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Overview

Drug combinations are critical in many diseases, including cancer. Synergistic drugs allow the use of lower doses in the treatment and therefore the adverse reactions would probably be reduced.

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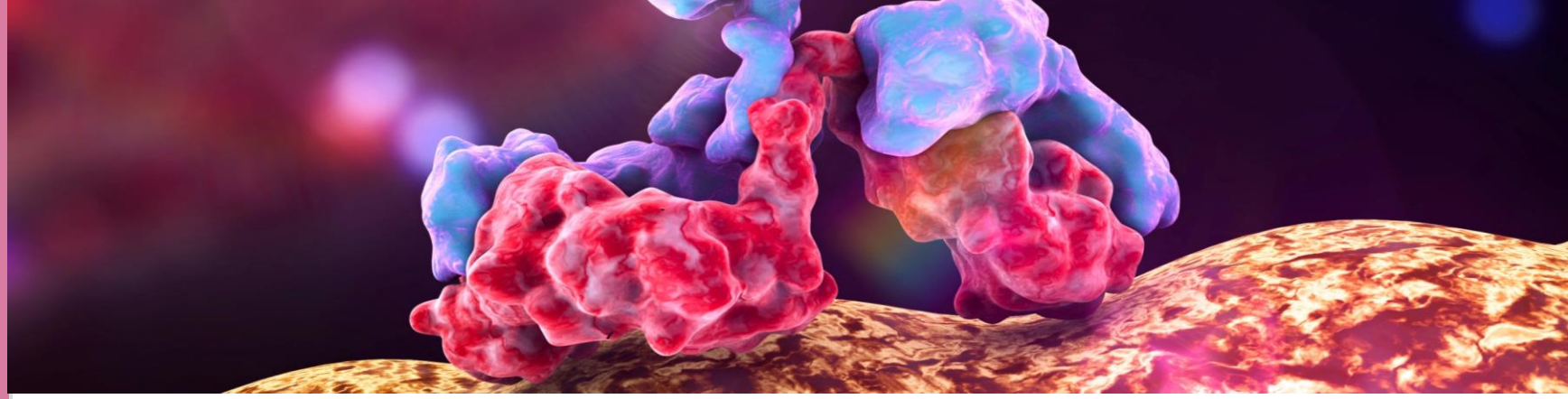

Innovative Drug Interaction Studies

Vivia has developed a workflow including different methods like traditional dose dependant indexes, surface modeling[1] (Greco et al., 1995) and the new MuSyC[2,3] algorithm to perform a complete drug interaction study.

Drug interaction study phases

- **Setup phase.** An initial phase to determine the optimal condition for drug interaction study.
  - Doses
    - Single Drug Doses. Single drugs are tested to select the most suitable doses for each drug.
    - Combination Doses. A dose matrix (4x4, 5x5, NxN) is created based on single drugs EC50s to have the more informative and reliable data to calculate the drug interaction.
  - Incubation times. The most suitable incubation time(s) are selected to grant the best data collection for the drug interaction synergy calculation.
- **Experimental phase.** Data information collected during the setup phase is used to perform the final experiment.
- **Analysis phase**
  - Dose-dependent
    - Combination Index
    - Loewe Combination Index
    - Loewe Delta
  - Interaction surface modeling
    - MuSyC[2,3] algorithm
    - Loewe[1]

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MuSyC algorithm different synergies for drug interaction

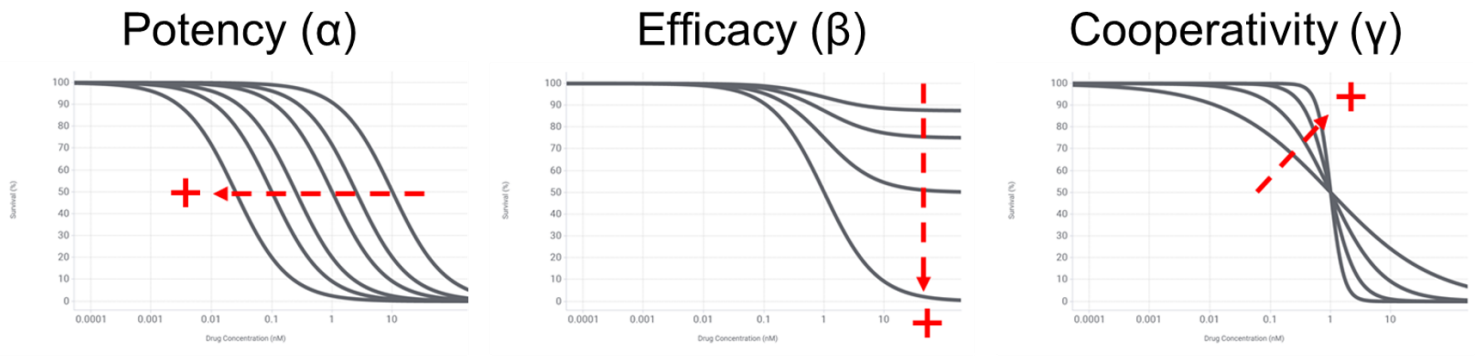

Figure 1. MuSyC algorithm is applicable to any metric of drug interaction effect and is able to differentiate between potency (α), efficacy (β) and cooperativity (γ) synergy.

Drug interaction study results dashboard

Figure 2. Drug interaction study analysis results in Spotfire. Combination Indexes, 3D surface model and synergy parameters results are displayed together for a better overview.

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Drug interaction 3D surface

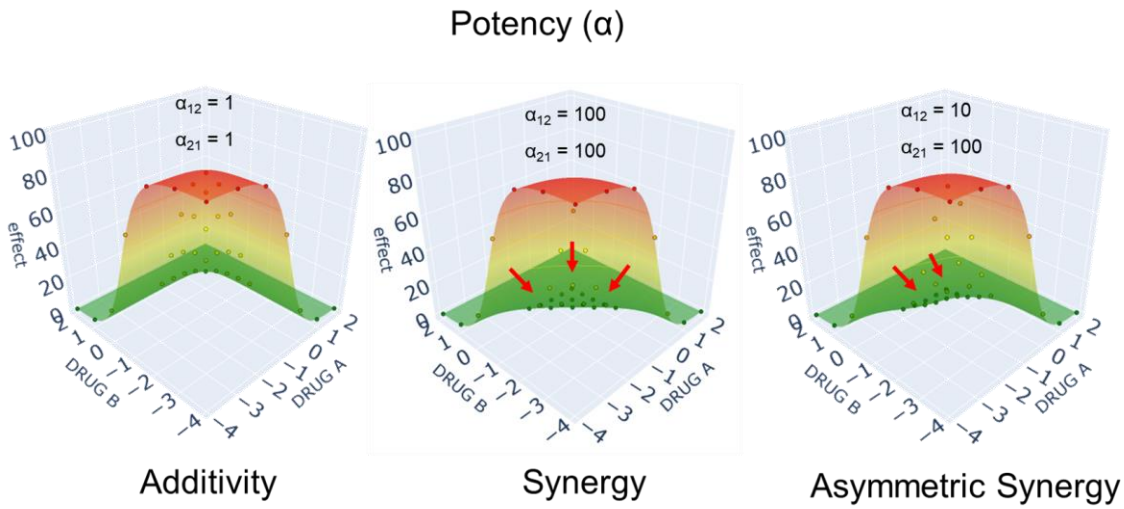

Figure 3. 3D interaction surface examples for potency synergy. MuSyC algorithm calculates fold changes in the potency on drug B induced by drug A (α_{12}) and vice versa (α_{21}).

Highlights

- Innovative workflow using a complete set of synergy calculation methods.
- Pre-analysis phase to maximize per well information collection without quality loss. (Single drug & combination doses selection, incubation time…)
- Efficacy and cooperativity synergy added to the traditional potency synergy.
- Asymmetric synergy detection (α_{12}, α_{21}, γ_{12} & γ_{21})
- Interactive Spotfire synergy data analysis and visualization (3D Surface viewer, drug interaction parameters, synergy score, single drug dose response curves …)

References

1. Greco, W.R., Bravo, G., and Parsons, J.C. (1995). The search for synergy: a critical review from a response surface perspective. Pharmacol. Rev. 47, 331–385.
2. Meyer, C.T., Wooten, D.J., Paudel, B.B., Bauer, J., Hardeman, K.N., Westover, D., Lovly, C.M., Harris, L.A., Tyson, D.R., and Quaranta, V. (2019). Quantifying drug combination synergy along potency and efficacy axes. Cell Syst. 8, 97–108.e16. https://doi.org/10.1016/j.cels.2019.01.003
3. Wooten, David J, and Albert, Réka. synergy - A Python library for calculating, analyzing, and visualizing drug combination synergy. (2020) Bioinformatics. https://doi.org/10.1093/bioinformatics/btaa826