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.
• 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
• 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

Why use a Benchmark Response of 1.349 x SD?

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?