NTP
National Toxicology Program

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

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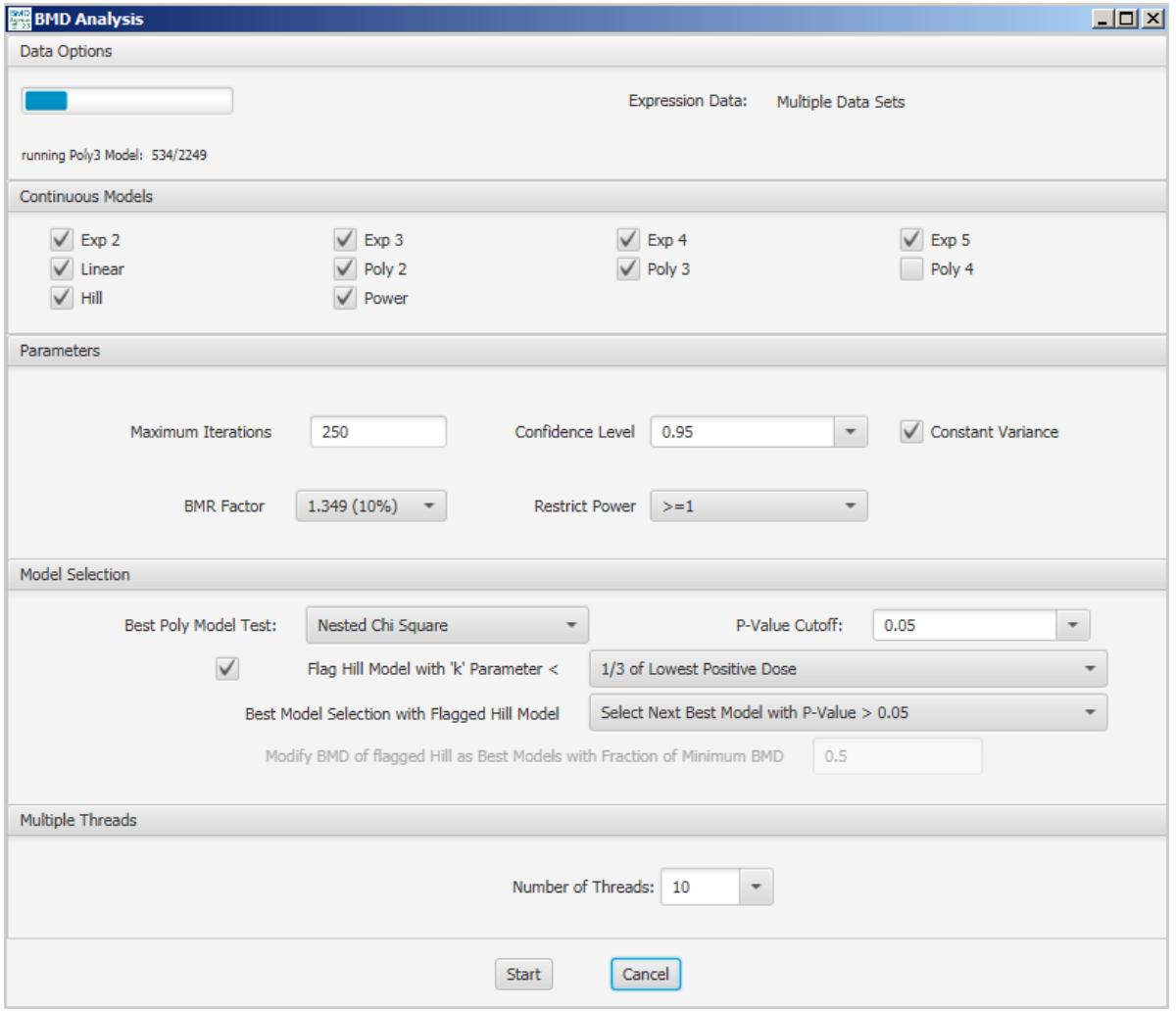
Fitting Features to Dose-Response Curves

- 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 x 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

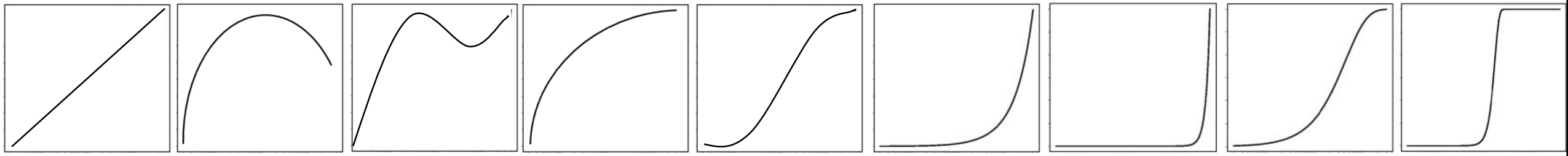


Why Parametric Models?

- 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

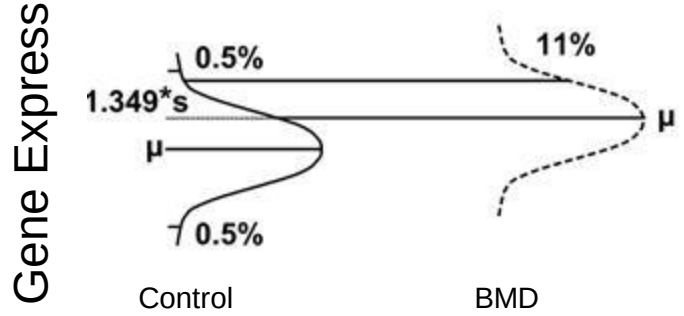


Why use a 2 Step Model Selection?

- 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

Points to Consider

- 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?