Comparison of Area Under the Curve and Mixed Effects Models Methodologies for Profile Analysis

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Abstract

Assume that study subjects are randomly assigned to one of *K* treatments and assessed for a specific response at time 0 (baseline) and each of *T* post-treatment times that are not necessarily equally spaced. Further, assume the objective is to compare the treatments with respect to their response profiles across time. The first issue is to determine if there is significant treatment by time interaction. If there is convincing evidence that interaction is negligible, the next issue is to determine if the treatment and time main effects are significant. If there is evidence of interaction, the treatments typically are compared at each assessment time with adjustments for multiple comparisons. Currently, the analytical method of choice is to employ mixed effects models for repeated measures. Nevertheless, many analysts prefer comparing the treatments in terms of area under the curve (AUC). Despite its long history and widespread use, there appear to be many misconceptions about the merits of using AUC for profile analysis. In this presentation, we use comparative studies of response profiles from an oral glucose tolerance test to show situations in which some analytical methods are more (or less) appropriate than others.

Introduction

y_{itk} denotes the response for the i^{th} treatment at the t^{th} time for the k^{th} subject

- $i=1, 2$
- $t=0, 60, 120, 180$

Adjust response using baseline values for each subject

- y_{itk}-y_{it1}

The goal of researchers is to determine if the two glucose profiles are different

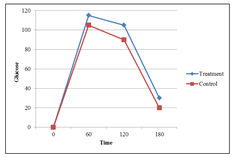


Figure 1. Glucose profiles for two treatment groups

Methodology

AUC

Calculate AUC for each subject

- Trapezoid rule
- $z_{ik} \approx y_{i2k}+y_{i3k}+0.5y_{i4k}$

H_0: $\mu_{c1}=\mu_{c2}$

- Two-sample t-test
  - Equal variance

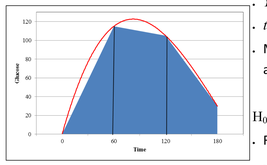


Figure 2. Area under the curve using trapezoid rule

Mixed

- $Y=\beta_0+\beta_1(t)+\beta_2(trt*t)+\varepsilon$
- t and trt are categorical
- Model repeated measures with an unstructured covariance

H_0: $\beta_2=0$

- F-test
  - Kenward Roger degrees of freedom

Simulation

$$H_0: \begin{pmatrix} \mu_{160} \\ \mu_{1120} \\ \mu_{1180} \end{pmatrix} = \begin{pmatrix} \mu_{260} \\ \mu_{2120} \\ \mu_{2180} \end{pmatrix}$$

- 25 subjects for each treatment
  - No missing values
- 1000 replications
- Values for population parameters at each time based on data obtained from Pennington Biomedical Research Center

Accuracy of a p-value

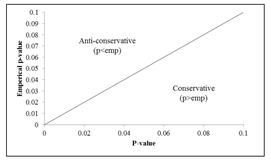
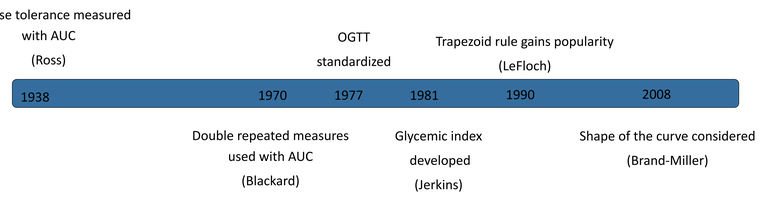


Figure 3. P-values plotted against their empirical p-values

History of AUC and Oral Glucose Tolerance test



Results

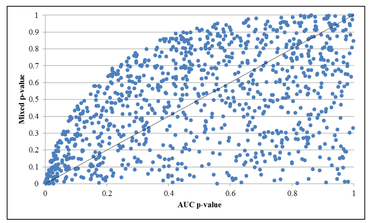


Figure 4. P-values based on the same sample

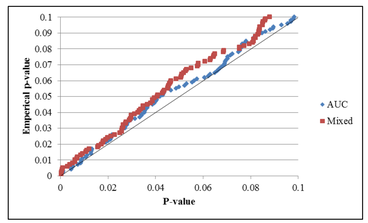


Figure 5. Accuracy of p-values

Crossing profiles

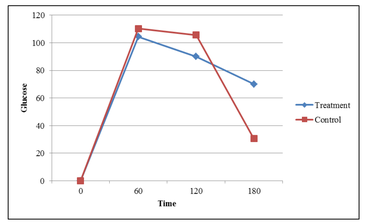


Figure 6. An example of a sample where the glucose profiles cross

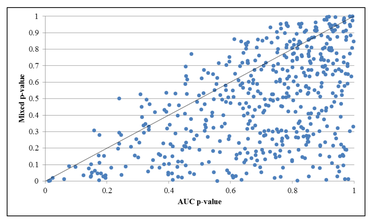


Figure 7. P-values for crossing profiles

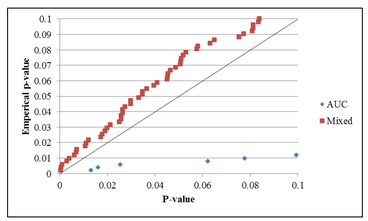


Figure 8. Accuracy of p-values for crossing profiles

Conclusion

Both methods may give vastly different p-values

- No cases where mixed p-value is high and AUC p-value is low
- Both methods are fairly accurate

Results differ when sample profiles cross

- Mixed p-values are generally smaller than those based on AUC
- Accuracy of the mixed p-value are about the same
- AUC are quite conservative

Future analysis includes investigating the power of these tests in various setting

- Overall and only when profiles cross

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Acknowledgments

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