

Using GAMs to assess effect of biomarkers on treatment effect (2)

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Previously...

Aims:

- ▶ To determine a biomarker threshold to divide patients into those who do and do not receive treatment.
- ▶ Use proportional hazards model with a nonlinear function of the biomarker to find treatment effect as a function of the biomarker.

$$\log\left(\frac{h_i(t)}{h_0(t)}\right) = \beta \text{treat}_i + f_{\text{treat}_i}(\text{biomarker}_i)$$

- ▶ f is a thin plate regression spline with wiggleness penalty.

Target Product Profile (TPP):

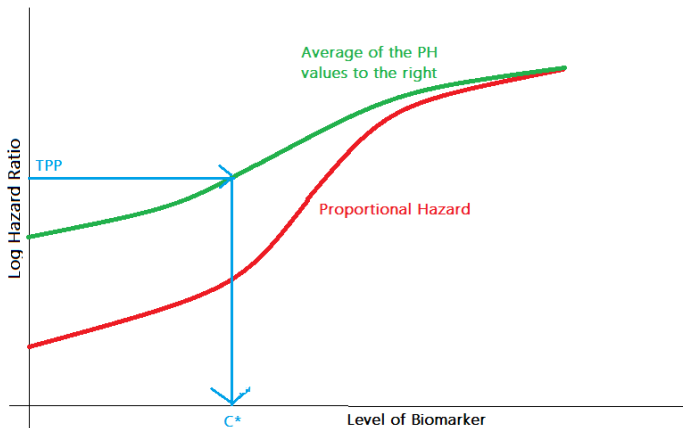
- ▶ The TPP is the minimum level of efficacy required.
- ▶ Example: The drug must reduce the treatment vs. control hazard ratio to 75%

General Procedure

Finding the biomarker threshold

- Once the model has been fitted, the curve must be integrated to find the mean value of the log hazard ratio above a given threshold.

$$I(c) = \int_c \log(HR), \quad c^* = I^{-1}(TPP)$$



Permutation test

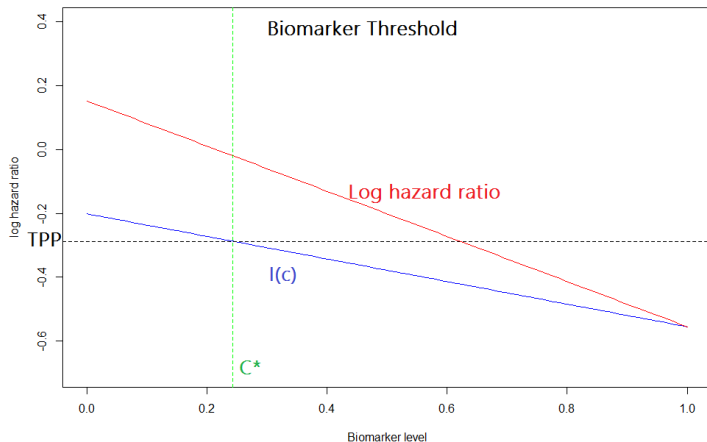
Type one error inflation

- ▶ Type one error is inflated when the same data is used to select a biomarker and test for efficacy.

Permutation Test:

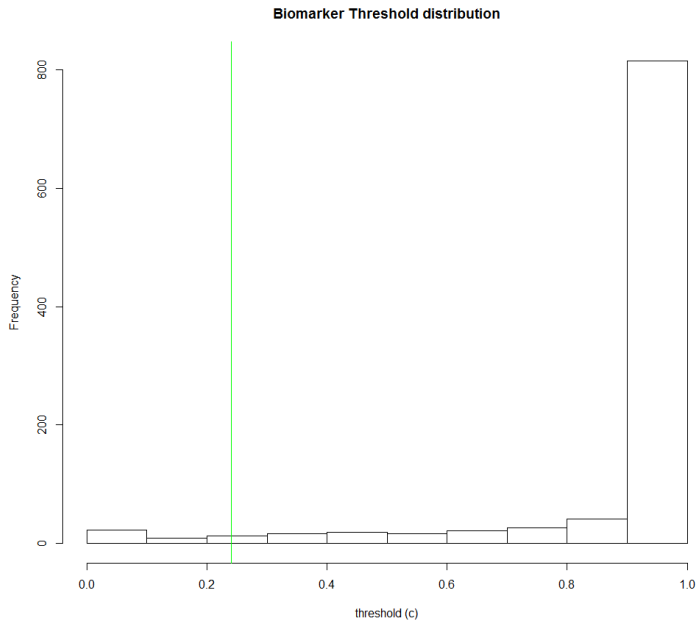
- ▶ If treatment and control are from the same group (with regards to the effect of the biomarker) then reassigning labels should have no effect.
- ▶ Relabel the observations repeatedly e.g. treatment or control. and carrying out the analyses as before.
- ▶ Obtain p -value from the permutation distribution.
- ▶ If significant, then the biomarker threshold may be used.

Simulated Example



- ▶ The TPP is $\log(0.75)$

Histogram of permutation test



What next?

Possible next steps:

- ▶ Look at alternatives to the permutation test for the type one error rate.
- ▶ Run simulations to check that the type one error rate is controlled.
- ▶ Use other models than proportional hazards.
- ▶ Consider Biomarkers which change in time.
- ▶ Look at possible confidence intervals for the cutoff point.
- ▶ Account for model selection uncertainty.