Guiding dose escalation studies in Phase 1 with **unblinded** modeling

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Innovative model-based dose escalation designs: what next?

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Abstract

Guiding dose escalation studies in Phase 1 with unblinded modeling

Clinical studies in early drug development are commonly small-sized with very quick turn-around times. Single- and multiple-ascending dose studies can incorporate 6 healthy subjects on active treatment and 2 on placebo with groups treated every other week. Traditionally, dose escalations were fixed prior to study start and the study stopped when doses showed intolerability.

The incorporation of an unblinded modeling and simulation scientist allows for greater flexibility. A model can incorporate prior information from pre-clinical experiments and the model can be updated after each group. Based on simulations and predictions from the model it can then be decided if the doses are increased at larger or smaller steps. Such an approach is particularly helpful in a situation of large uncertainty about the clinically relevant doses.

This presentation provides an introduction to algorithms for the selection of the next dose with case studies and discusses practical aspects of implementing an unblinded modeling and simulation scientist in clinical studies.

Overview

- Double-blind study conduct
- Phase I characteristics
  - SAD and MAD
  - MTD concept
- Approaches
  - Visualization
  - Estimation
  - Optimization
  - Population PK/PD modeling
- Summary
  - Pros and cons
  - Maintaining the blind
  - Experiences

Double-blinded study conduct

Medical evaluation of safety data and adverse events

- Must be conducted in fully blinded fashion
  - By the MD or CP
  - To avoid any bias towards the evaluation of safety data
- Otherwise: severe protocol violation -> study corruption

On the other hand

- Uncertainty can be large, in particular in first-in-man studies
- Knowledge accumulates with dose groups (SAD, MAD)
- Certainty on selection of next dose increases with knowledge during the study

SAD and MAD: Dose Escalation

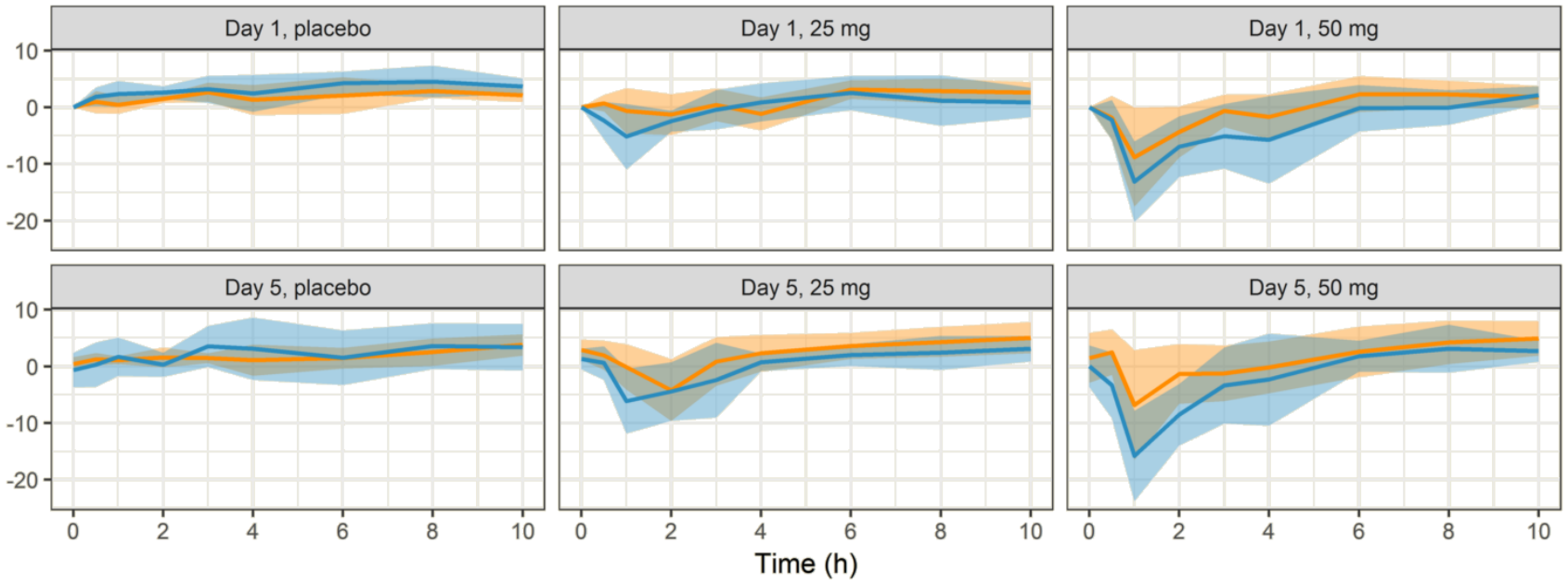
- Groups (cohorts) of subjects are treated in a dose escalation procedure
- Each group: all subjects receive the same dose or placebo
- One aim: determine the MTD
- Doses are defined at the start of the trial (example: 5, 10, 20, 30, 50 mg)
- Study stops when MTD is determined or all groups treated
- Frequently: multiple safety endpoints
- Occasionally (if efficacy in healthy subjects is similar to patients)
  - Safety and efficacy evaluation in healthy subjects

Stopping Criteria (example)

- Dose escalation will be discontinued if one or more of the following safety and tolerability stopping criteria is fulfilled in the most recent dose group:
- QTcF change from baseline > 60 ms (persistent over more than 30 min) in ≥ 2 subjects **or**
- QTcF > 500 ms and a change from baseline > 40 ms (persistent over more than 30 min) in ≥ 2 subjects **or**
- …

Approach 1: Visualization

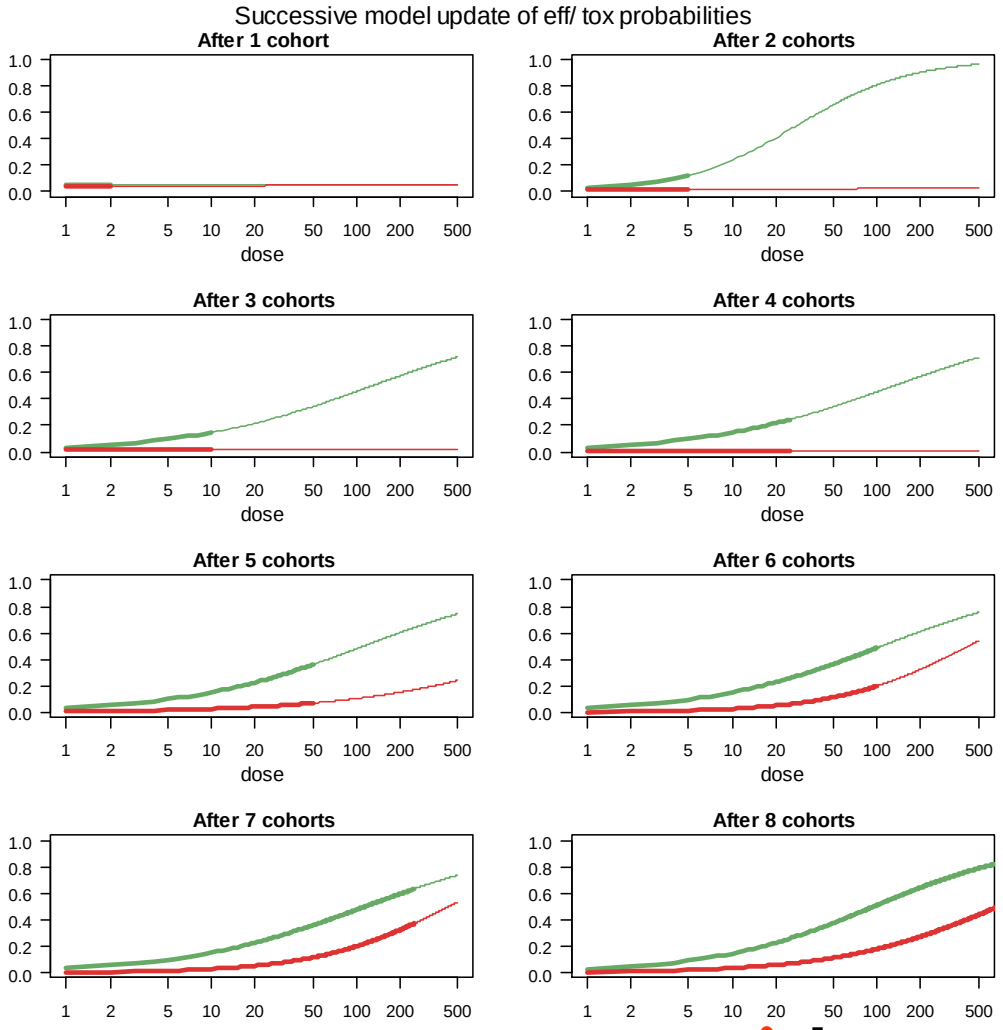
- Means and standard deviations by treatment group
  - Makes use of trt allocation information (active, placebo)
  - Start only after group 3 (group size placebo sufficiently large)



2: Iterative MTD estimation (Tibaldi, 2008)

Group	n	Dose	Efficacy	Toxicity
1	8	2	0	0
2	8	5	1	0
3	8	10	1	0
4	8	25	2	0
5	8	50	3	1
6	8	100	4	2
7	8	250	5	3
8	8	500	7	3

- Green: efficacy
- Red: safety (toxicity)
- Optional: use a Bayesian prior
  - Helps numerical stability (X^TX)
- Dose-response without use of trt information
  - Unblinding is a real concern here
  - Consider first occurrence of efficacy or safety



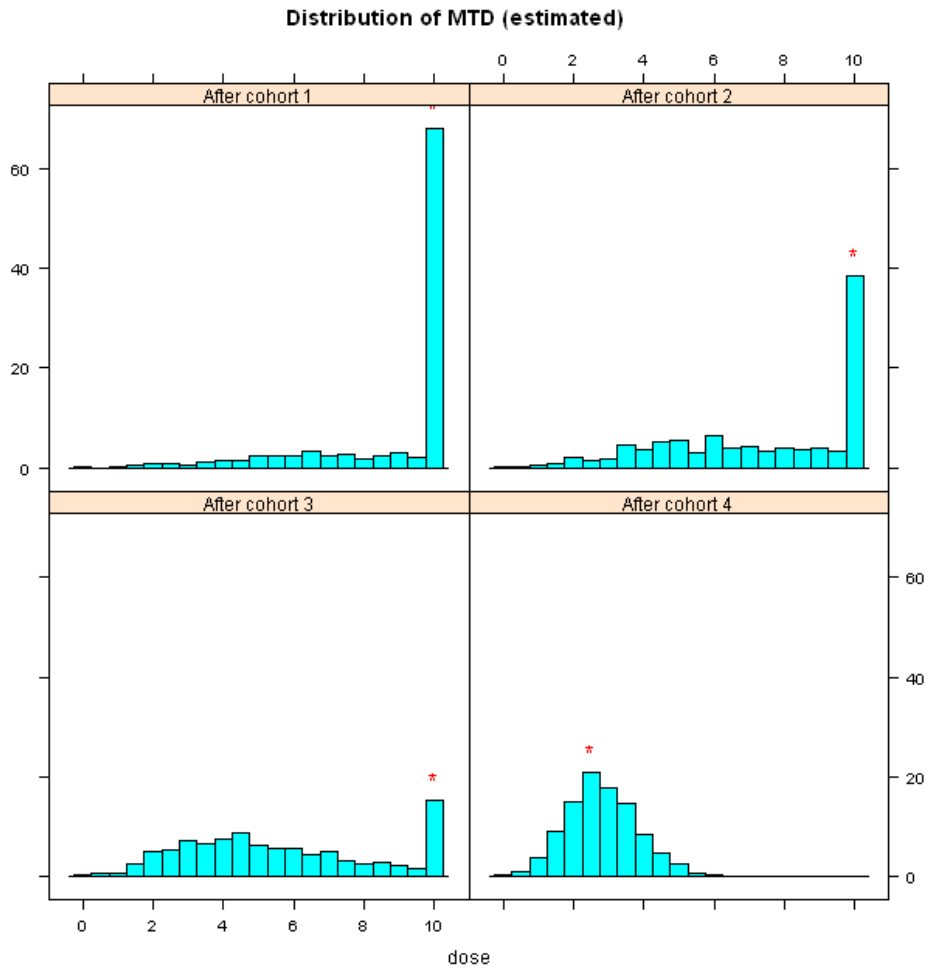
Iterative MTD estimation (2)

After each group

- Simulate the study a large number of times
- Each time, determine the MTD
- Obtain a distribution of the MTD

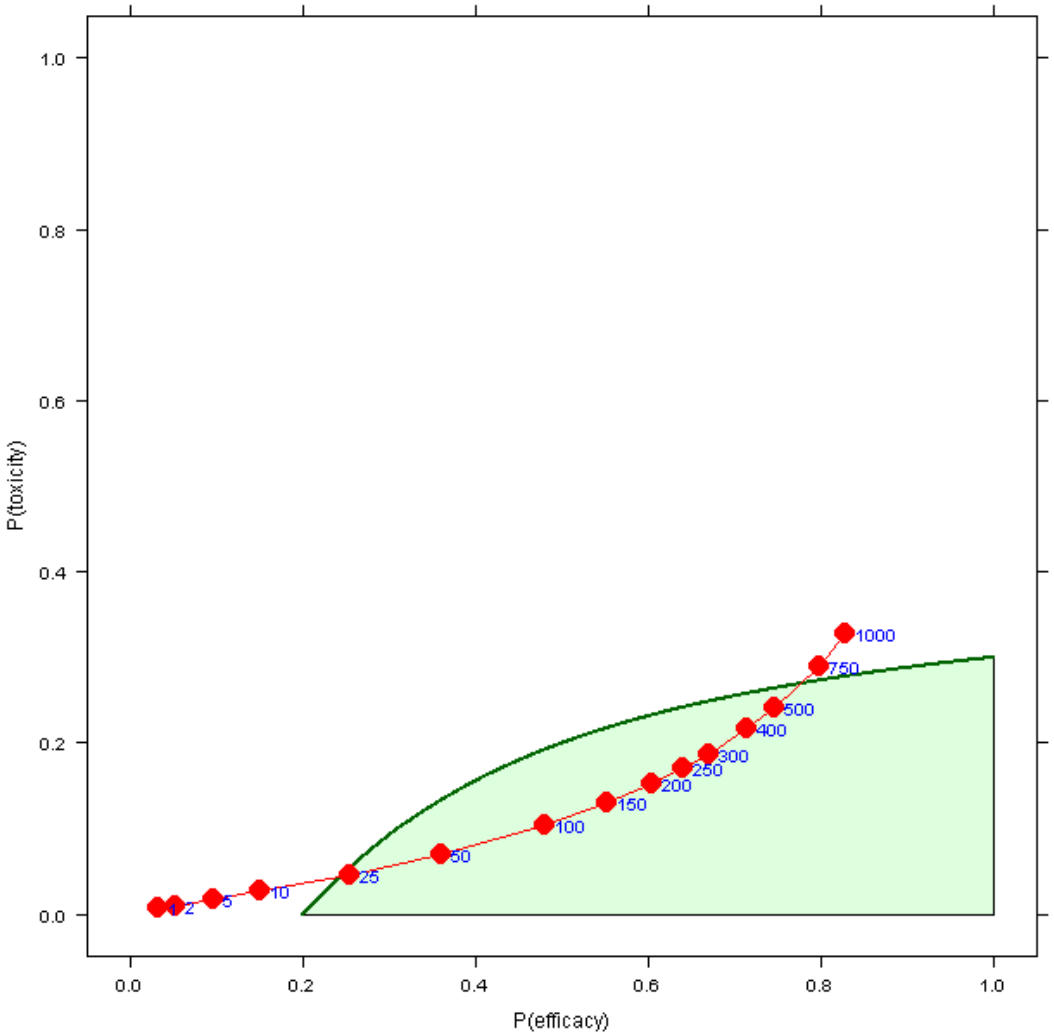
* most likely MTD

Example here: prior based on preclinical data, E_{max} model



Dingemanse J, Krause A: Impact of pharmacokinetic-pharmacodynamic modelling in early clinical drug development. European Journal of Pharmaceutical Sciences 2017

3. Efficacy-safety trade-off (Thall & Cook, 2004)

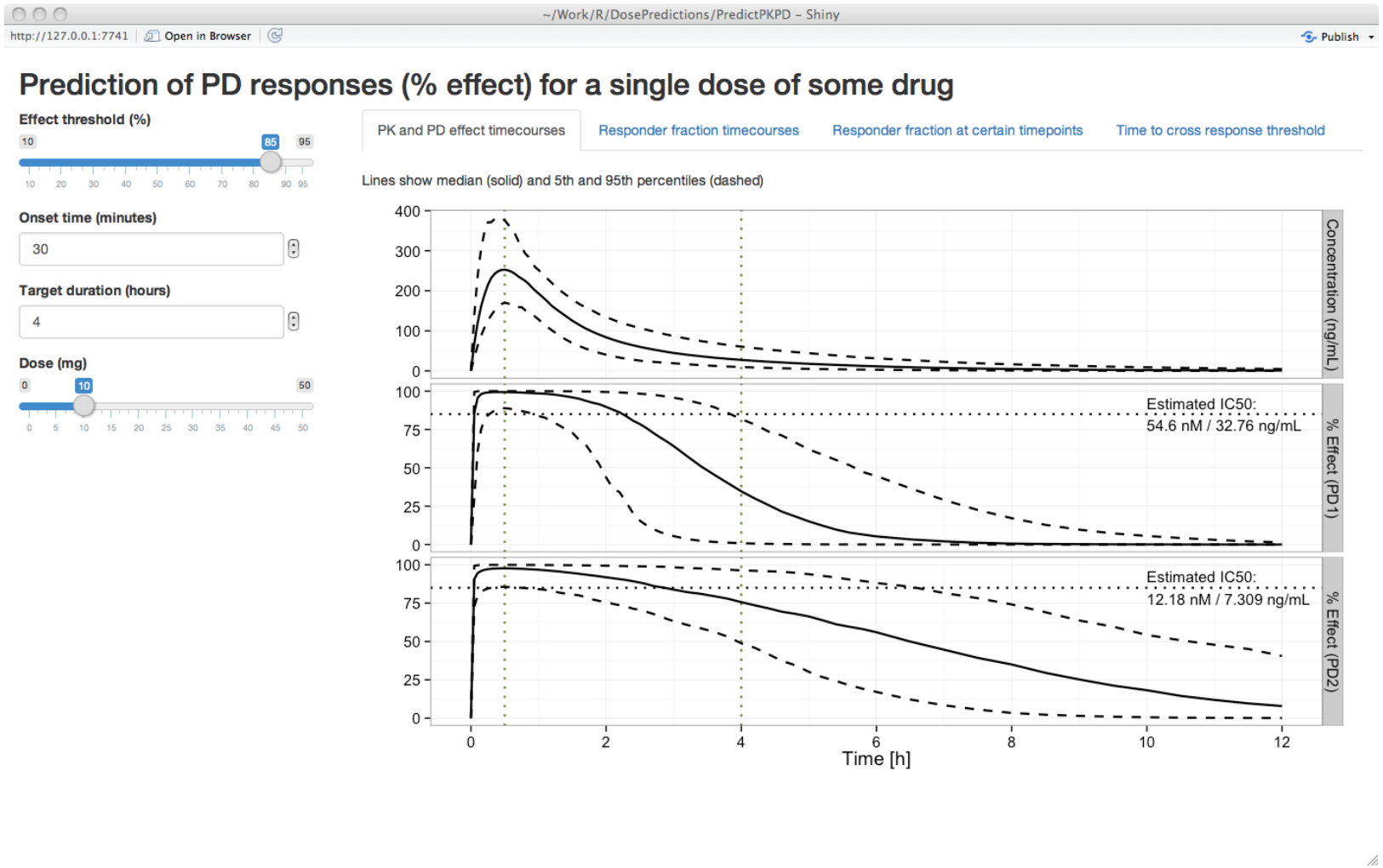


- Axes: efficacy (x), toxicity (y)
- Each dot: efficacy and toxicity for each candidate dose (estimate!)
- Optimum=bottom right: 100% efficacy, 0% toxicity.
- Green: acceptable area
- Desirability measure: close to optimum and far from acceptance line inside green area

4. Concentration-response modeling

- Use a population PK/PD model to estimate PK and PD
- Simulate PK and PD for a large number of subjects
- Make full use of treatment information
  - placebo and active doses
- Give the MD/CP an interactive tool (R & Shiny) to explore themselves
  - **While the study is ongoing!**

4. Concentration-response modeling

- 

Acknowledgement: Anne Kümmel

Discussion (1): Modeling contribution

- Decision making is supported
  - By estimating effects for candidate doses
- Example for a dose escalation criterion:
  - The maximum dose below the estimated MTD is administered
  - The dose will not be higher than 3x the largest dose administered so far
- The MTD can be estimated
  - Data-based: largest dose below the MTD.
  - Estimate: between data-based MTD and lowest dose above MTD (e.g., 172 mg)
- All data are used, not just the last group
  - SAD and MAD can be combined

Discussion (2): Different approaches

- Visualize summary statistics (means, std deviations)
  - Do not show individual data, in particular not (PK, PD)
  - Beware of single missing observations (one obs. missing at time t: take out all)
- Estimation of efficacy and safety
  - Dose-response without use of trt allocation (placebo vs active)
  - Use of trt allocation information is dangerous (in particular for safety data)
  - Can use priors (helpful for stability)
- Dose optimization
  - Can be fully automated (efficacy-safety trade-off, Thall and Cook)
- Concentration-response population model
  - Can make full use of the data (including placebo/active separation)
  - More work

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Discussion (3): Experiences

- Procedural colleagues must be won over to introduce a process with an unblinded modeling scientist
- Experience
  - The influence on the actual dose selection is limited
  - All available data are used, not just the last group -> consistency
- Concentration-response
  - Allows for full use of treatment allocation (placebo and active)
  - Disguises individual data
  - Concentration adjusts for differences in body weight and compliance
- **Much appreciated collaboration with early clinical colleagues**
  - **Feedback:**
    we feel much more safe and comfortable in dose selection

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Thank You!