A comprehensive comparative study of methods and models for synergy

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Introduction

Many diseases are cured by using single agents that affect single targets. However, now that the underlying pathways of some (complex) diseases are better known, the use of combination drug therapies are lifting. Usage of such combination therapies may be more effective with less side effects.

There are many data analysis methods that can be chosen by scientist to elucidate the potential of combination therapies. There is however no general framework that tells which method is better applicable in which circumstances.

Objectives

The latest version of the BIGL R package includes four null models that predict responses under the hypothesis of additivity, requiring only monotherapy dose-response data. The implemented null models are:

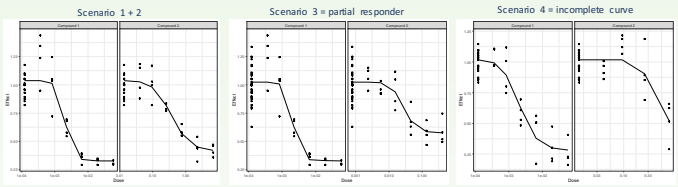
- Biochemically Intuitive Generalized Loewe (**BIGL**)
- **Loewe2:** Loewe model assuming $D_i = \infty$ when i is a partial responder and evaluating effects above the maximal response of the partial compound.
- Highest Single Agent (**HSA**)
- **BLISS independence**

When prediction deviates from observed responses from combination experiments, there may be evidence for synergy. Statistical tests can be used.

We used Monte Carlo simulations to mimic synergistic effects starting from each of these null models after which we tested the simulated data for synergy under each of the null models using statistical tests.
We compared the meanR and maxR tests from the BIGL package (non-parametric test to call synergistic points) with the Zhao model from the drugCombo package (parametric test to call synergistic points). Furthermore we looked at the influence of variance, outliers, partial responders and incomplete monotherapies on the performance of the different null models and statistical tests.

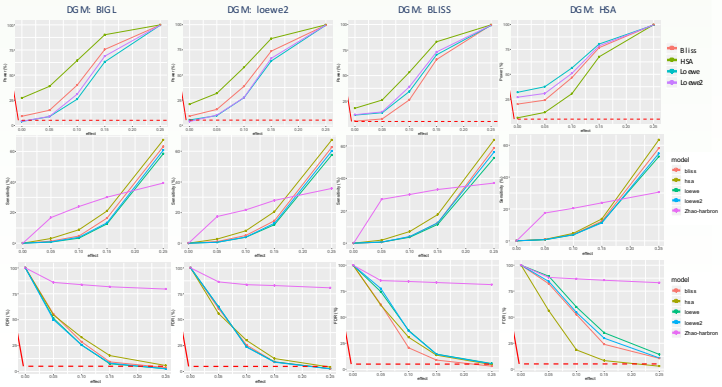
Results

Monotherapies used as pilot data during the simulations



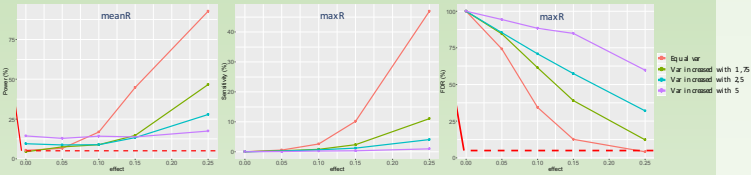
Scenario 1

Data were simulated under a certain data generating model (DGM) and a range of effect sizes were evaluated. Synergistic effects were added at random. The power of the meanR test statistic was evaluated for the analysis with all four null models, as well as the sensitivity, specificity and FDR of the maxR and the Zhao model. Specificity was for all models (except the zhao) > 97% and is not shown.



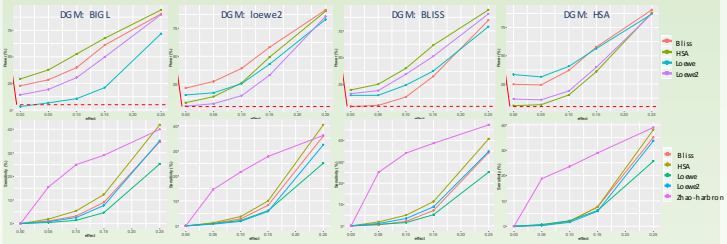
Scenario 2

The effect of an increasing off-axis variance on the behavior of null models and statistical tests was studied. Only the results of the BIGL DGM are shown, BIGL/Loewe was also the model used in the analysis of the data. The results of the other models are very similar.



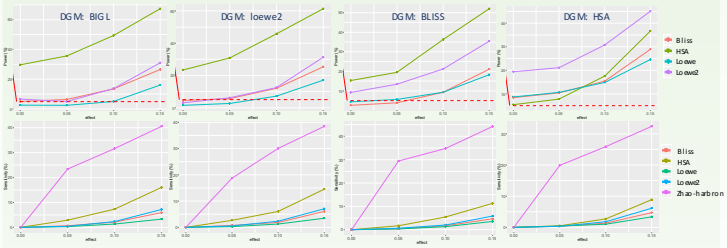
Scenario 3 – Partial responders

One monotherapy was changed to a partial responder and the same simulations were run.



Scenario 4 – Incomplete curves

One monotherapy was changed to an incomplete curve and the same simulations were run.



Conclusions

- The effect of the null model used in the data analysis on the performance of the statistical tests, depends on the DGM. HSA will call synergy more easily when the DGM is not HSA as it is the most liberal null model. Other null models behave rather similarly in scenario 1.
- A method works best when its own null model was used during data generation. Which means that it controls the type I error and has reliable power.
- Zhao calls too many of synergistic points. Sensitivity is high but so is the false discovery rate. Zhao seems to be most sensitive, but suffers in the current simulations most probably from model misspecification
- All models perform poorer when they have to deal with a partial responder. With complete curves there is no difference between Loewe and loewe2 because it's the same underlying model. However with a partial responder we see a discrepancy.
- All methods suffer if variability is too high. The type one error rate is not controlled at no synergy.

R packages

BIGL (not yet on CRAN): https://cran.r-project.org/web/packages/BIGL/
rugCombo: https://cran.rstudio.com/web/packages/drugCombo/index.html

References

1. Van der Borght, K., Tourny, A., Bagdziunas, R., Thas, O., Nazarov, M., Turner, H., ... & Ceulemans, H. (2017). BIGL: Biochemically Intuitive Generalized Loewe null model for prediction of the expected combined effect compatible with partial agonism and antagonism. *Scientific reports*, 7(1), 17935.
2. Harbron, C. (2010). A flexible unified approach to the analysis of pre-clinical combination studies. Statistics in medicine, 29(16), 1746-1756.
3. DrugCombo Vignette Cran

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