

NTP's Proposed Approach to Curve Fitting and Determination of Feature Potency

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Expert Panel Meeting on the Peer Review of Draft NTP
Approach to Genomic Dose-Response Modeling
October 24, 2017



Fitting Features to Dose-Response Curves

- Features are fit to 9 parametric continuous models
 - Derived from US EPA's BMDS software
 - Hill, Power, Linear, Poly2,3, Exp2,3,4,5
- $BMR = 1.349 \times SD$ of controls
 - Approximates 10% shift area under the normal distribution
- 2 step process for best model selection
 - Nested Chi Square – Best Poly model
 - Lowest AIC
- From the best fit model a BMD, BMD_L and BMD_U is determined

BMD Analysis

Data Options
Expression Data: Multiple Data Sets

running Poly3 Model: 534/2249

Continuous Models

| | | | |
|--|--|--|---|
| <input checked="" type="checkbox"/> Exp 2 | <input checked="" type="checkbox"/> Exp 3 | <input checked="" type="checkbox"/> Exp 4 | <input checked="" type="checkbox"/> Exp 5 |
| <input checked="" type="checkbox"/> Linear | <input checked="" type="checkbox"/> Poly 2 | <input checked="" type="checkbox"/> Poly 3 | <input type="checkbox"/> Poly 4 |
| <input checked="" type="checkbox"/> Hill | <input checked="" type="checkbox"/> Power | | |

Parameters

Maximum Iterations: 250
Confidence Level: 0.95
 Constant Variance

BMR Factor: 1.349 (10%)
Restrict Power: ≥ 1

Model Selection

Best Poly Model Test: Nested Chi Square
P-Value Cutoff: 0.05

Flag Hill Model with 'k' Parameter < 1/3 of Lowest Positive Dose

Best Model Selection with Flagged Hill Model: Select Next Best Model with P-Value > 0.05

Modify BMD of flagged Hill as Best Models with Fraction of Minimum BMD: 0.5

Multiple Threads

Number of Threads: 10

Start Cancel



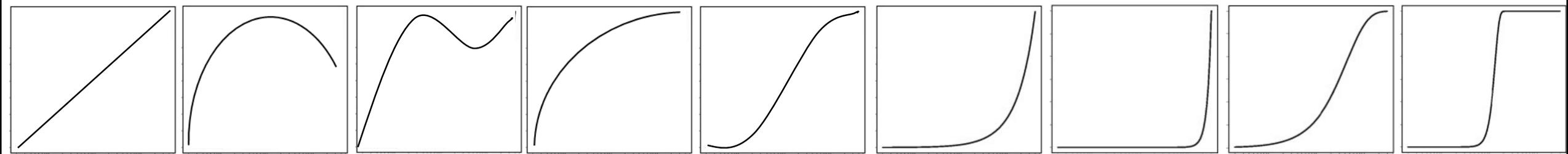
Why Parametric Models?

- Common standard for modeling toxicity data for use in risk assessment
- Simple to understand and therefore easy to translate
- Computationally affordable
- We don't anticipate seeing significant value added by using non-parametric models because of the diversity of model types we are using



Why 9 models?

- For any given feature there is not a pre-defined response model
 - Due to the complexity associated with control of gene expression
- The model that fits the data best will provide the most accurate estimate of the BMD for that feature



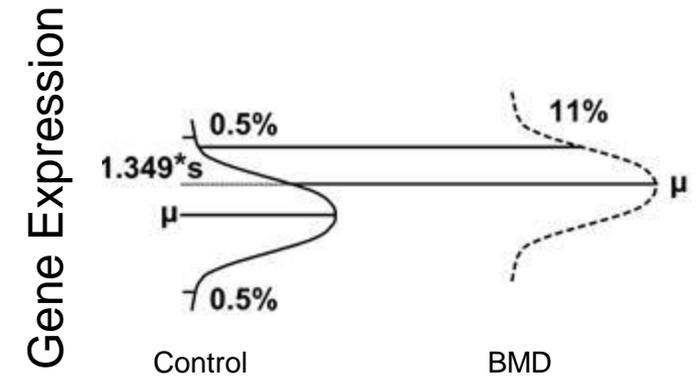
Why use a 2 Step Model Selection?

- Prefer to use a statistical method when possible such as in the case of the nested poly models, because it is a more rigorous test for comparison of fit compared to using AIC



Why use a Benchmark Response of 1.349 x SD?

- BMR = Pre-defined level change in measured feature that is used to determine the BMD
- Typically 10% response rate over control in toxicity studies
- BMR = 1.349 x standard deviation at control
- Assumptions
 - Normal distribution of intensities or counts in the control and treated groups
 - Changes in expression could occur in either tail, with a 1% chance of that occurring in the absence of exposure (0.5% in each tail)
- A shift in the mean of the treated distribution by 1.349*SD is the amount required to shift the treated distribution by 10% relative to the control distribution



Adapted from Thomas et. al., Tox Sci, 2007



- Parametric models
- Fit 9 models
- A BMR of 1.349*standard deviation at control
- Two step process for model selection
- Other variables to consider
 - EC10 vs. BMR?
 - Model averaging?
 - Potential for overfitting?
 - More models and less models?
 - BMD outside the dose range, use grid search to identify value?
 - Spline-based metaregression?