Unlocking synergy: Navigating Type I Error Control & Heterogeneous Variance in Simulation Studies

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Combination therapy, a treatment modality that combines two or more therapeutic agents is common in cancer treatment. Combination treatments have the possibility to enhance efficacy and reduced drug resistance compared to monotherapy treatments. The potential of such combinations is often evaluated *in-vitro* by quantifying the deviation of the observed combination response compared to the expected combination response, *i.e.*, effect size. The expected combination responses are derived solely from the monotherapy data. However, these evaluations face challenges due to heterogeneous variance in biological data and the multiple testing problem.

Within Janssen Research & Development, data are analyzed using the in-house developed R-package BIGL[1,2]. As replication in combination experiments is labor intensive, often limited data are available. Currently, the BIGL package uses a single estimate for the variance of the monotherapy data. The summarization of the heterogenous variance can lead to difficulties when quantifying the amount of uncertainty of the effect sizes. We propose a local bootstrapping method to improve the estimation of the heterogenous variance of the monotherapy data.

The evaluation is further hampered by the multiple testing problem as comparisons are made in each dose combination. Initially, the R BIGL package controlled the multiple testing using family wise error rate (FWER), a conservative error control. An alternative error rate control is proposed. Through a simulation study, we explore these methodologies' improvements compared to the original approach, providing valuable insights for the evaluation of potential combination therapies.

[1] Van der Borght, Koen, et al. "BIGL: Biochemically Intuitive Generalized Loewe null model for prediction of the expected combined effect compatible with partial agonism and antagonism." *Scientific reports* 7.1 (2017): 1-9.

[2] Thas, Olivier, et al. "Statistical detection of synergy: New methods and a comparative study." *Pharmaceutical Statistics* (2021).