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Type	Oral communication
Session	Pharmacogenomics
Title	SiCoDEA: a simple, fast and complete app for analyzing the effect of individual drugs and their combinations
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Motivation

The administration of combinations of drugs is a method widely used in the treatment of different pathologies as it can lead to an increase in the therapeutic effect and a reduction in the dose compared to the administration of the single drugs. It is particularly useful in cancer, that displays a great genetic heterogeneity and frequently develops drug resistance thus requiring a multi-target therapeutic approach. Combinatorial treatments delay the onset of drug resistance, and the reduction of the administered dose also allows a reduction of any toxic effects. For these reasons, it is of interest to study combinations of drugs and in particular to determine whether a specific combination has a synergistic, antagonistic or additive effect, i.e greater, less than or equal to the effect expected by the sum of the individual drugs.
For this purpose, various mathematical models have been developed, which use different methods to evaluate the synergy of a combination of drugs. Most of these methods are based on the Loewe Additivity Principle (Loewe S. et al., 1953), according to which additivity is given by the relationship a/A+b/B=1 where a and b are the concentrations of the two drugs in combination for a given effect while A and B are the expected concentrations necessary for individual drugs to achieve that same effect. From that it is possible to define a combination index CI=a/A+b/B which will indicate synergy if CI<1, antagonism if CI>1, and additivity if CI=1. The key step is therefore the model used for predicting the equivalent doses for the two drugs, namely A and B.
The most commonly used model for calculating the combination index is the Chou-Talalay Method (Chou T.C., Talalay P. et al., 1984) which is based on the median-effect equation, derived from the mass-action law principle. Although this kinetic approach is appropriate for assessing effects of drug combinations in enzymatic catalysis, it is not rigorous to apply it in the setting of cell viability and cytotoxicity experiments, as these biological variables rely on complex networks of multiple, interacting, cellular pathways. Consequently, a more accurate and hypothesis free model is needed.
Creating a model for this purpose and calculating its parameters, however, requires a certain level of mathematical and programming knowledge or the use of commercial software. For this purpose, therefore, we have developed an open access and easy to use app that allows to explore different models and to choose the most fitting for the specific experimental data: SiCoDEA (Single and Combined Drug Effect Analysis).

Methods

The data used to test SiCoDEA comes from cell line samples treated with different drug combinations and analyzed through metabolic or viability assays.
SiCoDEA is developed through a Shiny interactive and easy-to-use interface (R based); it provides both the simple calculation of the IC50 for different drugs and also the calculation of the combination index with the display of the respective plots.
There are six models taken into consideration for the analysis of single drugs and the calculation of combination index. The first is one of the most used, that of the median-effect; while the others are different forms of the log-logistic equation, with two, three and four parameters.

Results

The purpose of SiCoDEA is, on the one hand, to provide an easy-to-use tool for analyzing drug combination data and, on the other hand, also to have a view of the various steps and to offer different results based on the model chosen. An important prerequisite in analyzing drug combinations is in fact the dose-response curve calculated for individual drugs. For this purpose, SiCoDEA allows you to view the plots of the individual drugs both to evaluate the distribution of the calculated points and therefore identify any outliers, and to view the curve of the different models taken into consideration and evaluate which one

best fits the data. A table showing all the R2 values for the six different models is created with the curve plot. In addition to the type of model, it is also possible to choose between two different normalization methods, one based on the maximum or minimum value and the other on the value calculated at drug concentrations equal to zero. For the chosen options, a plot is then created that shows the trend of the combination index for the different drug combinations and consequently whether it is synergy, antagonism or additivity. Finally, it is possible to export the results in single png files or in a summary report in pdf. SiCoDEA is an open-source app among the most complete and offers more functions even than the famous CompuSyn (Chou, T.C., 2010), as it allows you to analyze drug curves with different models, rather than just one, and it also allows the analysis of single drug curves.

Info
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Figure
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Availability	-

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