Supporting information for
“Boosting the concordance index for survival data – a unified framework

to derive and evaluate biomarker combinations”

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Gradient boosting of the C-index

The concept of boosting was first introduced in the field of machine learning [1, 2]. The basic idea is
to boost the accuracy of a relatively weak performing classifier (termed “base-learner”) to a more
accurate prediction via iteratively applying the base-learner and aggregating its solutions. Generally, the
correlation of boosting leads to a drastically improved prediction accuracy compared to a single solution of
the base-learner [3]. This basic concept was later adapted to fit statistical regression models in a forward
stagewise fashion [4, 5]. One of the main advantages of this approach is the interpretability of the final
solution, which is basically the same as in any other statistical model [6]. This can not be achieved
with competing machine learning algorithms as Support Vector Machines [7] or Random Forests [8].
Specifically, the boosting approach can be used to develop prediction rules for survival outcomes [9–11].
Although there exist also likelihood-based approaches for boosting [12], we will her focus on gradient-
based boosting [6] as it is the better fitting approach for boosting the distribution-free C-index.

The most flexible implementation of gradient boosting is the mboost [13] add-on package for the Open
Source programming environment R [14]. The mboost package contains a large variety of different pre-
implemented base-learners and loss functions that can be combined by the user via different fitting
functions. For a tutorial on how to apply the package for practical data analysis, see [15].

To apply gradient boosting to optimize linear biomarker combinations w.r.t. the C-index in the version
of Uno et al. [16], it is necessary to specify the newly developed Cindex() family inside the glmboost() function.

The Cindex family object includes the sigmoid function \( K(u) = 1/(1 + \exp(-u/\sigma)) \) as approximation of
the indicator functions in the estimated C-index. The sigmoid function is evaluated inside the R functions
approxGrad() and approxLoss(), which are part of the Cindex object. The weights

\[
    w_{ik} := \frac{\Delta_i(\hat{g}_i^L(T))^{-2}\mathbb{1}(\hat{T}_i < \hat{T}_k)}{\sum_{i,k} \Delta_i(\hat{g}_i^L(T))^{-2}\mathbb{1}(\hat{T}_i < \hat{T}_k)}
\]

(1)

are computed via the internal function compute_weights() for both the empirical risk

\[
    -\hat{C}_{\text{smooth}}(T, \eta) = -\sum_{i,k} w_{ik} \cdot \frac{1}{1 + \exp\left(\frac{\hat{\eta}_k - \hat{\eta}_i}{\sigma}\right)}
\]

(2)

(implemented in the risk() function) as well as for the negative gradient

\[
    -\frac{\partial \hat{C}_{\text{smooth}}(T, \eta)}{\partial \eta_i} = -\sum_k w_{ik} \frac{-\exp(\frac{\hat{\eta}_k - \hat{\eta}_i}{\sigma})}{\sigma \left(1 + \exp\left(\frac{\hat{\eta}_k - \hat{\eta}_i}{\sigma}\right)\right)}
\]

(3)
(implemented in the \texttt{ngradient}() function).
Those different functions that define the optimization problem are finally plugged into the \texttt{mboost} specific \texttt{Family}() function to build a new \texttt{boost_family}. Details on how to implement user-specific families in \texttt{mboost} are presented in the Appendix of [15]. The complete \texttt{Cindex} object is then given as follows:

\begin{verbatim}
Cindex <- function (sigma = 0.1) {
  approxGrad <- function(x) { ## sigmoid function for gradient
    exp(x/sigma) / (sigma * (1 + exp(x/sigma))^2)
  }
  approxLoss <- function(x) { ## sigmoid function for loss
    1 / (1 + exp(x / sigma))
  }
  compute_weights <- function(y, w = 1){ # compute weights
    ipcw_wow <- IPCWeights(y[w != 0,])
    ipcw <- numeric(nrow(y))
    ipcw[w!=0] <- ipcw_wow
    survtime <- y[,1]
    n <- nrow(y)
    wweights <- matrix( (ipcw)^2, nrow = n, ncol = n)
    weightsj <- matrix(survtime, nrow = n, ncol = n)
    weightsk <- matrix(survtime, nrow = n, ncol = n, byrow = TRUE)
    weightsI <- (weightsj < weightsk) + 0
    wweights <- wweights * weightsI
    Wmat <- w *o* w
    wweights <- wweights * Wmat
    wweights <- wweights / sum(wweights)
    return(wweights)
  }
  ngradient = function(y, f, w = 1) { # negative gradient
    if (!all(w %in% c(0,1)))
      stop(sQuote("weights"), " must be either 0 or 1 for family ",
           sQuote("UnoC"))
    survtime <- y[,1]
    event <- y[,2]
    if (length(w) == 1) w <- rep(1, length(event))
    if (length(f) == 1) {
      f <- rep(f, length(survtime))
    }
    n <- length(survtime)
    etaj <- matrix(f, nrow = n, ncol = n, byrow = TRUE)
   etak <- matrix(f, nrow = n, ncol = n)
    etamat <- etak - etaj
    rm(etaj); rm(etak);
    weights_out <- compute_weights(y, w)
    M1 <- approxGrad(etaMat) * weights_out
    ng <- colSums(M1) - rowSums(M1)
  }
}
\end{verbatim}
return(ng)
}

risk = function(y, f, w = 1) {  ## empirical risk
  survtime <- y[,1]
  event <- y[,2]
  if (length(f) == 1) {
    f <- rep(f, length(y))
  }
  n <- length(survtime)

  etaj <- matrix(f, nrow = n, ncol = n, byrow = TRUE)
  etak <- matrix(f, nrow = n, ncol = n)
  etaMat <- (etak - etaj)
  rm(etaj); rm(etak);
  weights_out <- compute_weights(y, w)
  M1 <- approxLoss(etaMat) * weights_out
  return(- sum(M1))
}

Family(  ## build the family object
  ngradient = ngradient,
  risk = risk,
  weights = "zeroone",
  offset = function(y, w = 1) {0},
  check_y = function(y) {
    if (!inherits(y, "Surv"))
      stop("response is not an object of class ", sQuote("Surv"),
          " but ", sQuote("family = UnoC()"))
    y},
  rclass = function(f){},
  name = paste("Concordance Probability by Uno")
)

Application

We will briefly demonstrate how to apply the Cindex family in practice to derive the optimal combination of pre-selected biomarkers. We will use the van de Vijver et al. [17] data set of 144 lymph node positive breast cancer patients that was also considered in the main article. The data set is publicly available as part of the R add-on package penalized [18]. The 70-gene signature for metastasis-free survival after surgery was originally developed by van’t Veer et al. [19].

We first split the data set in 100 training observations and 44 test observations. To ensure better readability of the code, we do not carry out stratified subsampling but just use the first 100 patients as training sample. Model fitting is carried out by the glmboost() function of the mboost package. As linear models are the default base-learners for glmboost(), no additional base-learner has to be specified.
As appropriate family object we specify the Cindex family described above.

For evaluating the discriminatory power of the resulting prediction on test data, we use the UnoC() function of the survAUC package [20]. It implements the unbiased estimator $\hat{C}_{Uno}$, as proposed by Uno et al. [16].

```r
## load add-on packages
library(penalized) ## for the data set
library(mboost) ## for boosting
library(survAUC) ## for evaluation

data(nki70) ## loading the data

source("Cindex.R") ## loading the family defined above

## split the data set in training and test sample (simplified):
dtrain <- nki70[1:100,]
dtest <- nki70[101:144,]

## fit a model via the glmboost() function
## formula : defines the candidate model; the response is the survival
## object Surv(time, event); via "," all remaining variables
## in the data set serve as possible predictors
## family : defines the optimization problem (in this case the C-index)
## sigma is the smoothing parameter of the sigmoid function that
## approximates the indicator functions. The default value is 0.1.
## control : defines other boosting-specific tuning parameters like the
## stopping iteration mstop or the step-length nu; trace = TRUE is
## only for convenience (shows the trace of the empirical risk).
## data : defines the data set -> training sample

mod1 <- glmboost(Surv(time, event) ~ ., family = Cindex(sigma = 0.1),
                 control = boost_control(mstop = 500, trace = TRUE, nu = 0.1),
                 data = dtrain)

## The stopping iteration can be changes via simple indexing:
mod1 <- mod1[50000] ## Long runtime: 50000 iterations
                      ## takes at least a couple of minutes on a standard machine

## Now take a look at the resulting combination
coeff(mod1)

## Prediction on test data
preds <- predict(mod1, newdata = dtest)

## Evaluate the discriminatory power
UnoC(Surv(dtrain$time, dtrain$event), Surv(dtest$time, dtest$event), lpnew = -preds)
```
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