Low-dose Extrapolation Models for Reliable Human Health Assessment

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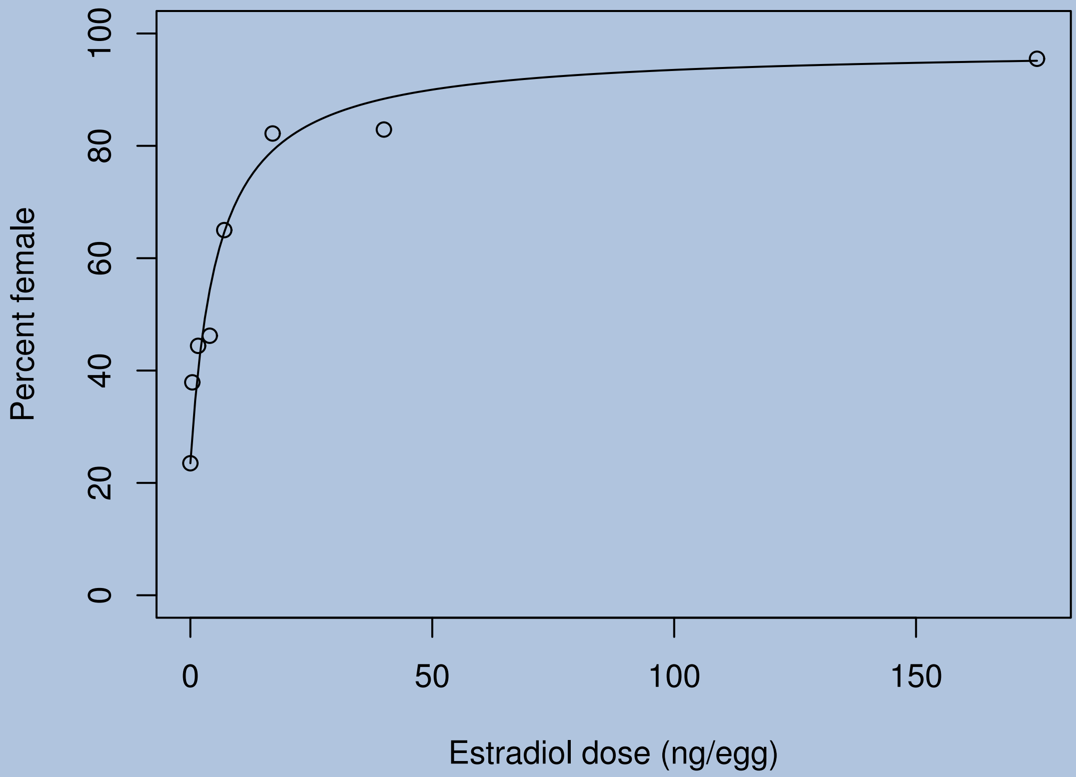
Toxic chemicals in the food chain

- Sources: Pesticides, manufacturing waste, and microbes
- At high concentrations are dangerous to human health
- Low concentrations are found in food
- At low concentrations effect is difficult to quantify

Dose-response modeling



Fitted with Michaelis-Menton enzyme kinetic model
Data Source: Environ Health Perspect 107:155-159 (1999)

Low-dose extrapolation models

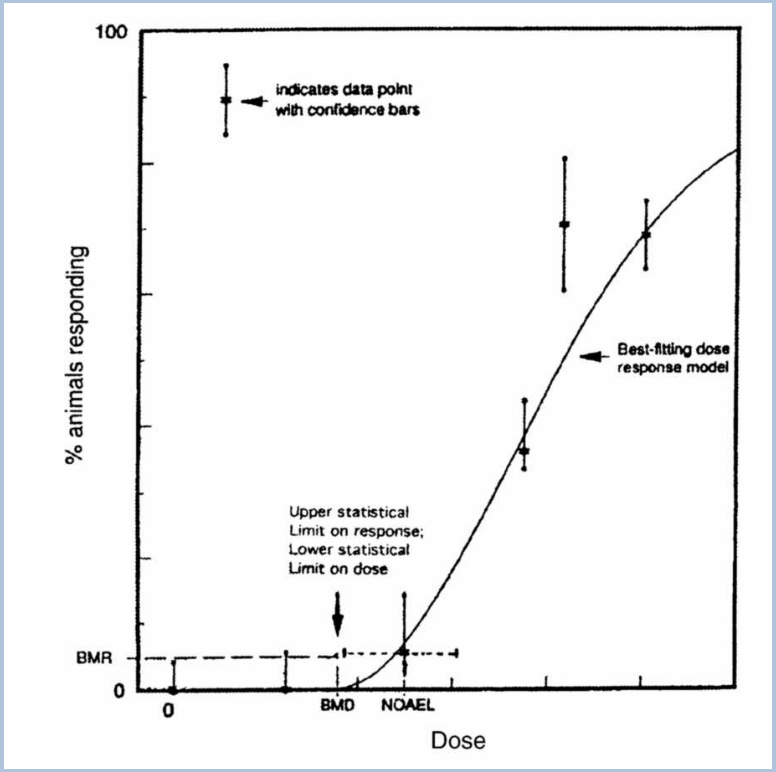


Figure from: Food and Chemical Toxicology 40: (2002) 283–326

Building a low-dose response model

1. Add uncertainty to point estimates of the response.
2. Select the appropriate function or functions to model response.
3. Compute the set of parameters which is consistent with the observed data.
4. Use the parameter set and original function to extrapolate to low-doses.

Accurate estimation of parameters for models is difficult

- Translation of a model parameter to an actual measurement is difficult.
- Measurements are indirect.
- Measurements are made with finite precision instruments.

There are ways to reduce measurement uncertainty but it cannot be entirely eliminated.

A fixed-error model of uncertainty

Let x denote the exact value of a measurement. $x \pm \epsilon,$ where ϵ is $\frac{1}{2}$ the measurement uncertainty, are bounds on the measurement. Because x is not known we have an interval denoted: $[a, b],$ where $a \leq x \leq b$.

Interval arithmetic

addition

$$[a, b] + [c, d] = [a + c, b + d]$$

$$[5, 8] + [1, 2] = [6, 10]$$

subtraction

$$[a, b] - [c, d] = [a - d, b - c]$$

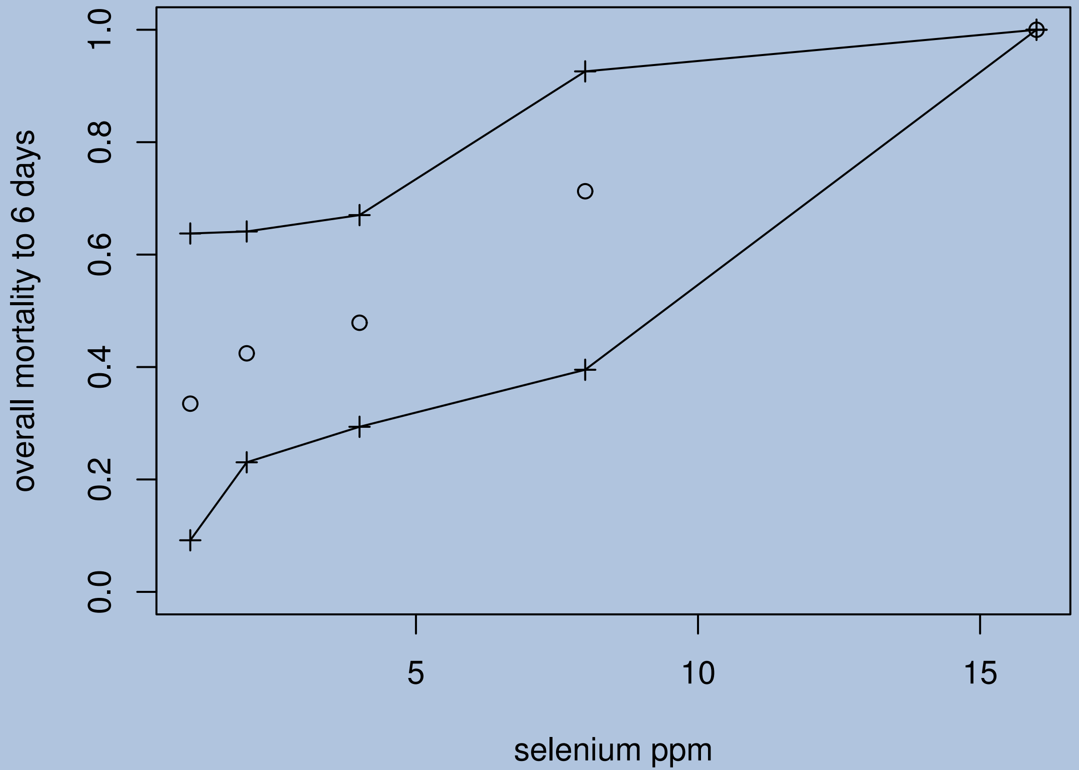
$$[10, 11] - [5, 6] = [10 - 6, 11 - 5] = [4, 6]$$

multiplication

$$[a, b] \times [c, d] = [\min(ac, ad, bc, bd), \max(ac, ad, bc, bd)]$$

$$[-3, -1] \times [-1, 2] = [\min(3, -6, 1, -2), \max(3, -6, 1, -2)] = [-6, 3]$$

Overall mortality of 6 day-old ducks



Assume linear response

For low doses ($d \leq 8$ ppm) assume:

$$\text{response} = m \times \text{dose} + b.$$

SIVIA (*Set Inverter Via Interval Analysis*)

Define:

$$F(\mathbf{X}) = \mathbf{Y} = \{f(\mathbf{x}) : \forall x \in \mathbf{X}\}.$$

Given the set $\mathbf{Y}$:

$$F^{-1}(\mathbf{Y}) = \mathbf{X} = \{f^{-1}(y) : \forall y \in \mathbf{Y}\}.$$

- Do not need f^{-1} to be defined just an interval extension of f.
- Requires an initial search box $\mathbf{x} \supseteq F^{-1}(\mathbf{Y})$.
- Computes a union of interval boxes which contain $F^{-1}(\mathbf{Y})$.

SIVIA based on inclusion test t

1. if $t(\mathbf{x}) = 0$; return;
2. if $t(\mathbf{x}) = 1$ then $\underline{\mathbf{X}} = \underline{\mathbf{X}} \cup \mathbf{x}$ and $\overline{\mathbf{X}} = \overline{\mathbf{X}} \cup \mathbf{x}$; return;
3. if $\max(\text{width}(\mathbf{x})) < \epsilon$ then $\overline{\mathbf{X}} = \overline{\mathbf{X}} \cup \mathbf{x}$; return;
4. $\text{SIVIA}(L(\mathbf{x}))$ and $\text{SIVIA}(R(\mathbf{x}))$

$L()$ and $R()$ bisect $\mathbf{x}$ into left and right halves.

$\underline{\mathbf{X}}$ and $\overline{\mathbf{X}}$ are the union of interval vectors which bound the solution set.

Simplified from Jaulin et al. 2001.

Parameter bounding

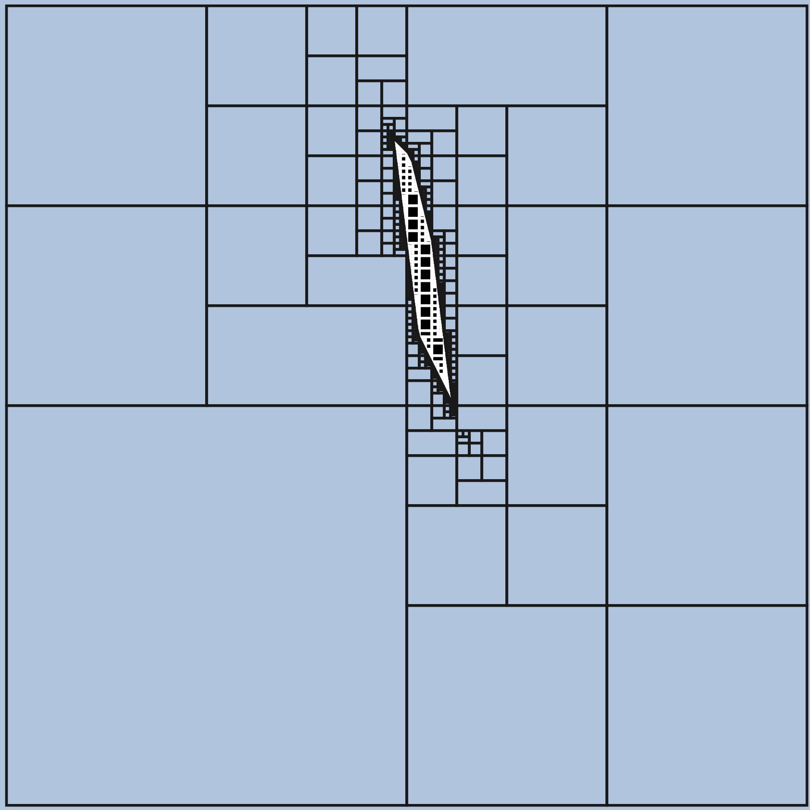
Computes bounds on the set $F^{-1}(\mathbf{Y})$ which is consistent with the response $\{\mathbf{y}_1, \ldots, \mathbf{y}_n\}$.

Define:

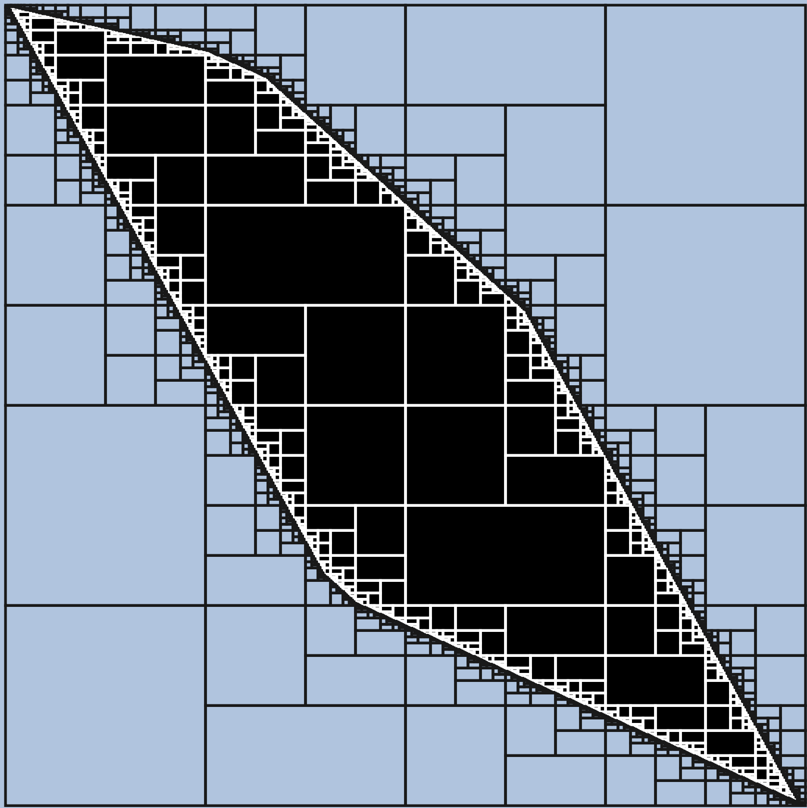
$$t_p(\mathbf{x}) = \begin{cases} \text{if } f(\mathbf{x}, d_i) \notin \mathbf{y}_i \text{ then } 0 \\ \text{if } f(\mathbf{x}, d_i) \in \mathbf{y}_i \text{ then } 1 \\ \text{else } [0, 1] \end{cases},$$

where $\mathbf{y}_i$ is the measured response at dose d_i.

Posterior parameter set



Up-close



SIVIA stats

- $\epsilon = 0.001$
- Initial search box: $[-1, 1] \times [-1, 1]$
- Outer approximation of the set $(\overline{\mathbf{X}})$ composed of 3149 boxes:
  $[-0.035, 0.118] \times [-0.003, 0.673]$
- Inner approximation of the set $(\underline{\mathbf{X}})$ composed of 1463 boxes:
  $[-0.034, 0.116] \times [0.002, 0.670]$
- Total number of boxes excluded 1602.

Predicting the bounds on response from dose

$$\mathrm{envelope}(F(\mathbf{x}_j, \mathbf{d})); \forall \mathbf{x}_j \in \overline{\mathbf{X}}$$

where $\mathbf{d}$ is an interval dose value.

Bounds on the response

For $\mathbf{d} = [0, 1]$ ppm. The bounds on the response are $[-0.003, 0.69]$ overall mortality.

Advantages and Limitations

- Accounts for measurement error
- Allows selection of multiple models
- SIVIA complexity
- Outliers: $\emptyset$