An overview of dose-response analysis

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About dose and response

Basic data structure:

dose: certain amount of biological, chemical or radiation stress
(also called explanatory variable or predictor or x
– usually a non-negative quantity)

response: biological reaction to a given dose of stress
(also called endpoint or outcome or y)

Various ways to quantify the response:

- continuous/quantitative (length, optical density, weight)
- discrete/quantal
  - binary (dead/alive, immobile/mobile, present/absent)
  - counts (number of offspring, roots)
  - multinomial (severity of damage, ordinal score)
- survival in terms of event times (e.g., Ritz *et al.* (2013))
- ...

Dose-response modelling

Basic building block:

- a **parametric** model for each observed dose-response curve

Extensions:

- combining data from several dose-response curves obtained from the same experiment into a single dose-response model
- nonlinear mixed-effects dose-response models for combining dose-response curves from different experiments
- model averaging to include model selection uncertainty
- mixture models describing the joint action of several substances
- ...

Parametric models

- log-logistic (and logistic) models
  - special cases: exponential decay, logit and Michaelis-Menten models
  - asymmetric extension: generalized log-logistic

- other monotonous models:
  - log-normal models *(probit analysis with log-dose a special case)*
  - asymmetric Weibull models *(related to extreme value distributions)*
  - fractional polynomial models (Namata *et al.*, 2008)
  - threshold models (Pires *et al.*, 2002)

- non-monotonous models (often tend to be too flexible):
  - inverse j-shaped/u-shaped *hormesis* models (Cedergreen *et al.*, 2005)
  - biphasic models (Cornou *et al.*, 2013)

(see also Ritz (2010) for additional details)

Log-logistic model: Definition

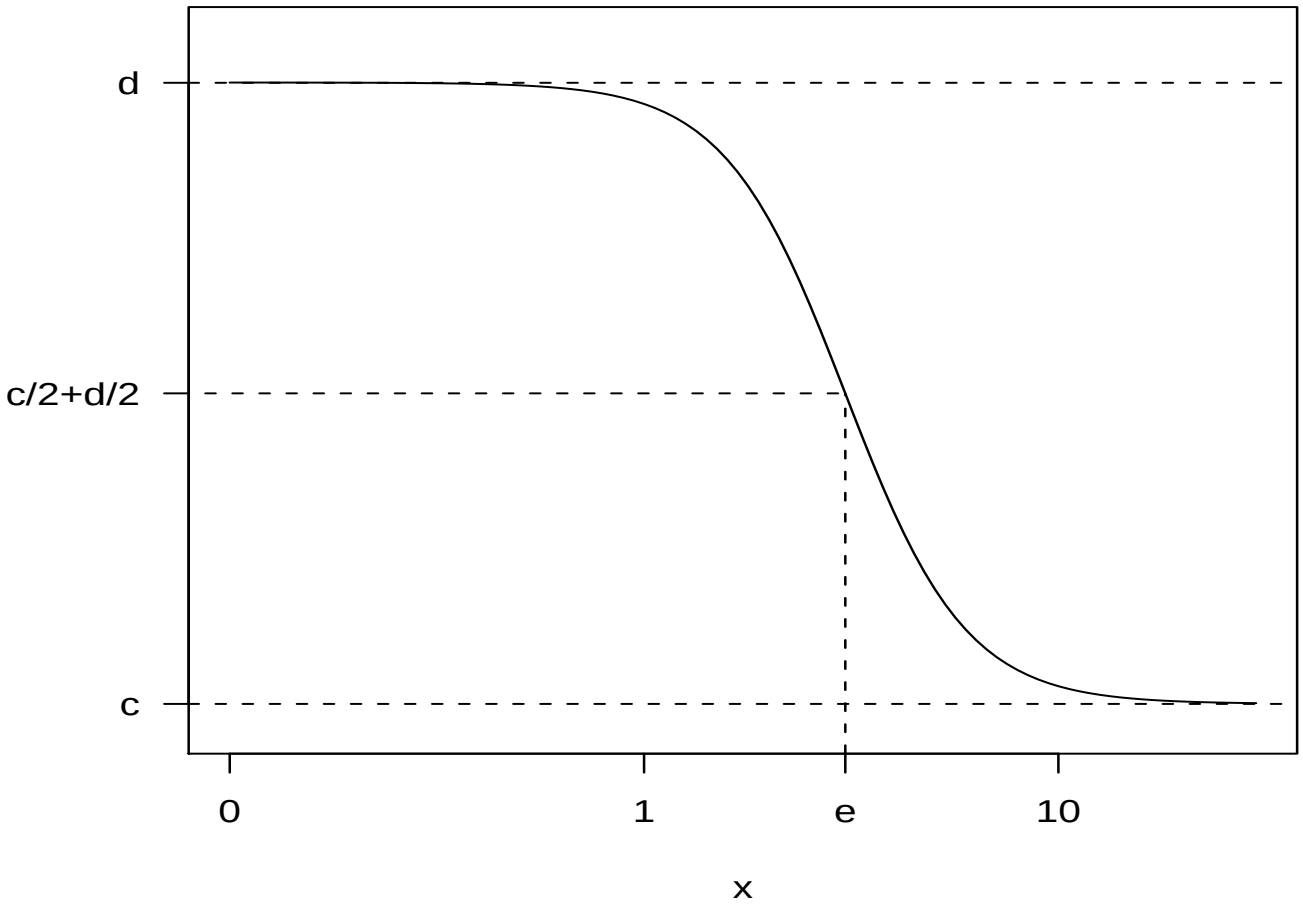
The classic: Four-parameter log-logistic model:

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

Details:

- *empirically established* for s-shaped dose-response data
- parameters have biological interpretation
- used in biology, hearing and speech science, medicine, pharmacology
- used extensively in toxicology for evaluating toxicity
- for binary data with $c = 0$ and $d = 1$ the *logistic regression model* is obtained (but in a somewhat different parameterization)

Log-logistic model: Parameter interpretation



Alternative asymmetric models

... if you know the type of asymmetry!

Slow descent from upper limit (Weibull type 1):

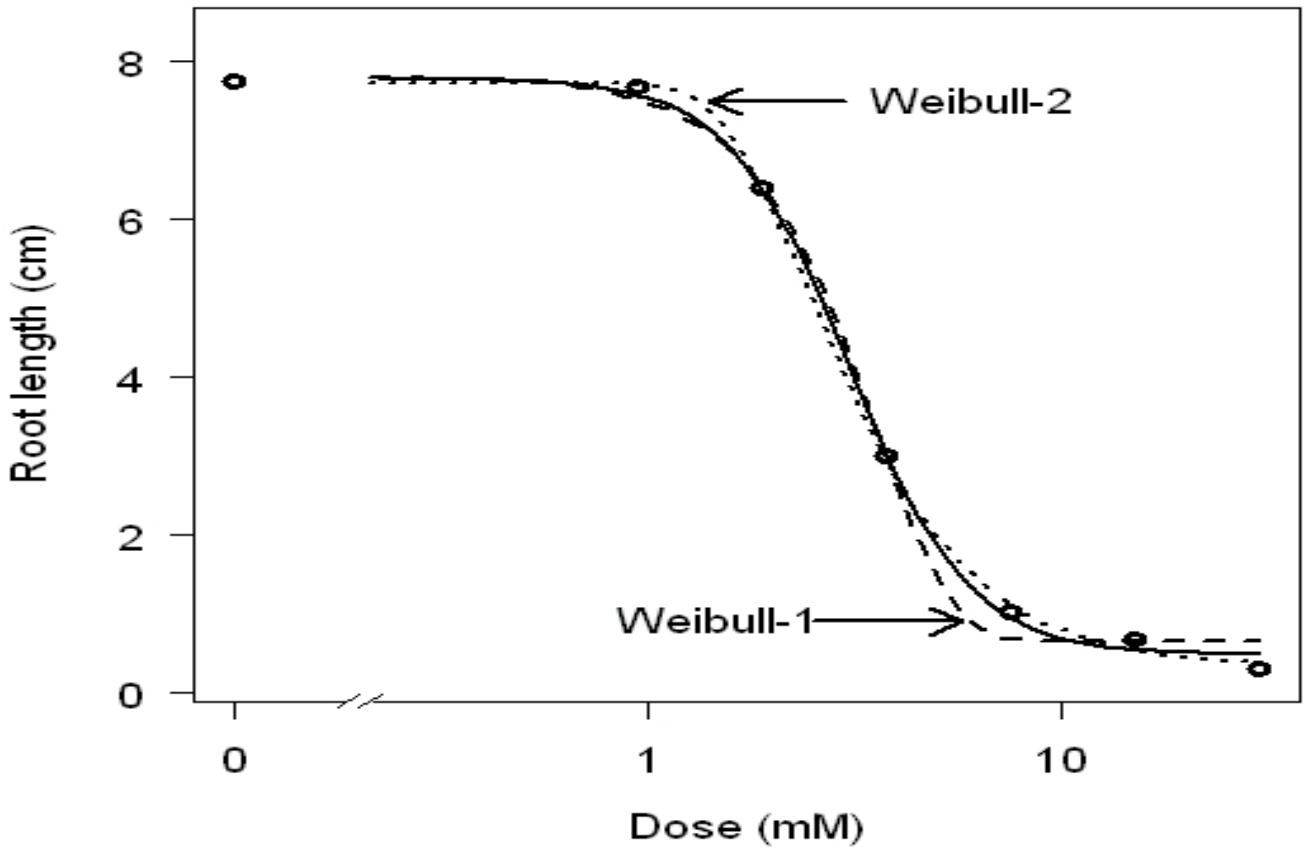
$$f(\text{dose}) = c + (d - c)exp(-exp[b\{log(\text{dose}) - log(e)\}])$$

Rapid descent from upper limit (Weibull type 2):

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

Note: Only the model parameters c and d have biological interpretations

Asymmetric dose-response curves



Hormesis models – formulas

Brain-Cousens model:

$$f(\text{dose}) = c + \frac{d - c + f\,\text{dose}}{1 + \exp\{b(\log(\text{dose}) - \log(e))\}}$$

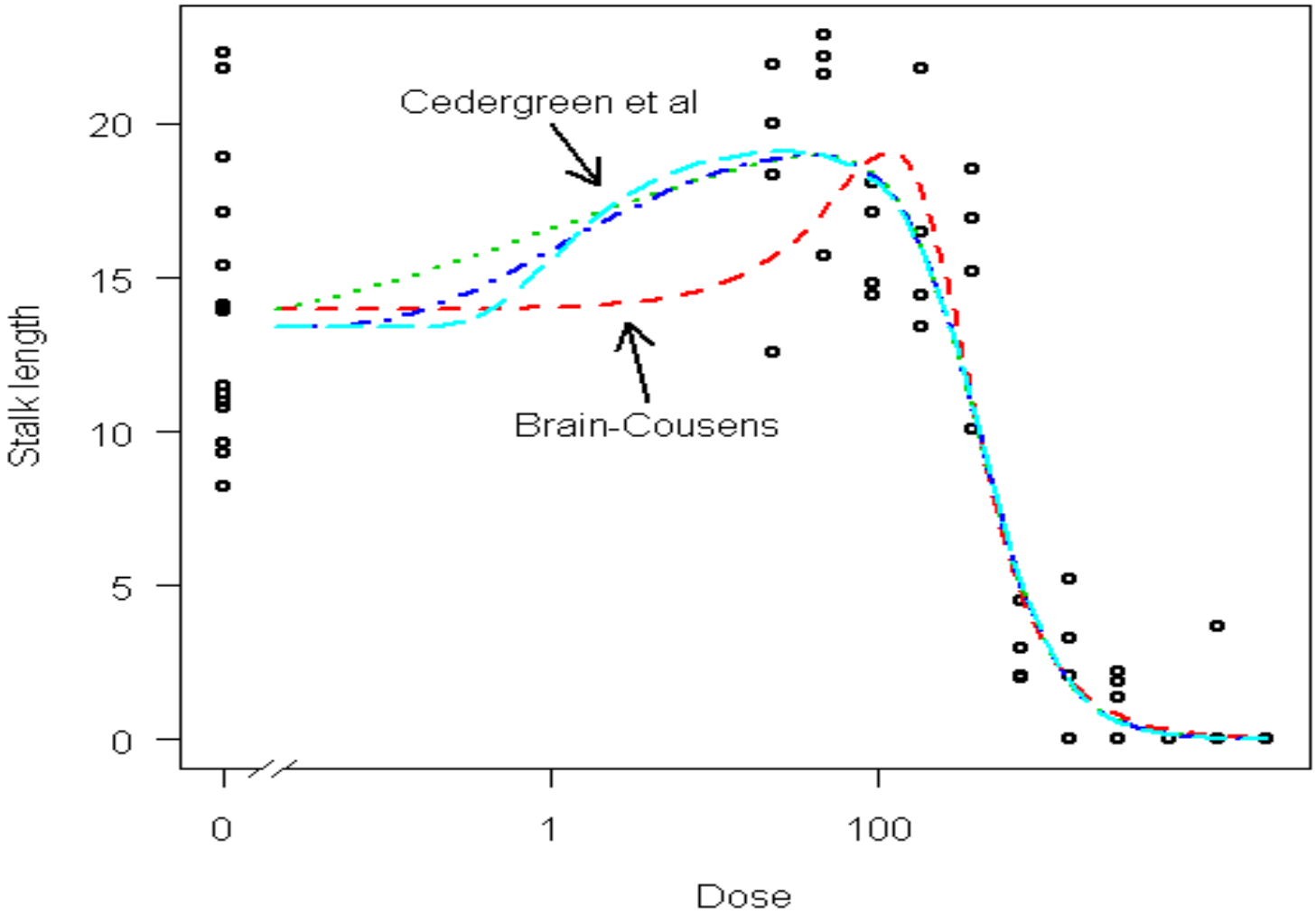
Cedergreen *et al.* (2005) model:

$$f(\text{dose}) = c + \frac{d - c + f\exp\{-1/\text{dose}^{\alpha}\}}{1 + \exp\{b(\log(\text{dose}) - \log(e))\}}$$

Note: The resulting curve has always both a minute local minimum and a global maximum that corresponds to the maximum hormesis response

There exist other hormesis models with even more model parameters (Beckon *et al.* (2008))

Hormesis models – visualization



What are dose-response models used for?

- A single dose-response curve:
  - estimating relevant parameters such as *effective concentrations/doses* (inverse regression problem)
  - quantifying the uncertainty associated with the estimates
- Several dose-response curves:
  - calculating *relative potency* between curves (ratios of effective concentrations/doses)
  - comparing entire dose-response curves
  - comparing only specific model parameters or derived parameters

Resources in **R**

Bits and pieces found in several packages:

- `nls()` – part of the standard **R** installation
- `nls2`, `nlstools`, `MASS`
- `drc` and extentions: `bmd`, `medrc`
- `calib`, `drfit`, `grofit`, `qpcR`, `PK`
- ...

Key features of `drc`

- Unified framework for different types of responses
- Convenient model specification through a range of built-in mean functions
- Special cases can be obtained by fixing parameters at given values (so not estimated)
- All standard **R** methods available (e.g., `anova`, `confint`, `predict`, `summary`, `vcov`)
- Estimation in most cases as smooth as for `lm()`
  (no need to think about starting values for the model parameters ... a consequence of the programming flexibility in **R***!)*
- Convenient plotting functionality (in contrast to `nls()`)
- Built-in calculation of derived parameters

References

- Beckon, W. N., Parkins, C., Maximovich, A., and Beckon, A. V. (2008). A General Approach to Modeling Biphasic Relationships. *Environ. Sci. Technol.* **42**, 1308–1314.
- Cedergreen, N., Ritz, C., and Streibig, J. C. (2005). Improved empirical models describing hormesis. *Environ. Toxicol. Chem.* **24**, 3166–3172.
- Cornou, C., Hindrichsen, I. K., Worgan, H., Bakewell, E., Ruiz, D. R. Y., Abecia, L. Tagliapietra, F., Cattani, M. Storm, I. M. L. D., Ritz, C. and Hansen, H. H. (2013). A ring test of a wireless in vitro gas production system. *Animal Production Science* **53**, 585–592.
- Namata, H., Aerts, M., Faes, C. and Teunis, P. (2008). Model Averaging in Microbial Risk Assessment Using Fractional Polynomials. *Risk Anal.* **28**, 891–905.
- Oris, J. T. and Bailer, A. J. (1997). Equivalence of concentration-response relationships in aquatic toxicology studies: Testing and implications for potency estimation. *Environ. Toxicol. Chem.* **16**, 2204–2209.
- Pires, A. M., Branco, J. A., Picado, A. and Mendonca, E. (2002). Models for the estimation of a 'no effect concentration', *Environmetrics* **13**, 15–27.
- Ritz, C. (2010). Towards a unified approach to dose-response modeling in ecotoxicology. *Environ. Toxicol. Chem.* **29**, 220–229.
- Ritz, C., Pipper, C. B., and Streibig, J. C. (2013). Analysis of germination data from agricultural experiments *European Journal of Agronomy* **45**, 1–6.
- Weimer, M., Jiang, X., Ponta, O., Stanzel, S., Freyberger, A., Kopp-Schneider, A (2012). The impact of data transformations on concentration-response modeling *Toxicology Letters* **213**, 292–298.