

Continuous Toxicological Dose-Response Relationships are Pretty Homogeneous

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Overview

- How heterogeneous are continuous dose-responses (from Slob and Setzer, *Critical Reviews in Toxicology* 44(3): 270-297; 2014)?
 - Data
 - Results
 - Continuous endpoints \leftrightarrow 4-parameter sigmoid models
 - Shape parameters show regularities
 - Dose-group level variability is non-trivial, and usually ignored.
- Bayesian methods fitting 4-parameter models to 3-dose data sets.

How big a problem is model uncertainty?

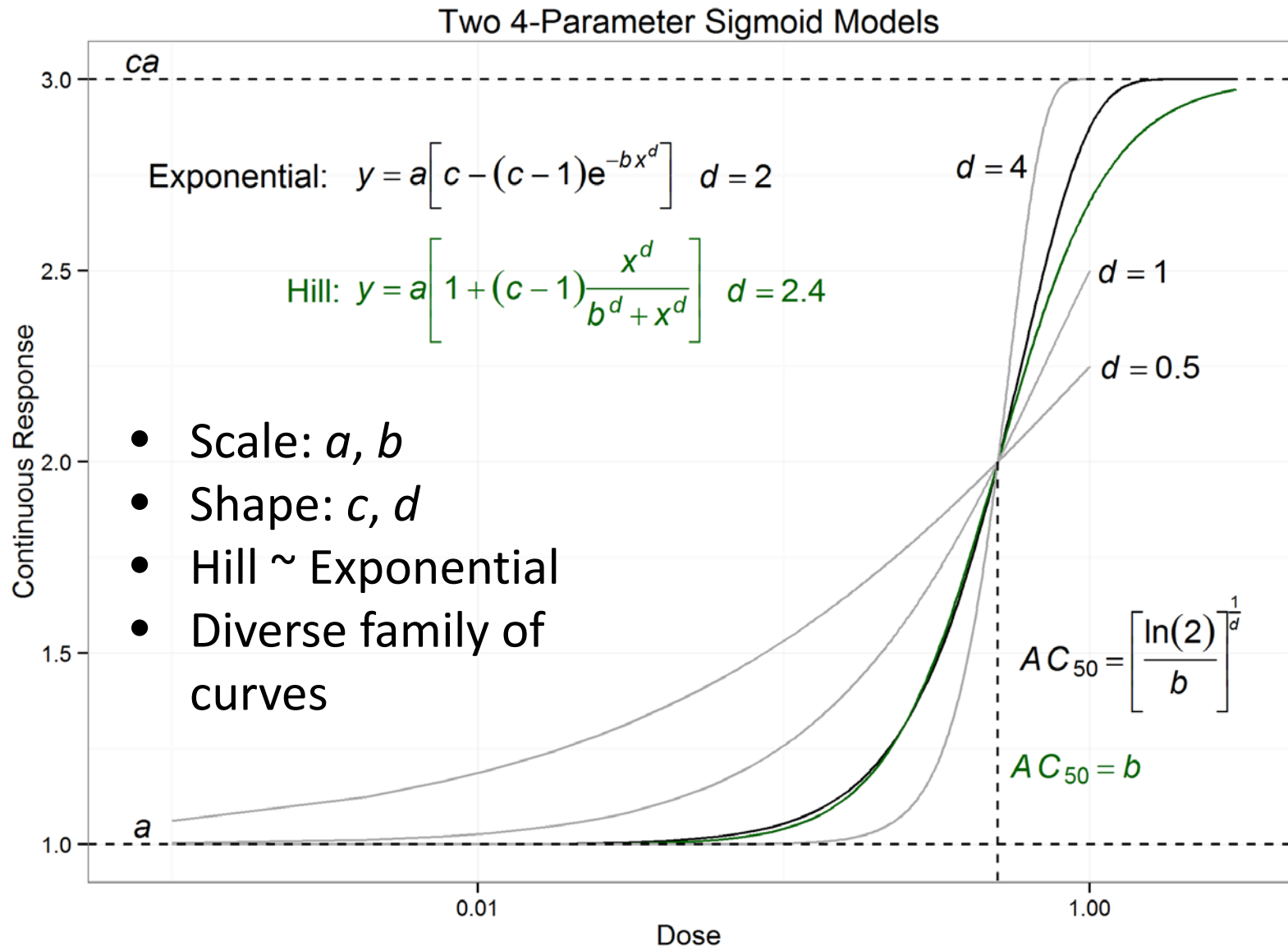
- How heterogeneous are the shapes of dose-response curves?
 - How well can we do with 4-parameter “sigmoid” models, specifically Hill and 4-parameter exponential?

$$\text{Exponential: } y = a \left[c - (c - 1)e^{-bx^d} \right]$$

$$\text{Hill: } y = a \left[1 + (c - 1) \frac{x^d}{b^d + x^d} \right]$$

- Are there regularities in dose-response shapes we can take advantage of?
- Are there features of dose-response data, usually ignored, that we need to be aware of?

Dose-Response Scale and Shape



Data Sets

<u>Cluster A: Subchronic NTP</u>	<u>♂ rat</u>	<u>♀ rat</u>	<u>♂ mouse</u>	<u>♀ mouse</u>
BW	38	34	22	18
Rel. Liver weight	29	26	15	23
Kidney weight	18	15	5	6

<u>Cluster B: OP ester</u>	<u>♂ rat</u>	<u>♀ rat</u>
AChE	16	16

Cluster C: In vivo micronucleus test

MN frequency 139

<u>Cluster D: LLNA test</u>	<u>Rubber chem.s</u>	<u>Low mol. weight chem.s</u>
proliferation	15	10

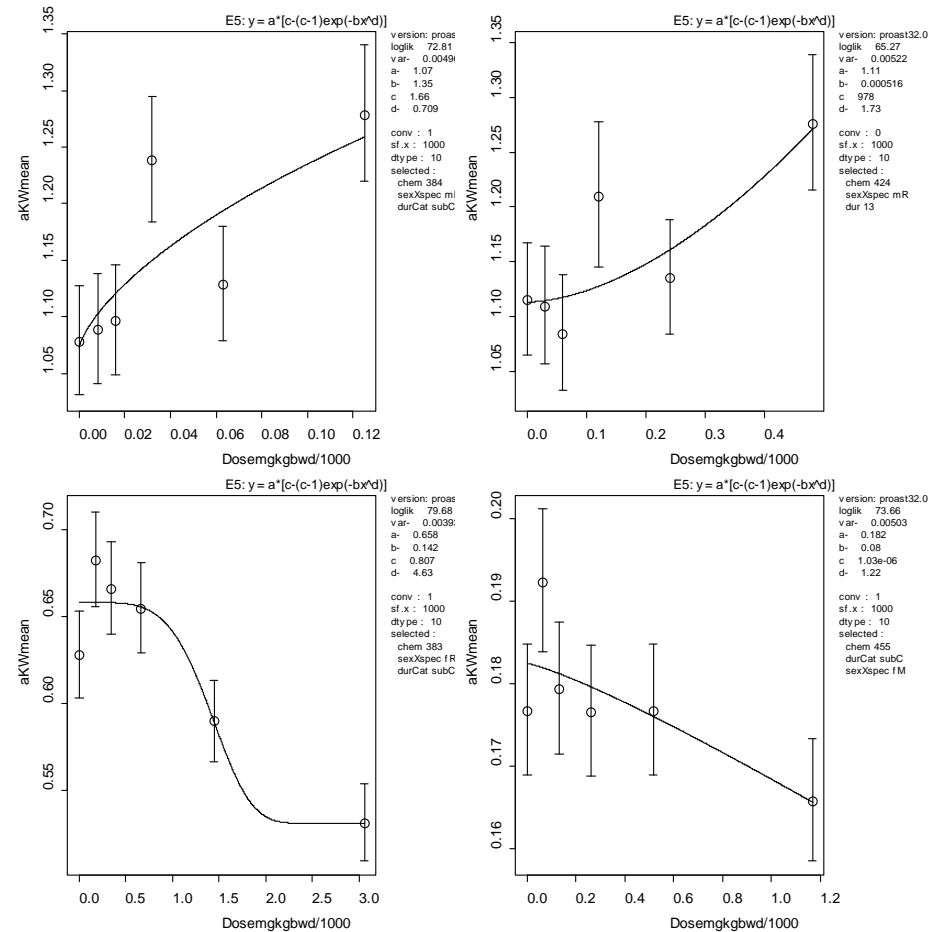
<u>Cluster E: WEC test</u>	<u>Lab 1</u>	<u>Lab 2</u>	<u>Lab 4</u>
Crown-rump length	13	13	12

Cluster F: In vitro micronucleus test

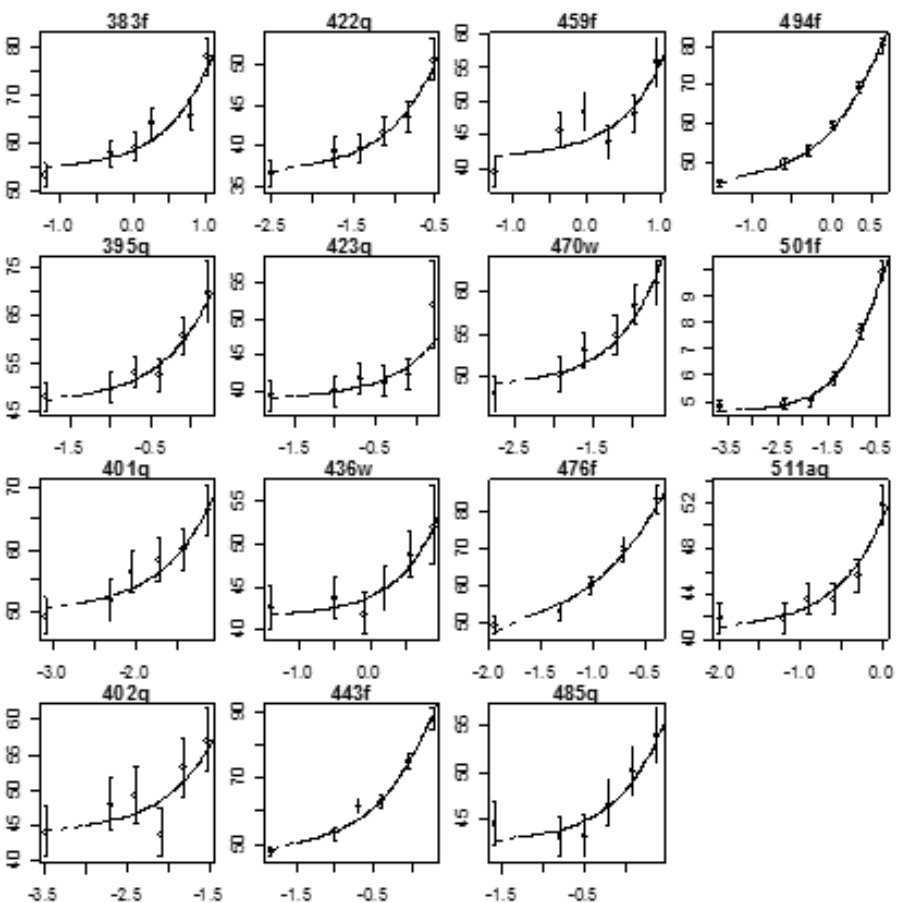
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Extra Variability at the Dose-Group-Level

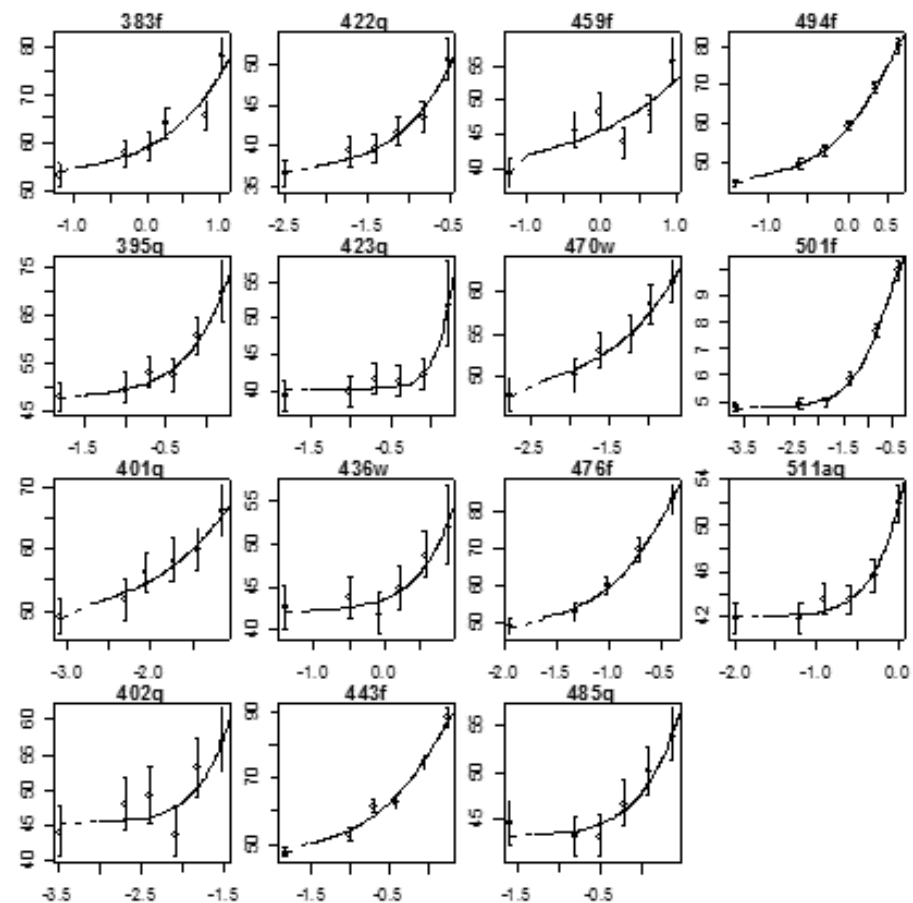
- Often invisible with just 3 or 4 doses, but
- Detectable when there are enough doses to visualize a trend
- **Confound parameter estimates and goodness of fit tests**



Shape is Consistent



a, b vary across chemicals



a, b, d vary across chemicals

Relative liver weight, male mice, subchronic NTP

Shape Parameters Fall in Narrow Ranges



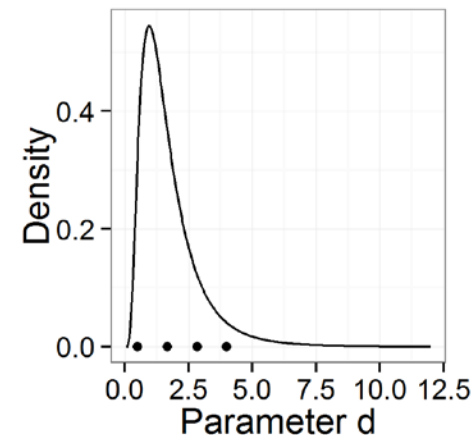
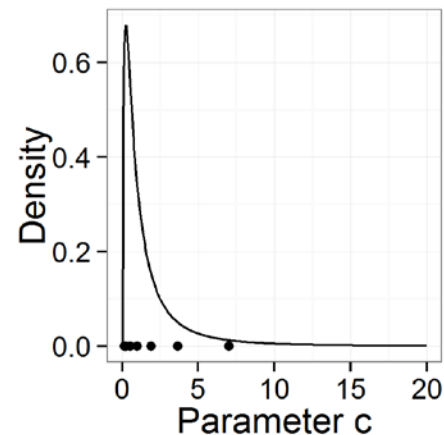
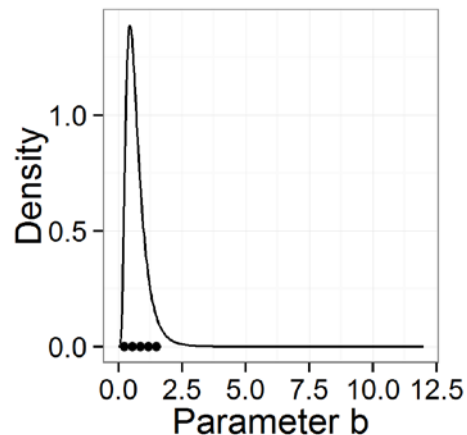
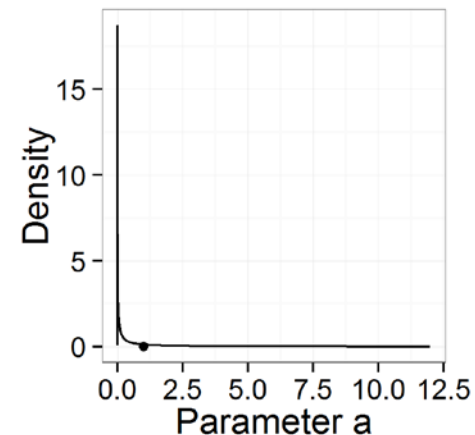
Conclusions:

- For continuous endpoints, standard four-parameter sigmoid models are generally adequate
- Extra variability at the dose-group level is common, and will confound parameter estimates, **especially in typical toxicological experimental designs (3 – 4 dose groups)**
- Model shape parameters appear to be narrowly constrained
- *BUT*, what about legacy datasets with only 3 dose groups?

Fitting a 4-Parameter Model to 3-Dose-Group Data

- Model parameters are not identifiable under conventional maximum likelihood estimation with only 3 dose groups
- Use Bayes with informative priors
 - Is coverage (measured conventionally) adequate?
 - Computationally feasible (effort involved, i.e., time)?
 - A preliminary simulation, with priors:

$$\text{Hill model: } m_g(y) = a \left[1 + (c - 1) \frac{x^d}{b^d + x^d} \right]$$



Simulation Provisional Summary

- Median time/dataset: 1.6 sec; 99% of times < 11.3 sec.
- Overall coverage of nominal 90% BMD CI: 85%
- Coverage varies considerably over the set of conditions – any given BMD CI may be very long, or very short.
 - Hypothesis: nominal overall coverage depends on the priors really characterizing the distribution of parameter values likely in real world applications
- Some questions:
 - How informative do priors need to be to get answers?
 - Can we better pick priors to reduce the variability in coverage?

Further Thoughts and Future Work:

- Model uncertainty for continuous variables is well characterized by the parameter uncertainty from fitting 4-parameter sigmoid models.
- More generally, we should systematically explore the variety of models needed to describe data sets, keeping in mind that we need unusually large studies to do this.
- Future model development should incorporate approaches for handling dose-group-level extra variability and informative priors.
- Future guidance on experimental design for toxicology data should be aimed at better estimating dose-response curves, taking into account the (probably inevitable) presence of dose-group-level extra variation.