Bayesian analysis of analyte data

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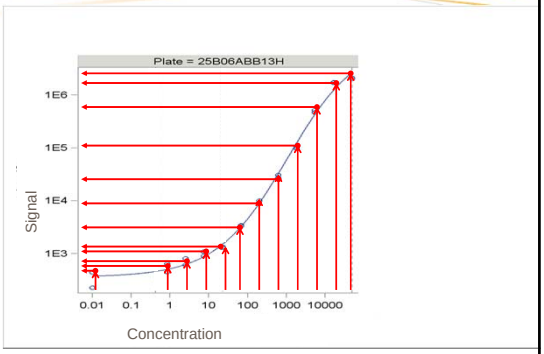
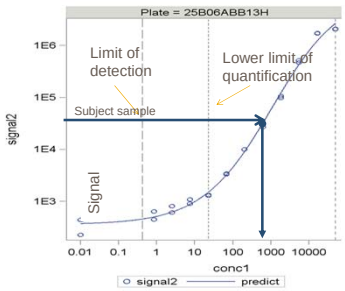
Background

- Ligand binding assays for analyte quantification of biomarkers
  - Use of a calibration curve to estimate the response of interest e.g concentration of an analyte
  - Examples :IL5 protein, glucose, histamine
- Bayesian approach
  - Incorporates all uncertainty
  - Focus on concentrations below the 'lower level of quantification'

Defining a standard curve



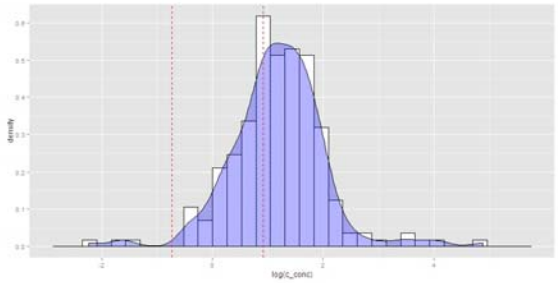
Using a standard curve



Note:

- See FDA recommendations on assay validation, etc
- LLoQ is the lowest std concentration which meets set criteria on accuracy and precision
  - Precision based on CV of the unlogged back calculation std concentration data
  - accuracy based on the estimated back-calculated std concentration over the true std concentration
  - Values below level of LLoQ set to LLoQ/2

Example



Modelling

- Typically something like a 4 parameter logistic model:

$$\mathrm{E}(y \mid x, \beta) = g(x, \beta) = \beta_1 + \frac{\beta_2}{1 + (x/\beta_3)^{-\beta_4}},$$

- Assume y Gaussian
- Sensible to make beta random effects eg to allow plate effects
- May allow variance to depend on E(y|x,beta)

Bayesian approach

- Above models P(signal | concentration)
- Applying Bayes rule,
  - P(concentration | signal) = P(signal | concentration).P(concentration) / P(signal)
- Specifying a prior for concentration allows inference about concentration conditional on signal
- If model is correct, this properly reflects uncertainty about concentration
  - No need to discard/adjust data below LLQ/LLD
  - Inference (eg on treatment effects) can be done within the same model and allows for uncertainty about concentration
- Not new: see eg Gelman et al, Biometrics 2004
- Doesn't seem to be much applied in practice
  - Here show some examples

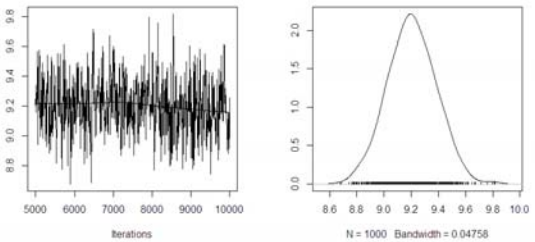
Priors

- 'Default' weakly informative priors on regression parameters/variance components
- For experimental concentrations:
  - conc.exp[i] ~ dlnorm(mu, tau)
  - 'Default' weakly informative priors on mu, tau
  - Typically mu will be a linear predictor incorporating parameters which are objects of inference

Computation: WinBUGs

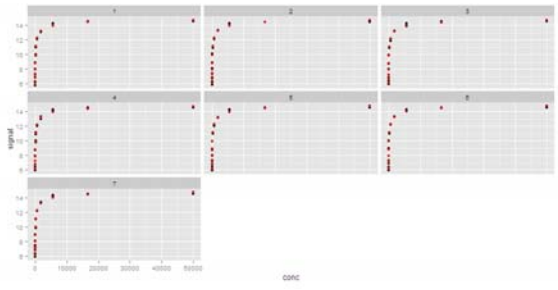
```
model{
  for (i in 1:m.stand){
              signal.stand[i]  ~ dnorm(mu.stand[i], tau.e)
              mu.stand[i] <- d[plate.stand[i]] + a[plate.stand[i]] / (1 +
pow(conc.stand[i] / c[plate.stand[i]],-b[plate.stand[i]]))
              }
.........

 for (i in 1:m.exp){
    signal.exp[i]  ~ dnorm(mu.exp[i], tau.e)
    mu.exp[i] <- d[plate.exp[i]] + a[plate.exp[i]] / (1 + pow(conc.exp[i] /
c[plate.exp[i]],-b[plate.exp[i]]))
   conc.exp[i] ~ dlnorm(mu.prior, tau.prior)
#    conc.exp[i] ~ dunif(0,500)
  }
```

Convergence

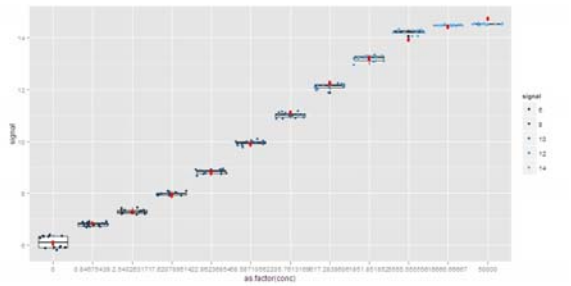


- Good convergence: total run time typically seconds/minutes
- Need good initial values if using default (slice sampler)
  - Initial fit to standards or via a simpler model

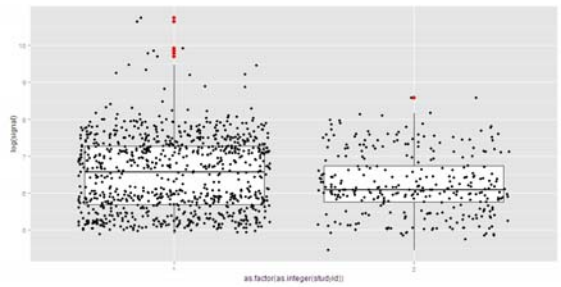
Fit to standards



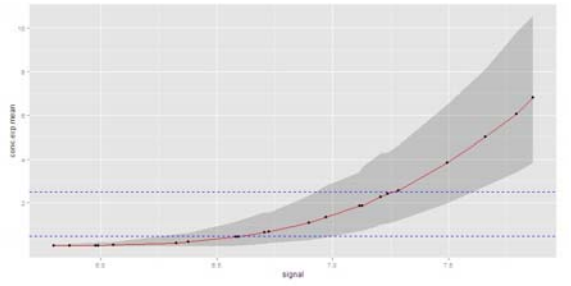
Fit to standards



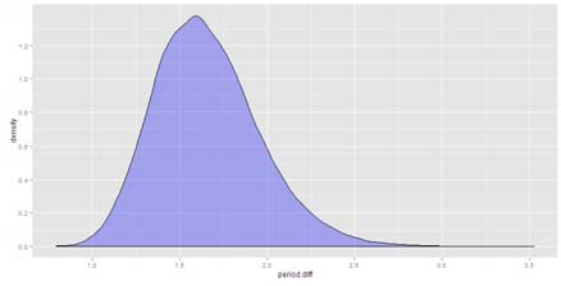
Experimental data



Fit to experimental (study 2)



Period effect



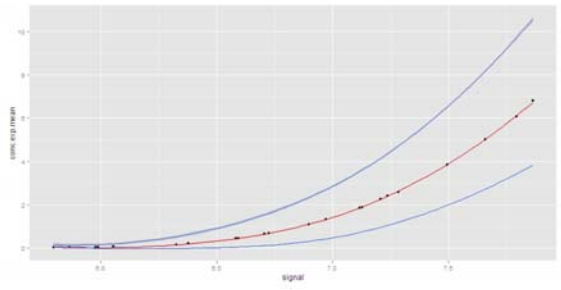
Discussion

- LLQ/LLD are often unnecessarily conservative and may discard valuable data
  - Check modelling assumptions
- Bayes approach works well
  - Care with starting values
  - WinBUGs adequate, other approaches may be faster
- Allows easy extension
  - Replace N() with t() to robustify
  - Model mean-variance relationships
  - Etc
- Challenge persuading colleagues to use this approach?

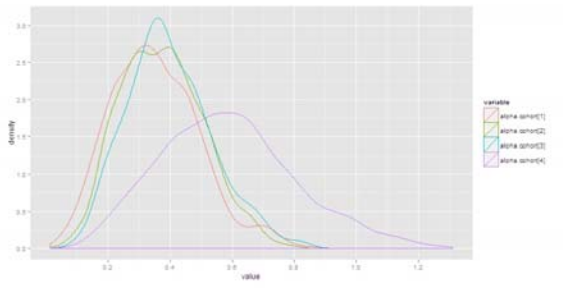
Ethics

- "The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents"

Fit to experimental (study 2)



Cohort effects



Fit to experimental (study 2)