BIGL: assessing and visualizing drug synergy

About

Biochemically **I**ntuitive **G**eneralized **L**oewe, or **BIGL**, package for **R** proposes a workflow to study synergy in drug combinations with methods that rely on response surface construction.

What is drug synergy?

When combining multiple drugs, **drug synergy** occurs when drugs can interact in ways that enhance or magnify the effects of those drugs. It is especially relevant in pharmacology since

- certain drugs can be effective in treatment but cause adverse effects in higher doses. Finding its synergistic pair allows lowering the dose.
- human body may learn to obstruct the action of a single drug but it will be more difficult to do so in case of multiple ones with different mechanisms of action

Procedure

We would like to assess the synergistic effects of a combination consisting of two compounds. This means our data has 3 columns: `"d1"`, `"d2"` (doses of Compounds 1 and 2) and `"effect"` (numerical measure of response).

1. Understand the action of each compound when it acts alone.
   - Estimate dose-response curves for each of the compounds.
2. Given information in point 1), predict the combined action of compounds using a null model of your choice. Under the null model, there is no drug interaction.
   - **BIGL** takes a response surface model approach, i.e. it constructs a 3-D surface as a null model over the domain of available dose combinations.
3. Compare response surface predictions with observed `"effect"` and test for statistically significant differences.
   - **BIGL** formalizes this step by introducing statistical testing methodology, notably `meanR` and `maxR` tests.

1. Marginal models

First, it is important to investigate the dose-response relationship of the individual compounds as it will constitute the basis of the null model. Experiment data should thus include data points where one or both compounds are dosed at zero.

If we observe activity y of a single compound, we expect it to follow a standard dose-response relationship, e.g.

$$y\left(d_i\right) = \text{Baseline} + \frac{\text{Max.Response} - \text{Baseline}}{1 + \left(d_i/\text{EC50}\right)^h}$$

Baseline is calculated at points where both compounds are dosed at zero and is the same for each compound. However, each compound has its own Hill slope h and mid-point EC50 parameter. Depending on the null model for the response surface, maximal response can be either shared or vary freely.

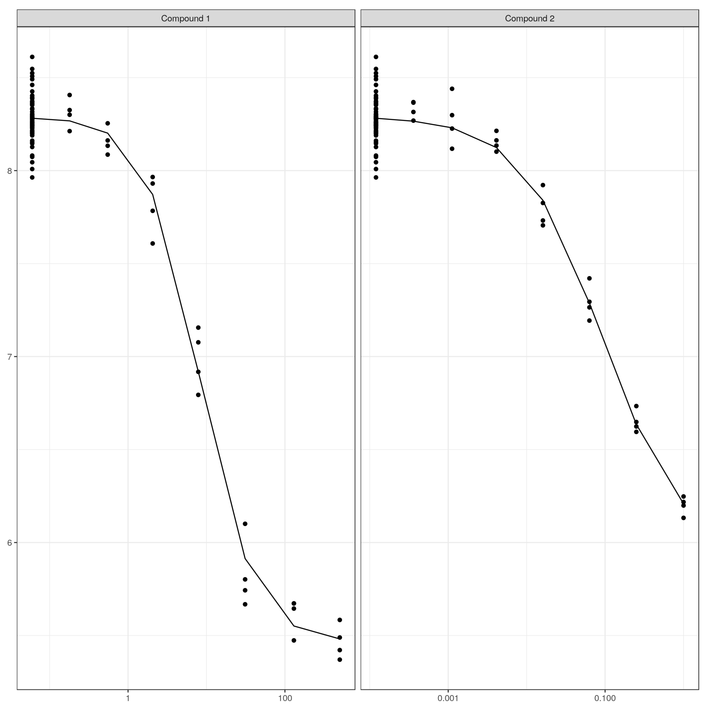

Figure 1: Dose-response curves for Compound 1 (left) and Compound 2 (right). Both curves are estimated simultaneously and share the same baseline.

2. Null model

Multiple biological models exist to make use of dose-response curve parameter estimates in order to construct a null model under which there is no interaction between compounds.

BIGL package uses estimates of dose-response models to construct the predicted 3-D response surface under 3 null models:

1. Highest Single Agent
2. Loewe Additivity
3. Generalized Loewe Additivity
   - It extends Loewe Additivity by allowing for differing maximal response across compounds

3. Response surface

After construction of the null model, the predicted response surface is compared with observed data points by means of a global (`meanR`) and local (`maxR`) statistical tests.

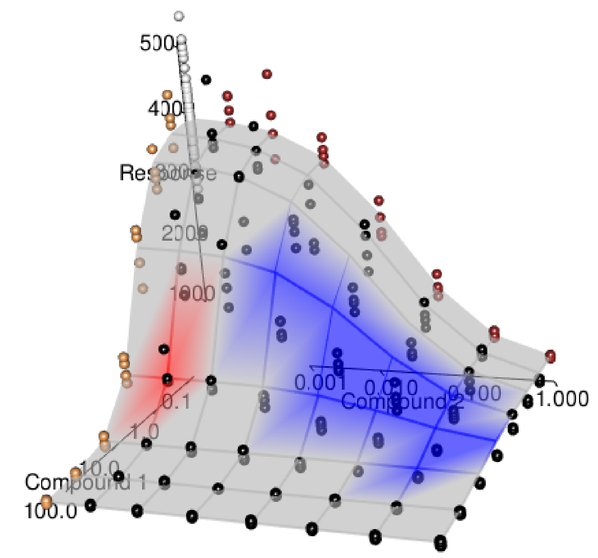

Figure 2: Null model response surface in grey. Blue coloring indicates observed effects (black points) higher than expected (synergy) whereas red coloring indicates observed effects lower than expected (antagonism) according to the `maxR` test scores. 3-D plot is interactive, can be zoomed in/out and rotated.

Also available in BIGL

- Dealing with data that has (or hasn't) replicates
- Transforming `"effect"` to stabilize variance
  - **BIGL** proposes pre-defined biologically-sensible transformations but also allows for automated transformation selection.
- Constraints on dose-response curve parameters
- Parallel computation for the bootstrapping procedure

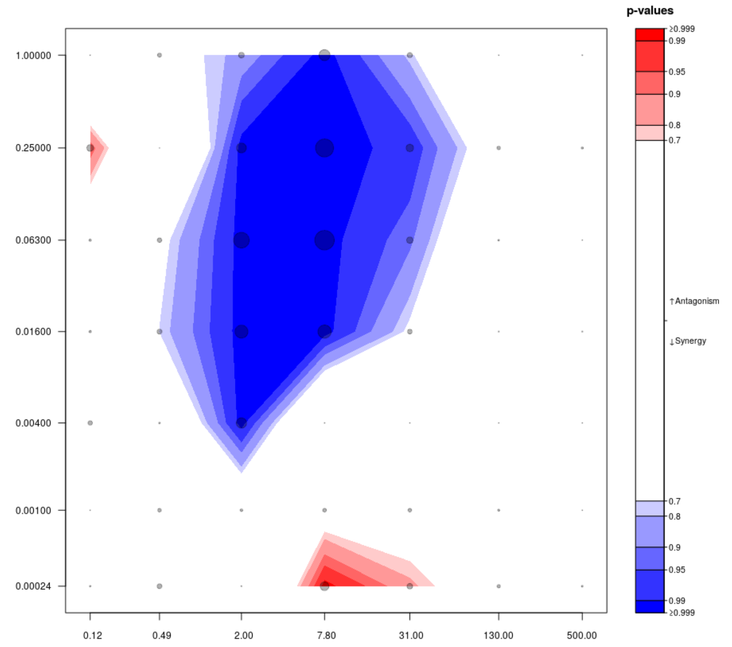

Figure 3: Projection of the 3-D plot onto 2-dimensional space. Here coloring is based on p-values of the `maxR` test statistic.

References

BIGL: *Biochemically Intuitive Generalized Loewe null model for prediction of the expected combined effect compatible with partial agonism and antagonism* (in preparation)
by K. Van der Borght, A. Tourny, R. Bagdžiūnas, O. Thas, M. Nazarov, H. Turner, B. Verbist & H. Ceulemans.

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