

R package *nplr* *n-parameter logistic regressions*

Frederic Commo^{1,2} and Briant M. Bot¹

¹*Sage Bionetworks, Fred Hutchinson Cancer Research Center, Seattle, Washington*

²*INSERM U981, Institut Gustave Roussy, 114 rue Edouard Vaillant, 94805 Villejuif, France*

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1 Introduction

1.1 Overview

In in-vitro experiments, the aim of drug response analyses is usually to estimate the drug concentration required to reach a given cell line growth inhibition rate - typically the 50% inhibitory concentration (IC_{50}), which inhibits 50% of the proliferation, compared with an untreated control. This estimation can be achieved by modeling the inhibition rate observed under a range of drug concentrations. Once the model is fitted, the x values (drug concentrations) can be estimated from the y values (inhibition rates) by simply inverting the function.

The most commonly used model for drug response analysis is the Richards' equation [1], also referred to as a 5-parameter logistic regression [2]:

$$y = B + \frac{T - B}{[1 + 10^{b(x_{mid} - x)}]^s}$$

where B and T are the bottom and top asymptotes, and b , x_{mid} and s are the Hill slope, the x -coordinate at the inflexion point and an asymmetric coefficient, respectively.

The `nplr` package is based on the full 5-parameter model, where all of the parameters are optimized, simultaneously, using a Newton-Raphson method (`nlm`, R package `stats`). The objective function to minimize is a weighted sum of squared errors:

$$sse(Y) = \sum_i w_i \cdot (\hat{y}_i - y_i)^2, i = 1, \dots, n$$

The weights, w_i , used in the objective function can be computed using 3 possible methods, as follows:

- residuals weights: $w_i = \left(\frac{1}{res_i}\right)^p, i = 1, \dots, n$ values
- standard weights: $w_{ir} = \frac{1}{Var(y_r)}, r = 1, \dots, r$ replicated conditions
- general weights: $w_i = \left(\frac{1}{y_i}\right)^p, i = 1, \dots, n$ values

where p is a tuning parameter. The `standard weights` and the `general weights` methods are described in [3, 4].

`nplr` provides several options in order to compute flexible weighted n -parameter logistic regression: `nparams="all"` can be explicitly specified, from 2 to 5, or set to `all`. In that case, all the possible models are evaluated, and the optimal one is returned, with respect to the minimal error returned by `nlm`.

The final model performance is estimated by a weighted and non-weighted standard error, as well as the weighted and non-weighted goodness-of-fit:

- standard error: $\frac{1}{(n-2)} \cdot \sum_i (\hat{y}_i - y_i)^2, i = 1, \dots, n$
- weighted standard error: $\frac{1}{(n-2)} \cdot \sum_i w_i \cdot (\hat{y}_i - y_i)^2, i = 1, \dots, n$
- goodness-of-fit: $1 - \frac{SS_{res}}{SS_{tot}}$
- weighted goodness-of-fit: $1 - \frac{\sum_i w_i (\hat{y}_i - y_i)^2}{\sum_i (y_i - \bar{y})^2}$

1.2 Functions in nplr

The main function is simply `nplr()`. It requires 2 main arguments: a vector of `x` and a vector of `y`. Several other arguments have default values.

The `npars` argument allows a user to run specific n-parameter models, n from 2 to 5, while the default value, `npars="all"`, asks the function to test which model fits the best the data, according to a weighted Goodness-of-Fit estimator.

In some situations, the `x` values may need to be log-transformed, e.g. `x` is provided as original drug concentrations. In such case, setting `useLog=TRUE` in `nplr()` will apply a Log_{10} transformation on the `x` values.

The `nplr()` function has been optimized for fitting curves on `y`-values passed as proportions of control, between 0 to 1. If data are supplied as original response values, e.g. optic density measurements, the `convertToProp()` function may be helpful. In drug-response curve fitting, a good practice consists in adjusting the signals on a T_0 and a *control* (`Ctrl`) values. Providing this values, the proportion values, y_p , are computed as:

$$y_p = \frac{y - T_0}{Ctrl - T_0}$$

where y , T_0 and `Ctrl` are the observed values, the 'time zero' and the 'untreated control', respectively.

Note that if neither T_0 nor `Ctrl` are provided, `convertToProp()` will compute the proportions with respect to the *min* and *max* of y . In that case, the user should be aware that $y = 0.5$ may not correspond to a IC_{50} , but rather to a EC_{50} (the half-effect between the maximum and the minimum of the observed effects).

In a drug-response (or progression) curve fitting context, typical needs are to invert the function in order to estimate the `x` value, e.g. the IC_{50} , given a y value, e.g. the 0.5 survival rate. To do so, the implemented `getEstimates()` method takes 2 arguments: the model (an instance of the class `nplr`), and one (or a vector of) `target(s)`. `getEstimates()` returns the corresponding `x` values and their estimated confidence intervals, as specified by `conf.level`.

2 Examples

The examples below use some samples of the NCI-60 Growth Inhibition Data. The full data can be downloaded at [5]. For the purpose of the demonstration, the supplied drug concentrations have been re-exponentiated.

2.1 Example 1

2.1.1 Fitting a model

```
> require(nplr)
```

The first example fits a simple drug-response curve: the PC-3 cell line treated with Thioguanine, 19 points without replicates.

```
> path <- system.file("extdata", "pc3.txt", package="nplr")
> pc3 <- read.delim(path)
> np1 <- nplr(x=pc3$CONC, y=pc3$GIPROP)
```

Testing pars...

The 5-parameters model showed better performance

Calling the object returns the fitting summary for the model.

```
> np1
Instance of class nplr

Call:
nplr(x = pc3$CONC, y = pc3$GIPROP)

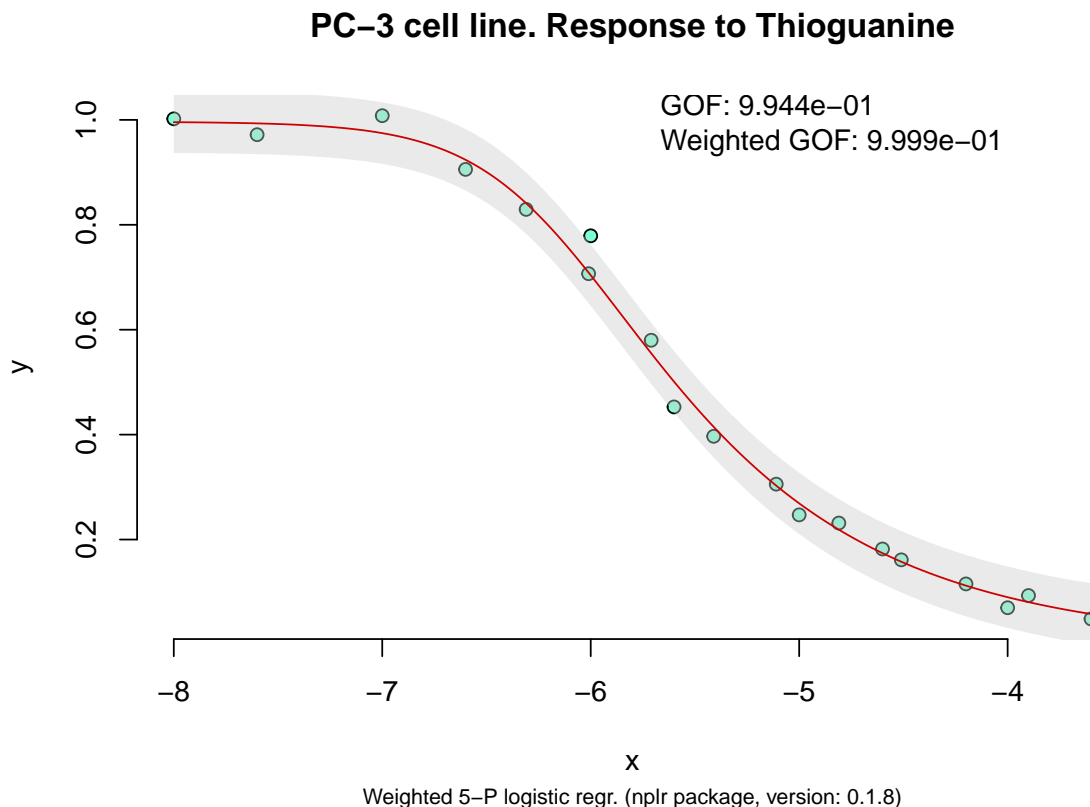
weights method: residuals

5-P logistic model
Bottom asymptote: 0.0001829475
Top asymptote: 0.9964906
Inflexion point at (x, y): -5.850105 0.6270841
Goodness of fit: 0.9944421
Weighted Goodness of fit: 0.9998545
Standard error: 0.02699085 0.01800316
```

2.1.2 Visualizing the model

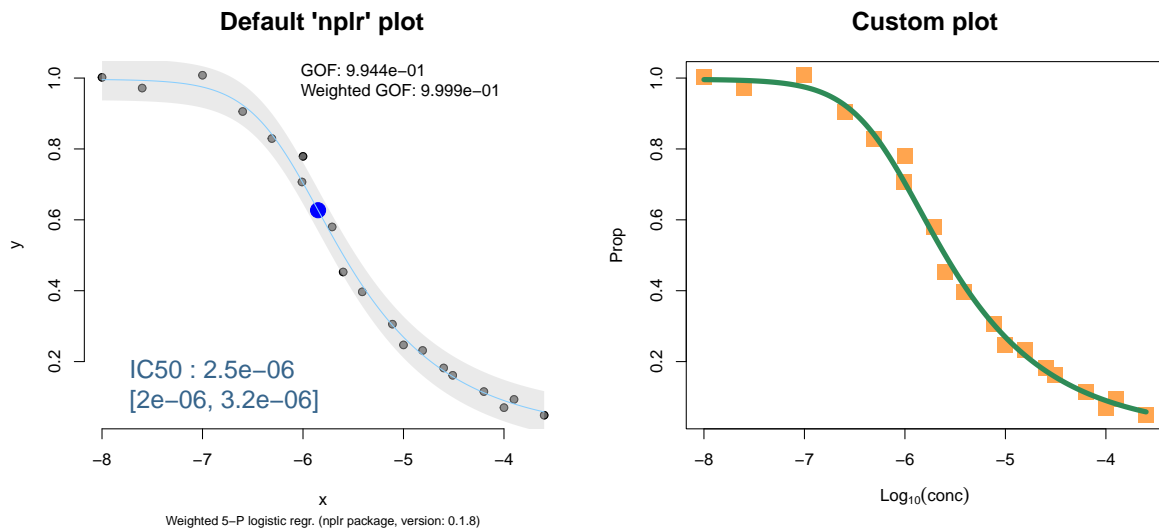
A specific plot() function has been implemented in order to visualize the results.

```
> plot(np1, cex.main = 1.2,
+       main="PC-3 cell line. Response to Thioguanine")
```



This function has several predefined graphical parameters, and some of them can be overwritten. However, a convenient way to draw simplest or customized plots is shown in the example below:

```
> plot(np1, pcol="grey40", lcol="skyblue1", showEstim=.5, showInfl=TRUE,
+       main="Default 'nplr' plot", cex.main=1.5)
> x1 <- getX(np1); y1 <- getY(np1)
> x2 <- getXcurve(np1); y2 <- getYcurve(np1)
> plot(x1, y1, pch=15, cex=2, col="tan1", xlab=expression(Log[10](conc)),
+       ylab="Prop", main="Custom plot", cex.main=1.5)
> lines(x2, y2, lwd=5, col="seagreen4")
```



2.1.3 Accessing the performances

Once the model is built, several accessor functions allow to get access to the performances of the model, and its parameters.

```
> getGoodness(np1)
$gof
[1] 0.9944421

$wgof
[1] 0.9998545
```

```
> getStdErr(np1)
      stdErr weighted stdErr
1 0.02699085      0.01800316
```

```
> getPar(np1)
$npar
[1] 5

$params
      bottom      top      xmid      scal      s
1 0.0001829475 0.9964906 -6.182545 -1.428009 0.3351753
```

Here, the 5-parameter model have been chosen as it showed better performances, according to the goodness-of-fit (`npar=5`). The optimal values for the parameters are reported in `params`.

2.1.4 Estimating the drug concentrations

The purpose of such fitting is to estimate the response to the drug. To do so, `nplr` provides 2 estimates: the area under the curve (AUC), and the drug concentration for a given response to reach.

The `getAUC()` function returns the area under the curve (AUC) estimated by the trapezoid rule and the Simpson's rule, while `getEstimates()` invert the function and returns the estimated concentration for a given response. If no target is specified, the default output is a table of the x values corresponding to responses from 0.9 to 0.1.

```
> getAUC(np1)
  trapezoid Simpson
1  2.507094 2.527395
```

```
> getEstimates(np1)
  y      x.025      x      x.975
1 0.9 1.887929e-07 3.181425e-07 4.537895e-07
2 0.8 4.759161e-07 6.223618e-07 7.931375e-07
3 0.7 8.216978e-07 1.017702e-06 1.253717e-06
4 0.6 1.300875e-06 1.593305e-06 1.951605e-06
5 0.5 2.033190e-06 2.522415e-06 3.154908e-06
6 0.4 3.274823e-06 4.219737e-06 5.555883e-06
7 0.3 5.827998e-06 7.916255e-06 1.129827e-05
8 0.2 1.215027e-05 1.873892e-05 3.234779e-05
9 0.1 3.714708e-05 8.030162e-05 2.937146e-04
```

A single value (a target), or a vector of values, can be passed to `getEstimates()`, and a confidence level can be specified (by default, `conf.level` is set to `.95`).

```
> getEstimates(np1, .5)
  y      x.025      x      x.975
1 0.5 2.041978e-06 2.522415e-06 3.147628e-06
```

```
> getEstimates(np1, c(.25, .5, .75), conf.level=.90)
  y      x.05      x      x.95
1 0.25 8.684319e-06 1.168667e-05 1.657270e-05
2 0.50 2.100420e-06 2.522415e-06 3.038789e-06
3 0.75 6.631842e-07 8.041128e-07 9.607243e-07
```

2.2 Example 2

The next example analyses a drug-response experiment with replicated drug concentrations: the MCF-7 cell line treated with Irinotecan.

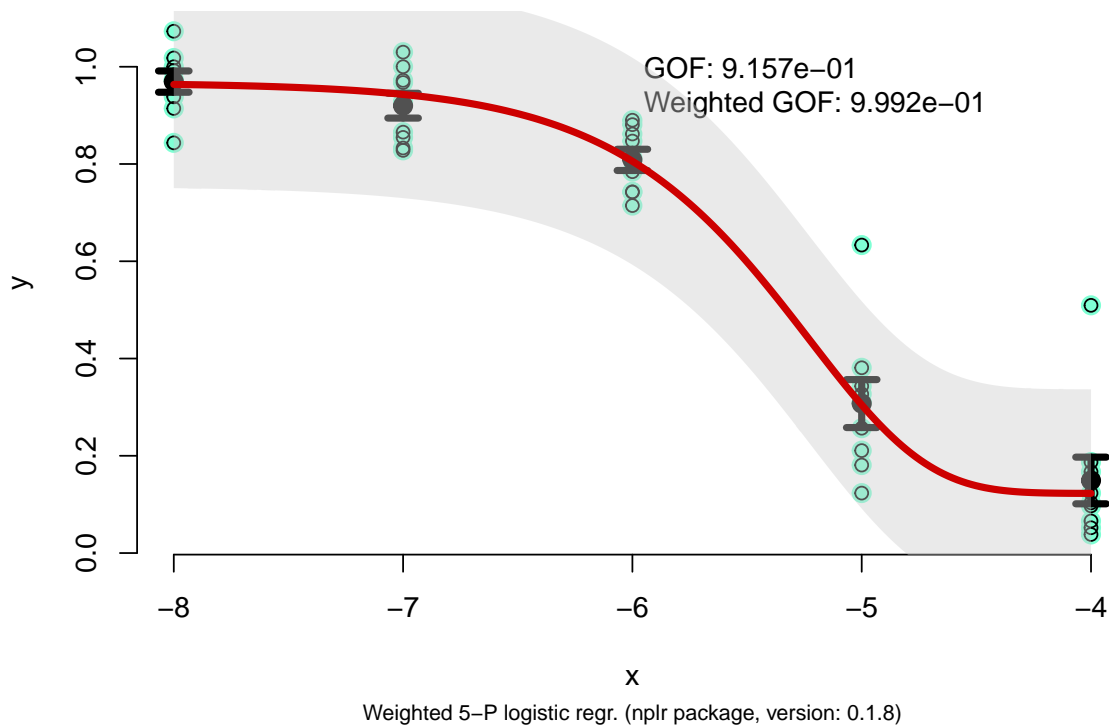
```
> path <- system.file("extdata", "mcf7.txt", package="nplr")
> mcf7 <- read.delim(path)
> np2 <- nplr(x=mcf7$CONC, y=mcf7$GIPROP)
```

Testing pars...

The 5-parameters model showed better performance

```
> plot(np2, showSDerr = TRUE, lwd = 4, cex.main=1.25,
+       main="Cell line MCF-7. Response to Irinotecan")
```

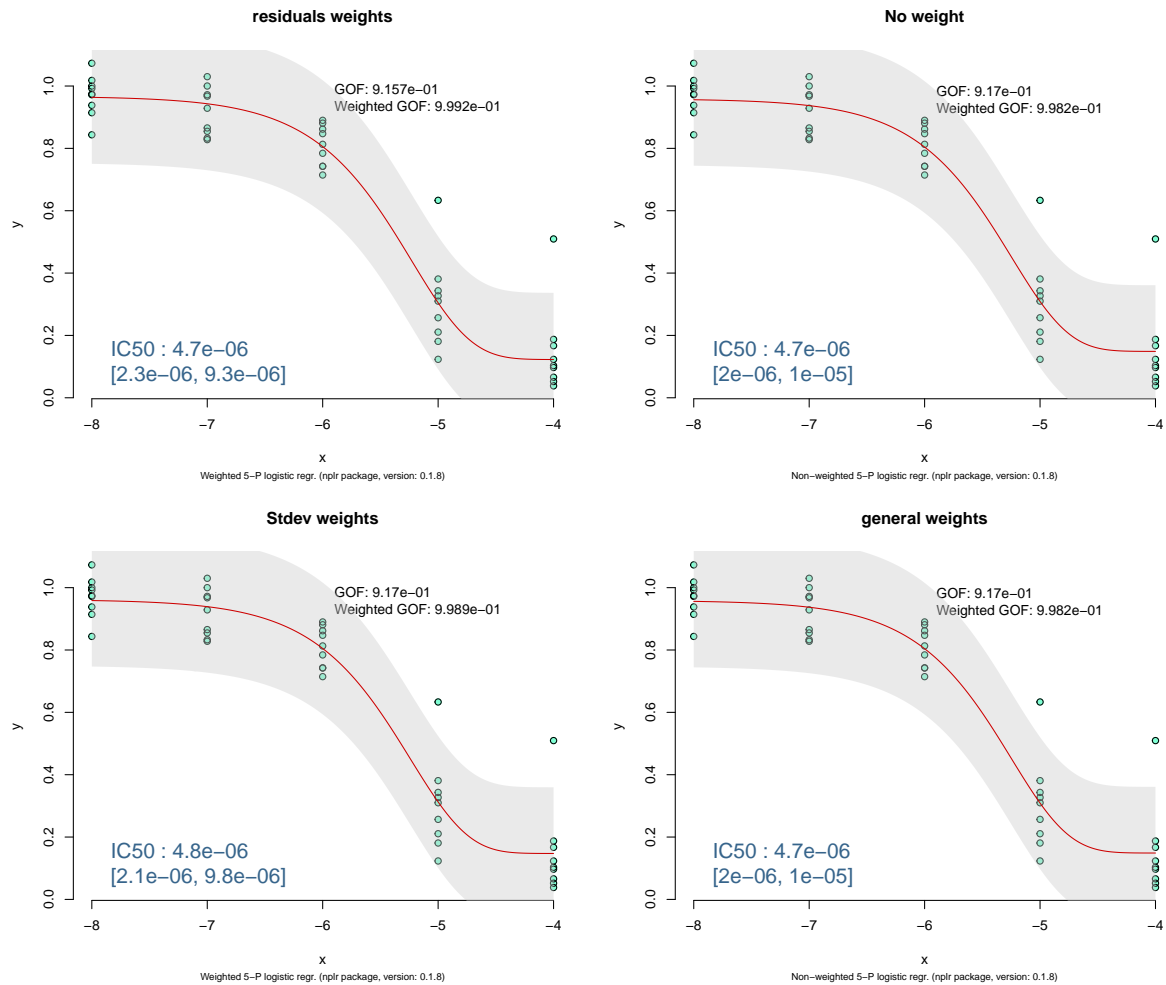
Cell line MCF-7. Response to Irinotecan



As there are replicates, we can compare the effect of the different weighted methods: the default method is **residuals weights**, "res". A **no-weight** condition can be tested by setting the `LPweight` argument to 0: The vector of weights is then just a vector of 1's.

```
> x <- mcf7$CONC
> y <- mcf7$GIPROP
> noweight <- nplr(x, y, LPweight=0, silent=TRUE)
> sdw <- nplr(x, y, method="sdw", silent=TRUE)
> gw <- nplr(x, y, method="sdw", LPweight=1.5, silent=TRUE)
```

```
> plot(np2, showEstim=.5, main="residuals weights")
> plot(noweight, showEstim=.5, main="No weight")
> plot(sdw, showEstim=.5, main="Stdev weights")
> plot(noweight, showEstim=.5, main="general weights")
```



Note that the curves do not seem to change dramatically. However, the different weights can give different performances.

2.3 Example 3

2.3.1 Fitting a Progression/Time model

This last example illustrates a Progression/Time experiment: these are simulated data.

```
> path <- system.file("extdata", "prog.txt", package="nplr")
> prog <- read.delim(path)
```

Here, the progression values are given in some unknown unit, and the x values are Time in hours. So we don't need to use a Log_{10} transformation. Let us assume that we have access to the T_0 and the *control* values. We can use `convertToProp()` in order to convert the y values to proportions.

```
> x <- prog$time
> yp <- convertToProp(prog$prog, T0 = 5, Ctrl = 102)
> np3 <- nplr(x, yp, useLog=FALSE)
```

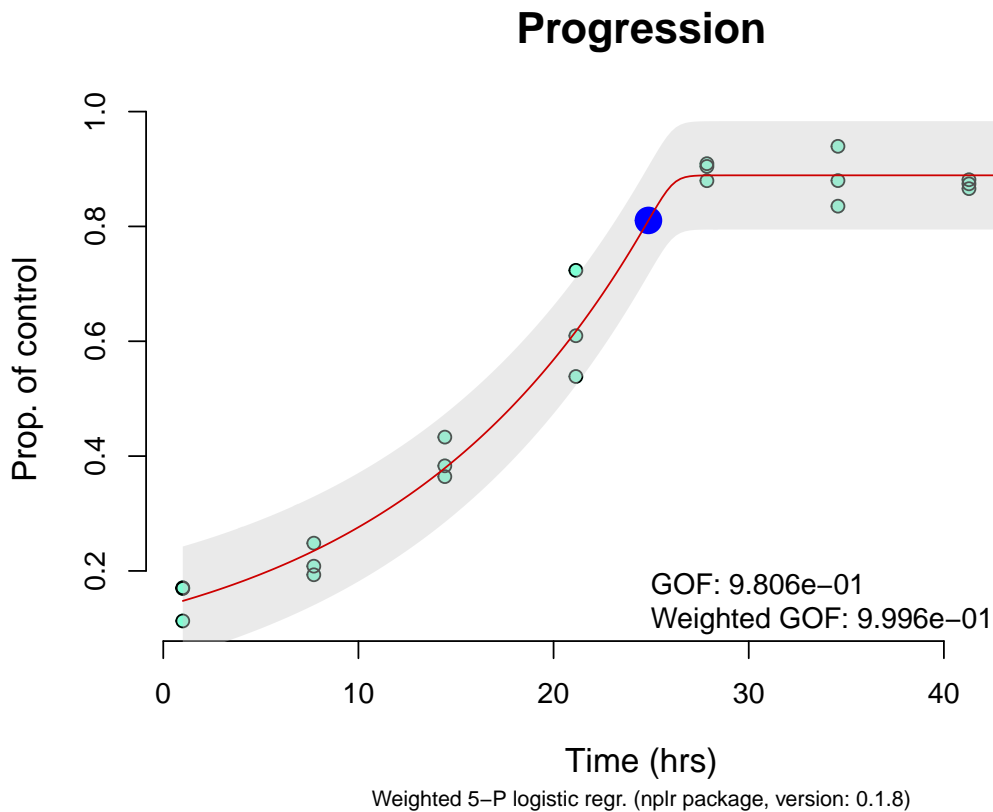
Testing pars...

The 5-parameters model showed better performance

When progression is at stake, it may be interesting to get the coordinates of the inflexion point, as it corresponds to the point where the slope (the progression) is maximal.

```
> getInflexion(np3)
      x      y
1 24.8605 0.8104354
```

```
> plot(np3, showInfl=TRUE, xlab="Time (hrs)", cex.main=1.5, cex.lab=1.2,
+      ylab="Prop. of control", main="Progression")
```

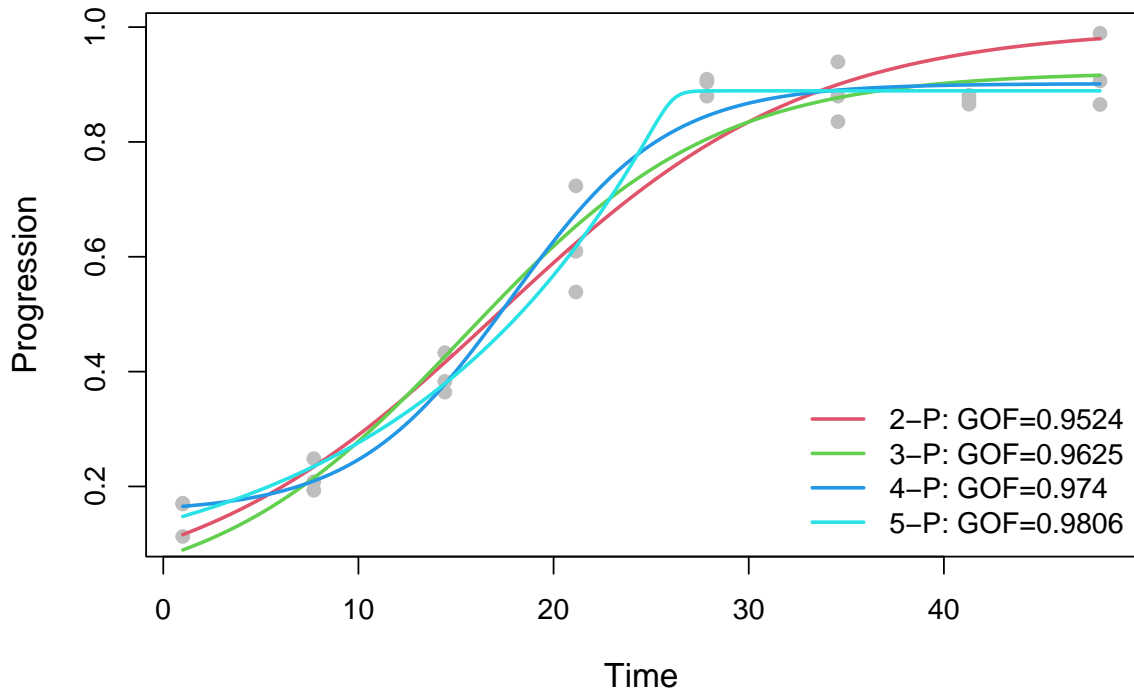


2.3.2 Evaluating the number of parameters

When a 5-p logistic regression is used, and because of the asymmetric parameter, the curve is no longer symmetrical around its inflexion point. Here is an illustration of the impact of the number of parameters on the fitting.

```
> plot(x, yp, pch=19, col="grey" , cex.main=1.5, cex.lab=1.2,
+      main="The n-parameter effect", xlab="Time", ylab="Progression")
> le <- c()
> for(i in 2:5){
+   test <- nplr(x, yp, npars = i, useLog = FALSE)
+   lines(getXcurve(test), getYcurve(test), lwd = 2, col = i)
+   goodness <- getGoodness(test)
+   gof <- goodness$gof
+   le <- c(le, sprintf("%s-P: GOF=%s", i, round(gof, 4)))
+ }
> legend("bottomright", legend=le, lwd=2, col=2:5, bty="n")
```

The n-parameter effect



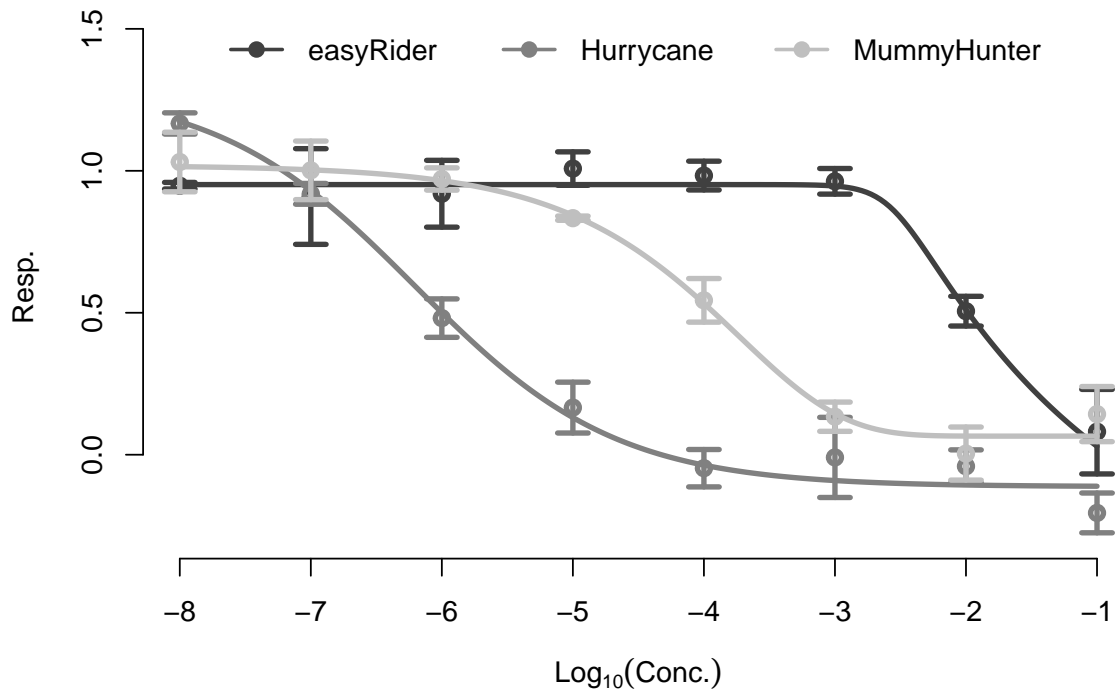
Note that the 5-P model may not be always the best choice.

2.4 Superimposing multiple curves

When multiple cell lines, or multiple compounds are compared, it can be useful to superimpose the response curves on a single plot.

```
> path <- system.file("extdata", "multicell.tsv", package="nplr")
> multicell <- read.delim(path)
>
> # Computing models (to be stored in a list)
> cellsList <- split(multicell, multicell$cell)
> Models <- lapply(cellsList, function(tmp){
+   nplr(tmp$conc, tmp$resp, silent = TRUE)
+ })
>
> # Visualizing
> overlay(Models, xlab = expression(Log[10](Conc.)), ylab = "Resp.",
+   main="Superimposing multiple curves", cex.main=1.5, lwd = 3)
```

Superimposing multiple curves



2.5 Web-server version

nplr is available as a free online application at <https://fredcommo.shinyapps.io/curveFitter>

This application is built on top of shiny and nplr, and allows a user to upload a file as the same form as those provided as examples in the nplr package. A multicell.tsv example file is also available for download through the App (click on Example file).

Plot and results can be exported after the models have been built.

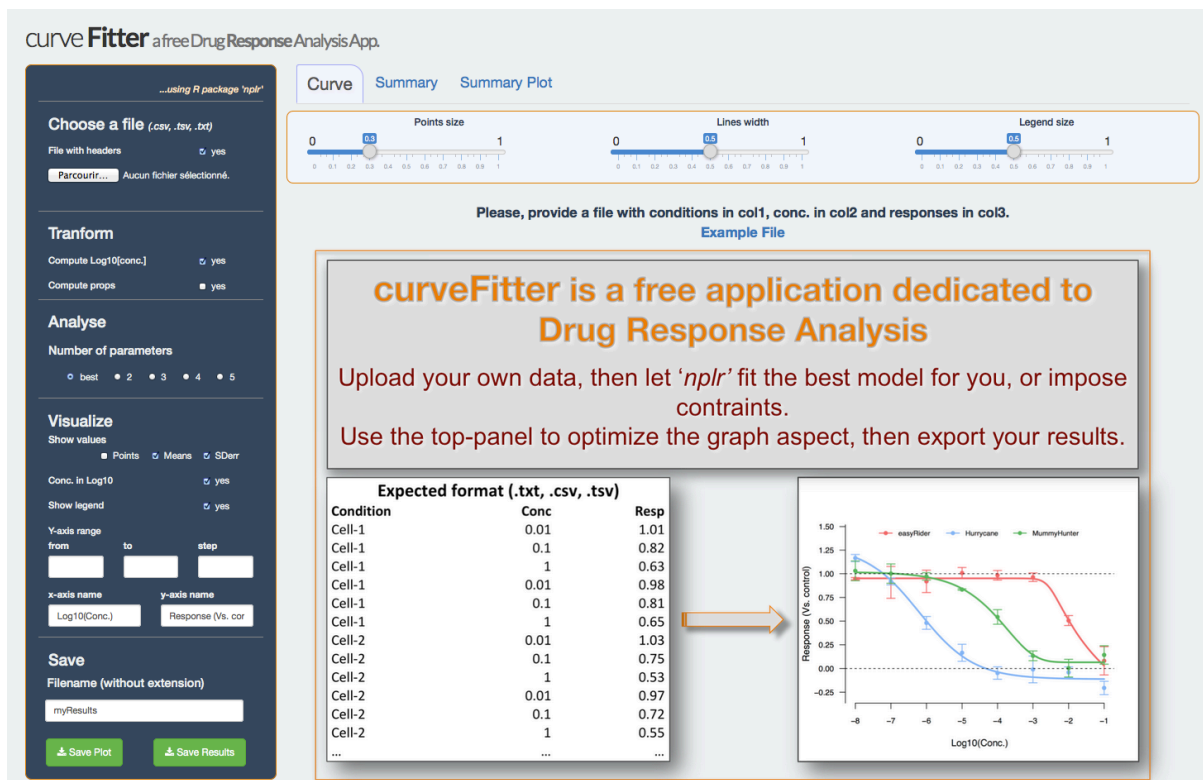


Figure 1: nplr at <https://fredcommo.shinyapps.io/curveFitter>

3 Accessing R code

nplr R code is available on github: <https://github.com/fredcommo/nplr>

References

- [1] Richards FJ. "A flexible growth function for empirical use." In: *J Exp Bot.* 10 (1959), pp. 290–300.
- [2] Giraldo J et al. "Assessing the (a)symmetry of concentration-effect curves: empirical versus mechanistic models." In: *Pharmacol Ther.* 95.1 (2002), pp. 21–45.
- [3] Motulsky HJ and Brown RE. "Assessing the (a)symmetry of concentration-effect curves: empirical versus mechanistic models." In: *BMC Bioinformatics* 9 (2006), pp. 7–123.
- [4] Laurence M. Lévasseur et al. "Implications for Clinical Pharmacodynamic Studies of the Statistical Characterization of an In Vitro Antiproliferation Assay." In: *Journal of Pharmacokinetics and Biopharmaceutics* 26.6 (Dec. 1998), pp. 717–733.
- [5] URL: <https://wiki.nci.nih.gov/display/NCIDTPdata/NCI-60+Growth+Inhibition+Data>.