Issues in the Statistical Inference of Stability Data

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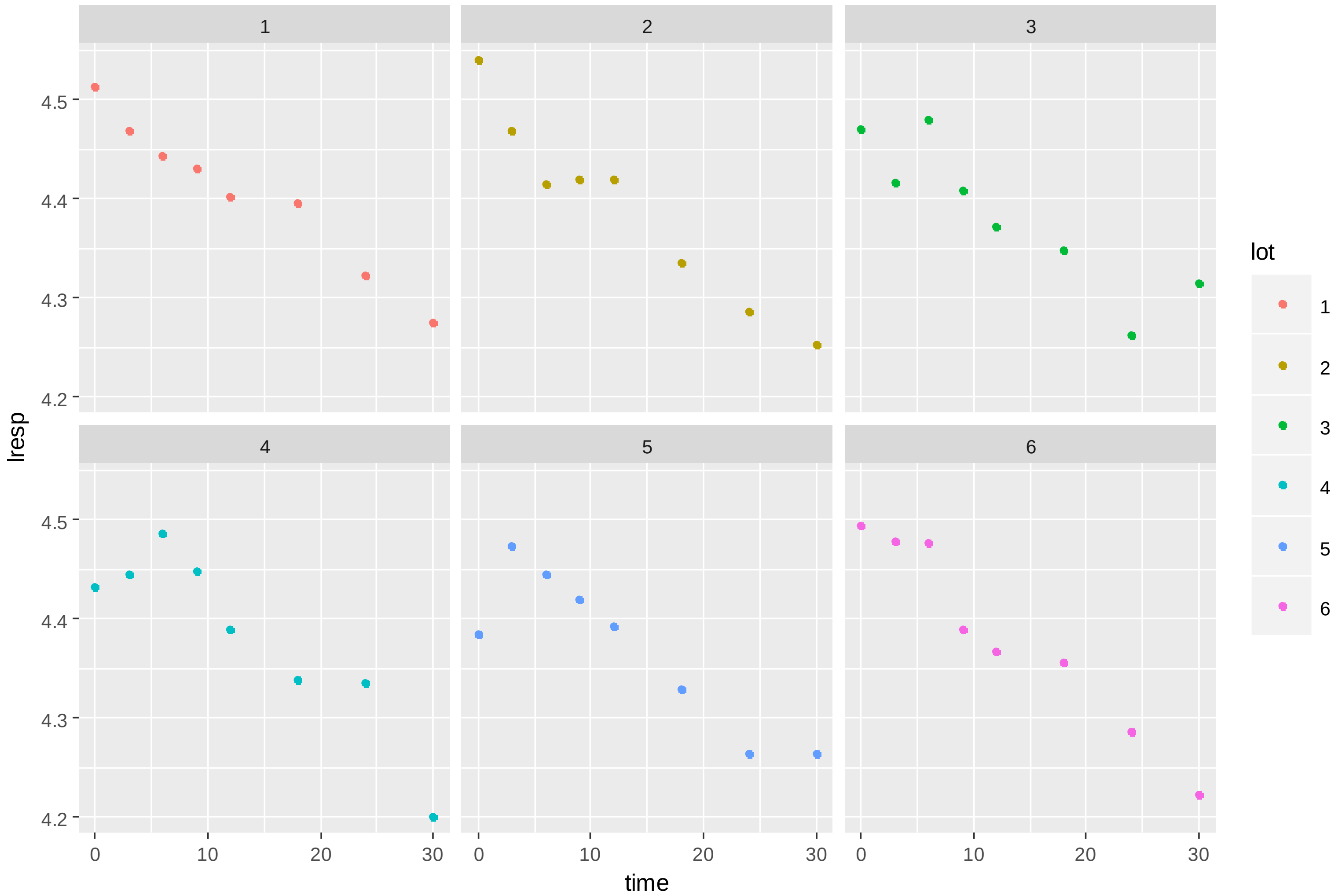
Outline

- Example stability datasets
- The past
- Product release mixed model

Example 1: $\sigma_b = 0.001$

- Simulated data based on real results
- Low variability among slopes
- Response is on log scale
- Overall slope is -0.008
- Slope variability (Std dev) is 0.001

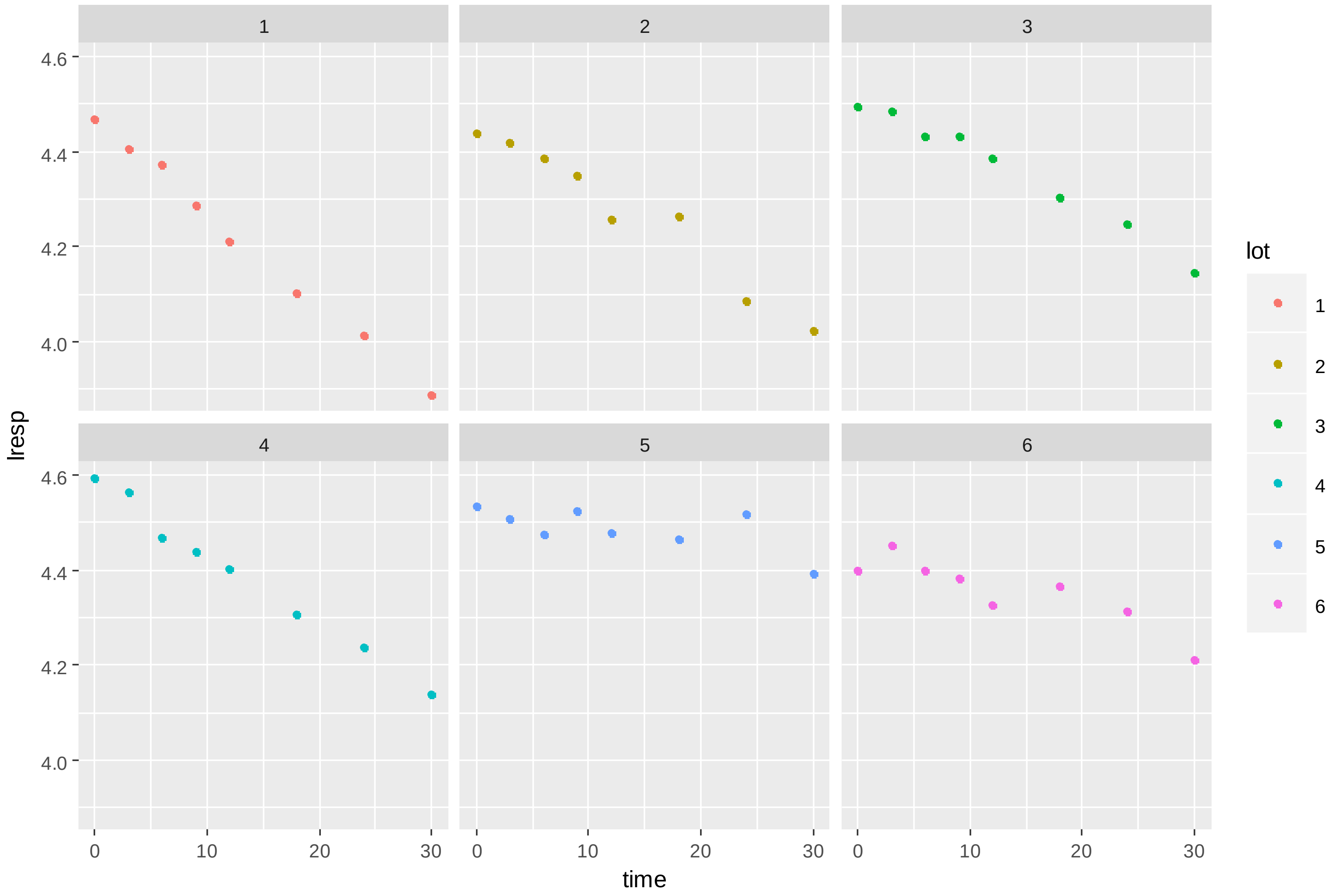
Example 1:



Example 2: $\sigma_b = 0.006$

- Higher variability among slopes
- Response is on log scale
- Overall slope is -0.008
- Slope variability (Std dev) is 0.001

Example 2



Past Recommendations

- Fit a fixed effects model including an intercept and slope for each lot.
- Using $p >= 0.25$ perform significance tests to suggest that a common slope and intercept could be used instead.
- If $p >= 0.25$ then calculate the shelf life limit combining all lots and using a single slope and intercept.
- If $p < 0.25$ then calculate the shelf life for each lot and use the most conservative result.
- The shelf life is estimated by the intersection of the lower specification limit and the confidence interval about the regression line.

Example 1

- Applying these methods to the data results in the following:

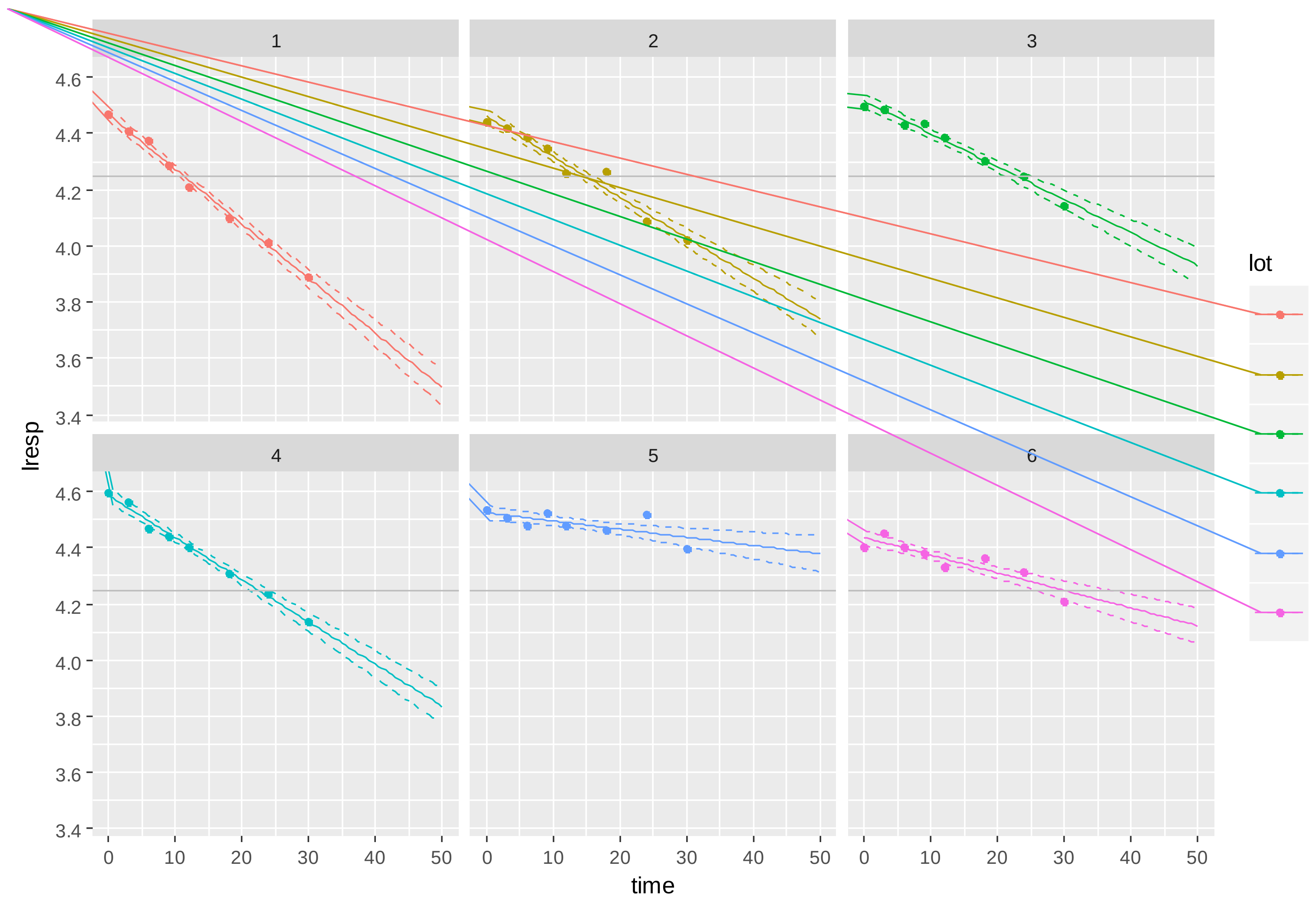
```
Model 1: lresp ~ 1 + time
Model 2: lresp ~ -1 + lot + time + lot:time
  Res.Df      RSS Df Sum of Sq      F Pr(>F)
1     46 0.045931
2     36 0.035710 10  0.010221 1.0304 0.4385
```

- Since p>0.25 for testing the lot by time interaction, we can fit a single slope and intercept for all of the lots.

Example 2:

```
Model 1: lresp ~ -1 + lot + time
Model 2: lresp ~ -1 + lot + time + lot:time
  Res.Df      RSS Df Sum of Sq      F    Pr(>F)
1     41 0.168441
2     36 0.026902  5   0.14154 37.881 2.271e-13
```

Example 2:



Problems

- Since $p<0.25$ then take the most conservative shelf life estimate from all of the lots.
- Results apply to the lots observed and not necessarily to future lots.
- Results are dependent on the observed intercepts
- Tests discriminate against assays with small variance
- Tests discourage the testing of more lots.

One Solution

- Use a model that addresses the problems
- The product release model with a variance component for slopes across lots.
- If the model accounts for the variability in slopes, do we still need to worry about testing slope equality?

Product Release Model

- Only use slopes and variances from the stability lots -- intercepts are not used.
- Incorporate the release limits and shelf life together in model.
- Mixed effects model

$$LL = MRP + t_1(\beta + b) - U,$$

where $U = z_{1-\alpha}\sqrt{\sigma^2 + t^2 V(\beta) + t^2 \sigma_b^2}$

Example 2:

- Fitting the Product Release Model to the data of Example 2 produces the following results:

MRP	slope	SDslopes	SEslope	sigma
4.2738	-0.01160843	0.005984652	0.002476125	0.02733637

Extension

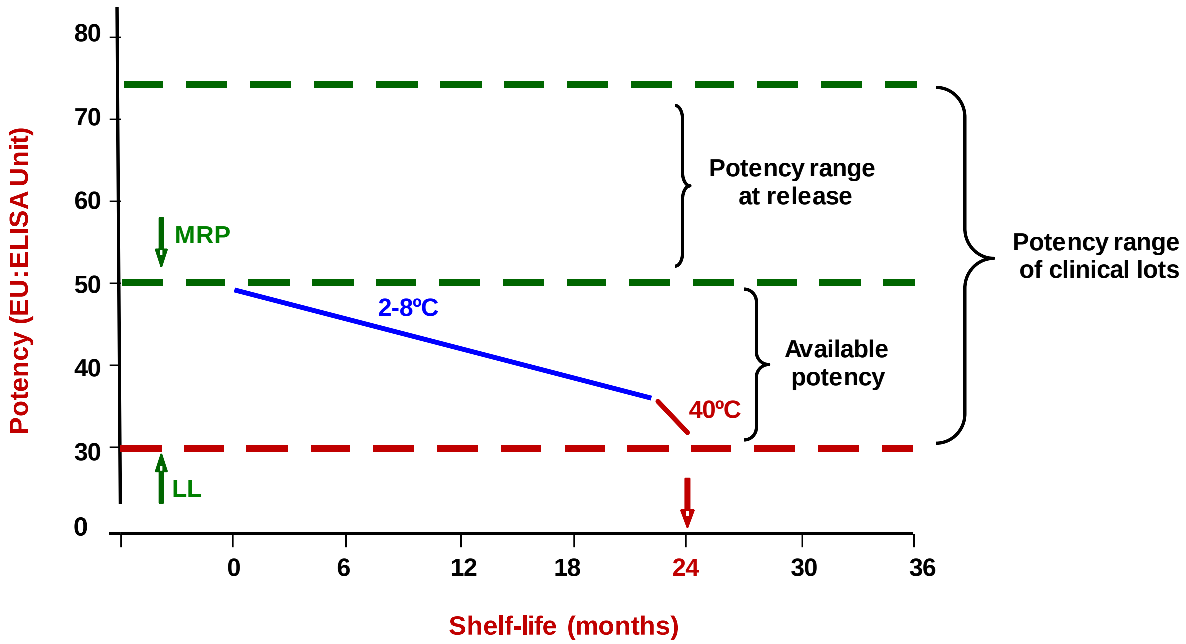
This can be extended to handle Extended Controlled Temperature Conditions similar to the WHO draft guidelines

$$LL = MRP + \sum t_i(\beta\_i + b) - U,$$

where $U = z_{1-\alpha} \sqrt{\sigma^2 + \sum t_i^2 V(\beta\_i) + \sum t_i^2 \quad} \sigma_{bi}^2$

WHO draft

- Example



Notes:

- If the model includes a random slope factor, then sigma^2 can be considered the assay variability.
- If a random slope factor is not included in the model, then sigma^2 must be estimated by the residual error and not just assay variability.
- Is it necessary to test the importance of the random slope factor? If it is included in the model when it is very small, then it will have little effect on the results.
- Since we are dealing with variance components, how many lots should be tested?

Summary

- Old ways of analysis had many drawbacks
- The Product Release mixed model addresses many of these drawbacks

Thank you.