Hierarchical models

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Nov 3 2019

Example data

In vitro effects of the fungicide vinclozolin: Chinese hamster ovary cells were exposed to nine different concentrations of vinclozolin (in μM) for 22 hours and the resulting luminescence effects were recorded in an AR reporter gene assay (in luminescence units) (Nellemann *et al.*, 2003)

This basic dose-response experiment was repeated 6 times on different days (with the same concentrations)

Data look like this:

```
library(drc)

library(devtools)
install_github("DoseResponse/drcData")
library(drcData)

head(vinclozolin, 3)
```

```
##   exper  conc effect
## 1 10509 0.000   1003
## 2 10509 0.025    908
## 3 10509 0.050    997
```

Fitting a mixed-effects model

We need to use the packages *drc* and *medrc*:

```
library(drc)
vinclo.nonlin <- drm(effect ~ conc, data = vinclozolin, fct = LL.4())

library(devtools)
install_github("DoseResponse/medrc") # package from github

library(medrc)
vinclo.nlmm <- medrm(effect ~ conc, data = vinclozolin, fct = LL.4(),
                             random = d ~ 1|exper, start = coef(vinclo.nonlin))
```

A few comments:

- Model specification as in `drm()` in the package *drc*
- Fixed and random effects specification as in `nlme()`
- In this example: Starting values supplied using the initial nonlinear regression fit

(see Baty *et al.* (2016, 2017) and da Cunha *et al.* (2019))

Looking at the output

A condensed version of the summary output:

```
coef(summary(vinclo.nlmm))
```

```
##           Value    Std.Error DF    t-value      p-value
## b    0.44702501   0.05971651 44  7.4857861 2.232959e-09
## c  -47.00086373 129.86832972 44 -0.3619117 7.191504e-01
## d 1979.84000564 297.77647987 44  6.6487454 3.748172e-08
## e    0.08730831   0.02850549 44  3.0628591 3.733198e-03
```

Between-day variation is much larger than within-day variation

Estimating EC values (cond. 0 and marginal)}

```
ED(vinclo.nlmm, c(5, 10, 20, 50), interval = "delta")
```

```
##
## Estimated effective doses
##
##           Estimate  Std. Error       Lower       Upper
## e:1:5   1.2036e-04  9.1516e-05 -6.3750e-05  3.0446e-04
## e:1:10  6.4033e-04  3.6274e-04 -8.9403e-05  1.3701e-03
## e:1:20  3.9286e-03  1.5013e-03  9.0849e-04  6.9488e-03
## e:1:50  8.7308e-02  2.7409e-02  3.2169e-02  1.4245e-01
```

```
EDmarg(vinclo.nlmm, c(5, 10, 20, 50), interval = "delta")
```

```
##
## Estimated effective doses
##
##         Estimate  Std. Error       Lower       Upper
## 1:5   1.0981e-04  5.0226e-05  8.7642e-06  2.1085e-04
## 1:10  6.2432e-04  3.9162e-04 -1.6351e-04  1.4122e-03
## 1:20  3.9355e-03  1.4827e-03  9.5258e-04  6.9184e-03
## 1:50  8.7308e-02  2.7413e-02  3.2160e-02  1.4246e-01
```

Not much of a difference in this case

References

- Baty, F., Ritz, C., van Gestel, A., Brutsche, M., Gerhard, D. (2016). Modeling the oxygen uptake kinetics during exercise testing of patients with chronic obstructive pulmonary diseases using nonlinear mixed models. *BMC Med Res Methodol*, **16**, 66. https://dx.doi.org/10.1186%2Fs12874-016-0173-8

- Baty, F., Ritz, C., Jensen, S. M., Kern, L., Tamm, M., Brutsche, M. (2017). Multimodel inference applied to oxygen recovery kinetics after 6-min walk tests in patients with chronic obstructive pulmonary disease. *PLoS ONE*, **12**, e0187548. https://doi.org/10.1371/journal.pone.0187548

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- Nellemann C., Dalgaard M., Lam H.R., Vinggaard A.M. (2003). The combined effects of vinclozolin and procymidone do not deviate from expected additivity in vitro and in vivo. *Toxicological Sciences*, **71**, 251-262. https://doi.org/10.1093/toxsci/71.2.251