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Using desirability indices for decision making in drug development

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Motivations

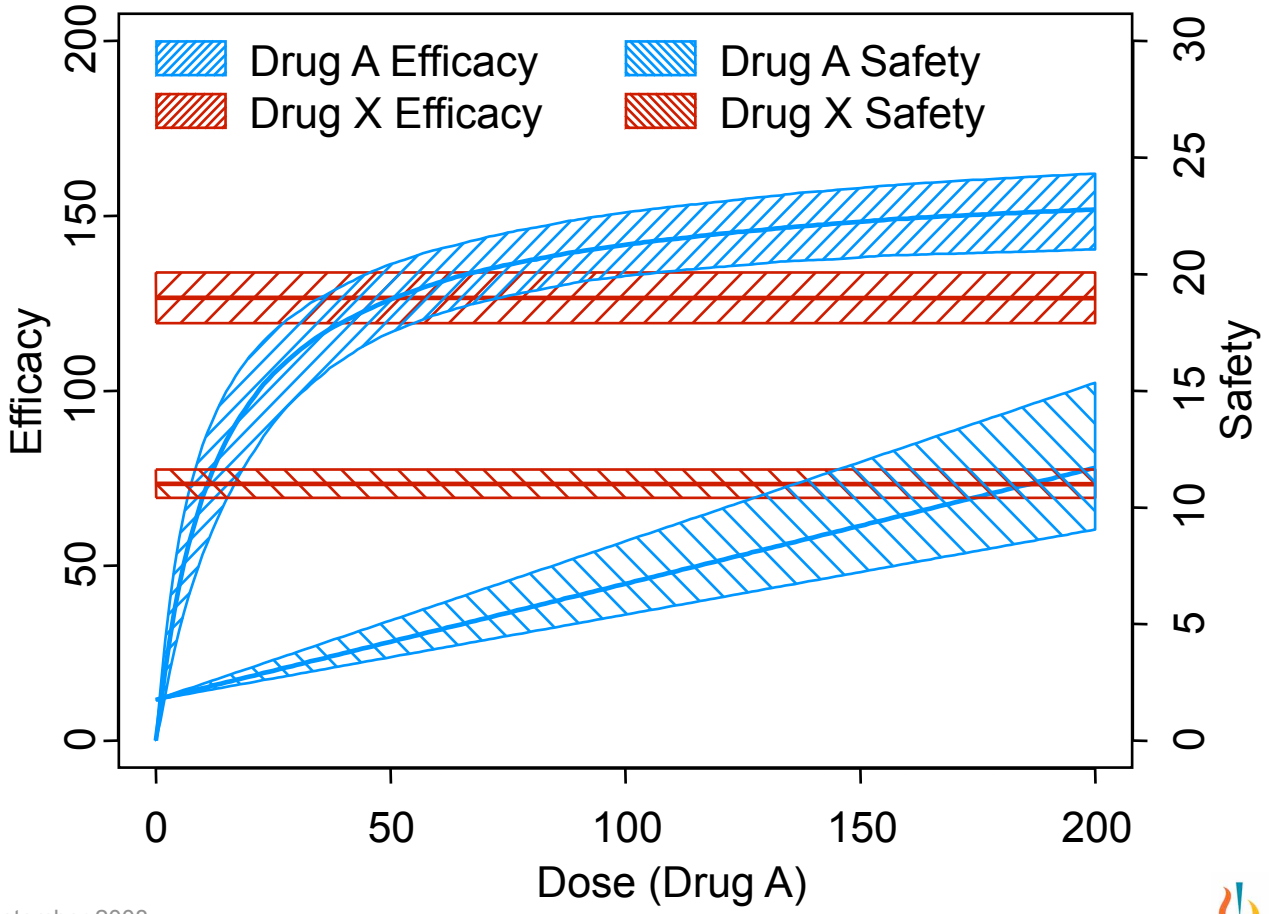
Which type of decisions ?

- Dose optimization:
  - Determining the optimal dose of a compound based on various outcomes.
  - These will typically be, but not restricted to, efficacy and safety outcomes.
- Compound comparison:
  - Comparing compounds based on various attributes.
  - These can be clinical outcomes (efficacy, safety), quality of life benefits, but also very general attributes (drugability properties, economic factors, etc).

An example

Dose response curves (Drug A) / Reference (Drug X)

- Drug A is a new candidate compared to Drug X, a marketed compound.



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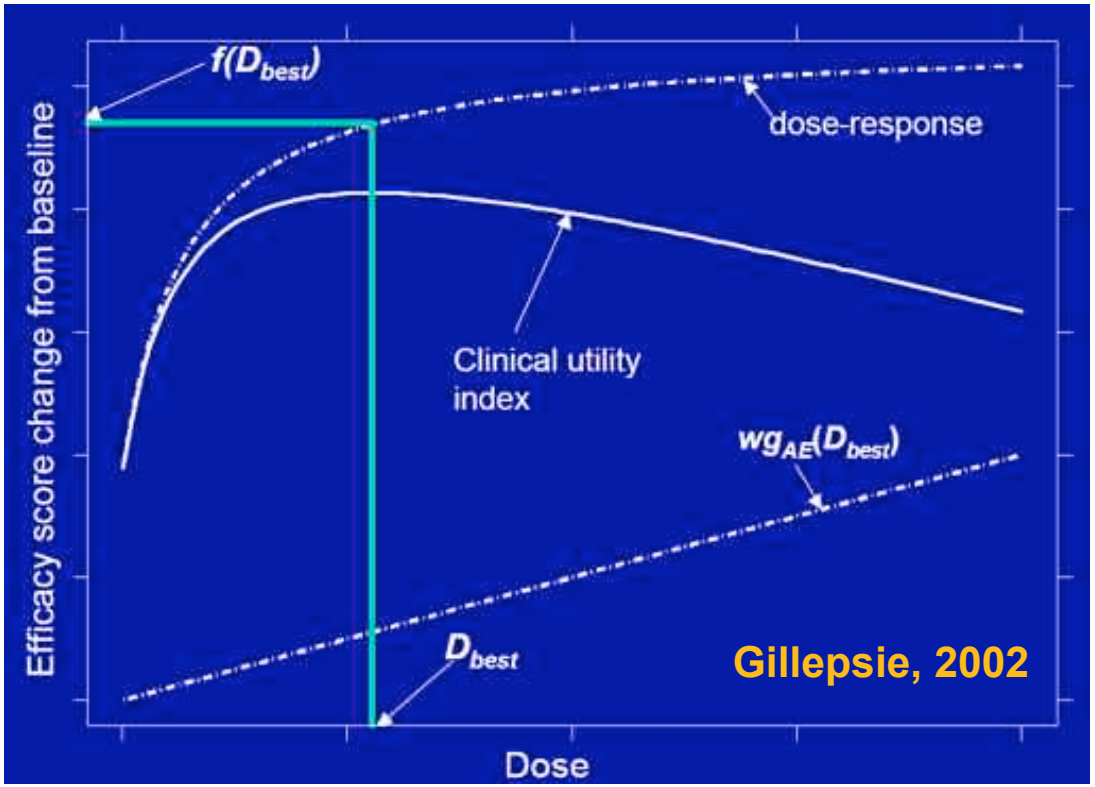
Measuring benefit and risk

The Clinical Utility Index (CUI)

- The CUI has been proposed as an integrated measure of benefit/ risk for the determination of optimal doses (illustration below) or the comparison of competing treatments.
- The CUI is defined as a weighted sum.

$$CUI = f(D) - w.g_{AE}(D)$$



Borrowing ideas from another field…

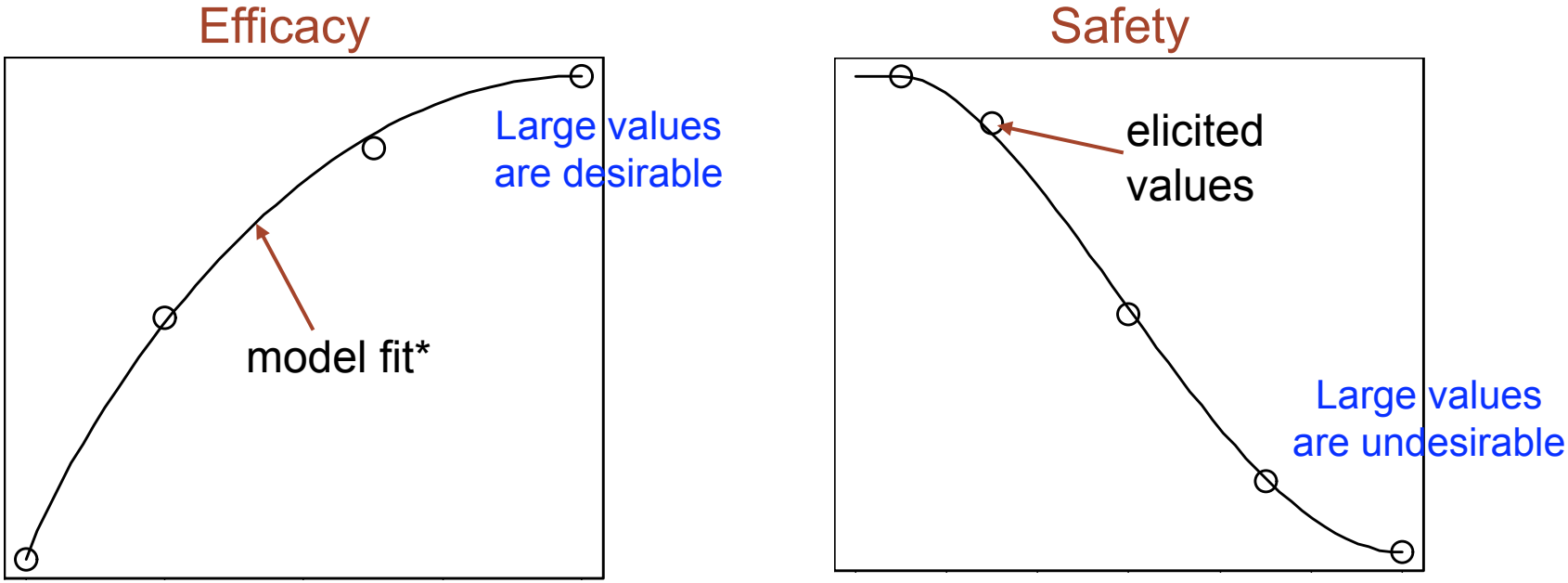
Multi-criteria optimization (MCO)

- Typically arises in the optimization of industrial production processes, e.g. to improve the quality of a product.
- Problem: a set of factors (X_j) is related to product properties (Y_k): $E(Y_k) = f_k(\boldsymbol{X}, \theta_k)$… Which factor settings optimize simultaneously the possibly competing properties?
- Desirability concept (Harrington, 1965) :
  - the Y_k's are transformed into a unitless (desirability) scale, and combined through some kind of summary measure.
- The MCO problem is then transformed into a response surface one, yielding pareto-optimal solutions.

Desirability functions

Example

- Desirability functions are used to quantify how desirable certain outcomes are on an absolute scale ([0,1])
- Elicited desirability functions:



* Beta growth function: $$y = \left(1 + \frac{x_e - x}{x_e - x_m}\right)\left(\frac{x - x_b}{x_e - x_m}\right)^{\frac{x_e - x_b}{x_e - x_m}}$$

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The desirability index

Combining desirability values

- Desirability values are combined using some kind of mean value, the Desirability Index (DI).
- The weighted geometric mean has desirable properties:

$$DI(d) = D_{Eff}(f_{Eff}(d))^{w_1} \times D_{Saf}(f_{Saf}(d))^{w2}$$

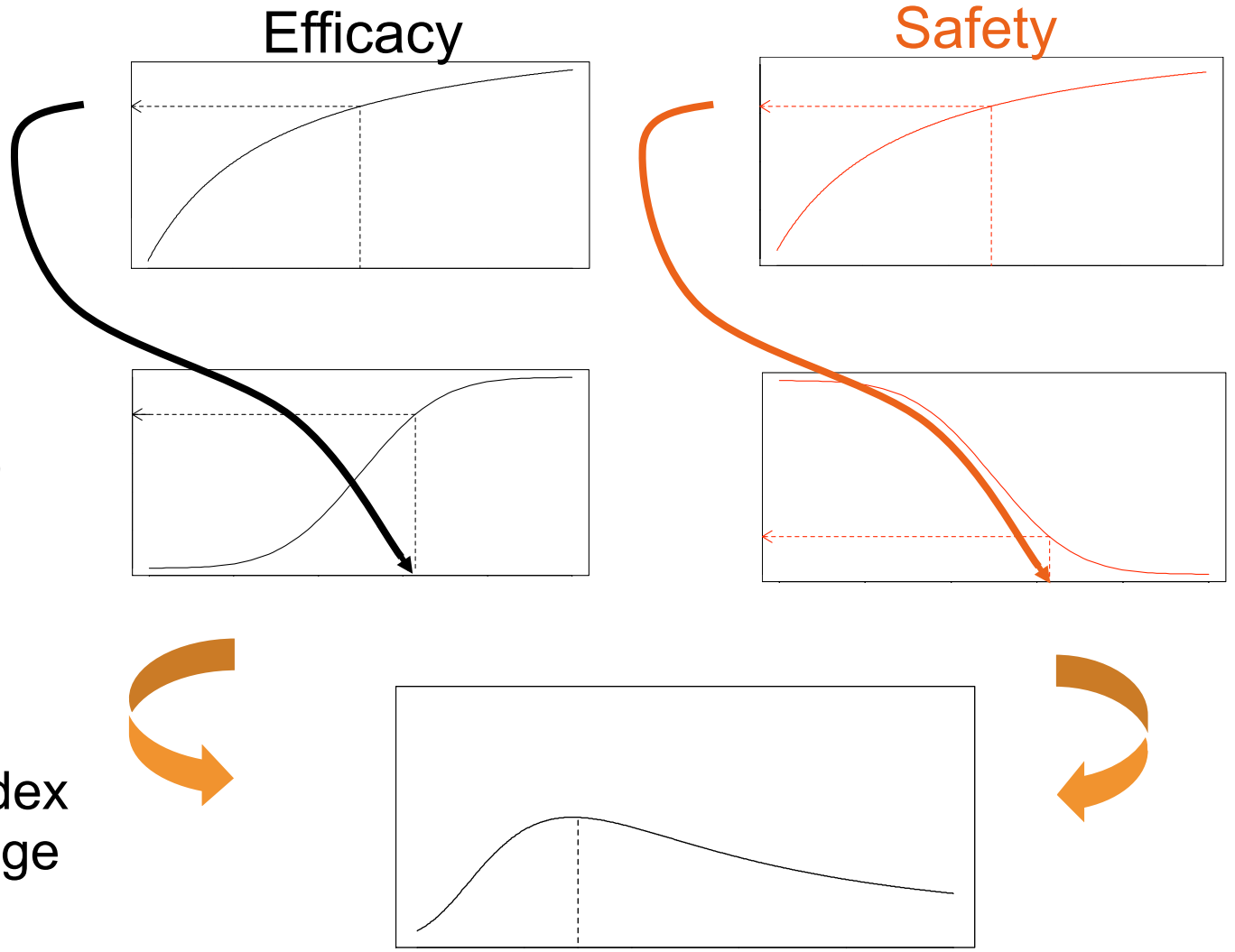
"If one of the product's properties is completely unacceptable, the product as a whole is unacceptable."

- DI can serve as an absolute measure to answer questions of interest here.

Desirability for dose optimization

In three steps…

- Derive dose response curves
- Convert responses to desirability
- Optimize desirability index over dose range



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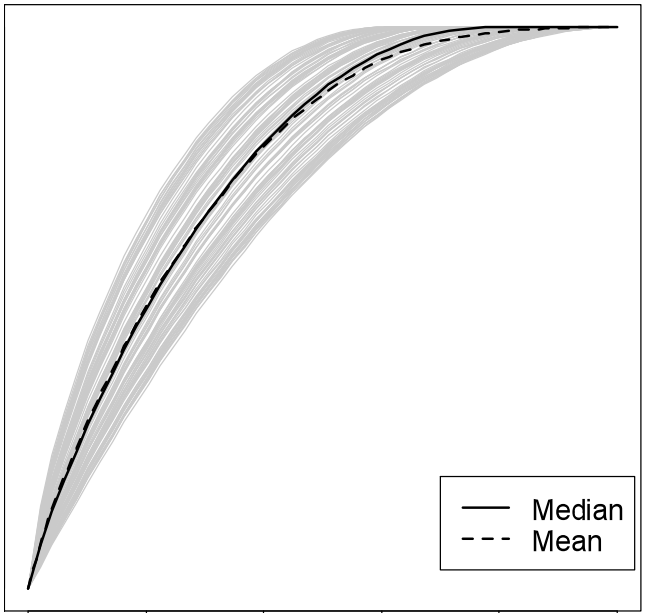
Sources of uncertainty

Toward a more robust assessment

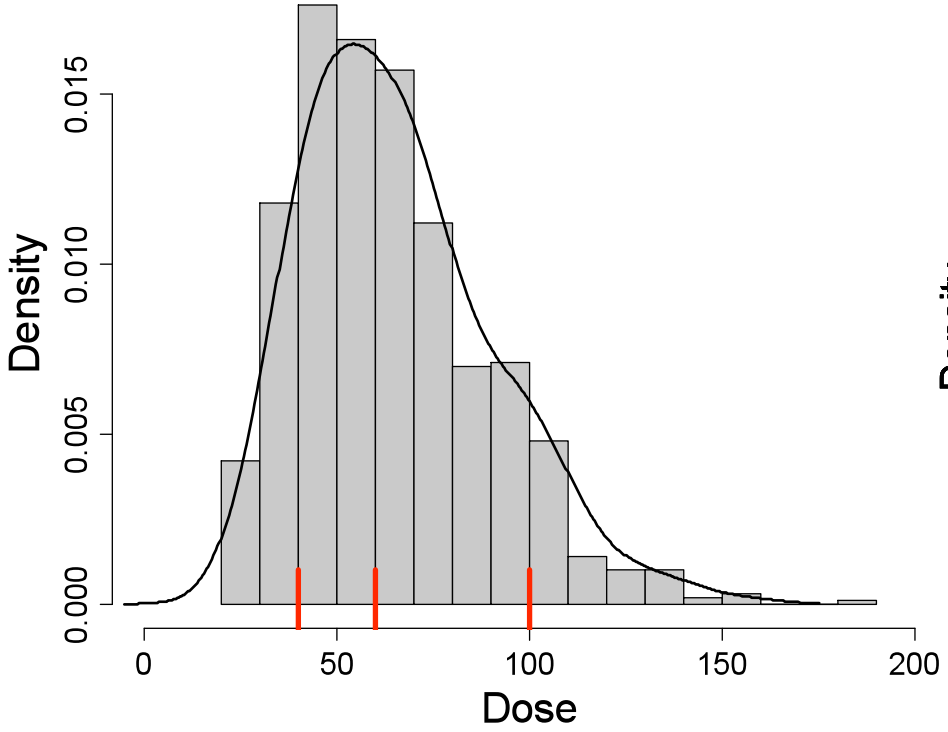
- Two sources of uncertainty are integrated in the analysis:
  - Variability in estimated dose response curves.
  - Desirability functions are inherently subjective and random variation is added to achieve a more robust assessment.



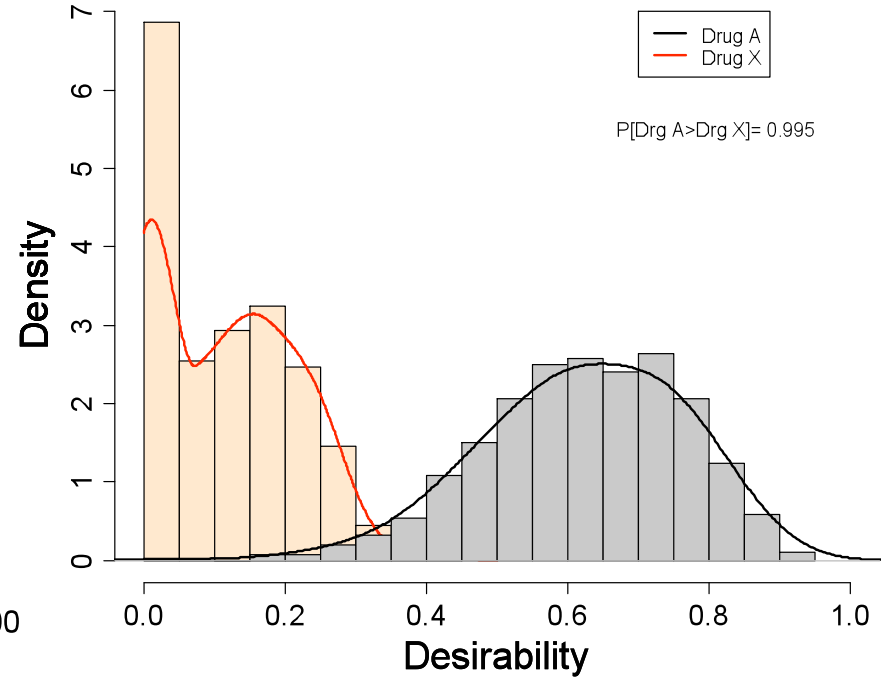
Illustration

Histograms are generated by simulating from sources of uncertainty

Distribution of optimal dose



Compound comparison Distribution of DI



Red marks correspond to 10th, 50th, 90 th quantiles

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Discussion

- Desirability indices can help support dose and compound decisions in drug development.
- Provides a general and flexible framework.
- Can be cast into a Bayesian decision theory setting, where the desirability index acts as a gain function.
- Practical difficulty in eliciting desirability functions (and weights) is partly overcome here by adding uncertainty, but requires expert opinion nevertheless.
- Should one characterize the 2D desirability surface directly to better represent the risk-benefit assessment ?

Acknowledgements

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