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Exploration of a new method and a new tool for the characterization of in vitro combinations of two compounds for screening purpose in oncology

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19 . October . 2022

Content

This presentation is the result of a work initiated during an internship and continued within an internal working group

→ Reflection on the statistical analysis of in vitro combination experiments on two different aspects

Aspect 1: Statistical model

- *Context*
- *Quick presentation of Loewe model*
- *Loewe model limitations*
- *Hand model: Theory - Graphical representation - Examples*

Aspect 2: Process of the analysis of in vitro combination experiments

- *Context of the development of a new tool*
- *Our Rshiny application*

Aspects 1 and 2 interconnecting

- *Hand model tests and limitations*
- *Conclusion*

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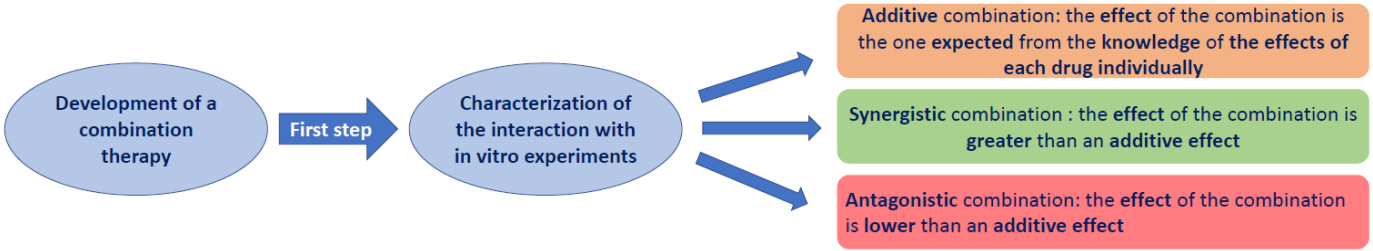
Context and definition

- In oncology, the development of drug combinations is widespread: they can increase efficacy or maintain it at lower doses with reduced adverse events.



- Very large literature on the "synergy/antagonism"
  - Concept of additivity/synergy/antagonism : definition well-accepted
  - BUT not consensus on the formal/mathematical definition of additivity
    - → Different reference models identified
    - → Huge variety of methodologies regularly published to demonstrate synergy

- One of the main historical models to express synergy: the Loewe additivity model (Loewe and Muischnek, 1926)
  - Thinking using concentrations needed to reach an effect: synergy if the same effect is reached with smaller concentrations

Quick presentation of Loewe model

- Equation for Loewe additivity model between compounds A and B: $\frac{C_A}{ICX_A} + \frac{C_B}{ICX_B} = 1$

With C_A, C_B: concentrations of each compound in the mixture necessary to obtain X% of effect

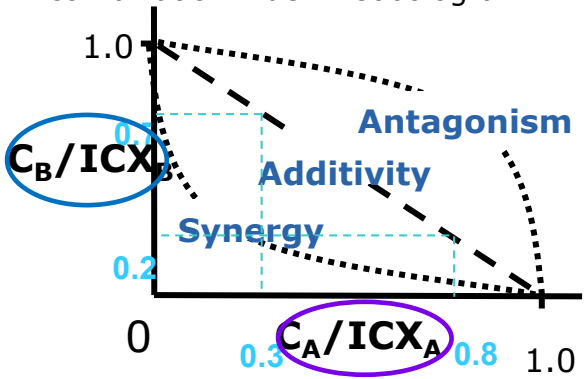
ICX_A, ICX_B: concentrations of compounds A and B necessary to obtain X% of effect for each compound alone (often absolute IC50, but not mandatory)

- From the additivity equation of Loewe, a combination index was developed

$$K = \frac{C_A}{ICX_A} + \frac{C_B}{ICX_B}$$

- K is then compared to 1 (additivity hypothesis)
  - K <1 => synergy (upper bound of K's CI <1)
  - K =1 => additivity
  - K >1 => antagonism (lower bound of K's CI >1)

- Graphical representation associated to the combination index: Isobologram



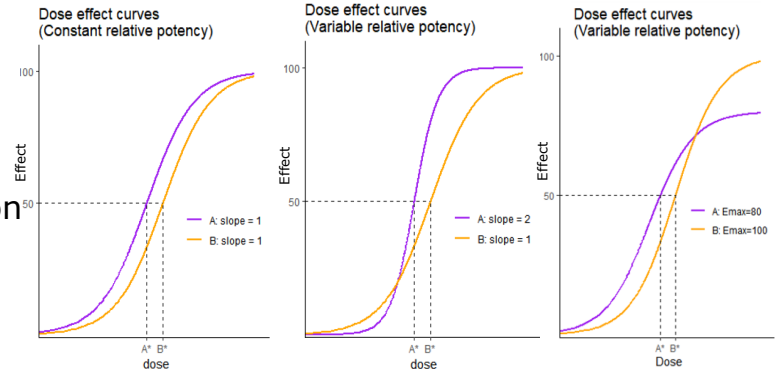
- What is needed to calculate K ?
  - the whole dose-effect curves of the single compounds and of the combination needed
    → four-parameter logistic model used to fit these dose-effect curves

Loewe model limitations and alternatives

- The equation of Loewe additivity is based on the hypothesis of a constant relative potency → $\mathrm{R} = \frac{\mathrm{IC}X_{\mathrm{A}}}{\mathrm{IC}X_{\mathrm{B}}} = \frac{\mathrm{ICY_A}}{\mathrm{ICY_B}} = \frac{\mathrm{IC50_A}}{\mathrm{IC50_B}}$

- The relative potency is often not constant
  - The slopes of single compounds curves are not equal
  - Maximum effects of single compounds differ

  → In this case, the additivity line of the isobologram becomes a curvilinear additive isobole and the calculation of the combination index is more complex.



- Alternatives
  - In the literature, a lot of models are regularly developed: some very complicated, some not very rigorous
  - A model was explored
    - **Hand model** → developed by David J. Hand in 2000, and rediscovered and described by Sinzger and al, in 2019

Hand model

- **Hand model:** formulation of the additivity in terms of instantaneous effect gains rather than effect level

- Dose-effect curve: $f(x)=E_{min}+\frac{E_{max}-E_{min}}{1+\left(\frac{IC50}{x}\right)^{m}}$ **Derivation** → Sensitivity: $S(x)=f'\left(f^{-1}(x)\right)$ → Instantaneous gain in effect per dose giving the effect x

- Equation for Hand additivity model : $S_{AB,\lambda}(x)=\lambda S_A(x)+(1-\lambda)S_B(x)$, λ: proportion of compound A in the mixture

  → At each effect level both compounds contribute linearly to the instantaneous gain in effect of the combined curve
  → The effect-sensitivity curve of the combination is a weighted average of the single effect-sensitivity curves

→ From the inverse derivative formula: $S_{AB,\lambda}(x)=f'_{AB,\lambda}\left(f_{AB,\lambda}^{-1}(x)\right)=\frac{1}{f_{AB,\lambda}^{-1'}(x)}=\frac{\lambda}{f_A^{-1'}(x)}+\frac{1-\lambda}{f_B^{-1'}(x)}$

- Estimation of the dose-effect curve for the expected additive combination **Integration** ↓

→ The inverse dose-effect curve for the expected additive combination: $f^{-1}_{AB,\lambda}(x)=\int_0^x\left(\frac{\lambda}{f_A^{-1'}(y)}+\frac{1-\lambda}{f_B^{-1'}(y)}\right)^{-1}dy$

The dose-effect curve for the expected additive combination can be obtained !

Hand model – Graphical representation

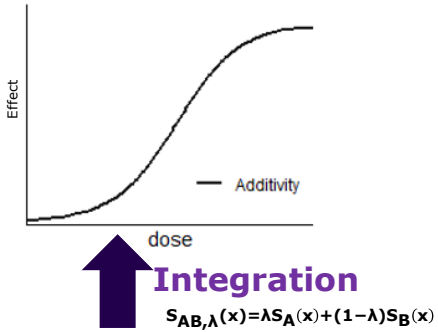
Dose-effect curves of single compounds

Derivation

Effect-sensitivity curves of single compounds

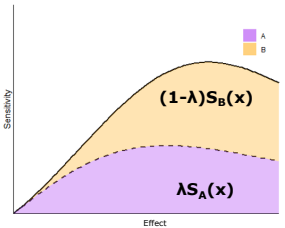
Weighted average

Dose-effect curve of the expected additive combination



Integration

$S_{AB,\lambda}(x)=\lambda S_A(x)+(1-\lambda)S_B(x)$



Effect-sensitivity curve of the expected additive combination

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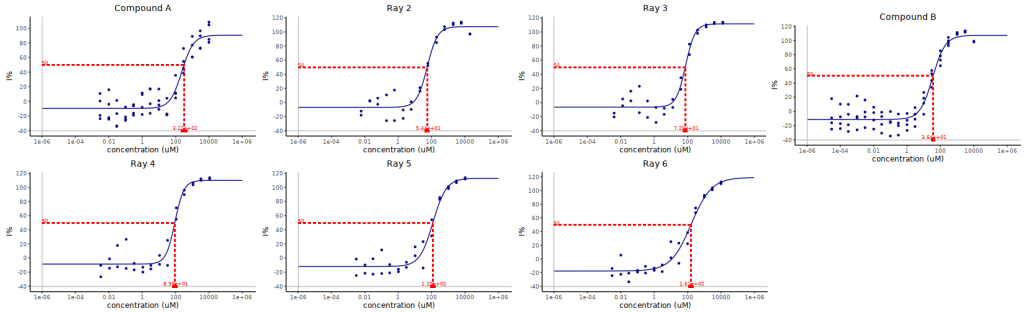
Hand model- Example

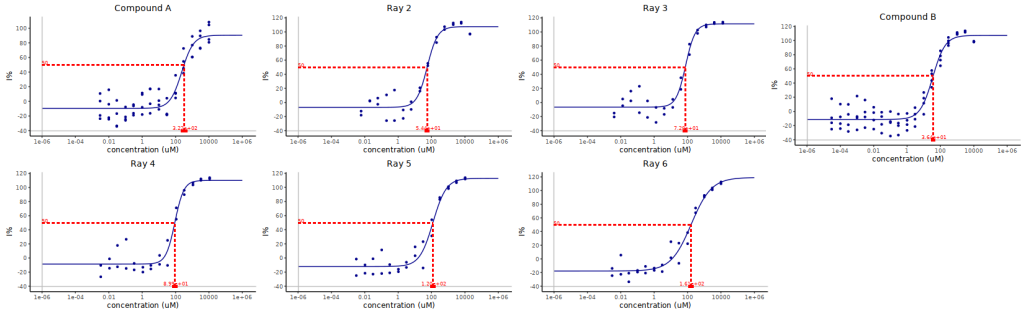
- 7 dose-effect curves (2 with single compounds + 5 with mixtures with constant proportion of both compounds)



Ray Index	slope	IC50 rel	CV%	IC50 abs	IC50 abs (LCB95%)	IC50 abs(UCB95%)	Top	Bottom
Compound A	1.24	2.35e+02	26.82%	3.22e+02	2.05e+02	5.07e+02	90.4	-9.62
Ray 2	1.39	5.48e+01	18.34%	5.44e+01	3.94e+01	7.52e+01	107.49	-6.89
Ray 3	1.54	7.69e+01	18%	7.28e+01	5.31e+01	9.99e+01	111.48	-6.62
Ray 4	1.62	9.12e+01	18.34%	8.99e+01	6.51e+01	1.24e+02	110.01	-8.58
Ray 5	1.09	1.22e+02	21.43%	1.20e+02	8.57e+01	1.69e+02	112.79	-12.13
Ray 6	0.71	1.66e+02	32.36%	1.61e+02	1.11e+02	2.35e+02	119.18	-17.77
Compound B	1.15	3.42e+01	16.07%	3.64e+01	2.78e+01	4.75e+01	107.23	-11.34

Hand model- Example

- 7 dose-effect curves (2 with single compounds + 5 with mixtures with constant proportion of both compounds)



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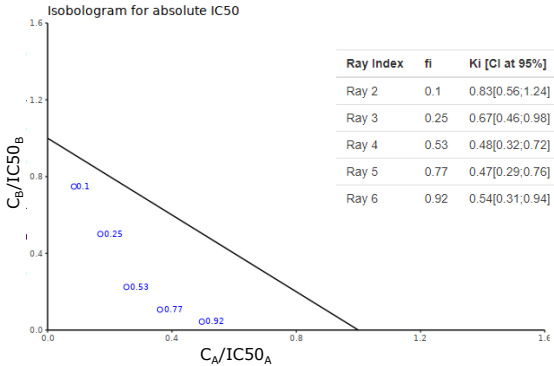
- Loewe model



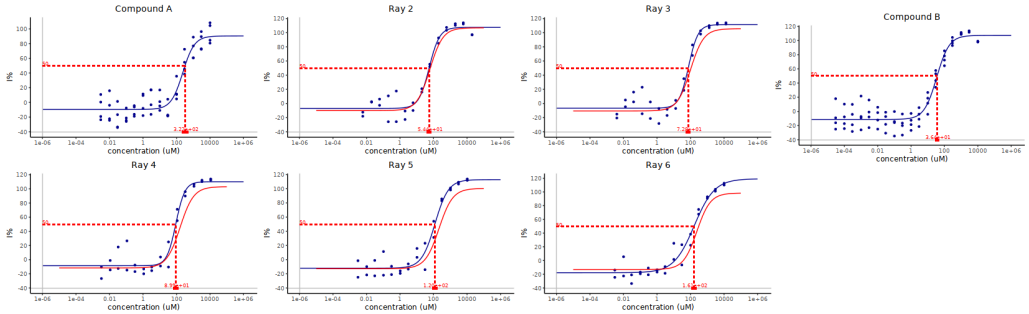
Ray Index	fi	Ki [CI at 95%]
Ray 2	0.1	0.83[0.56;1.24]
Ray 3	0.25	0.67[0.46;0.98]
Ray 4	0.53	0.48[0.32;0.72]
Ray 5	0.77	0.47[0.29;0.76]
Ray 6	0.92	0.54[0.31;0.94]

Ki: combination indexes (with their confidence intervals)

fi: effective fraction, proportion defined in terms of unit of effect of each compound alone according to their respective IC50

Hand model- Example

- 7 dose-effect curves (2 with single compounds + 5 with mixtures with constant proportion of both compounds)



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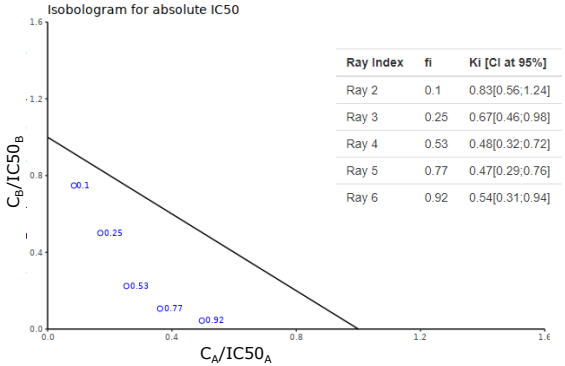
- Loewe model



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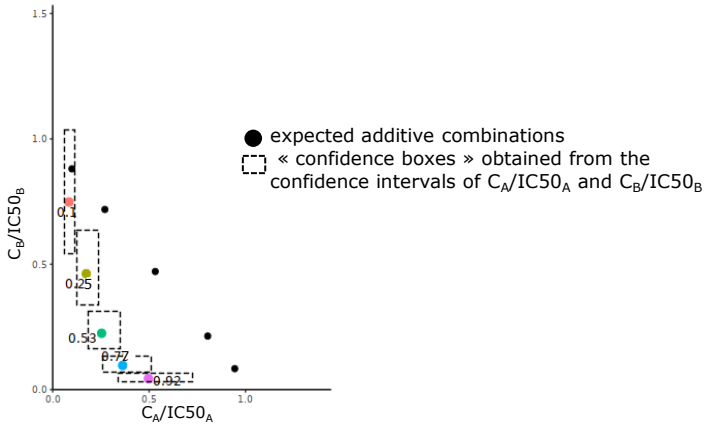
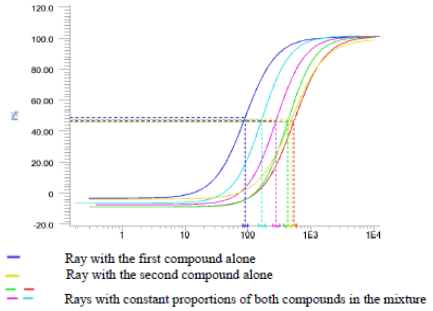
- Hand model



Why a new tool ?

- Process of in vitro combination experiments

Design set up	Experiment	Analysis
Scientist and statistician	**Scientist**	**Statistician**
Ray design (constant proportion of compounds mixture)	Repeated, recommended 3 times to take into account the experimental variability	Estimation of dose-effect curves of single compounds and for each ratio of compound

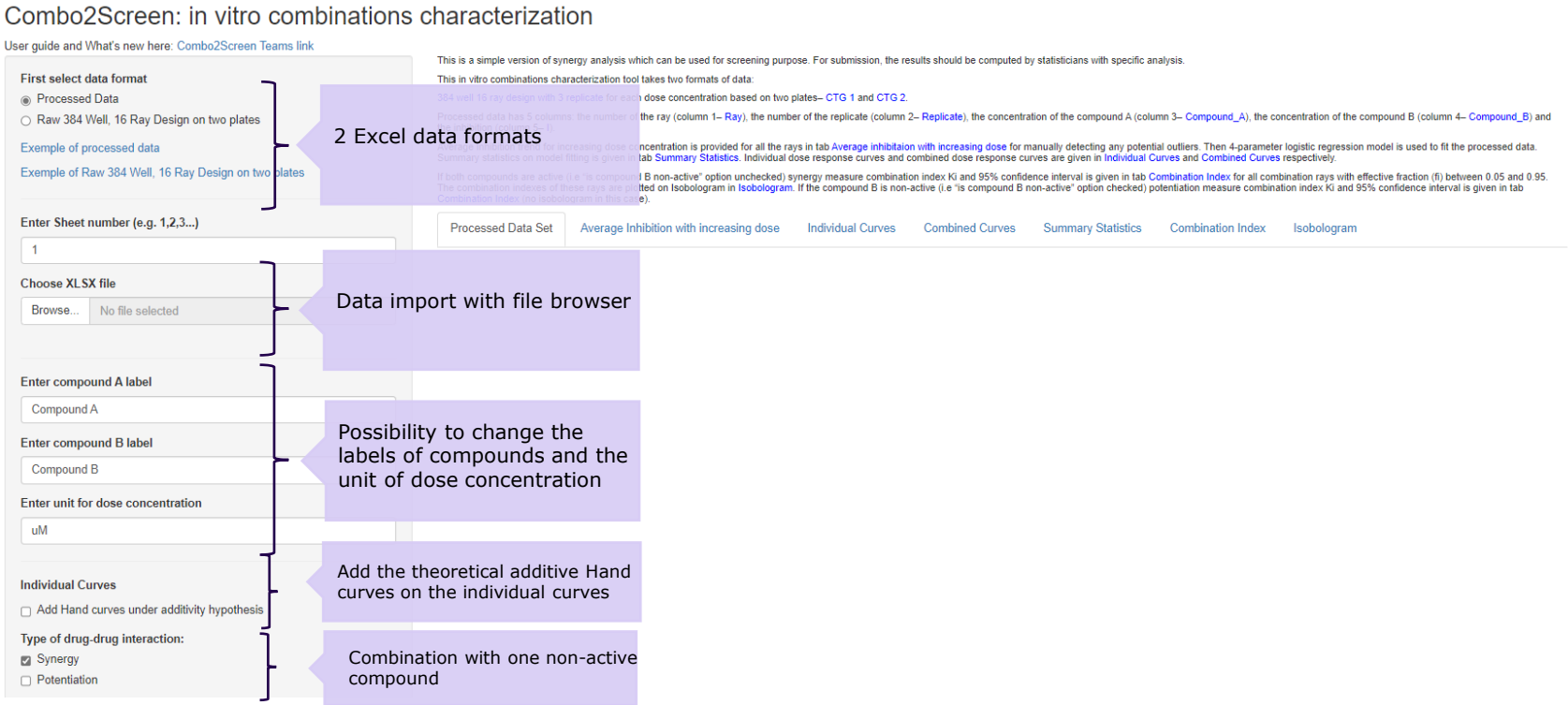


$$f(x)=E_{min}+\frac{E_{max}-E_{min}}{1+\left(\frac{IC50}{x}\right)^{m}}$$

- The search of new combinations starts with a screening phase
  - Time consuming for the biostat team to analyse all these combinations
  - Delay for the scientists to have the results

→ Need to develop a tool to characterize the in vitro combinations of two compounds for screening purpose
  → Speed increase
  → Autonomy of scientists
  → **Opportunity to explore and test the Hand model as an alternative to the Loewe model and to implement it in this new tool**

A Rshiny application to characterize combinations



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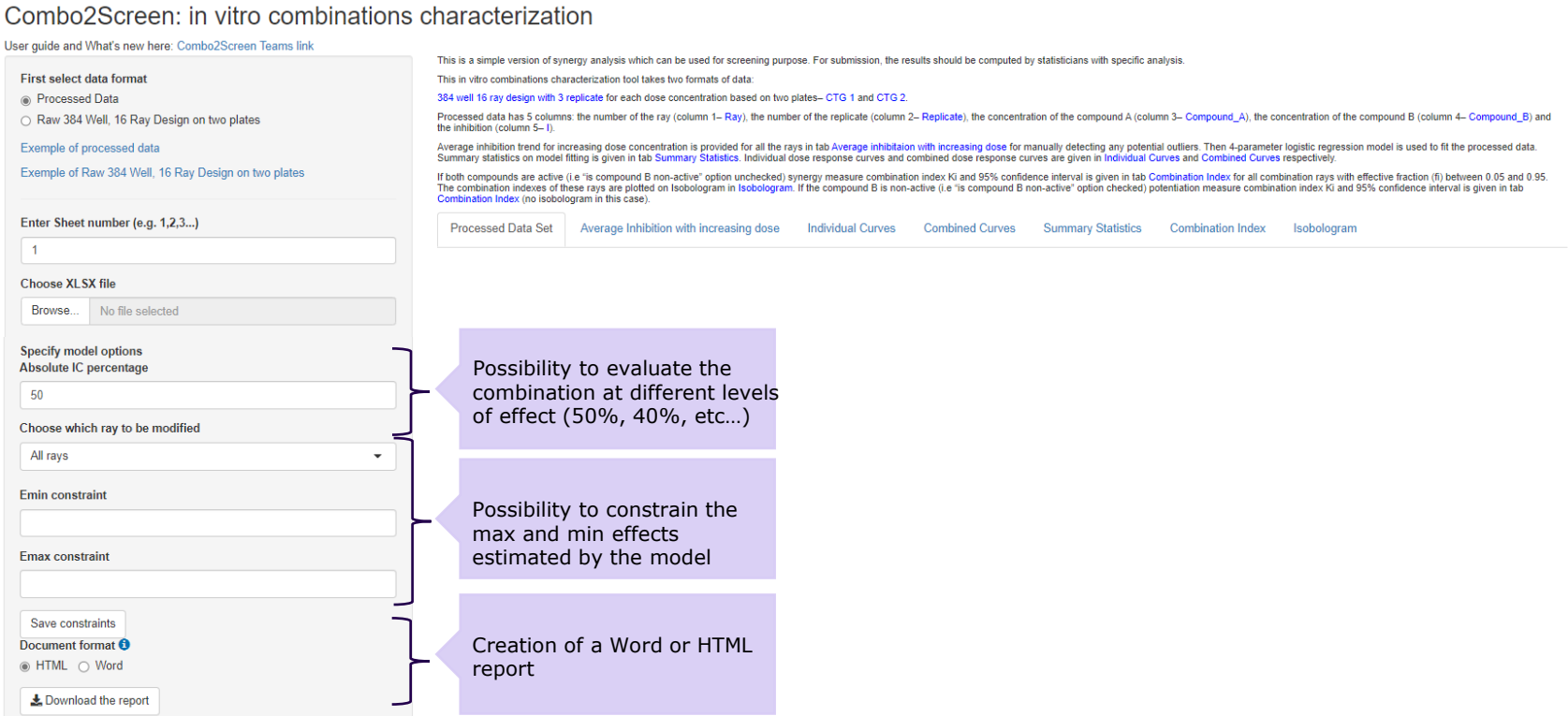

A Rshiny application to characterize combinations

Combo2Screen: in vitro combinations characterization

User guide and What's new here: Combo2Screen Teams link

First select data format

- (•) Processed Data
- ( ) Raw 384 Well, 16 Ray Design on two plates

Exemple of processed data

Exemple of Raw 384 Well, 16 Ray Design on two plates

Enter Sheet number (e.g. 1,2,3...)

1

Choose XLSX file

Browse... data10.xlsx

Upload complete

Enter compound A label

Compound A

Enter compound B label

Compound B

Enter unit for dose concentration

uM

Individual Curves

- [x] Add Hand curves under additivity hypothesis

Type of drug-drug interaction:

- [x] Synergy
- [ ] Potentiation

Specify model options
Absolute IC percentage

50

Choose which ray to be modified

All rays

This is a simple version of synergy analysis which can be used for screening purpose. For submission, the results should be computed by statisticians with specific analysis.

This in vitro combinations characterization tool takes two formats of data:

384 well 16 ray design with 3 replicate for each dose concentration based on two plates– CTG 1 and CTG 2.

Processed data has 5 columns: the number of the ray (column 1– Ray), the number of the replicate (column 2– Replicate), the concentration of the compound A (column 3– Compound_A), the concentration of the compound B (column 4– Compound_B) and the inhibition (column 5– I).

Average inhibition trend for increasing dose concentration is provided for all the rays in tab Average inhibitaion with increasing dose for manually detecting any potential outliers. Then 4-parameter logistic regression model is used to fit the processed data. Summary statistics on model fitting is given in tab Summary Statistics. Individual dose response curves and combined dose response curves are given in Individual Curves and Combined Curves respectively.

If both compounds are active (i.e "is compound B non-active" option unchecked) synergy measure combination index Ki and 95% confidence interval is given in tab Combination Index for all combination rays with effective fraction (fi) between 0.05 and 0.95. The combination indexes of these rays are plotted on Isobologram in Isobologram. If the compound B is non-active (i.e "is compound B non-active" option checked) potentiation measure combination index Ki and 95% confidence interval is given in tab Combination Index (no isobologram in this case).

Processed Data Set | Average Inhibition with increasing dose | Individual Curves | Combined Curves | Summary Statistics | Combination Index | Isobologram

Ray	Replicate	Compound A(uM)	Compound B(uM)	Inhibition%
1	1	1.00e+00	0.00e+00	45.31
1	1	3.33e-01	0.00e+00	42.7
1	1	1.11e-01	0.00e+00	45.71
1	1	3.70e-02	0.00e+00	45.2
1	1	1.23e-02	0.00e+00	37.22
1	1	4.12e-03	0.00e+00	17.48
1	1	1.37e-03	0.00e+00	2.71
1	1	4.57e-04	0.00e+00	-1.81
1	1	1.52e-04	0.00e+00	-8.95
1	2	1.00e+00	0.00e+00	49.61
1	2	3.33e-01	0.00e+00	49.85
1	2	1.11e-01	0.00e+00	50.09
1	2	3.70e-02	0.00e+00	48.8
1	2	1.23e-02	0.00e+00	39.15
1	2	4.12e-03	0.00e+00	25.02
1	2	1.37e-03	0.00e+00	4.73
1	2	4.57e-04	0.00e+00	3.27
1	2	1.52e-04	0.00e+00	-2.8
1	3	1.00e+00	0.00e+00	48.18
1	3	3.33e-01	0.00e+00	54.08
1	3	1.11e-01	0.00e+00	47.81
1	3	3.70e-02	0.00e+00	54.21
1	3	1.23e-02	0.00e+00	42.23

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Enter Sheet number (e.g. 1,2,3...)

1

Choose XLSX file

Browse... data10.xlsx

Upload complete

Enter compound A label

Compound A

Enter compound B label

Compound B

Enter unit for dose concentration

uM

Individual Curves

☑ Add Hand curves under additivity hypothesis

Type of drug-drug interaction:

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If both compounds are active (i.e "is compound B non-active" option unchecked) synergy measure combination index Ki and 95% confidence interval is given in tab Com
The combination indexes of these rays are plotted on Isobologram in Isobologram. If the compound B is non-active (i.e "is compound B non-active" option checked) pote
Combination Index (no isobologram in this case).

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Ray	Replicate	Compound A(uM)	Compound B(uM)	Inhibition
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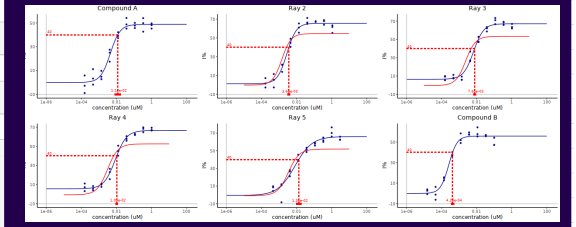
1	1	3.33e-01	0.00e+00	42.7
1	1	1.11e-01	0.00e+00	45.71
1	1	3.70e-02	0.00e+00	
1	2	4.57e-04	0.00e+00	3.27
1	2	1.52e-04	0.00e+00	-2.8
1	3	1.00e+00	0.00e+00	48.18
1	3	3.33e-01	0.00e+00	54.08
1	3	1.11e-01	0.00e+00	47.81
1	3	3.70e-02	0.00e+00	54.21
1	3	1.23e-02	0.00e+00	42.23

1 2 3 4 5

1



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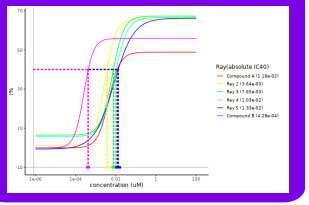


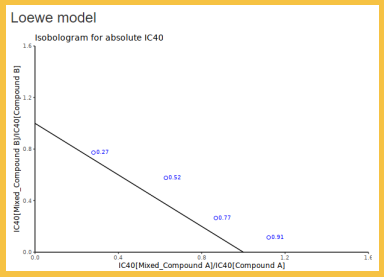
3

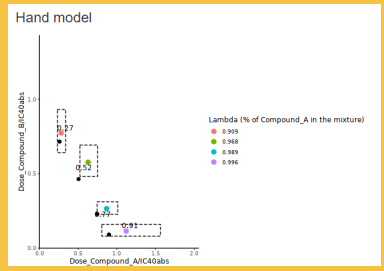
Ray Index	slope	IC50 rel	CV%	IC40 abs	IC40 abs (LCB95%)	IC40 abs(UCB95%)	Top	Bottom
Compound A	1.55	4.45e-03	14.84%	1.18e-02	7.92e-03	1.75e-02	48.81	-0.08
Ray 2	1.62	2.82e-03	11.58%	3.64e-03	3.02e-03	4.38e-03	65.6	1.27
Ray 3	1.51	6.67e-03	10.66%	7.65e-03	6.39e-03	9.16e-03	67.25	6.48
Ray 4	1.36	8.55e-03	9.12%	1.03e-02	8.86e-03	1.21e-02	66.6	5.6
Ray 5	0.89	8.08e-03	27.02%	1.33e-02	9.52e-03	1.85e-02	66.2	-0.7
Compound B	1.84	2.58e-04	11.33%	4.28e-04	3.43e-04	5.33e-04	55.82	-0.05

4

Ray Index	fi	Ki [CI at 95%]	ConcenCompound A	ConcenCompound B	interaction Characterization
Ray 2	0.27	1.05[0.81;1.37]	3.31e-03	3.31e-04	No decision
Ray 3	0.52	1.21[0.91;1.6]	7.40e-03	2.47e-04	No decision
Ray 4	0.77	1.13[0.81;1.58]	1.02e-02	1.14e-04	No decision
Ray 5	0.91	1.24[0.77;1.98]	1.32e-02	4.89e-05	No decision

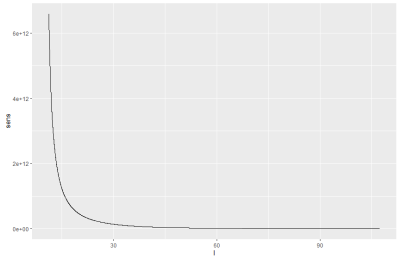
5





The Hand model: attractive but limited usage in practice

- With tests on real cases, a HUGE limitation appears: the integration of the sensitivity functions is not feasible when the slope is ≤ 1 for at least one single compound
  - In this case, the sensitivity has the following form



and the integral $f^{-1}_{AB,\lambda}(x) = \int_0^x \left(\frac{\lambda}{f_A^{-1'}(y)} + \frac{1-\lambda}{f_B^{-1'}(y)} \right)^{-1}$ dy does not converge

- **Big deception** → in a lot of cases in our experiments, the slope is lower or equal to 1

- In our Rshiny application, for the moment we limit the use of Hand model to the case with a slope >1

Conclusion

- Lessons learned of this work
  - Not easy to evaluate the Hand model (no mathematical definition of additivity) → What is the reference ?
  - A nice and attractive mathematical model can not be selected if it is not in adequation with the biological reality

- Next steps
  - Find a mathematical solution to the limitation of slope >1
  - Explore a new model

- Special thank
  - → Jiyoung OH, the trainee who initiated the work on the Hand model
  - → Maxime BELLAMI (IT&M stat) who strongly contributed to the development of the Rshiny app
  - → Jakob VANHOEFER and Jan HASENAUER, two of the authors of the Sinzger M. et al., 2019 publication who kindly answered to our questions

References for the Hand model

- Hand, D. J. Synergy in drug combinations. In Gaul, W., Opitz, O. & Schader, M. (eds) Data Analysis: Scientific Modeling and Practical Application, 471–475, 10.1007/978-3-642-58250-9_38 (Springer Berlin Heidelberg, 2000).
- **Sinzger M. et al. (2019) Comparison of null models for combination drug therapy reveals Hand model as biochemically most plausible. Sci. Rep 9, 3002.**

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Thank you for your attention

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Back-up slides

Details on Loewe model

- Equation for Loewe additivity model between compounds A and B: $\frac{C_A}{ICX_A} + \frac{C_B}{ICX_B} = 1$

With C_A, C_B: concentrations of each compound in the mixture necessary to obtain X% of effect

ICX_A, ICX_B: concentrations of compounds A and B necessary to obtain X% of effect for each compound alone (often absolute IC50, but not mandatory)

- This equation is based on the dose equivalence principle
  - There are one concentration D_A of A alone and one concentration D_B of B alone such as $Effect_A(C_A)=Effect_B(D_B)$ and $Effect_B(C_B)=Effect_A(D_A)$
  - Hypothesis : constant relative potency → $R = \frac{ICX_A}{ICX_B} = \frac{C_A}{D_B} = \frac{D_A}{C_B}$

- There is additivity if the same effect is obtained with the combination and with single compounds at equipotent concentration i.e if $Effect_{AB}(C_A+C_B)=Effect_A(C_A+D_A)=Effect_B(C_B+D_B)$

$$\mathbf{Effect_{AB}}(\mathbf{C_A}+\mathbf{C_B})=\mathbf{X}\%\rightarrow C_A+\mathbf{D_A}=\mathbf{ICX_A}\leftrightarrow C_A+\mathbf{R}\cdot\mathbf{C_B}=ICX_A\leftrightarrow\frac{\mathbf{C_A}}{\mathbf{ICX_A}}+\frac{\mathbf{C_B}}{\mathbf{ICX_B}}=\mathbf{1}$$

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Details on Hand model (1/2)

- Hand model: formulation of the additivity in terms of instantaneous effect gains rather than effect level
- Prerequisites
  - Dose-effect curve: $f(x)=E_{min}+\frac{E_{max}-E_{min}}{1+\left(\frac{IC50}{x}\right)^{m}}$ with its inverse $f^{-1}(y)=IC50\left(\frac{E_{max}-y}{y-E_{min}}\right)^{\frac{-1}{m}}$
    - $f^{-1}(y)$: dose giving the effect y
    - $f'(x)$ measures the variation of the effect per dose

Derivation

  - Sensitivity
    - $f'\left(f^{-1}(x)\right)$ noted S(x) : instantaneous gain in effect per dose giving the effect x
    - $S(x)=\frac{m}{IC50(E_{max}-E_{min})}(x-E_{min})^{1-\frac{1}{m}}(E_{max}-x)^{1+\frac{1}{m}}$

Details on Hand model (2/2)

- Under the additivity assumption of Hand, the combination must satisfy the following equation:

$$S_{AB,\lambda}(x)=\lambda S_A(x)+(1-\lambda)S_B(x) \Leftrightarrow f'_{AB,\lambda}\left(f_{AB,\lambda}^{-1}(x)\right)=\lambda f'_A\left(f_A^{-1}(x)\right)+(1-\lambda)f'_B\left(f_B^{-1}(x)\right)$$

λ: proportion of compound A in the mixture (mixture ratio)

→ At each effect level both compounds contribute linearly to the instantaneous gain in effect of the combined curve

→ The effect-sensitivity curve of the combination is a weighted average of the single effect-sensitivity curves

- Dose effect curve for expected additive combination
  - From the inverse derivative formula

$$S_{AB,\lambda}(x)=f'_{AB,\lambda}\left(f_{AB,\lambda}^{-1}(x)\right)=\frac{1}{f_{AB,\lambda}^{-1'}(x)}=\frac{\lambda}{f_A^{-1'}(x)}+\frac{1-\lambda}{f_B^{-1'}(x)}$$

→ The inverse dose-effect curve for expected additive combination:

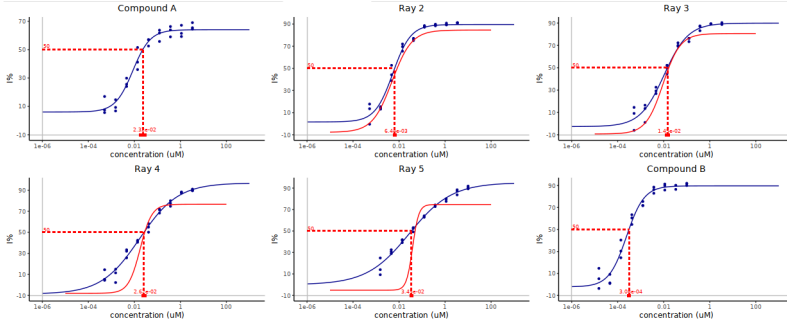
$$f^{-1}{}_{AB,\lambda}(x)=\int_0^x\left(\frac{\lambda}{f_A^{-1'}(y)}+\frac{1-\lambda}{f_B^{-1'}(y)}\right)^{-1}dy$$

→ The dose-effect curve for expected additive combination can be obtained

Integration

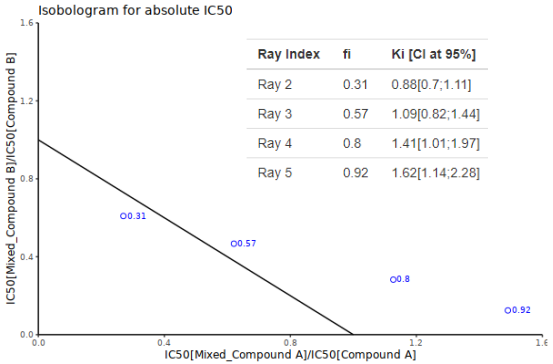
Hand model- Example 2

- 6 dose-effect curves (2 with single compounds + 4 with mixtures with constant proportion of both compounds)



Ray Index	slope	IC50 rel	CV%	IC50 abs	IC50 abs (LCB95%)	IC50 abs(UCB95%)	Top	Bottom
Compound A	1.14	8.52e-03	17.32%	2.32e-02	1.65e-02	3.25e-02	64.03	6.05
Ray 2	1.12	5.38e-03	14.6%	6.44e-03	5.41e-03	7.66e-03	89.59	1.59
Ray 3	0.83	1.04e-02	18.93%	1.45e-02	1.19e-02	1.77e-02	89.95	-2.69
Ray 4	0.52	1.71e-02	29.94%	2.62e-02	2.12e-02	3.23e-02	96.91	-8.66
Ray 5	0.47	2.78e-02	16.83%	3.45e-02	2.91e-02	4.11e-02	95.1	0 *
Compound B	1.13	2.42e-04	13.65%	3.08e-04	2.55e-04	3.72e-04	89.65	-2.19

- Loewe model



Ray Index	fi	Ki [CI at 95%]
Ray 2	0.31	0.88[0.7;1.11]
Ray 3	0.57	1.09[0.82;1.44]
Ray 4	0.8	1.41[1.01;1.97]
Ray 5	0.92	1.62[1.14;2.28]

- Hand model