Profile likelihood confidence intervals for ECx

Philip M. Dixon
_iowa State University_, pdixon@iastate.edu

Katherine J. Goode
_iowa State University_, kgoode@iastate.edu

C. Lay
_Abt Associates_

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Profile likelihood confidence intervals for ECx

Dixon, P.M.$^1$, Goode, K.J.$^1$, Lay, C.$^2$

$^1$Department of Statistics, Iowa State University, Ames IA
$^2$Abt Associates, Boulder, CO

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Summary

Confidence intervals for effective concentrations (EC’s) are commonly computed in dose response curve analyses. Profile intervals offer an alternative method for computing the confidence intervals in situations where delta method based confidence intervals produce intervals with values outside of a practical range. In this document, we describe the computation of profile intervals for EC’s. We then introduce an R function, profile.ECx(), for computing these intervals from a dose response model fit by the drm() function in the drc package. Supplemental material includes three files of R code that define profile.ECx() and its helper functions and R code and data for the two examples.

Introduction

The drc R package (Ritz et al., 2019) provides a comprehensive set of tools to model dose response curves. The primary model-fitting function, drm(), can fit a large number of potential curves to continuous, count, or binary data and return the estimated parameters from the curve fits. Additionally, the ED() function will estimate effective doses (EDs). EDs are the estimated dose producing a specified response. In the case of a two-parameter model for a binary response of alive or dead, the ED_{10} is the dose producing 10% mortality. Because dose and concentration are interchangeable for modeling purposes (but not interpretation), EDs are also called effective concentrations (ECs).

The drm() function uses ED_{50} (or EC_{50}) as one of the model parameters. Standard errors and confidence intervals for ED_{50} are easily obtained from the model fit. Estimates for other percentages are derived from the estimated model parameters. The ED function computes Wald confidence intervals using a delta-method approximation to the variance of the estimated ED. A disadvantage of Wald confidence intervals is that the method of computing a Wald confidence interval allows the interval to sometimes extend outside of the range of possible parameter values. For example, a dose must be greater than or equal to zero, but a Wald confidence interval for an ED could include negative values. An alternative approach is to use a profile confidence interval, which will not extend outside of the parameter space. A profile confidence interval is derived directly from the likelihood function, and it has better statistical properties in many situations (Cox and Hinkley 1974, pp. 342-3, Crump and Howe 1985). An option to compute a profile confidence interval for an ED is not available in the drc package.

This document describes profile confidence intervals for EDs. First, the estimation of an ED for a specified proportion is discussed, and then the theory and implementation of profile likelihood confidence intervals for an ED are described. The profile.ECx() function is provided to estimate profile confidence intervals for an ED using the output from a fitted drm() model. We provide two examples to illustrate the use of the profile.ECx() function.
**Estimating EC\(_x\)**

The concentration or dose at which the estimated response equals a specified value is a commonly desired quantity in the analysis of toxicological data. When the response is a probability ranging from 0 to 1, the EC\(_{50}\), which is the concentration at which the probability equals 0.5, is often used to rate the toxicity of a compound. In ecotoxicology, there may be interest in other response probabilities, e.g., the EC\(_{10}\) or EC\(_{20}\), i.e., the concentration at which there is a 10% or 20% probability of a dose-related response. Given a fitted dose-response curve, e.g. a 2 parameter log-logistic curve:

\[
P[event] = \frac{1}{1 + \exp\left[-\left(\hat{\beta}_0 + \hat{\beta}_1 \log \text{dose}\right)\right]},
\]

the EC\(_{50}\) can be estimated as:

\[
\hat{\text{EC}}_{50} = \exp\left(\frac{-\hat{\beta}_0}{\hat{\beta}_1}\right)
\]

Alternatively, the log logistic model can be parameterized in terms of the EC\(_{50}\). The drm() function uses this approach. The two drm() parameters are \(b\), the slope of the logistic regression, and \(e\), the EC\(_{50}\). The reparameterized model using drm() parameter names is:

\[
P[event] = \frac{1}{1 + \exp[b(\log \text{dose} - \log e)]}.
\]

The 2 parameter model, equation (3), can be generalized to a 3 parameter model, equation (4), that accounts for non-zero background mortality or to a 4 parameter model, equation (5), that allows the mean of a continuous outcome to have a lower and upper asymptote.

\[
P[event] = c + \frac{1 - c}{1 + \exp[b(\log \text{dose} - \log e)]}
\]

\[
\mu = c + \frac{d - c}{1 + \exp[b(\log \text{dose} - \log e)]}
\]

Equations (4) and (5) are written using the drm names for parameters where \(c\) is the lower limit and \(d\) is the upper limit.

In the two parameter log logistic model, the effective concentration for probabilities other than 0.5 can be calculated as:

\[
\hat{\text{EC}}_x = \exp\left[\frac{1}{b} \log \left(\frac{1 - x}{x}\right) - \log e\right],
\]

where \(x\) is the specified event probability. When the dose-response curve is decreasing, the EC\(_x\) is commonly interpreted as an \(x\)% drop from 100%, i.e. the dose producing a predicted response of \((100-x)\)%.

One example would be a model for the probability of successful reproduction. In this case, the EC\(_{10}\) is the dose producing a 90% probability. Equation (6) would be used with \(\frac{x}{1-x}\) replacing \(\frac{1-x}{x}\).

The computation of EC\(_x\) in models with upper limits other than 1 and/or lower limits other than 0 depends on whether \(x\) is interpreted as an added risk or an extra risk. Added risk and
extra risk will be described in the next section, along with the necessary modifications to the computation of $EC_x$.

## Added and extra risk

When the lower and upper asymptotes of the dose-response curve are not 0 and 1, risk can be described as an extra risk or an added risk. To illustrate the difference, consider an increasing dose response curve with a lower asymptote of 4 and an upper asymptote of 12. Extra risk describes risk as a proportion of the difference between upper and lower asymptotes. A 10% extra risk would have a mean response that is 10% of the way from 4 to 12. Extra risk is commonly used when the response is a proportion. Added risk describes a multiple of the lower asymptote and does not depend on the upper asymptote. A 10% added risk would have a mean response that is 1.1 times the lower asymptote. Added risk is commonly used with continuous responses.

When risk is defined as extra risk, the $EC_x$ is the concentration (or dose) at which the proportional response, $\frac{Y(x) - c}{d - c}$, equals $x$. This is for the common case where $d$ is the upper asymptote and $c$ is the lower asymptote. To illustrate the computation of extra risk, consider a dose response curve with a lower asymptote, $c$, of 4 and an upper asymptote, $d$, of 12, which is shown in Figure 1.

![Figure 1: Log likelihood surface for the example five dose data set.](image)
The mean response for an extra risk of 0.7, \( Y(0.7) \), is \( 4 + 0.7 \times (12-4) = 9.6 \), and \( \text{EC}_{0.7} \) is the dose producing that mean response. This is illustrated by the dotted lines in Figure 1.

When risk is defined as added risk, the \( \text{ECA}_a \) is the concentration (or dose) at which the response is the specified proportion above the lower asymptote. In other words, \( \text{ECA}_a \) is the value of \( Y(a) \) for which \( \frac{Y(a) - c}{c} = a \). Added risk can be converted into an equivalent extra risk for specified lower and upper asymptotes, \( c \) and \( d \). For an increasing curve with \( d > c \), that conversion is:

\[
x = \frac{c}{d - c} a.
\]  

(7)

When \( c=4 \) and \( d=8 \), an added risk of 0.7 is the dose for which the mean response is 6.8, i.e. 1.7 times the control mean response. An added risk of 0.7 is equivalent to an extra risk of \( x = 4 \times 0.7/(12 - 4) = 0.35 \). This is illustrated by the dashed lines in the figure. Added risk is undefined when the lower asymptote of an increasing dose-response curve is 0.

**Maximum likelihood estimates of \( \text{EC}_x \)**

When model parameters are estimated by maximum likelihood, the estimated \( \text{EC}_x \) is a maximum likelihood estimate (mle). A particular \( \text{EC}_x \) may be an explicit parameter in the model, as in equations (3), (4), or (5). It may also be calculated from mle’s of the fitted parameters of a model, as in equations (2) or (6), where the \( \text{EC}_x \) is computed from the mle’s from models (1) and (3), respectively. The computed \( \text{EC}_x \), e.g., using equation (6), is still a maximum likelihood estimate because of the invariance property of mle’s.

The mle of \( \text{EC}_x \) is a single number that gives no indication of its precision. An estimated \( \text{EC}_x \) of 31 ppm may be precise when estimated from large numbers of observations, many doses, and data with low variability. That same estimated \( \text{EC}_x \) will not be precise when estimated from few observations at few doses with large variability in the data. A confidence interval reports both the magnitude and precision of the \( \text{EC}_x \). Although calculating an \( \text{EC}_x \) from mle’s of model parameters is straightforward, determining a confidence interval for \( \text{EC}_x \) is not.

**Confidence intervals for parameters**

Confidence intervals for \( \text{EC}_x \) can be constructed using the delta method, using Fieller’s theorem, or by using profile likelihood. The three methods make different assumptions about the estimates or functions of the estimates (Piegorsch and Bailer 1997). The delta method assumes that the estimated \( \text{EC}_x \) is normally distributed. Fieller’s method assumes that the estimated regression parameters, \( \hat{\beta}_0 \) and \( \hat{\beta}_1 \) in equation (1), are normally distributed. The profile likelihood method is based on inverting a likelihood ratio test. Both the delta and Fieller’s method are sensitive to whether \( \text{EC}_x \) is estimated on the log scale (so the parameter in the model is log \( \text{EC}_x \)) or
dose scale (so the parameter in the model is EC\textsubscript{x}), because both are based on assumptions about the distribution of the estimates. The profile likelihood method is not sensitive to how EC\textsubscript{x} is reported (i.e. as EC\textsubscript{x} or log EC\textsubscript{x}). Of the three methods, profile likelihood intervals are often found to have empirical coverage that is the best behaved, in the sense of being closest to nominal (Crump and Howe 1985, Williams 1986, Bailar and Smith 1994, Alho and Valtonen 1995, Huang 2001, Faraggi et al. 2003), but the differences between intervals are sometimes small (Kelly 2001).

All confidence intervals can be constructed by inverting a hypothesis test. The (1 − \alpha) \times 100\% confidence interval for some quantity θ is the set of all parameter values θ\textsubscript{0} for which a hypothesis test of H\textsubscript{0}: θ = θ\textsubscript{0} is accepted at the significance level of α. For example, a delta method confidence interval can be constructed by repeatedly using a Z test (assuming a normal distribution) for many hypothesized values. Those hypothesized values that result in a p-value < α are inside the 100(1 − α)\% confidence interval. In practice, the endpoints of delta method confidence intervals are usually calculated directly because of the algebraic relationship between the test and the interval.

**Principles of profile likelihood confidence intervals for EC\textsubscript{50}**

The profile likelihood confidence interval for EC\textsubscript{50} is constructed using the same relationship with hypothesis tests of EC\textsubscript{50} = θ\textsubscript{0}, except that those tests use a likelihood ratio test (LRT) instead of a Z test. In general, a LRT makes fewer assumptions than does a T test or Z test. In particular, the LRT makes no assumptions about the distribution of the parameter estimates, so the LRT is unaffected by changing the parameterization of EC\textsubscript{50} from a dose scale value (EC\textsubscript{50}) to a log scale value (log EC\textsubscript{50}).

The 100(1 − α)\% confidence interval for EC\textsubscript{50} includes all values of θ\textsubscript{0} for which the LRT accepts H\textsubscript{0}: EC\textsubscript{50} = θ\textsubscript{0} at level α. The LRT of H\textsubscript{0}: EC\textsubscript{50} = θ\textsubscript{0} compares the log likelihood evaluated at the mle of all parameters to the maximum log likelihood given EC\textsubscript{50} = θ\textsubscript{0}. Calculating the second term requires fixing EC\textsubscript{50} at θ\textsubscript{0} and finding the conditional mle’s for all other parameters. Specifically, for a 2-parameter log-logistic model with parameters β\textsubscript{1} and EC\textsubscript{50}, the second term is max\textsubscript{β\textsubscript{1}} log L(θ, β\textsubscript{1}). The LRT of H\textsubscript{0}: EC\textsubscript{50} = θ\textsubscript{0} will accept that null hypothesis when

\[2 \left[ \log L(\hat{EC}_{50}, \hat{β}_1) - \max\textsubscript{β\textsubscript{1}} \log L(θ\textsubscript{0}, β\textsubscript{1}) \right] < χ^2_{1,1−α},\]

where \( \hat{EC}_{50} \) and \( \hat{β}_1 \) are the maximum likelihood estimates of EC\textsubscript{50} and β\textsubscript{1} and \( χ^2_{1,1−α} \) is the 100(1 − α)\% percentile of a Chi-square distribution with 1 degree of freedom. The 100(1 − α)\% confidence interval for EC\textsubscript{50} then is all values of θ\textsubscript{0} for which:

\[C = 2 \left( \log L(\hat{EC}_{50}, \hat{β}_1) - \max\textsubscript{β\textsubscript{1}} \log L(θ\textsubscript{0}, β\textsubscript{1}) \right) < χ^2_{1,1−α}. \]  (8)

The computation of the profile likelihood confidence interval is illustrated using a small data set of the count of number of adverse events when individuals are tested individually at one of five
doses: 1, 1.65, 2.72, 7.39, and 20.1 ppm. The data are 2, 10, 8, 37, and 47 adverse events out of 50 tested individuals at each dose. The assumed model for the probability of an adverse event is the two parameter log-logistic curve, equation (3). The counts are assumed to follow a binomial distribution with a probability that depends on the log dose and the two parameters (the slope coefficient, $\beta_1$ and the EC$_{50}$). The log-likelihood surface, as a function of the slope and EC$_{50}$, is shown in Figure 2. The mle's of the slope and EC$_{50}$ are the location of the maximum of this surface, which are $\hat{\beta}_1 = -1.91$ and $\hat{\text{EC}}_{50} = 4.66$.

The profile likelihood confidence interval can be found by considering different possible values for EC$_{50}$, e.g., 3.3, 3.5, · · · , 7.4. Each possible value for EC$_{50}$ defines a horizontal line across the plot of the log-likelihood surface. At each possible value of EC$_{50}$, there is a “best” value for the regression slope, defined by the slope that has the largest log-likelihood. The locations of the best regression slope for each value of EC$_{50}$ are given by the dots in Figure 3. The value of the log likelihood at each dot is the $\max_{\beta_1} \log L(\theta_0; \beta_1)$ term in equation (8). These profile log likelihood values can be plotted (Figure 4) as a function of the EC$_{50}$ value at which each log-likelihood was calculated. The profile log-likelihood curve has a maximum at $\hat{\text{EC}}_{50} = 4.66$, which is (and should be) the overall mle of the EC$_{50}$. The LRT test statistic, $C$, for testing $H_0 : \text{EC}_{50} = 5$ is twice the difference between the log likelihood at the maximum of the profile log likelihood curve at $\hat{\text{EC}}_{50} = 4.66$ and the value of the profile log likelihood curve at $\text{EC}_{50} = 5$. The values of EC$_{50}$ where the LRT rejects the null hypothesis with a p-value of exactly 0.05 are given by the EC$_{50}$ values where $C$ in equation (8) = 3.82, or equivalent when the log-likelihood is 1.92 units below the maximum. That log likelihood is indicated by the horizontal line in Figure 4. The intersections of that line and the profile curve are the end points of the profile likelihood
Figure 3: Log likelihood surface for the example five dose data set. Dots indicate the conditional mle for the slope given a particular value of EC50.

Figure 4: Partial log likelihood curve for the example five dose data set.
confidence interval. For these data, that interval is (3.88, 5.69). In contrast, the delta method confidence interval for EC$_{50}$ is (3.78, 5.56).

The definition of a profile likelihood confidence interval is easily extended to models with more than two parameters. In the two-parameter model, there is one “nuisance” parameter, the regression slope. In a 3 or 4 parameter model, there are 2 or 3 “nuisance” parameters. The key change is that the maximization over the regression slope in equation (8) is replaced by the maximum over all parameters other than $\theta_0$, the potential value for EC$_{50}$.

**Profile likelihood intervals for EC$_x$**

Calculating a profile likelihood interval for EC$_x$ where $x$ is not 50% is more complicated because the models in equations (3), (4), and (5) do not include EC$_x$ as a parameter. These models need to be rewritten to include EC$_x$ as a parameter. The details of this depend on whether the dose-response curve is increasing (P[event] or $\mu$ increase with dose) or decreasing (P[event] or $\mu$ decrease with dose) and whether risk is defined as excess risk or added risk.

**Increasing dose-response curve**

In terms of the drm() parameters, the dose-response curve is increasing when $d > c$ and $b < 0$ or $c > d$ and $b > 0$ (rare, inversion of parameters). For a binomial response with range from 0 to 1 or from $c$ to 1, the dose-response curve is increasing when $b < 0$.

The mean response (or P[event] for a binomial response) for a specified extra risk, $x$, is:

$$E[Y] = c + \frac{d - c}{1 + \exp \left[ b(\log \text{dose} - \log \text{EC}_x) - \log \left( \frac{x}{1-x} \right) \right]}, \quad (9)$$

in the usual case where $d > c$.

When risk is defined as added risk, an extra step is needed. The mean response (or P[event]) for added risk $a$ is obtained by substituting equation (7) into equation (9) to get:

$$E[Y] = c + \frac{d - c}{1 + \exp \left[ b(\log \text{dose} - \log \text{ECA}_a) - \log \left( \frac{ca}{d-c-ca} \right) \right]}, \quad (10)$$

where ECA$_a$ is the dose resulting in an added risk of $a$. In effect, equation (10), is repeatedly converting added to extra risk each time the mean response function is evaluated because the conversion depends on the current values of $c$ and $d$. This repeated conversion is needed because the profile likelihood computations require maximizing the log likelihood over the nuisance parameters, which include $c$ and $d$. 

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In the rare case that the parameters are swapped, so \( c \) is the upper asymptote and \( d \) is the lower asymptote, the mean response function for extra risk is:

\[
E[Y] = c + \frac{d - c}{1 + \exp\left[b(\log \text{dose} - \log EC_x) + \log \left(\frac{x}{1-x}\right)\right]}.
\] (11)

The only difference between equations (9) and (11) is the sign of the shift term, \( \log \left(\frac{x}{1-x}\right) \).

**Decreasing dose-response curve**

The dose-response curve is decreasing when \( d > c \) and \( b > 0 \) or \( c > d \) and \( b < 0 \) (rare, inversion of parameters). For a binomial response with range from 0 to 1 or from \( c \) to 1, the dose-response curve is increasing when \( b > 0 \). Let us first consider extra risk and added risk when \( d > c \).

To illustrate the computation of extra risk and added risk for a decreasing dose response curve, consider the dose response curve with a lower asymptote, \( c \), of 4 and an upper asymptote, \( d \), of 12 shown in Figure 5.

![Decreasing dose-response curve](image)

Figure 5: Example of a decreasing dose response curve with upper asymptote, \( d = 12 \) and lower asymptote, \( c = 4 \).

When risk is defined as extra risk, the \( EC_x \) is the concentration (or dose) at which the proportional response, \( \frac{d-Y(x)}{d-c} \), equals \( x \). The mean response for an extra risk of 0.4, \( Y(0.4) \), is 12 -
0.4 \times (12-4) = 8.8, and EC_{0.4} is the dose producing that mean response. This is illustrated by the dotted lines in Figure 5.

When risk is defined as added risk, the ECA_a is the concentration (or dose) at which the response is the specified proportion below the upper asymptote. In other words, ECA_a is the value of Y(a) for which \( \frac{d - Y(a)}{a} = a \). The conversion to an extra risk for a decreasing curve with \( d > c \), that conversion is:

\[
x = \frac{d}{d - c} a.
\]

When \( c=4 \) and \( d=8 \), an added risk of 0.4 is the dose for which the mean response is 7.2, i.e. \((1-0.4)=0.6\) times the control mean response. An added risk of 0.4 is equivalent to an extra risk of \( x = 12 \times 0.4/(12 - 4) = 0.6 \). This is illustrated by the dashed lines in Figure 5.

The mean response (or P[event] for a binomial response) for a decreasing dose-response curve is:

\[
E[Y] = d - \frac{d - c}{1 + \exp \left[ b (\log \text{dose} - \log EC_x) - \log \left( \frac{x}{1-x} \right) \right]},
\]

which is equivalent to:

\[
E[Y] = d - \frac{d - c}{1 + \exp \left[ b (\log \text{dose} - \log EC_x) + \log \left( \frac{a d}{d - c - a d} \right) \right]},
\]

Both are for the usual case where \( d > c \). If the parameters are swapped, the sign on the shift term, \( \log \left( \frac{x}{1-x} \right) \), switches, as before.

**Implementation in R**

The drm() function in the drc package (Ritz et al. 2019) fits various dose-response curves to binomial or continuous data. The ED() function estimates EC_x using parameter estimates stored in a fitted drm object. ED() provides delta-method confidence intervals for EC_x but not profile likelihood intervals. The function introduced in this document, profile.ECx(), computes profile likelihood intervals starting from a fitted drm() object.

Various approaches for computing the profile likelihood intervals were considered. It was simplest and most reliable to use the profile() and confint() functions in the bbmle package (Bolker and R Development Core Team 2017). The profile() function calculates the profile likelihood trace for a parameter in an mle2() fit. The confint() function then calculates the confidence interval bounds from that profile trace.

The drm() function fits a model using least-squares (or weighted least-squares), although various robust alternatives are also implemented (Ritz et al. 2019). Calculating a profile interval requires a likelihood. The profile.ECx() function starts by refitting the drm() model using maximum
likelihood. This is done using the mle2() function in the bbmle package (Bolker et al. 2017). For some types of data and models, it was numerically more robust to express the drm() parameters on a different scale, e.g. a logistic transformation of the $c$ parameter or a log transformation of the EC$_x$.

The profile.ECx() code determines the appropriate log-likelihood function based on information in the drm() fit (Table 1). Variations on the models listed in Table 1 are supported or can easily be added to profile.ECx(). Some details on adding new models are in the Appendix.

<table>
<thead>
<tr>
<th>Data type</th>
<th>drm model</th>
<th>Risk</th>
<th>Likelihood function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binomial</td>
<td>LL.2</td>
<td>extra</td>
<td>lnl2()</td>
</tr>
<tr>
<td></td>
<td>LL.3</td>
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<td></td>
<td>LL.4</td>
<td>extra</td>
<td>lnl4()</td>
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<tr>
<td>Continuous</td>
<td>LL.3</td>
<td>extra</td>
<td>lnl3c()</td>
</tr>
<tr>
<td></td>
<td>LL.4</td>
<td>extra</td>
<td>lnl4c()</td>
</tr>
<tr>
<td>Continuous</td>
<td>LL.3</td>
<td>added</td>
<td>lnl3ca()</td>
</tr>
<tr>
<td></td>
<td>LL.4</td>
<td>added</td>
<td>lnl4ca()</td>
</tr>
</tbody>
</table>

Table 1: Likelihood functions for specified type of data, drm() model, and definition of risk.

For some data sets, the maximum likelihood fit gives somewhat different parameter estimates. A warning is issued when this happens.

**Arguments to the profile.ECx() function**

The profile.ECx() function requires a fitted drm() model. This is provided as the first argument to profile.ECx(). Additional arguments are:

- **x**: desired quantile, as a proportion, e.g. 0.5 for EC50, 0.1 for EC10. Note, this is different from the ED() function in drc, which expects a percentage, e.g. 50 or 10.  
  default value: 0.5

- **coverage**: confidence interval coverage  
  default value: 0.95

- **interval**: possible values: “two”, “lower”, “upper”  
  whether to compute two-sided interval or one-sided bound  
  default: “two”

- **risk**: possible values: “extra” or “added”, or NULL  
  which type of risk is desired.
if NULL, use extra risk for binomial and added risk for continuous data models
default: NULL

• full: possible values: TRUE or FALSE
  FALSE: return only the confidence interval
  TRUE: return a list with the interval and intermediate results, e.g. the mle fit
default: FALSE

• std.err: NULL, or a vector of approximate standard errors for parameters
  only needed when Hessian from mle fit is poorly behaved
default: NULL

The profile.ECx() function and support functions are packaged into three R files: profile.r, helper.r, and lnl.r. All R code is available as supplemental material to this document in the Iowa State University Digital Repository.

The Appendix provides further details on the implementation.

Profile likelihood confidence intervals for other parameters in the drm() model

The maximum likelihood fit of the drm() model includes estimates for all model parameters. Profile likelihood confidence intervals for any of these parameters can be computed by returning the mle fit using profile.ECx(···, full=T) then using profile() and confint() on that mle fit. An example illustrating this is at the end of example 2 below.
Examples using profile.ECx()

The examples.r file is a plain text version of the code below. The examples.Rmd file is an R markdown version of the same code. If you want to run the code, please use one of these two files instead of using copy/paste from this pdf file. Quotes and some other symbols are represented differently in pdf files.

# examples using profile.ECx()

# installation - assumes have files in working directory
source('profile.r')  # main function
source('helper.r')   # helper functions
source('lnl.r')      # and likelihood functions

# attach necessary libraries
library(drc)
library(bbmle)

# --------------------------------
# example 1: continuous response. Ritz et al. 2019 book, section 1.1.1
# Root inhibition by secalonic acid

# data in drcData on github repo

library(drcData)
data(secalonic)

# fit a 4 parameter log logistic

sec.LL4 <- drm(rootl ~ dose, data=secalonic, fct=LL.4())

summary(sec.LL4)

# 10'th percentile using a delta method CI
ED(sec.LL4, 10, 'delta')

# 10'th percentile using profile CI:
# default is added risk for continuous data
profile.ECx(sec.LL4, 0.1)

# curve is decreasing,
so this is the dose giving 90% of the upper asymptote

10'th percentile using profile CI:
using extra risk

profile.ECx(sec.LL4, 0.1, risk='extra')

this is the dose giving 90% of the difference between asymptotes
very similar here because lower asymptote almost 0

example 2: binary response.
Minnow mortality with Fluoranthene exposure
Data from Piegorsch and Bailer 1997, example 7.6

minnow <- read.table('minnow.txt', header=T, as.is=T)

Piegorsch and Bailer fit a logistic with linear dose
But L3 profile interval not yet implemented
use log logistic model instead

# fit a two parameter logistic
min.LL2 <- drm(mort/n ~ conc, data=minnow, weights=n, fct=LL.2(),
              type='binomial')

delta method CI for 5% and 10%
ED(min.LL2, c(5, 10), 'delta')

profile interval for 5%
profile.ECx(min.LL2, 0.05)

and 10%
profile.ECx(min.LL2, 0.10)

fake a logistic model using exp(conc) in model
min.L2 <- drm(mort/n ~ exp(conc), data=minnow, weights=n, fct=LL.2(),
              type='binomial')

Delta method intervals quite bad
log( ED(min.L2, c(5, 10), 'delta') )

but profile intervals reasonable after transforming back to raw scale
log( profile.ECx(min.L2, 0.05) )
log( profile.ECx(min.L2, 0.10) )
# check against delta method intervals for L.3 with a fixed d=1
min.L2b <- drm(mort/n ~ conc, data=minnow, weights=n,
   fct=L.3(fixed=c(NA,1,NA)),
   type='binomial')

# coefficients are exactly the same as previous fit using "fake"
# but L.3 not (yet) one of the profile models

# to compute profile intervals on all parameters:
min.full <- profile.ECx(min.LL2, full=T)

min.prof <- profile(min.full$mle)
# the mle component is the bbmle fit
# by default, profile() does all parameters
# NOTE ECx here is for the proportion used in the profile.ECx() call
confint(min.prof)

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## References


**Appendix**

**Details of implementation**

The profile.ECx() function supports multiple choices of drm model, multiple transformations of parameters, and two possible definitions of risk (extra or added). These are implemented using helper functions not intended to be called directly by the user. These helper functions are defined in the `helper.r` code file. The check.fct() function looks at the drm() model and the desired definition of risk (extra or added) and returns the appropriate choices for each of helper functions. Table 2 describes the various functions, their purpose, and the file containing their definition. The log likelihood functions for each model are defined in `lnl.r`. 
Table 2: Primary functions

<table>
<thead>
<tr>
<th>Function</th>
<th>Found in</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>profile.ECx</td>
<td>profile.r</td>
<td>Main function</td>
</tr>
<tr>
<td>check.fct</td>
<td>helper.r</td>
<td>Assign log likelihood function</td>
</tr>
<tr>
<td>newparam</td>
<td>helper.r</td>
<td>Convert between drm parameterization and lnl</td>
</tr>
<tr>
<td>newparamc</td>
<td>helper.r</td>
<td>Same for continuous data</td>
</tr>
<tr>
<td>newparamca</td>
<td>helper.r</td>
<td>Same for continuous data with added risk</td>
</tr>
<tr>
<td>oldparam</td>
<td>helper.r</td>
<td>Convert back to drm parameterization</td>
</tr>
<tr>
<td>oldparamc</td>
<td>helper.r</td>
<td>Same for continuous responses</td>
</tr>
<tr>
<td>oldparamca</td>
<td>helper.r</td>
<td>Same for continuous responses with added risk</td>
</tr>
<tr>
<td>various</td>
<td>lnl.r</td>
<td>Log likelihood computations</td>
</tr>
</tbody>
</table>

Adding additional models

Another drm model or type of data can be implemented by extending the chain of if conditions in check.fct() to detect the new model or type of data and then defining the appropriate log likelihood, newparam, and oldparam functions. The choice to report EC\(_x\) or log EC\(_x\) is decided in a second if/else block that defines the three transformation parameters.