Risk-based Parallelism test for Parallel Curve Assays

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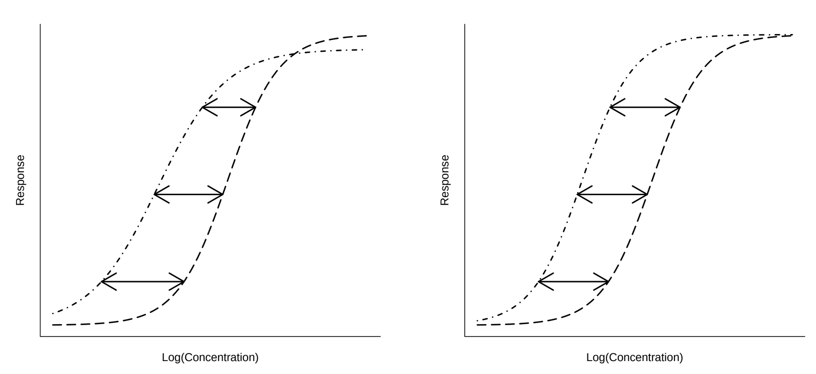
NonClinical Biostatistics Conference 2019 | New Brunswick, NJ, USA

1. Context

The Relative Potency (RP) of a biological product is estimated from a concentration or log(concentration)-response function, as the horizontal difference between sample and standard curves.



Four parameterlogistics (4PL) :

$$y = yMax + \frac{yMin - yMax}{1 + \left(\frac{x}{C_{50}}\right)^H}$$

Parallelism between the functions is required to compute the RP. Curves must share similar **upper asymptotes**, **range between asymptotes** and **slopes**.

Current approach:

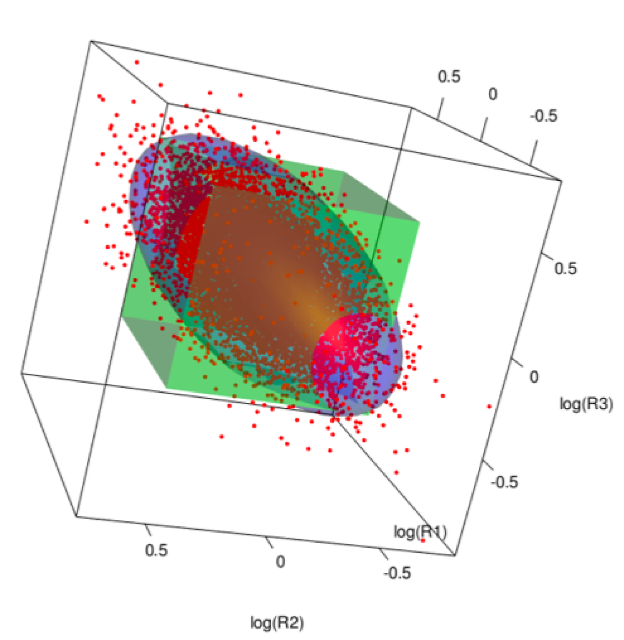
- Calculate
  - $r_1 = \frac{\widehat{yMax_1}}{\widehat{yMax_2}}$
  - $r_2 = \frac{\widehat{yMax_1} - \widehat{yMin_1}}{\widehat{yMax_2} - \widehat{yMin_2}}$
  - $r_3 = \frac{\left(\widehat{yMax_1} - \widehat{yMin_1}\right)\widehat{H_1}}{\left(\widehat{yMax_2} - \widehat{yMin_2}\right)\widehat{H_2}}$
- Declare parallelism if $D_{Lk} \leq r_k \leq D_{Uk} \quad \forall k \in 1, 2, 3$

Challenges with this test:

1. The ratio estimates **in case of true parallelism** are correlated.
   ⇒ 'Empty space' in the 3D acceptance zone. **Marginal limits are not adapted to the problem.**
2. How to chose limits D_{Lk} and D_{Uk} ?

2. Solution: Ratio correlation

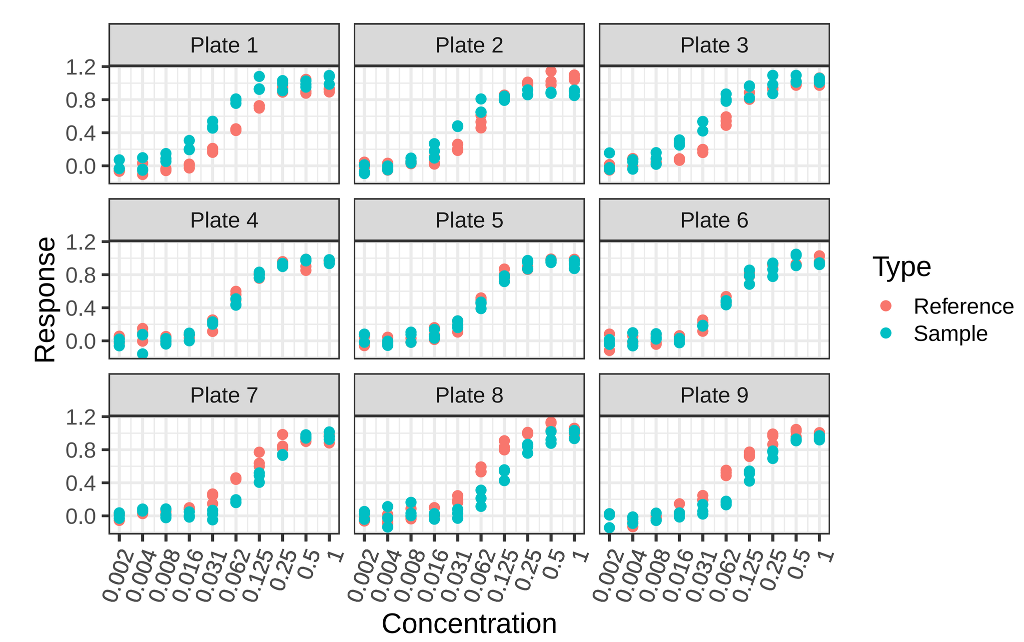
- Assess if the new set of $\log(\hat{r}_k)s$ are contained within the **ellipsoid** around the joint posterior distribution of $log(r_k)s$ in case of **true parallelism**. Test:
- $\hat{\lambda}^T \hat{\Sigma} \hat{\lambda} \leq q_{\alpha,3}$ where $\hat{\lambda} = \log[\hat{r}_1, \hat{r}_2, \hat{r}_3]$, $\hat{\Sigma}$ is the VCV matrix of the posterior distribution of λ, and $q_{\alpha,3}$ is the $100\alpha^{th}$ percentile of the χ^2 distribution with 3 df.



3. Solution: Acceptance limits

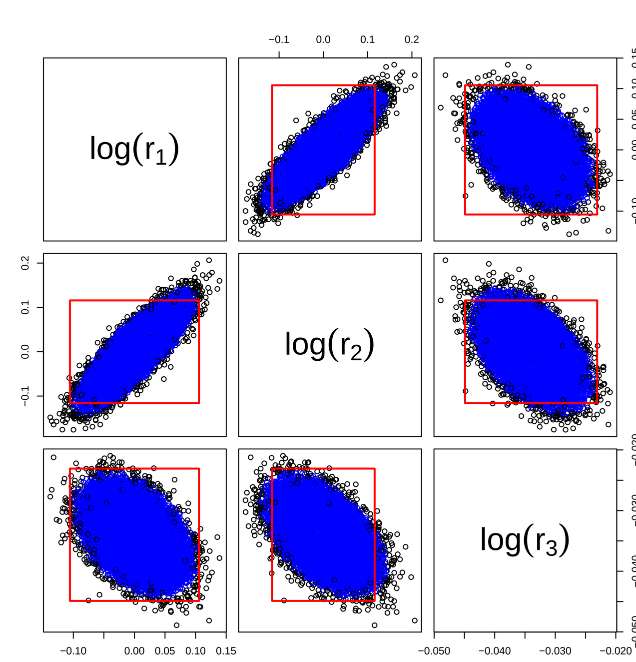
- **USP 1032 proposal :** use historical data to develop equivalence margins ⇒ **Comparison of the reference product to itself**.
- **Problem: historical data not always available, and generating plates full of reference product can be very expensive!**

Using a **case study**, consider a **Bayesian** alternative to reference-to-reference comparison. We have a qualification set of 9 plates with each a **reference curve** and a **test curve**.



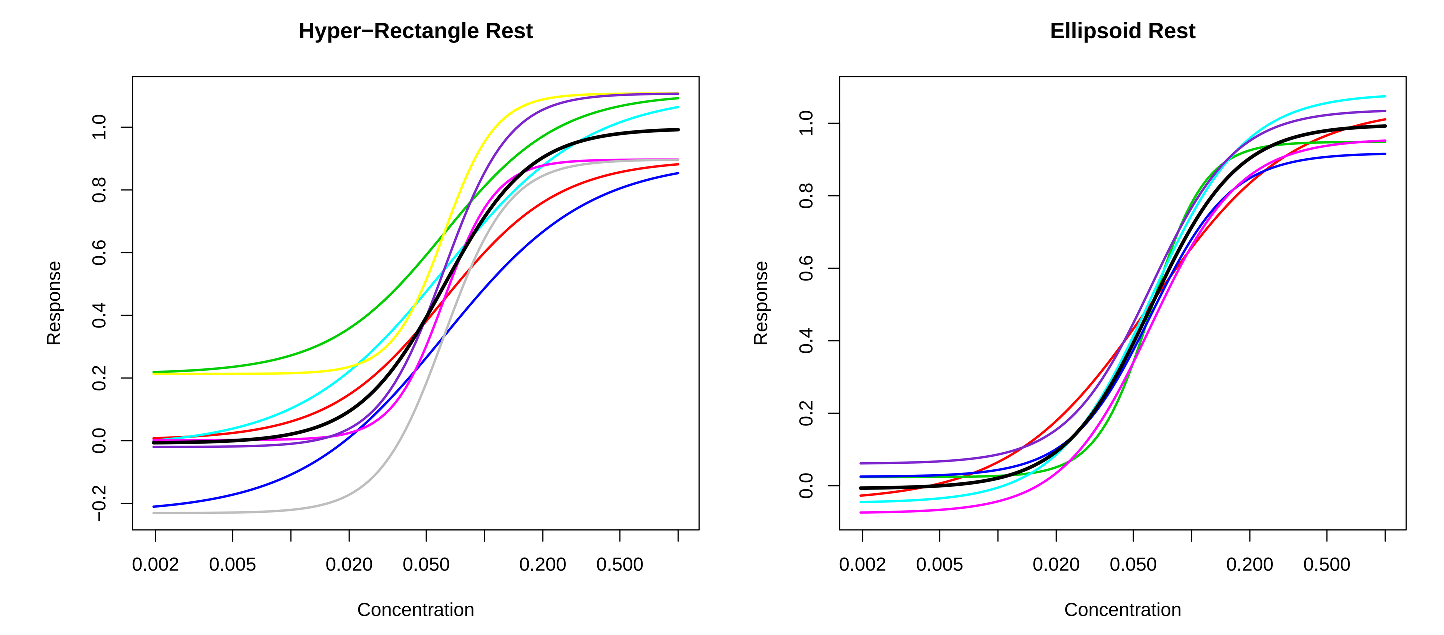
- Using only the reference curves, fit the following model with Stan, using flat **prior distributions**
  $y = yMax_j + \frac{yMin - yMax_j}{1 + \left(\frac{x}{c_50}\right)^H} \quad j = 1, \ldots, 9$: a plate-to-plate variability affects the upped asymptote.
- From the **joint posterior distribution** of the curve parameters and variance components, generate $10,000$ plates with two **reference curves**.
- Calculate $\hat{\lambda}$ for each plate to obtain the **joint posterior distribution of the log ratios in case of true parallelism** (noted Λ).
- Calculate $\hat{\Sigma} = VCV(\Lambda)$ for the ellipsoid test.
- For a chosen **lab risk** α of rejecting truly parallel curves - here 1% - use Nelder and Mead to find the smallest hyper-rectangle that contains $100(1-\alpha)\%$ of Λ.

This figure shows Λ. The **red lines** are the calculated limits for the hyper-rectangle, and the **blue points** show the posterior draws inside the 99% coverage ellipsoid.



4. Test comparisons

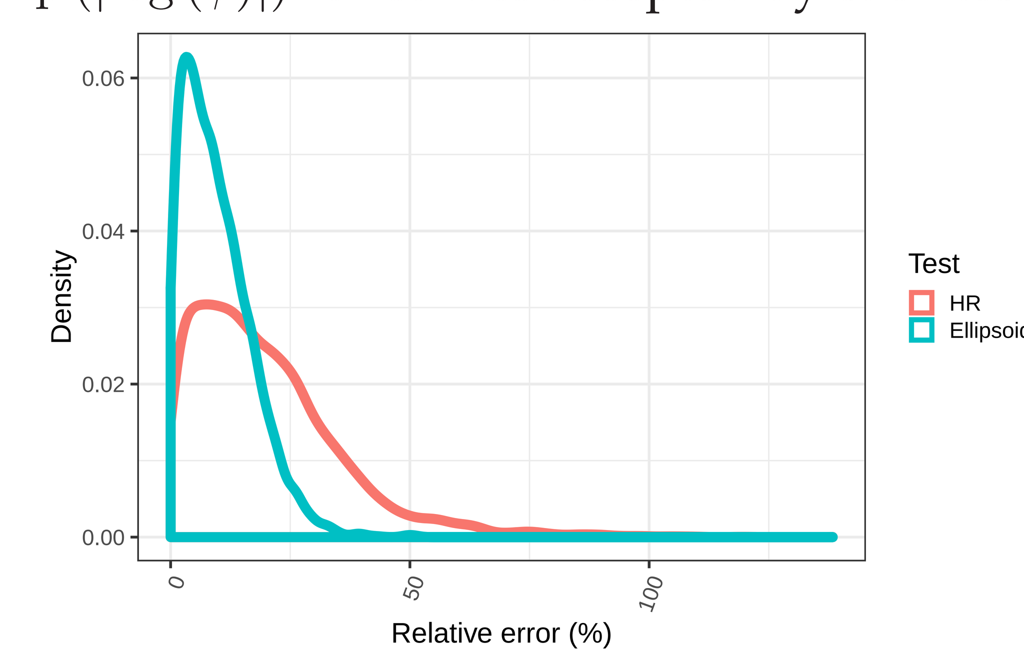
The figure below shows the worst possible curves accepted by each test. The reference is the black curve and the colored curves are the samples.



Both test control the **lab risk**. We want to assess the **consumer risk**. To do so, we simulate 10,000 reference and sample curves. For each pair of curves, we calculate

$$\phi = \frac{ObservedRP}{TrueRP}$$

The figure below shows the density of $\exp(|\log(\phi)|)$ for curves accepted by each test.



5. Discussion

- MCMC simulation are a cost-efficient alternative to reference-to-reference comparison.
- The hyper-rectangle test can lead to very unsimilar curves to pass parallelism and therefore a high relative error in RP estimation.
- The ellipsoid test also controls for lab risk, while better managing the consumer risk than the hyper-rectangle test.
- This poster purposely does not present parallelism tests as classic hypothesis tests. Contact author for explanation.
- Other tests for parallelism exists, this poster doesn't mention them for simplicity.

Selected References

1. Yang et al., "Implementation of Parallelism Testing for 4PL Model in Bioassays", *PDA*.
2. USP < 1032 >, "Design and Development of Biological Assays", 2010.
3. Kruschke, *Doing Bayesian Data Analysis*. Academic Press, 2014.

Acknowledgement

Pierre Lebrun, Bruno Boulanger, Tara Scherder