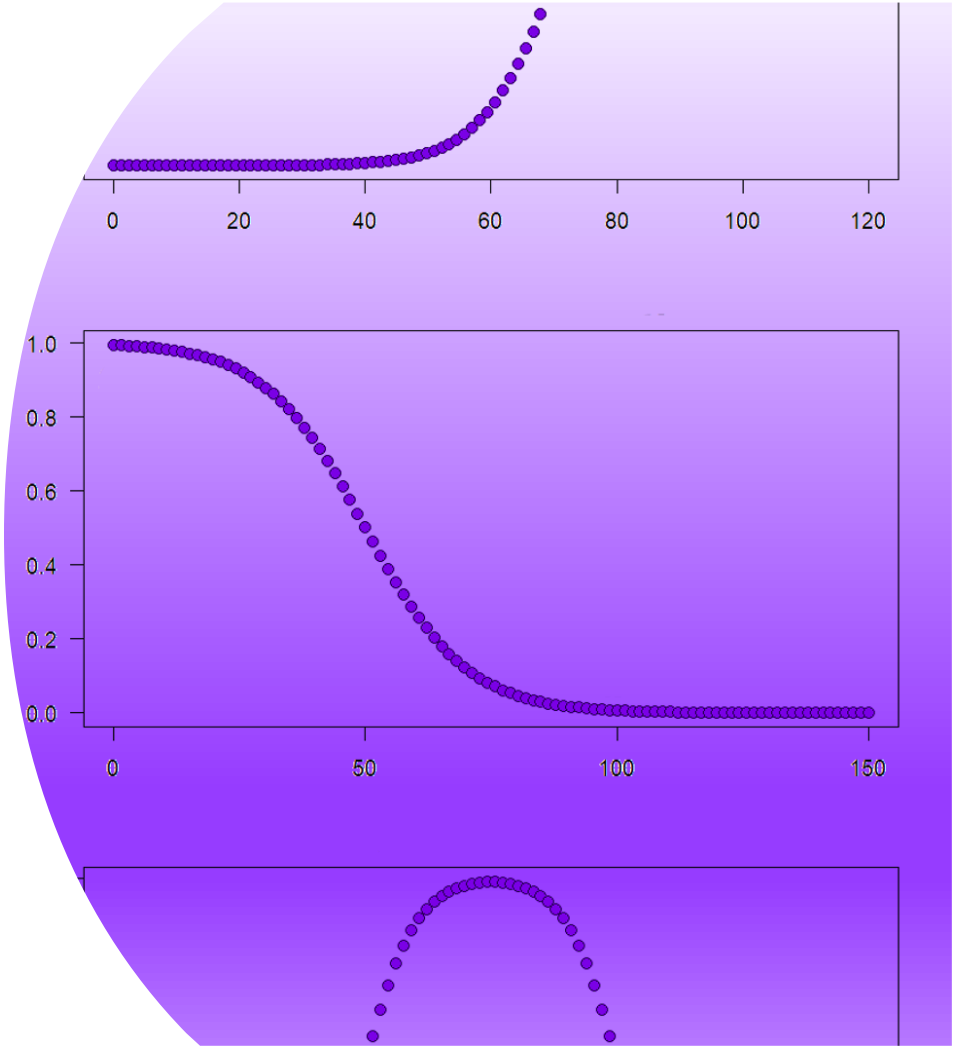
sanofi

Desirability functions: a case study to select promising candidates for optimal cytokines release

Alexandra Laugerotte
Non Clinical Efficacy and Safety Biostatistics



NCS Non-Clinical Statistics Conference
Wiesbaden, DE / 25-27 September, 2024

01 Objectives of the study

Objectives of the pharmacologist

- **Objectives**
  - For each compound, use percentage of lysis as parameter of interest to evaluate efficacy and cytokines as the parameters of interest to evaluate safety
  - Compare compounds based on both efficacy and safety and rank them

  - **What is lysis ?**
    - Cells death

  - **What is a cytokine ?**
    - regulators that play a major role in immune system, by affecting the growth of cells
    - key contributor to current clinical cancer research

02 Desirability functions : an introduction

The desirability function approach

The desirability function approach is a common technique for optimizing multiple response variables simultaneously.

It can be used also to rank compounds based on several characteristic variables. The compounds can be any type of entity of interest, such as antibodies or biomarkers.

The characteristic variables are any numeric (quantitative) variables that describe the properties of compounds.

Resulting in a global desirability score, with values between 0 and 1, where 1 represents perfect state in all characteristics and 0 represents unacceptable at least for 1 characteristic.

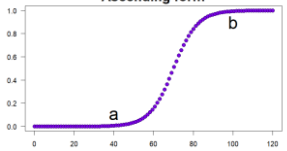
The global score computation

Step 1 - Build a desirability function per response

Step 2 - Build a global desirability function & Compute a global desirability score

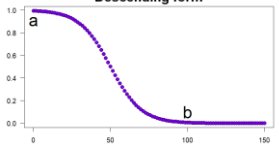
Step 1

Ascending form



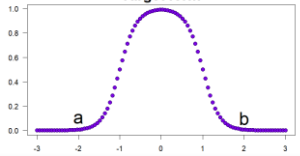
$$f_A(x) = \frac{1}{1 + e^{\frac{10}{b-a}\left(x - \frac{a+b}{2}\right)}}$$

Descending form



$$f_B(x) = \frac{1}{1 + e^{-\frac{10}{b-a}\left(x - \frac{a+b}{2}\right)}}$$

Target form



$$f_C(x) = \frac{1}{1 + e^{\frac{sign(x-c)\frac{10}{\frac{b-a}{2}}\left(x - c - sign(x-c)\frac{b-a}{4}\right)}}}$$

Step 2

Weighted geometric mean:

$$D = \left(\prod_{i=1}^{n} d_i^{w_i} \right)^{\frac{1}{\sum_i w_i}}$$

Where

i varied from 1 to n (the number of parameters)

d_i are the individual desirability values for variable i

w_i are the corresponding importance (weights) relatively to other parameters.

03 Efficacy and safety parameters

Efficacy and Safety parameters

30 compounds ranked

Efficacy parameter: Lysis (%)
7 donors

- Minimize Geometric Mean & max of **EC50**
- Maximize Arithmetic Mean & min of **Top**

4 parameters

Safety parameters: 6 cytokines
6 donors

- Minimize Mean & max of **cytokine level at EC20 of lysis**
- Minimize Mean & max of **cytokine level at max concentration**

24 parameters

Global desirability function with 26 parameters to minimize and 2 parameters to maximize.

Same global weight for parameters of efficacy and of safety were chosen.

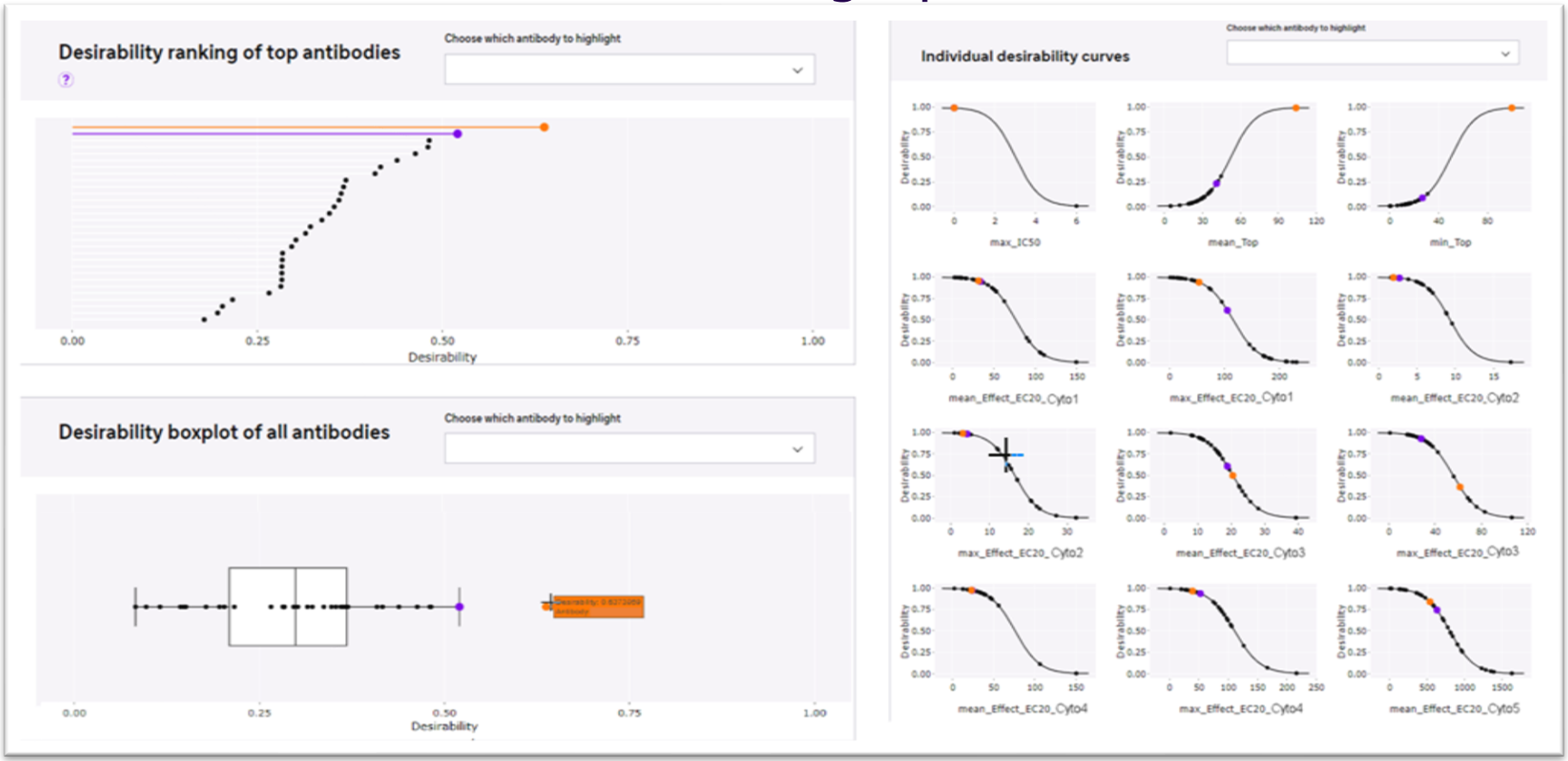
Missing data

As missing data are not allowed to calculate desirability function, imputation is a crucial step of the process.

Missing data are imputed using missForest package, a machine learning-based data imputation algorithm that operates on the Random Forest algorithm, using available information from all variables: for each variable with missing values, MissForest fits a random forest on the observed part and then predicts the missing part.

04 Results

Interactive graphs



From SANOFI internal application

05 Conclusion

To conclude

- Desirability functions have been used to select promising candidates for optimal cytokines release

- A software application has been developed internally – if any question feel free to ask during breaks

Thank you
&
Thanks to main contributors

Fanny Windenberger (use-case)

Valérie Martin (tool)
Andreas Schulz (tool)
Luc Esserméant (tool)

sanofi