

Multivariable Fractional Polynomials

Axel Benner

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1 Introduction

The `mfp` package is a collection of R [3] functions targeted at the use of fractional polynomials (FP) for modelling the influence of continuous covariates on the outcome in regression models, as introduced by Royston & Altman (1994) [4] and modified by Sauerbrei & Royston (1999) [6]. The model may include binary, categorical or further continuous covariates which are included in the variable selection process but without need of FP transformation. It combines backward elimination with a systematic search for a ‘suitable’ transformation to represent the influence of each continuous covariate on the outcome. An application of multivariable fractional polynomials (MFP) in modelling prognostic and diagnostic factors in breast cancer is given by [6]. The stability of the models selected is investigated in [5]. Briefly, fractional polynomials models are useful when one wishes to preserve the continuous nature of the covariates in a regression model, but suspects that some or all of the relationships may be non-linear. At each step of a ‘backfitting’ algorithm MFP constructs a fractional polynomial transformation for each continuous covariate while fixing the current functional forms of the other covariates. The algorithm terminates when no more covariate is excluded and the functional forms of the continuous covariates do not change anymore.

2 Inventory of functions

`mfp.object` is an object representing a fitted `mfp` model. Class `mfp` inherits from either `glm` or `coxph` depending on the type of model fitted. In addition to the standard `glm/coxph` components the following components are included in an `mfp` object

x the final FP transformations that are contained in the design matrix `x`. The covariate “z” with 4 df (second-degree FP) has corresponding columns “z.1” and “z.2” in `x`. A first-degree FP covariate “z” would have one column “z.1”.

powers a matrix containing the best FP powers for each covariate. If a covariate has less than two powers NAs will fill the appropriate cell of the matrix.

pvalues a matrix containing the P-values from the "closed test procedure" together with the best powers chosen. Briefly p.null is the P-value for the test of inclusion (see mfp), p.lin corresponds to the test of nonlinearity and p.FP the test of simplification by comparing first degree (FP1) and second degree (FP2) transformations. The best first degree FP power (power2) and best second degree FP powers (power4.1 and power4.2) are also given. The numbers 2 and 4 describe the corresponding degrees of freedom.

scale all covariates are shifted and rescaled before being power transformed if nonpositive values are encountered or the range of values of the covariates is reasonably large. If x' would be used instead of x where $x' = (x+a)/b$ the parameters a (shift) and b (scale) are contained in the matrix scale.

df.initial a vector containing the degrees of freedom allocated to each covariate corresponding to the degree of FP ($m=4$ for second degree FP, $m=2$ for first degree FP).

df.final a vector containing the degrees of freedom of each covariate at convergence of the backfitting algorithm ($m=4$ for second degree FP, $m=2$ for first degree FP, $m=1$ for untransformed variable, $m=0$ if covariate was excluded).

dev the deviance of the final model.

dev.lin the deviance of the model that uses the linear predictor of untransformed covariates.

dev.null the deviance of the null model.

fptable the table of the final fp transformations.

fit a call of the corresponding glm or cox model using the selected and (possibly) FP transformed variables of the final model.

3 Usage in R

Start with

```
>library(mfp)
```

```
Loading required package: survival
```

```
Loading required package: splines
```

An `mfp.object` will be created by application of function `mfp`.

A typical call of an `mfp` model has the form `response ~ terms` where `response` is the (numeric) response vector and `terms` is a series of terms, separated by `+` operators, which specifies a linear predictor for `response` provided by the `formula` argument of the function call.

```
>str(mfp)
```

```
function (formula = formula(data), data = parent.frame(), family = gaussian,
  method = c("efron", "breslow"), subset = NULL, na.action = na.omit,
  init = NULL, alpha = 0.05, select = 1, verbose = FALSE, x = TRUE,
  y = TRUE)
```

Fractional polynomial terms are indicated by **fp**.

For **binomial** models the response can also be specified as a **factor**. If a Cox proportional hazards model is required then the outcome need to be specified using the **Surv()** notation.

The argument **family** describes the error distribution and link function to be used in the model. This can be a character string naming a family function, a family function or the result of a call to a family function.

Argument **alpha** sets the global FP selection level for all covariates. Different selection levels for individual covariates can be chosen by using the **fp** function. The variable selection level for all covariates is set by **select**. Values for individual fractional polynomials may be set using the **fp** function.

The function **fp** defines a fractional polynomial object for a single input variable.

```
>str(fp)
```

```
function (x, df = 4, select = NA, alpha = NA, scale = TRUE)
```

In addition to **alpha** and **select** the **scale** argument of the **fp** function denotes the use of pre-transformation scaling to avoid possible numerical problems or for variables with non-positive values.

3.1 Model selection

The original Stata implementation of **mfp** uses two different selection procedures for a single continuous covariate x , a sequential selection procedure and a closed testing selection procedure (**ra2**, [1]). In the R implementation only the **ra2** algorithm is used which is also the default in the Stata and SAS implementations of **mfp**.

The **ra2** algorithm is described in [1] and [7]. It uses a closed test procedure [2] which maintains approximately the correct Type I error rate for each component test. The procedure allows the complexity of candidate models to increase progressively from a prespecified minimum (a null model) to a prespecified maximum (an FP) according to an ordered sequence of test results.

The algorithm works as follows:

1. Perform a 4 df test at the α level of the best-fitting second-degree FP against the null model. If the test is not significant, drop x and stop, otherwise continue.
2. Perform a 3 df test at the α level of the best-fitting second-degree FP against a straight line. If the test is not significant, stop (the final model is a straight line), otherwise continue.
3. Perform a 2 df test at the α level of the best-fitting second-degree FP against the best-fitting first-degree FP. If the test is significant, the final model is the FP with $m = 2$, otherwise the FP with $m = 1$.

The tests in step 1, 2 and 3 are of overall association, non-linearity and between a simpler or more complex FP model, respectively.

4 Example

4.1 Cox proportional hazards model

We use the dataset **GBSG** which contains data from a study of the German Breast Cancer Study Group for patients with node-positive breast cancer.

```
>data(GBSG)
>str(GBSG)
```

```
`data.frame':      686 obs. of  11 variables:
 $ id      : int   1 2 3 4 5 6 7 8 9 10 ...
 $ htreat  : Factor w/ 2 levels "0","1": 1 2 2 2 1 1 2 1 1 1 ...
 $ age     : int   70 56 58 59 73 32 59 65 80 66 ...
 $ menostat: Factor w/ 2 levels "1","2": 2 2 2 2 2 1 2 2 2 2 ...
 $ tumsize : int   21 12 35 17 35 57 8 16 39 18 ...
 $ tumgrad : Factor w/ 3 levels "1","2","3": 2 2 2 2 2 3 2 2 2 2 ...
 $ posnodal: int    3 7 9 4 1 24 2 1 30 7 ...
 $ prm     : int   49 62 53 61 27 1 182 193 1 1 ...
 $ esm     : int   67 78 272 30 66 14 1 26 60 4 ...
 $ rfst    : int  1814 2018 712 1807 772 448 2172 2161 471 2014 ...
 $ cens    : int    1 1 1 1 1 1 0 0 1 0 ...
```

The response variable is recurrence free survival time (`Surv(rfst, cens)`). Complete data on 7 prognostic factors is available for 686 patients. The median follow-up was about 5 years, 299 events were observed for recurrence free survival time. We use a Cox proportional hazards regression to model the hazard of recurrence by the 7 prognostic factors of which 5 are continuous, age of the patients in years (`age`), tumor size in mm (`tumsize`), number of positive lymphnodes (`posnodal`), progesterone receptor in fmol (`prm`), estrogen receptor in fmol (`esm`); one is binary, menopausal status (`menostat`); and one is ordered categorical with three levels, tumor grade (`tumgrad`). The additional variable `htreat` describes if a hormonal therapy was applied and is used as stratification variable.

We use `mfp` to build a model from the initial set of 7 covariates using the backfitting model selection algorithm. We set the global variable selection level to 0.05 and use the default FP selection level.

By using `fp()` in the model formula a fractional polynomial transformation with possibly pre-transformation scaling is estimated. This is done here for `tumsize`, `posnodal`, `prm`, and `esm`. Otherwise a linear form of the unscaled variable is used, as for `age`. Categorical factors are included without transformation. Hormonal therapy (`htreat`) was used as stratification variable.

By `verbose=TRUE` the process of FP and variable selection is printed.

```
>f <- mfp(Surv(rfst, cens) ~ strata(htreat) + age + fp(tumsize) +
+      fp(posnodal) + fp(prm) + fp(esm) + menostat + tumgrad, family = cox,
+      data = GBSG, select = 0.05, verbose = TRUE)
```

Variable	Deviance	Power(s)

Cycle 1		
posnodal		
	3135.218	
	3103.245	1
	3081.123	0
	3074.213	0.5 3
prm		
	3095.43	
	3074.213	1
	3067.746	0.5
	3066.502	-2 0.5
tumgrad2		
	3081.253	

	3074.213	1	
tumgrad3	3082.613		
	3074.213	1	
tumsize	3075.813		
	3074.213	1	
	3072.091	-1	
	3071.882	-1	3
menostat2	3076.922		
	3075.813	1	
age	3076.922		
	3076.922	1	
esm	3077.795		
	3076.922	1	
	3073.627	3	
	3071.028	-0.5	3
Cycle 2			
posnodal	3152.737		
	3108.965	1	
	3085.051	0	
	3077.795	0.5	3
prm	3099.562		
	3077.795	1	
	3071.74		0.5
	3070.548	0	0.5
tumgrad2	3085.024		

	3077.795	1
tumgrad3	3086.686	
	3077.795	1
tumsize	3077.795	
	3076.471	1
	3074.077	-1
	3073.759	-0.5 0
menostat2	3077.795	
	3076.973	1
age	3077.795	
	3077.737	1

Transformation

	shift	scale
posnodal	0	1
prm	0	100
tumgrad2	0	1
tumgrad3	0	1
tumsize	0	10
menostat2	0	1
age	0	1
esm	0	100

Fractional polynomials

	df.initial	select	alpha	df.final	power1	power2
posnodal	4	0.05	0.05	4	0.5	3
prm	4	0.05	0.05	1	1	.
tumgrad2	1	0.05	0.05	1	1	.
tumgrad3	1	0.05	0.05	1	1	.
tumsize	4	0.05	0.05	0	.	.
menostat2	1	0.05	0.05	0	.	.
age	1	0.05	0.05	0	.	.

```
esm                4    0.05  0.05          0    .    .
```

Null model: 3198.026

Linear model: 3103.245

Final model: 3077.795

After two cycles the final model is selected. Of the possible input variables tumor size (tumsiz), menopausal status (menostat), age and estrogen receptor (esm) were excluded from the model. Only for variable `posnodal` a nonlinear transformation was chosen. Prescaling was used for esm, prm and tumsiz.

Details of the model fit are given by `summary`.

```
>summary(f)
```

Call:

```
mfp(formula = Surv(rfst, cens) ~ strata(htreat) + age + fp(tumsiz) +
    fp(posnodal) + fp(prm) + fp(esm) + menostat + tumgrad, data = GBSG,
    family = cox, select = 0.05, verbose = TRUE)
```

n= 686

	coef	exp(coef)	se(coef)	z	p
posnodal.1	5.66e-01	1.762	6.75e-02	8.39	0.0e+00
posnodal.2	-3.25e-05	1.000	1.33e-05	-2.44	1.5e-02
prm.1	-2.13e-03	0.998	5.38e-04	-3.96	7.4e-05
tumgrad2.1	6.16e-01	1.852	2.49e-01	2.48	1.3e-02
tumgrad3.1	7.49e-01	2.115	2.68e-01	2.79	5.2e-03

	exp(coef)	exp(-coef)	lower .95	upper .95
posnodal.1	1.762	0.568	1.544	2.011
posnodal.2	1.000	1.000	1.000	1.000
prm.1	0.998	1.002	0.997	0.999
tumgrad2.1	1.852	0.540	1.137	3.016
tumgrad3.1	2.115	0.473	1.251	3.576

Rsquare= 0.161 (max possible= 0.991)

Likelihood ratio test= 120 on 5 df, p=0

Wald test = 116 on 5 df, p=0

Score (logrank) test = 123 on 5 df, p=0

Details of the FP transformations are given in the `fptable` value of the resulting `mfp.object`.

```
>f$fptable
```

	df.initial	select	alpha	df.final	power1	power2
posnodal	4	0.05	0.05	4	0.5	3
prm	4	0.05	0.05	1	1	.
tumgrad2	1	0.05	0.05	1	1	.
tumgrad3	1	0.05	0.05	1	1	.
tumsiz	4	0.05	0.05	0	.	.

menostat2	1	0.05	0.05	0	.	.
age	1	0.05	0.05	0	.	.
esm	4	0.05	0.05	0	.	.

The final model uses a second degree fractional polynomial for the number of positive lymphnodes with powers 0.5 and 3.

The value `fit` of the resulting `mfp` object can be used for survival curve estimation of the final model fit (1).

The function `plot.mfp` draws three plots: smoothed martingale based residuals of the null model, the linear predictor function and a plot of the partial residuals together with a lowess smooth (2).

References

- [1] AMBLER, G., AND ROYSTON, P. Fractional polynomial model selection procedures: investigation of Type I error rate. *Journal of Statistical Simulation and Computation* 69 (2001), 89–108.
- [2] MARCUS, R., PERITZ, E., AND GABRIEL, K. On closed test procedures with special reference to ordered analysis of variance. *Biometrika* 76 (1976), 655–660.
- [3] R DEVELOPMENT CORE TEAM. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria, 2004. ISBN 3-900051-00-3.
- [4] ROYSTON, P., AND ALTMAN, D. G. Regression using fractional polynomials of continuous co-variates: parsimonious parametric modelling (with discussion). *Applied Statistics* 43, 3 (1994), 429–467.
- [5] ROYSTON, P., AND SAUERBREI, W. Stability of multivariable fractional polynomial models with selection of variables and transformations: a bootstrap investigation. *Statistics in Medicine* 22 (2003), 639–659.
- [6] SAUERBREI, W., AND ROYSTON, P. Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. *Journal of the Royal Statistical Society (Series A)* 162 (1999), 71–94.
- [7] SAUERBREI, W., AND ROYSTON, P. Corrigendum: Building multivariable prognostic and diagnostic models: transformation of the predictors by using fractional polynomials. *Journal of the Royal Statistical Society (Series A)* 165 (2002), 399–400.

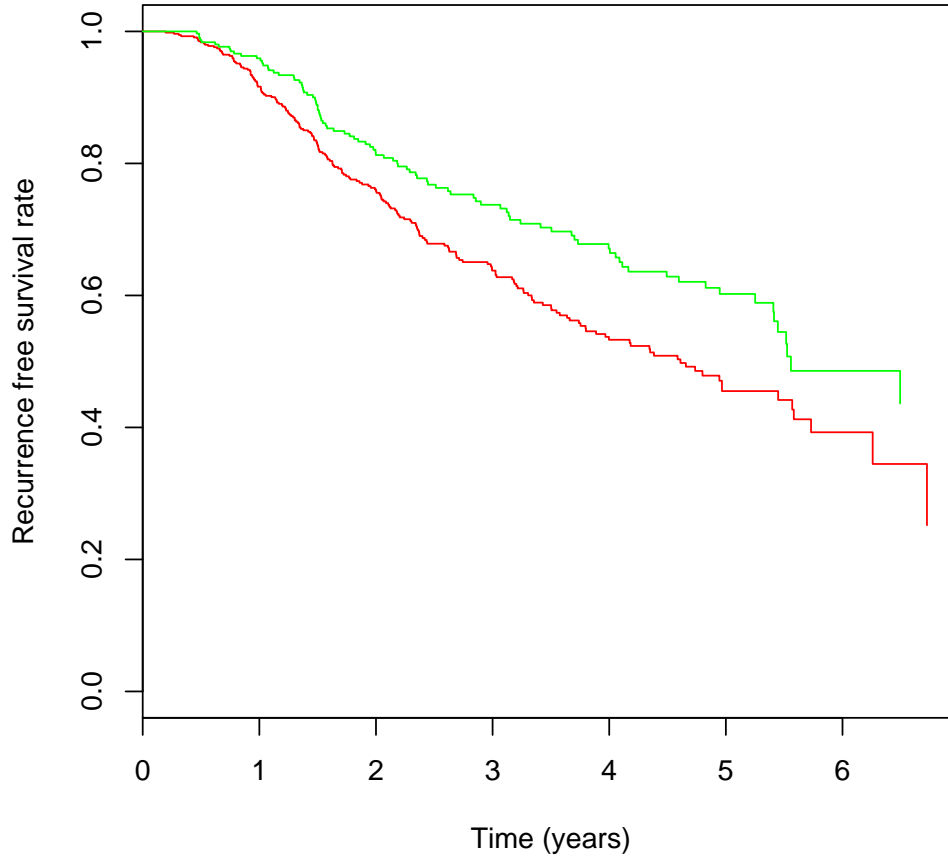


Figure 1: Predicted survival curves of the final mfp model for the two strata defined by hormonal treatment (red line = no hormonal treatment, green line = hormonal treatment).

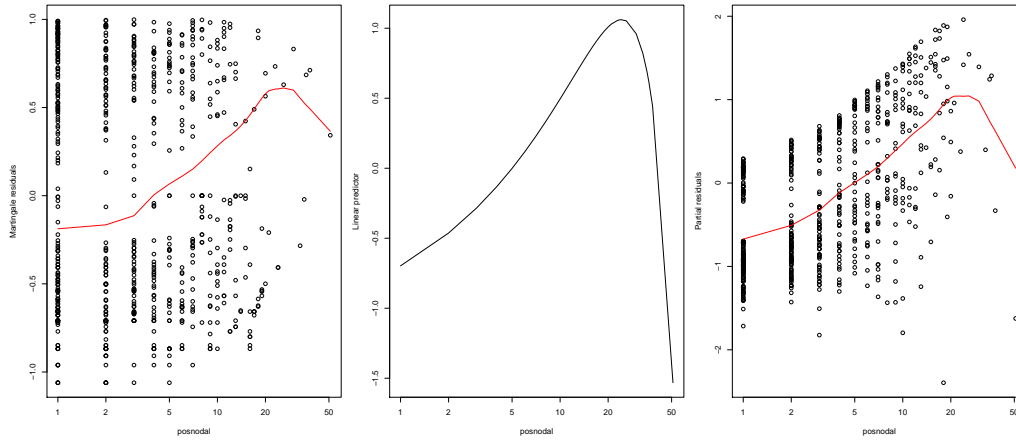


Figure 2: Smoothed null model martingale residuals, the plot of the estimated functional form of the influence of the number of positive lymph nodes (`posnodal`) on the log relative hazard of tumor recurrence, and the partial residuals plot for `posnodal`.