L1 and L2 Penalized Regression Models

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1 Citing penalized.

To cite the package *penalized*, please cite Goeman, J. J., L1 penalized estimation in the Cox proportional hazards model. *Biometrical Journal* 52(1), 70–84.

2 Introduction

This short note explains the use of the *penalized* package. The package is designed for penalized estimation in generalized linear models. The lasso and elastic net algorithm that it implements is described in Goeman (2010).

The supported models at this moment are linear regression, logistic regression, poisson regression and the Cox proportional hazards model, but others are likely to be included in the future. As to penalties, the package allows an L1 absolute value ("lasso") penalty (Tibshirani, 1996, 1997), an L2 quadratic ("ridge") penalty (Hoerl and Kennard, 1970; Le Cessie and van Houwelingen, 1992; Verweij and Van Houwelingen, 1994), or a combination of the two (the "naive elastic net" of Zou and Hastie, 2005). The package also includes facilities for likelihood cross-validation and for optimization of the tuning parameter.

L1 and L2 penalized estimation methods shrink the estimates of the regression coefficients towards zero relative to the maximum likelihood estimates. The purpose of this shrinkage is to prevent overfit arising due to either collinearity of the covariates or high-dimensionality. Although both methods are shrinkage methods, the effects of L1 and L2 penalization are quite different in practice. Applying an L2 penalty tends to result in all small but non-zero regression coefficients, whereas applying an L1 penalty tends to result in many regression coefficients shrunk exactly to zero and a few other regression coefficients with comparatively little shrinkage. Combining L1 and L2 penalties tends to give a result in between, with fewer regression coefficients set to zero than in a pure L1 setting, and more shrinkage of the other coefficients. The amount of shrinkage is determined by tuning parameters λ_1 and λ_2 . A value of zero always means no shrinkage (= maximum likelihood estimation) and a value of infinity means infinite shrinkage (= setting all regression coefficients to zero). For more details about the methods, please refer to the above-mentioned papers.

It is important to note that shrinkage methods are generally not invariant to the relative scaling of the covariates. Before fitting a model, it is prudent to consider if the covariates already have a natural scaling relative to each other or whether they should be standardized.

The main algorithm for L1 penalized estimation (lasso and elastic net) that used in this package is documented in Goeman (2010). It has been combined with ideas from Eilers et al. (2001) and Van Houwelingen et al. (2006) for efficient L2 penalized estimation.

3 Penalized likelihood estimation

The basic function of the package is the penalized function, which performs penalized estimation for fixed values of λ_1 and λ_2 . Its syntax has been loosely modeled on that of the functions glm (package stats) and coxph (package survival), but it is slightly more flexible in some respects. Two main input types are allowed: one using formula objects, one using matrices.

3.1 the nki70 data

As example data we use the 70 gene signature of Van 't Veer et al. (2002) in the gene expression data set of Van de Vijver et al. (2002).

```
> library(penalized)
> library(survival)
> data(nki70)
```

This loads a *data frame* with 144 breast cancer patients and 77 covariates. The first two covariates indicate the survival time and event status (time is in months), the next five are clinical covariates (diameter of the tumor, lymph node status, estrogen receptor status, grade of the tumor and age of the patients), and the other 70 are gene expression measurements of the 70 molecular markers. As we are interested in survival as an outcome, we also need the survival package.

```
> set.seed(1)
```

3.2 the penalized function

The penalized function can be used to fit a penalized prediction model for prediction of a response. For example, to predict the Estrogen Receptor status ER for the patients in the nki70 data with the two markers "DIAPH3" and "NUSAP1" at $\lambda_1=0$ and $\lambda_2=1$, we can say (all are equivalent)

```
> fit <- penalized(ER, ~DIAPH3 + NUSAP1, data = nki70, lambda2 = 1)
> fit <- penalized(ER, nki70[, 10:11], data = nki70, lambda2 = 1)
> fit <- penalized(ER ~ DIAPH3 + NUSAP1, data = nki70, lambda2 = 1)</pre>
```

The covariates may be specified in the second function argument (penalized) as a formula object with an open left hand side, as in the first line. Alternatively, they may be specified as a matrix or data.frame, as in the second line. If, as here, they are supplied as a data.frame, they are coerced to a matrix.

For consistency with glm and coxph the third option is also allowed, in which the covariates are included in the first function argument.

The penalized function tries to determine the appropriate generalized linear model from the *response* variable. This automatic choice may not always be appropriate. In such cases the model may be specified explicitly using the *model* argument.

For the examples in the rest of this vignette we use the Cox proportional hazerds model, using the survival time (Surv(time, event)) as the response to be predicted. This is a *Surv* object.

We use attach to avoid specifying the data argument every time.

```
> attach(nki70)
```

3.3 choice of lambda

It is difficult to say in advance which value of lambda1 or lambda2 to use. The penalized package offers ways of finding optimal values using cross-validation. This is explained in Section 5

Note that for small values of *lambda1* or *lambda2* the algorithm be very slow, may fail to converge or may run into numerical problems, especially in high-dimensional data. When this happens, increase the value of *lambda1* or *lambda2*.

It is possible to specify both *lambda1* or *lambda2*. In this case both types of penalties apply, and a so-called *elastic net*.

Sometimes it can be useful to have different values of lambda1 or lambda2 for different covariates. This can be done in penalized by specifying lambda1 or lambda2 as a vector.

```
> fit <- penalized(Surv(time, event) ~ DIAPH3 + NUSAP1, data = nki70,
lambda2 = c(1, 2))</pre>
```

3.4 penfit objects

The penalized function returns a *penfit* object, from which useful information can be extracted. For example, to extract regression coefficients, (martingale) residuals, individual relative risks and baseline survival curve, write

> residuals(fit)[1:10]

```
125 127 128 129 130 132 134

-0.1554545 0.7119251 -0.3710430 -0.2335851 -0.4101212 -0.3424704 0.7235891

135 136 137

-0.6391287 0.7468025 -0.4893899
```

> fitted(fit)[1:10]

```
125 127 128 129 130 132 134 135 0.4810103 1.0518078 0.9170982 0.7227633 1.2690045 1.1124577 0.8552757 1.4158589 136 137 1.1712807 0.6481456
```

> basesurv(fit)

A "breslow" object with 1 survival curve and 50 time points.

See $\mathtt{help}(\mathtt{penfit})$ for more information on penfit objects and Section 5.2 on breslow objects.

The coefficients function extracts the named vector of regression coefficients. It has an extra second argument *which* that can be used to specify which coefficients are of interest. Possible values of *which* are nonzero (the default) for extracting all non-zero coefficients, all for all coefficients, and penalized and *unpenalized* for only the penalized or unpenalized ones.

```
> coefficients(fit, "all")
DIAPH3 NUSAP1
0.2236060 1.1768069
```

To extract the loglikelihood of the fit and the evaluated penalty function,

The loglik function gives the loglikelihood without the penalty, and the penalty function gives the fitted penalty, i.e. for L1 lambda1 times the sum of the absolute values of the fitted coefficients.

The *penfit* object can also be used to generate predictions for new data using the **predict** function. Pretending that the first three subjects in the **nki70** data are new subjects, we can find their predicted survival curves with either of

```
> predict(fit, ~DIAPH3 + NUSAP1, data = nki70[1:3, ])
A "breslow" object with 3 survival curves and 50 time points.
> predict(fit, nki70[1:3, c("DIAPH3", "NUSAP1")])
A "breslow" object with 3 survival curves and 50 time points.
```

See Section 5.2 for more on breslow objects. We can get five year survival predictions by saying

3.5 standardization

If the covariates are not naturally on the same scale, it is advisable to standardize them. The function argument *standardize* (default: FALSE) standardizes the covariates to unit second central moment before applying penalization. This standardization makes sure that each covariate is affected more or less equally by the penalization.

The fitted regression coefficients that the function returns have been scaled back and correspond to the original scale of the covariates. To extract the regression coefficients of the standardized covariates, use the coefficients function with standardize = TRUE. This option is also available if the model was not fitted with standardized covariates, as the covariates are always standardized internally for numerical stability. To find the weights used by the function, use weights(fit).

```
> coefficients(fit)
    DIAPH3     NUSAP1
0.2236060 1.1768069
> coefficients(fit, standardize = TRUE)
    DIAPH3     NUSAP1
0.05243638 0.31416138
> weights(fit)
    DIAPH3     NUSAP1
0.2345035 0.2669609
```

3.6 unpenalized covariates

In some situations it is desirable that not all covariates are subject to a penalty. Any additional covariates that should be included in the model without being penalized can be specified separately. using the third function argument (unpenalized). For example (the two commands below are equivalent)

```
> fit <- penalized(Surv(time, event), nki70[, 8:77], ~ER, lambda2 = 1)
> fit <- penalized(Surv(time, event) ~ ER, nki70[, 8:77], lambda2 = 1)</pre>
```

This adds estrogen receptor status as an unpenalized covariate. Note in the second line that right hand side of the *formula* object in the *response* argument is automatically taken to be the *unpenalized* argument because the *penalized* argument was given by the user.

In linear and logistic regression the intercept is by default never penalized. The use of an intercept can be suppressed with penalized = 0. The intercept is always removed from the penalized model matrix, unless the penalized model consists of only an intercept.

It is possible to include an offset term in the model. Use the offset function in the *unpenalized* argument, which must then be of *formula* type. The Cox model implementation allows strata terms.

3.7 factors

If some of the factors included in the *formula* object *penalized* are of type *factor*, these are automatically made into dummy variables, as in glm and coxph, but in a special way that is more appropriate for penalized regression.

Unordered factors are turned into as many dummy variables as the factor has levels. This ensures a symmetric treatment of all levels and guarantees that the fit does not depend on the ordering of the levels. See help(contr.none) for details.

Ordered factors are turned into dummy variables that code for the difference between successive levels (one dummy less than the number of levels). L2 penalization on such factors therefore leads to small successive differences; L1 penalization leads to ranges of successive levels with identical effects. See help(contr.diff) for details.

When fitting a model with factors with more than two levels with an L1 penalty, it is advisable to add a small L2 penalty as well in order to speed up convergence. By varying the L2 penalty it can be checked that the L2 penalty is not so large that it influences the estimates.

To override the automatic choice of contrasts, use C (package stats).

The *response* argument may also be also be specified as a *factor* in a logistic regression model. In that case, the value levels(response) [1] is treated as a failure (0), and all other values as a success (1).

3.8 fitting in steps

In some cases it may be interesting to visualize the effect of changing the tuning parameter lambda1 or lambda2 on the values of the fitted regression coefficients. This can be done using the function argument steps in combination with the plotpath function. At this moment, this functionality is only available for visualizing the effect of lambda1.

When using the *steps* argument, the function starts fitting the model at the maximal value of λ_1 , that is the smallest value that shrinks all regression coefficients to zero. From that value it continues fitting the model for *steps* successively decreasing values of λ_1 until the specified value of *lambda1* is reached.

If the argument *steps* is supplied to penalized, the function returns a *list* of *penfit* objects. These can be accessed individually or their coefficients can be plotted using plotpath.

Following Park and Hastie (2007) it is possible to choose the values of λ_1 in such a way that these are the change-points at which the active set changes. This can be done by setting steps = "Park".

```
> fit <- penalized(Surv(time, event), nki70[, 8:77], lambda1 = 1,
    steps = "Park", trace = FALSE)</pre>
```

Note that plotpath plots the unstandardized coefficients by default. Standardized coefficients can be plotted (even when the model was not fitted with standardized coefficients) with the *standardize* argument.

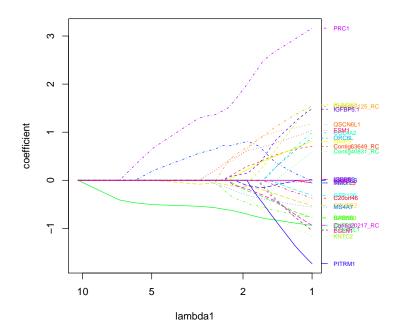
3.9 a positivity constraint

In some applications it is natural to restrict all estimated regression coefficients to be positive. Such a positivity constraint is an alternative type of constrained estimation that is easily combined with L1 and L2 penalization in the algorithm implemented in the *penalized* package.

To add a positivity restriction to the regression coefficients of all penalized covariates, set the function argument *positive* to TRUE (the default is FALSE). Note that it is not strictly necessary to also include an L1 or L2 penalty; the model can also be fitted with only a positivity constraint.

```
> fit <- penalized(Surv(time, event), nki70[, 8:77], positive = TRUE)
```

> plotpath(fit, log = "x")

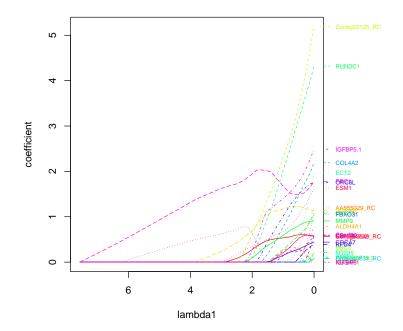


> coefficients(fit)

Contig63649_RC	AA555029_RC	ALDH4A1	QSCN6L1	FGF18
0.56883350	1.19479968	0.78893478	1.13549561	0.21511238
Contig32125_RC	BBC3	RP5.860F19.3	OXCT1	MMP9
5.19060693	0.32578805	0.09279051	1.08253778	0.90786251
RUNDC1	ECT2	WISP1	MTDH	Contig40831_RC
4.31995520	1.96799708	0.11182254	0.20738967	0.08058631
COL4A2	FBX031	ORC6L	RFC4	CDCA7
2.19059076	1.04830672	1.75330155	0.39074008	0.44076424
C9orf30	IGFBP5.1	PRC1	CENPA	NM_004702
0.59695825	2.48990214	1.77488012	0.57635421	0.56779362
ESM1				
1.63222843				

It is also possible to constrain only part of the regression coefficients to be positive by giving the positive argument as a logical vector.

> coef(penalized(Surv(time, event), nki70[, 8:16], positive = c(F, rep(T, 8))))



4 Pretesting

Before fitting a penalized regression model it can be worthwhile to test the global null hypothesis of no association between any of the predictor variables and the response. A package that can do this is, and which ties very closely to the *penalized* package is the *globaltest* package, available from www.bioconductor.org. The package can be installed using the bioconductor install script

```
> source("http://bioconductor.org/biocLite.R")
> biocLite("globaltest")
```

The interface of *globaltest* is very similar to the interface of *penalized*. To test for any evidence of association in the nki70 data, say

```
> library(globaltest)
> gt(Surv(time, event), nki70[, 8:77])

p-value Statistic Expected Std.dev #Cov
1 0.0076 2.95 0.694 0.93 70
```

The resulting p-value can be interpreted as a global indicator of predictive ability. Data sets that have a significant test result almost always have a an optimal lambda value smaller than infinity.

See the vignette of the *qlobaltest* package for details.

5 Cross-validation and optimization

Cross-validation can be used to assess the predictive quality of the penalized prediction model or to compare the predictive ability of different values of the tuning parameter.

The penalized package uses likelihood cross-validation for all models. Likelihood cross-validation has some advantages over other optimization criteria: it tends to be a continuous function of the tuning parameter; it can be defined in a general way for almost any model, and it does not require calculation the effective dimension of a model, which is problematic in L1 penalized models. For the Cox proportional hazards model, the package uses cross-validated log partial likelihood (Verweij and Van Houwelingen, 1993), which is a natural extension of the cross-validated log likelihood to the Cox model.

Five functions are available for calculating the cross-validated log likelihood and for optimizing the cross-validated log likelihood with respect to the tuning parameters. They have largely the same arguments. See help(cvl) for an overview.

5.1 cross-validation

The function cvl calculates the cross-validated log likelihood for fixed values of λ_1 and λ_2 .

It accepts the same arguments as penalized (except steps: see profL1 below) as well as the fold argument. This will usually be a single number k to indicate k-fold cross-validation. In that case, the allocation of the subjects to the folds is random. Alternatively, the precise allocation of the subjects into

the folds can be specified by giving fold as a vector of the length of the number of subjects with values form 1 to k, each indicating the fold allocation of the corresponding subject. The default is to do leave-one-out cross-validation.

The function cvl returns a names list with four elements:

cvl the cross-validated log likelihood.

fold the fold allocation used; this may serve as input to a next call to cvl to ensure comparability.

predictions the predictions made on each left-out subject. The format depends on the model used. In logistic regression this is just a vector of probabilities. In the Cox model this is a collection of predicted survival curves (a *breslow* object). In the linear model this is a collection of predicted means and predicted standard deviations (the latter are the maximum penalized likelihood estimates of σ^2).

```
fullfit the fit on the full data (a penfit object)
```

```
> fit <- cvl(Surv(time, event), nki70[, 8:77], lambda1 = 1, fold = 10)
```

> fit\$cvl

[1] -256.4273

> fit\$fullfit

Penalized cox regression object 70 regression coefficients of which 28 are non-zero

> fit <- cvl(Surv(time, event), nki70[, 8:77], lambda1 = 2, fold = fit\$fold)

5.2 breslow objects

The *breslow* class is defined in the *penalized* package to store estimated survival curves. They are used for the predictions in cross-validation and for the baseline survival estimated in the penalized function. See help(breslow) for details.

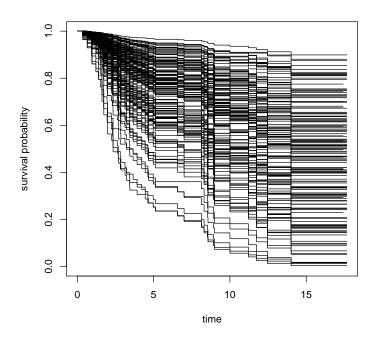
> fit\$predictions

A "breslow" object with 144 survival curves and 51 time points.

> time(fit\$predictions)

```
0.0000000 \quad 0.3531828 \quad 0.6488706 \quad 0.9363276 \quad 0.9609856
 [1]
                                                             1.2101300
 [7]
                           1.6098563
     1.3880903
                1.5003422
                                      1.6125941
                                                  1.7166324
                                                             1.7330595
[13]
     1.9466119
                1.9657769
                           1.9739904
                                      2.2231348
                                                 2.2970568
                                                             2.3353867
[19]
     2.3408624 2.6146475
                           2.6803559
                                      2.6967830
                                                 2.8117728
                                                             2.8528405
[25]
     3.1211499 3.2197125
                           3.4195756
                                      3.4387406
                                                 3.6550308
                                                             3.9151266
[31]
    4.2190281 4.4462697
                           4.6214921 4.6625599
                                                 4.9719370
                                                             5.1170431
[37] 6.5653662 6.9952088 8.1286790 8.3039014 8.5284052
                                                             8.5612594
[43] 8.9253936 8.9883641 9.9986311 11.2114990 11.7399042 12.4654346
[49] 14.0123203 17.4209446 17.6591376
```

> plot(fit\$predictions)



> as.data.frame(basesurv(fit\$fullfit))[1:10,]

survival time

1 1.0000000 0.0000000

2 0.9947948 0.3531828

3 0.9895787 0.6488706

4 0.9842225 0.9363276

5 0.9788527 0.9609856

6 0.9733970 1.2101300

7 0.9678684 1.3880903

8 0.9622905 1.5003422

9 0.9566938 1.6098563

10 0.9509489 1.6125941

> plot(fit\$predictions)

We can easily extract the 5 year cross-validated survival probabilities

> survival(fit\$predictions, 5)[1:10]

1 2 3 4 5 6 7 8 0.9262637 0.6931959 0.7409963 0.8858466 0.7183237 0.6951237 0.7737997 0.3766935 9 10 0.5476301 0.8940526

5.3 profiling the cross-validated log likelihood

The functions profL1 and profL2 can be used to examine the effect of the parameters λ_1 and λ_2 on the cross-validated log likelihood. The profL1 function can be used to vary λ_1 while keeping λ_2 fixed, vice versa for profL2.

The minimum and maximum values between which the cross-validated log likelihood is to be profiled can be given as minlambda1 and maxlambda1 or minlambda2 and maxlambda2, respectively. The default value of minlambda1 and minlambda2 is at zero. The default value of maxlambda1 is at the maximal value of λ_1 , that is the smallest value that shrinks all regression coefficients to zero. There is no default for maxlambda2.

The number of steps between the minimal and maximal values can be given in the *steps* argument (default 100). These steps are equally spaced if the argument *log* is FALSE or equally spaced on the log scale if the argument *log* is TRUE. Note that the default value of *log* differs between profL1 (FALSE) and profL2 (TRUE). If *log* is TRUE, *minlambda1* or *minlambda2* must be given by the user as the default value is not usable.

By default, the profiling is stopped prematurely when the cross-validated log likelihood drops below the cross-validated log likelihood of the null model with all penalized regression coefficients equal to zero. This is done because it avoids lengthy calculations at small values of λ when the models are most likely not interesting. The automatic stopping can be controlled using the option minsteps (default steps/2). The algorithm only considers early stopping after it has done at least minsteps steps. Setting minsteps equal to steps cancels the automatic stopping.

The functions profL1 and profL2 return a named list with the same elements as returned by cvl, but each of cvl, predictions, fullfit is now a *vector* or a *list* (as appropriate) as multiple cross-validated likelihoods were calculated. An additional vector lambda is returned which lists the values of λ_1 or λ_2 at which the cross-validated likelihood was calculated.

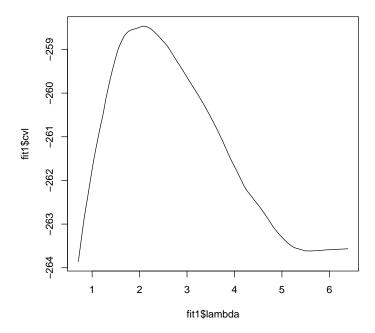
The allocation of the subjects into cross-validation folds is done only once, so that all cross-validated likelihoods are calculated using the same allocation. This makes the cross-validated log likelihoods more comparable. As in cvl the allocation is returned in fold.

It is also possible in these functions to set fold = 1. This will cause no cross-validation to be performed, but will let only the full data fits be calculated. This can be used in a similar way to the use of the penalized function with its *steps* argument, only with more flexibility.

The profiles can be plotted using the output of profL1 and profL2 or directly using the plot arguments of these functions.

The plotpath function can again be used to visualize the effect of the tuning parameter on the regression coefficients.

```
> plotpath(fit2$fullfit, log = "x")
```



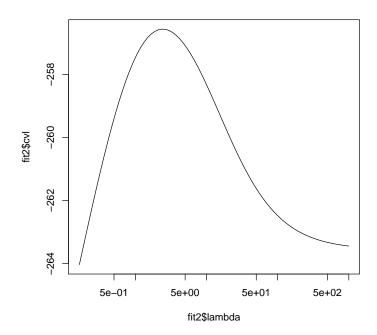
5.4 optimizing the cross-validated likelihood

Often we are not interested in the whole profile of the cross-validated likelihood, but only in the optimum. The functions optL1 and optL2 can be used to find the optimal value of λ_1 or λ_2 .

The algorithm used for the optimization is the Brent algorithm for minimization without derivatives (Brent, 1973, see also help(optimize)). When using this algorithm, it is important to realize that this algorithm is guaranteed to work only for unimodal functions and that it may converge to a local maximum. This is especially relevant for L1 optimization, as the cross-validated likelihood as a function of λ_1 very often has several local maxima. It is recommended only to use optL1 in combination with profL1 to prevent convergence to the wrong optimum. The cross-validated likelihood as a function of λ_2 , on the other hand, is far better behaved and practically never has local maxima. The function optL2 can safely be used even without combining it with profL2.

The functions optL1 and optL2 take the same arguments as cvl, and some additional ones.

The arguments minlambda1 and maxlambda1, and minlambda2 and maxlambda2 can be used to specify the range between which the cross-validated log likelihood is to be optimized. Both arguments can be left out in both functions, but supplying them can improve convergence speed. In optL1, the parameter range can be use to ensure that the function converges to the right maximum. In optL2 the user can also supply only one of minlambda2 and maxlambda2 to give the algorithm advance information of the order of mag-



nitude of λ_2 . In this case, the algorithm will search for an optimum around minlambda2 or maxlambda2.

The functions optL1 and optL2 return a named list just as cv1, with an additional element lambda which returns the optimum found. The returned cv1, predictions, fullfit all relate to the optimal λ found.

```
> opt1 <- optL1(Surv(time, event), nki70[, 50:70], fold = fit1$fold)
```

> opt1\$lambda

[1] 2.086035

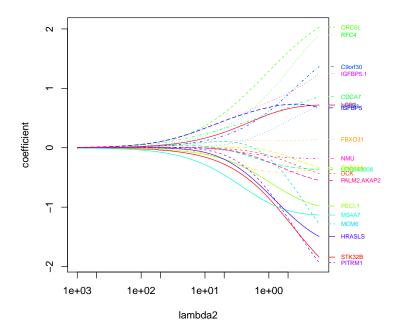
> opt1\$cv1

[1] -258.4657

> opt2 <- optL2(Surv(time, event), nki70[, 50:70], fold = fit2\$fold)

6 A note on standard errors and confidence intervals

It is a very natural question to ask for standard errors of regression coefficients or other estimated quantities. In principle such standard errors can easily be calculated, e.g. using the bootstrap.



Still, this package deliberately does not provide them. The reason for this is that standard errors are not very meaningful for strongly biased estimates such as arise from penalized estimation methods. Penalized estimation is a procedure that reduces the variance of estimators by introducing substantial bias. The bias of each estimator is therefore a major component of its mean squared error, whereas its variance may contribute only a small part.

Unfortunately, in most applications of penalized regression it is impossible to obtain a sufficiently precise estimate of the bias. Any bootstrap-based calculations can only give an assessment of the variance of the estimates. Reliable estimates of the bias are only available if reliable unbiased estimates are available, which is typically not the case in situations in which penalized estimates are used.

Reporting a standard error of a penalized estimate therefore tells only part of the story. It can give a mistaken impression of great precision, completely ignoring the inaccuracy caused by the bias. It is certainly a mistake to make confidence statements that are only based on an assessment of the variance of the estimates, such as bootstrap-based confidence intervals do.

Reliable confidence intervals around the penalized estimates can be obtained in the case of low dimensional models using the standard generalized linear model theory as implemented in lm, glm and coxph. Methods for constructing reliable confidence intervals in the high-dimensional situation are, to my knowledge, not available.

References

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