    data = big, interaction = FALSE, B = 100, R = 200)

Coefficients:
[1] -1.998012298  0.055776411  0.002379742

 ki67 Thresholds:
7.445795%
     2.39

Conditional regression coefficient given  ki67 biomarker =  2.39
Call:
coxph(formula = y ~ x.c_)

                coef exp(coef) se(coef)      z      p
x.c_ki67    -2.08371   0.12447  0.11876 -17.55 <2e-16
x.c_rxgroup  0.08527   1.08901  0.12069   0.71   0.48
x.c_age      0.00129   1.00129  0.00395   0.33   0.74
```

Fit a ki67 predictive biomarker model for ki67 and treatment

```
Call:
bhm.formula(formula = Surv(time, event) ~ ki67 + rxgroup, data = big,
    interaction = TRUE, B = 100, R = 200)

Coefficients:
[1] -3.0635603 -0.3160863  0.6580706

 ki67 Thresholds:
7.203793%
     2.38

Conditional regression coefficient given  ki67 biomarker =  2.38
Call:
coxph(formula = y ~ x.c_)

                    coef exp(coef) se(coef)     z       p
x.c_ki67         -3.1614    0.0424   0.3963 -7.98 1.6e-15
x.c_rxgroup      -0.2931    0.7459   0.1759 -1.67  0.0956
x.c_ki67:rxgroup  0.6724    1.9589   0.2381  2.82  0.0047
```

Fit a predictive biomarker model for ki67 and treatment, adjusted for age

```
Call:
bhm.formula(formula = Surv(time, event) ~ ki67 + rxgroup + age,
    data = big, B = 100, R = 200)

Coefficients:
[1] -3.330795462 -0.408588754  0.804952116 -0.002729243

 ki67 Thresholds:
6.947197%
     2.37

Conditional regression coefficient given  ki67 biomarker =  2.37
Call:
coxph(formula = y ~ x.c_)

                     coef exp(coef) se(coef)     z       p
x.c_ki67         -3.20882   0.04040  0.39818 -8.06 7.8e-16
x.c_rxgroup      -0.33310   0.71670  0.17850 -1.87  0.0620
x.c_ki67:rxgroup  0.69050   1.99472  0.23895  2.89  0.0039
x.c_age          -0.00339   0.99662  0.00388 -0.87  0.3825
```

Profile likelihood method

- For any given cut point c, let

$$W = I(biomarker > c)$$

- Fit model

$$g(Y|Z, W) \sim \beta_0 + \beta_1 Z + \beta_2 W + \beta_3 ZW$$

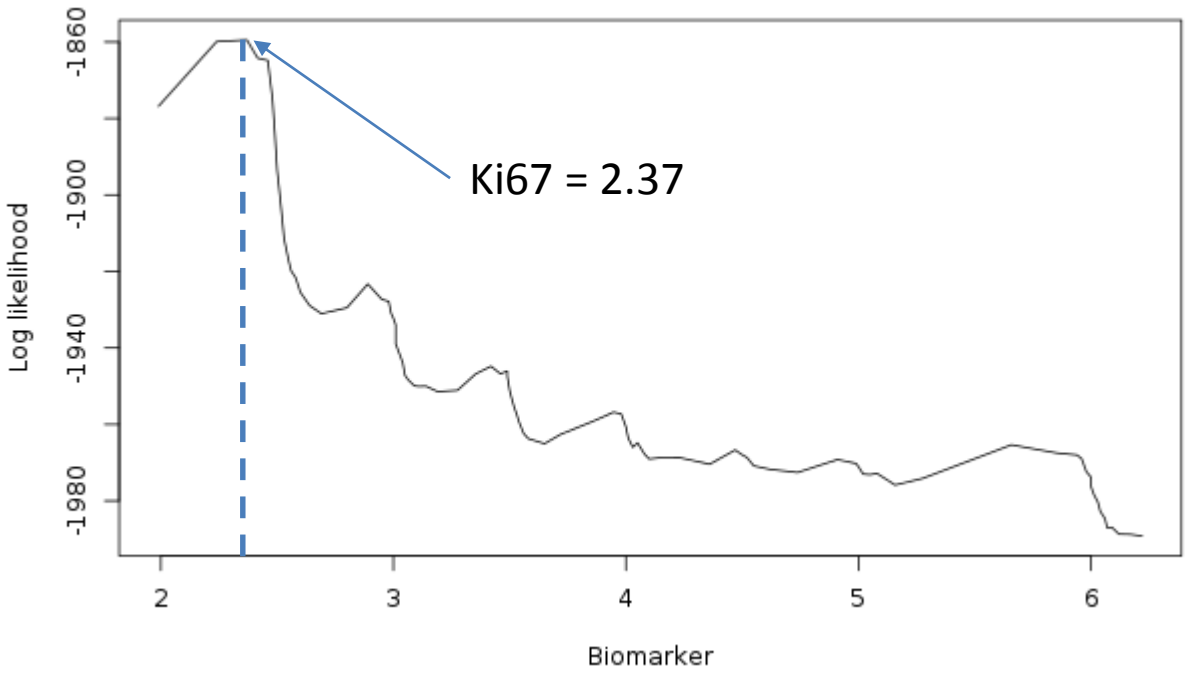
- Find maximum likelihood

$$\ell_p(c) = \ell(\widehat{\beta_c}, c)$$

- Find maximum profile likelihood $(\widehat{\beta_{\hat{c}}}, \hat{c})$

$$\max_c \ell_p(c)$$

Profile likelihood of ki67 biomarker



Fit a ki67 predictive biomarker model using profile likelihood method

```
Call:
bhm.formula(formula = Surv(time, event) ~ ki67 + rxgroup, data = big,
    method = "profile", R = 200, epsilon = 0.001)

Coefficients:
        x.c_ki67      x.c_rxgroup x.c_ki67:rxgroup
      -3.3490080       -0.3985869        0.7667508

 ki67 Thresholds:
6.8%
2.36

Conditional regression coefficient given  ki67 biomarker =  2.36
Call:
coxph(formula = y ~ x.c_)

                    coef exp(coef) se(coef)     z      p
x.c_ki67         -3.3490    0.0351   0.3976 -8.42 <2e-16
x.c_rxgroup      -0.3986    0.6713   0.1781 -2.24 0.0253
x.c_ki67:rxgroup  0.7668    2.1528   0.2386  3.21 0.0013
```

Using Bootstrap method to find confidence interval and standard error

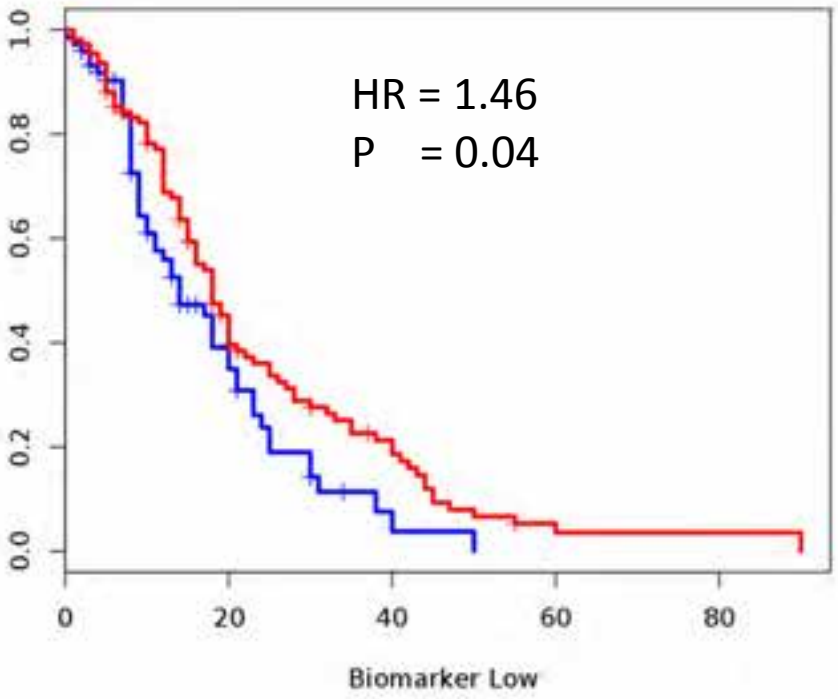
```
> summary(fit3)
Call:
bhm.formula(formula = Surv(time, event) ~ ki67 + rxgroup, data = big,
    R = 40, method = "profile", epsilon = 0.001)

Regression coefficients:
                 Estimate StdErr
x.c_ki67          -3.3490  0.398
x.c_rxgroup       -0.3986  0.178
x.c_ki67:rxgroup   0.7668  0.239

 ki67 biomarker threshold:
     Estimate 2.5% 97.5%
6.8%     2.36 2.03   2.4
```

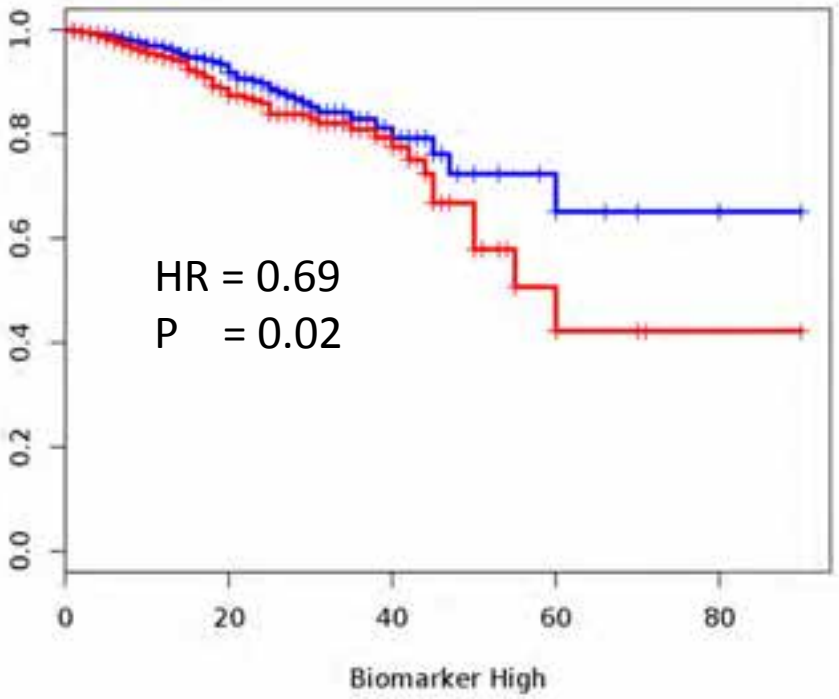
Profile likelihood method

Upload dataset to the web app for analysis

http://statapps.tk/biomarker_interaction/

Using cut point for Ki67 that maximizes MLE of the profile likelihood





Application

- Costa Rica Vaccine Trial (CVT) for HPV
  - A community-based double-blind randomized controlled phase III trial
- Study Population
  - Pregnant women from the CVT population
- Exclusion Criteria
  - Ongoing pregnancies at the end of the follow-up

Application

- Analyses
  - Primary analysis on 1st-pregnancy data
  - Confounding variables: maternal age, BMI, smoking status, marital status, monthly income, education
  - Model selection: Forward selection with BIC

$$bhm(y \sim riskWindow + treatment + age,\ family = \text{“binomial”},\ data = cvt,\ c.n = 2,\ B = 1000,\ R = 5000)$$

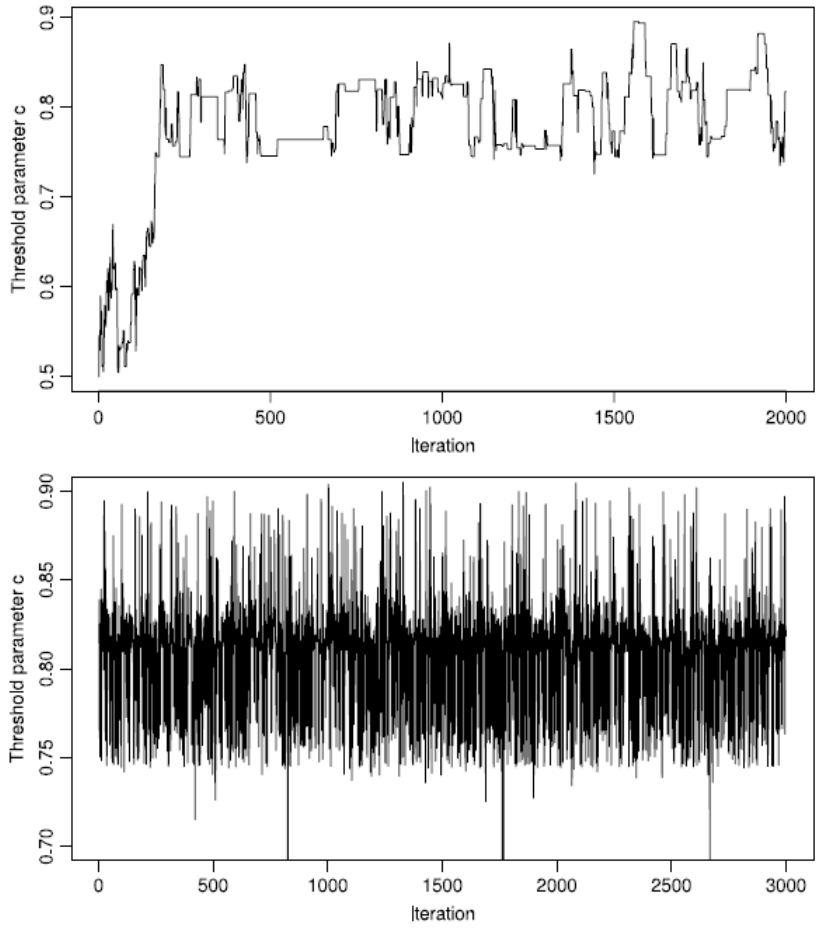
Results

Summary of the parameter estimates and 95% credible intervals using the Bayesian model on the Costa Vaccine trial ($n = 3433$).

Risk window	Parameter c_1, c_2		Cut points (years)	
	Estimates	95% CI	Estimates	95% CI
c_1	0.28	(0.09, 0.42)	0.62	(0.16, 1.14)
c_2	0.45	(0.25, 0.65)	1.27	(0.54, 2.01)
Coefficients	**Parameter β**		**$\exp(\beta)$**	
	Estimates	95% CI	Estimates	95% CI
β_0: Intercept	−3.05	(−3.97, −2.12)	0.05	(0.02, 0.12)
β_1: HPV effect	0.08	(−0.15, 0.31)	1.08	(0.86, 1.36)
β_2: Risk window effect	−0.40	(−1.13, 0.35)	0.67	(0.32, 1.42)
β_3: Interaction effect	0.06	(−0.98, 0.99)	1.06	(0.38, 2.69)
β_4: Age effect:	0.05	(0.01, 0.09)	1.05	(1.01, 1.09)
Prior parameters	**Parameter**			
	Estimates	95% CI		
q_1	2.05	(1.02, 5.40)		
q_2	1.60	(1.01, 3.37)		

The risk window estimation was based on the transformed scale in interval (0, 1). The estimated window was then transformed back to the original scale in years. Results were based on posterior distribution from $B = 5000$ MCMC iterations.

Application to prostate cancer data



Application to prostate cancer data

AP value = 46

Table 4
Prostate cancer example: the acid phosphatase (AP) biomarker.

Parameter	Estimate	S.E.	95% C. I.		p-value ($\beta_j = 0$)
c	0.803	0.036	0.745	0.871	
Marginal method					
β_1	−0.017	0.136	−0.279	0.258	0.8889
β_2	1.267	0.290	0.692	1.827	<0.0001
β_3	−0.851	0.321	−1.480	0.287	0.007

Conclusions

- The Bayes hierarchical model is applicable to other research with treatment biomarker interaction
  - Are patients in a particular subset benefit more from the experimental drug?
- The Bayes model has nice finite sample properties in term of bias and coverage properties
- Other related research topics
  - Spline smoothing and/or testing
  - Kernel smoothing and /or testing (Liu, Jiang and Chen, 2015, *Statistics in Medicine*)

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