Bayesian concept for combined Phase 2a/b trials

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Agenda

- Phase 2a: PoC studies
- Phase 2b: dose finding studies
- Simulation
- Results / Discussion

Phase 2a: PoC studies

Phase 2a: PoC studies

Definition of PoC

- “Earliest point in the drug development process at which the weight of evidence suggests that it is ‘reasonably likely’ that the key attributes for success are present and the key causes of failure are absent“ (Cartwright et al. 2010)
- Choice of endpoints may vary according to the type of decision to be made- usually good surrogates for Phase III or even phase III endpoints
- Usually 2-armed trial, highest safe dose of new drug vs. placebo (Frewer et al. 2016, Pulkstenis et al. 2017)

Phase 2a: PoC studies

Bayesian approach (Fisch et al. 2015):

- Declare PoC if the following criteria are fulfilled:
  - Significance: $Pr(\mu > 0 \mid data) \geq 1 - \alpha$
  - Relevance: $Pr(\mu > \text{minimally desired effect} \mid data) \geq \delta$

- Usually: choose small α (eg 10%) and moderate δ (ie$\geq$50%)
- If both significance and relevance are fulfilled: GO
- If only one of the criteria is fulfilled: CONSIDER

Phase 2b: dose ranging studies

Phase 2b studies

Objectives of Phase 2b studies

- Objectives (Ruberg 1995)
  - Find minimal dose with a better effect than control
  - Describe dose response relationship, usually by nonlinear regression model
  - Find dose that optimally satisfies safety and efficacy constraints

- Dose ranging studies: Estimate doses with interesting properties, eg
  - Minimal dose better than control (with a certain probability)
  - Minimal dose which is better than control plus Δ. (aka Minimal effective dose, MED)
    Several proposals how to define MED (Bretz et al. 2005), all depending on the confidence band around the regression curve

Phase 2b studies

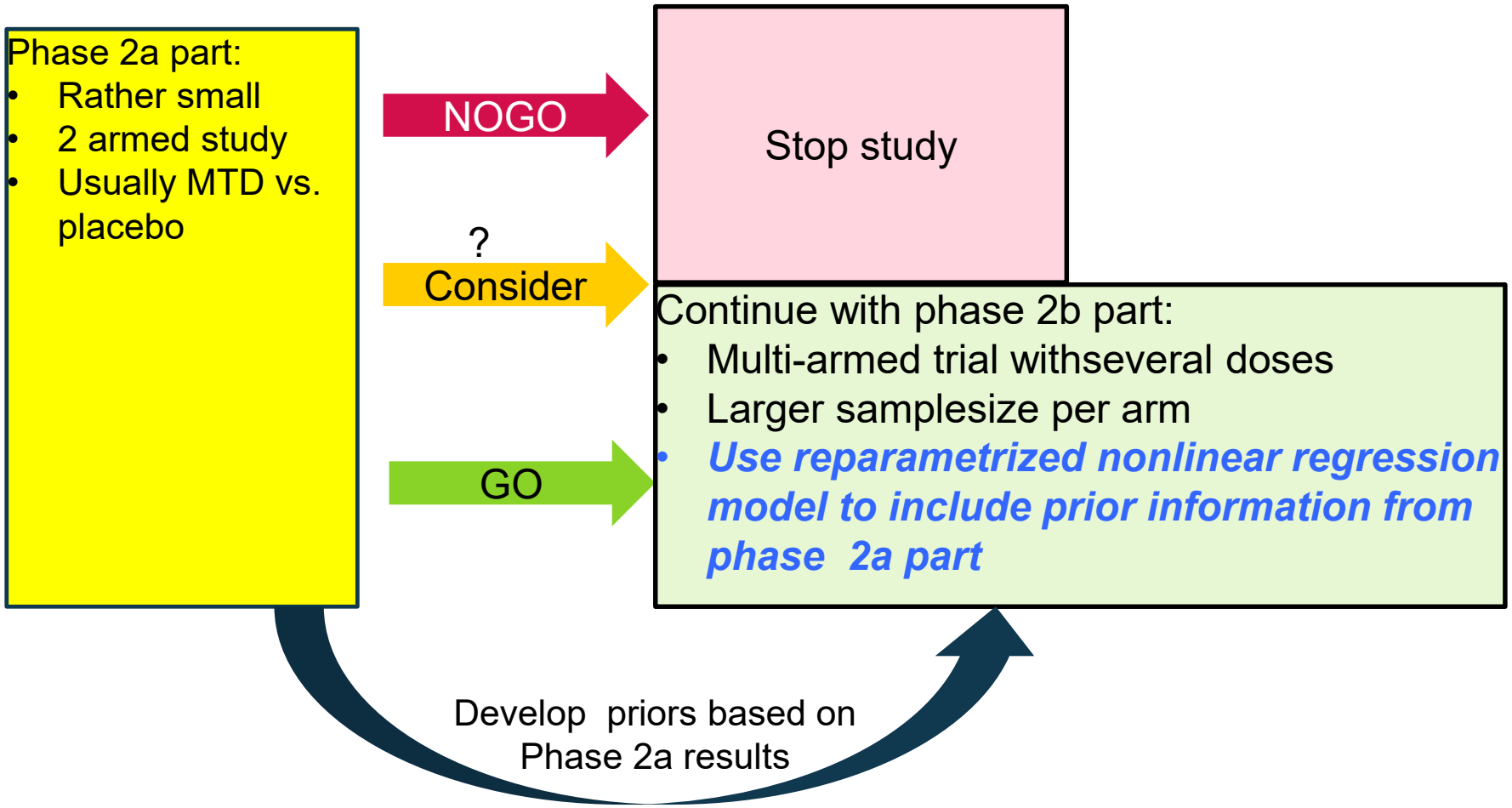
Design of Phase 2b studies

- Design (Ting 2006)
  - Fixed doses, parallel group design with placebo as control group
  - Eventually include active control
  - Usually at least 4 treatment arms
- Clinical endpoints or surrogate markers , depending on
  - practicability as well as on
  - secure translation to Phase 3

Combined Phase 2a/b studies

Combined Phase 2a/b studies

Schematic representation



Combined Phase 2a/b studies

General outline

The following sections will discuss

- How to include phase 2a information into the nonlinear model of a dose ranging study
- Simulation results concerning this approach.

- Combined phase 2a/b study will generally be faster than having two separate study protocols.
- Downside: increased inflexibility.

Combined Phase 2a/b studies

Phase 2a data as prior information for a dose ranging study with 3 parameter emax regression model

- Phase 2a: mean treatment effect for MTD and placebo (outcome assumed as $N(\mu_t,\sigma^2)$ distributed)
- Phase 2b: utilises nonlinear regression, eg 3 parameter Emax model:

$$y = E_0 + \frac{E_{max} * dose}{ED50 + dose} + \varepsilon$$

where ε is $N(0,\sigma^2)$ distributed

Goal:

Add information of Phase 2a in spite of modeling differences while preserving the possibility to downweight the phase 2a information

Combined Phase 2a/b studies

Phase 2a data as prior information for a dose ranging study with 3 parameter emax regression model (2)

- Consider Emax model for a prespecified dose d (where y_d denotes the expected outcome at d):
  - $y_d = E_0 + \frac{E_{max} * d}{ED50 + d}$

- Solving for E_{max} gives: $E_{max} = \frac{(y_d - E_0)(ED50 + d)}{d}$
- Reinsert this expression in the original Emax model equation:
  =>reparametrized model where y_d replaces Emax as model parameter

$$y = E_0 + \frac{(y_d - E_0)(ED50 + d) * dose}{d(ED50 + dose)}$$

Note that d is a known constant (ie the dose used in Phase 2a)

E0 and the new parameter y_d may be used to include the Phase 2a information

Combined Phase 2a/b studies

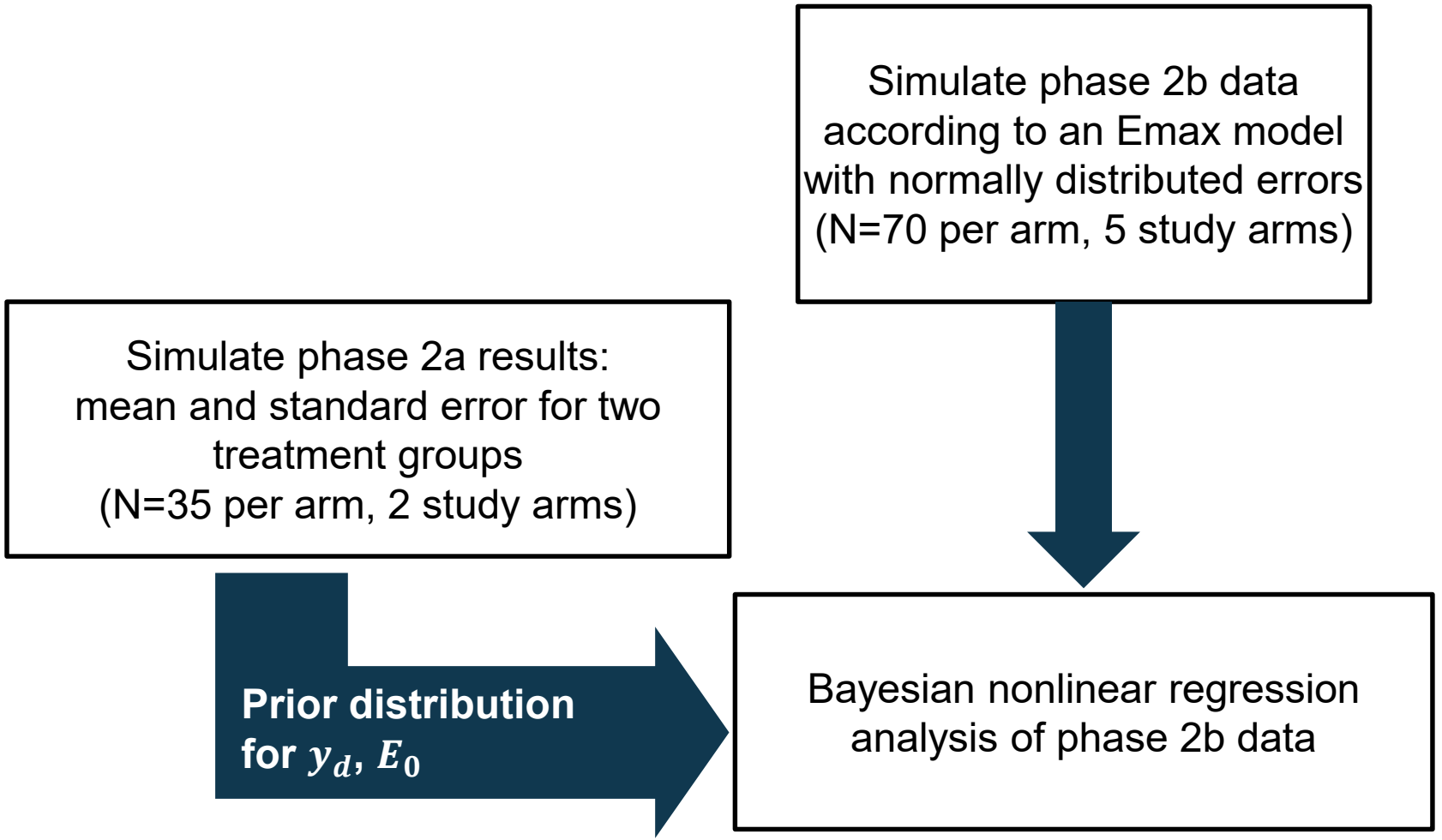
Phase 2a data as prior information for a dose ranging study with 3 parameter emax regression model (3)

- Posterior distributions for the group means in the phase 2a part can now be used as prior information for model parameters y_d, E_0 in the nonlinear regression of phase 2b.
- y_d, E_0 are examples for so-called expected value parameters which are sometimes proposed to reduce curvature in nonlinear regression models (Ratkowsky 1989)
- Expected value parameters can be found for many nonlinear regression models
- Open questions:
  - Prior information was not inserted for all model parameters. How large will be the effect in reducing variability of estimated model?
  - How large will be the bias in case of prior-data conflicts?

Assumptions for simulation

Simulation

Schematic representation of each simulation step



Simulation

General approach

- Simulation of Phase 2a
  - 2 arms: highest dose vs. placebo
  - Effect at highest dose if no bias present: 3.6
  - Effect at high dose if bias present: 4 (ie: 33% bias)
  - Effect at placebo: 2.4
- Simulation of Phase 2b:
  - simulated with 5 doses: 0 / 0.25 / 0.5 / 0.75 / 1
  - Mean response follows an Emax model
    - Effect at maximum dose: ≈ 3.6
    - E0: ≈ 2.4
    - Maximum effect compared to placebo: ≈ 1.2

Simulation

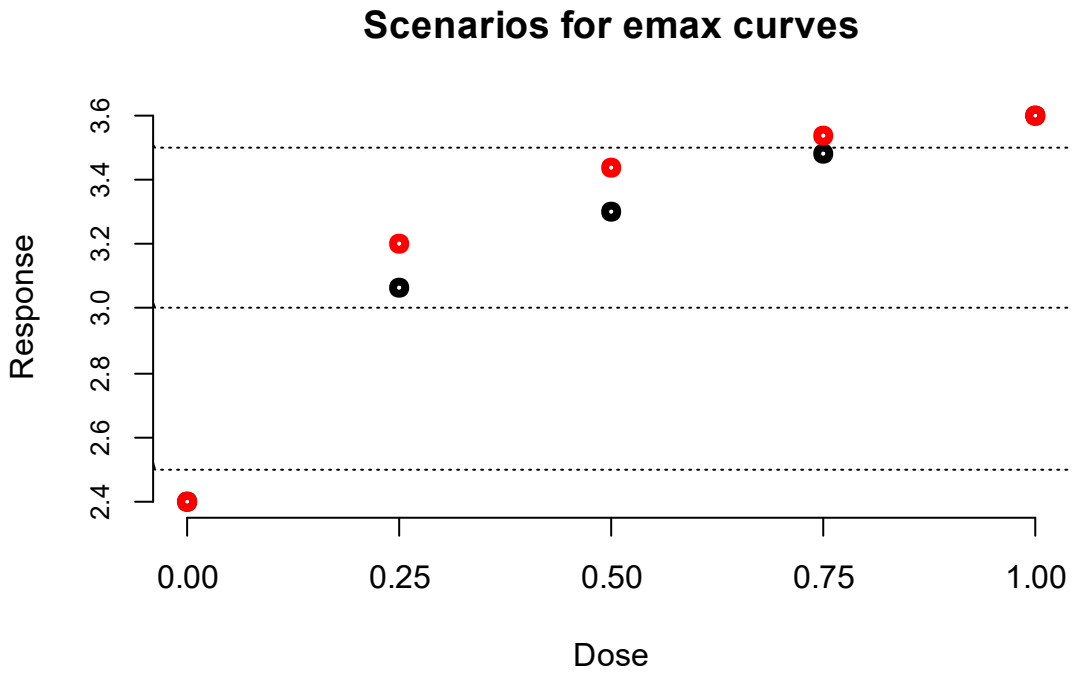
Overview on simulation scenarios

Fully weighted prior	Bias in phase 2a	moderate variability	low ED50
			high ED50
		high variability	low ED50
			high ED50
	No Bias in phase 2 a	moderate variability	low ED50
			high ED50
		high variability	low ED50
			high ED50
Half weighted prior	Bias in phase 2a	moderate variability	low ED50
			high ED50
		high variability	low ED50
			high ED50
	No Bias in phase 2 a	moderate variability	low ED50
			high ED50
		high variability	low ED50
			high ED50
Uninformative prior	Bias in phase 2a	moderate variability	low ED50
			high ED50
		high variability	low ED50
			high ED50
	No Bias in phase 2 a	moderate variability	low ED50
			high ED50
		high variability	low ED50
			high ED50

Simulation

Scenarios for Emax models

- 2 different representations of Emax model used:
  - ED50 at dose 0.2 (ie: red dots)
  - ED50 at dose 0.4 (ie: black dots)



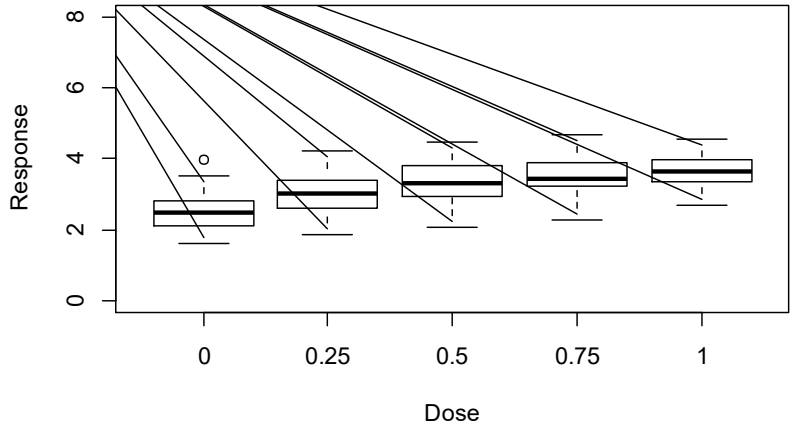
Simulation

Scenarios on variability

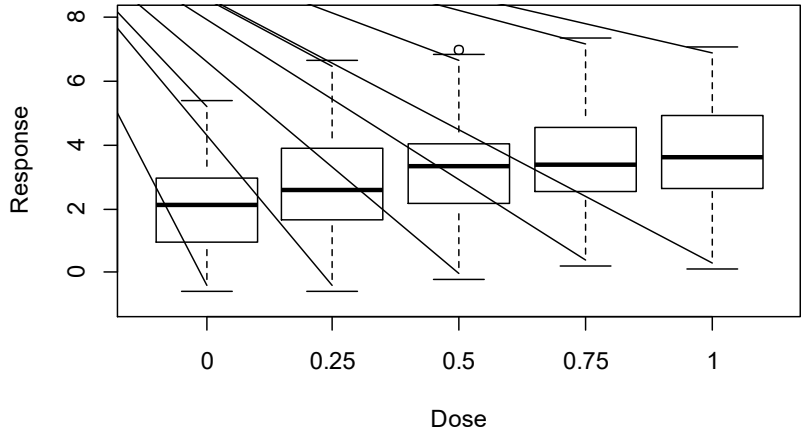
2 different variability scenarios used for simulation:

- Moderate variability ($\sigma \approx 40\%$ of maximum effect in Emax model)
- High variability ($\sigma \approx 125\%$ of maximum effect in Emax model)

Moderate variability example

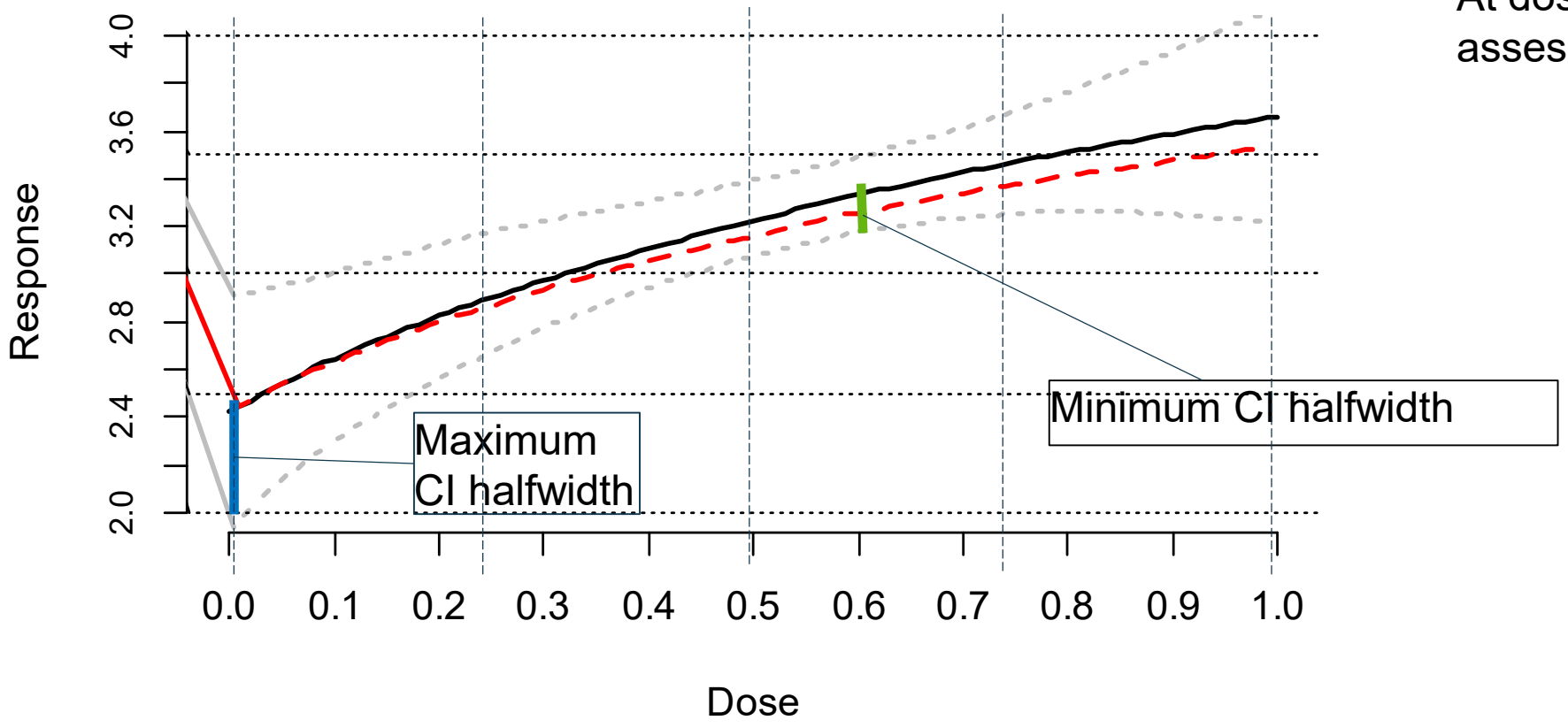


High variability example



Simulation
Quantities assessed

Simulation example: Emax curve and 90% credible band



At doses indicated by dotted lines:
assess bias to true curve

Results / Discussion

Results / Discussion

Summary of results

Criterion		Moderate variability	High variability
Width of credible band	Minimum width	Similar as for uninformative prior	6% more narrow using (full) prior information
	Maximum width	15% more narrow using full prior information 7% more narrow using downweighted prior information	25% more narrow using full prior information 10% more narrow using downweighted prior information
Effect of biased prior	Width of credible interval	Similar as for unbiased prior	Similar as for unbiased prior
	Bias of point estimates (fully weighted prior)	No bias for E0. Maximum dose: effect vs. placebo overestimated by 8%	Tendency of bias. Bias difficult to detect due to large variability but in the same range as for small variability
	Bias of point estimates (downweighted prior)	No bias for E0. Maximum dose: effect vs. placebo overestimated by 5%	Bias difficult to assess, probably overlayed by high variability

Results / Discussion

Further results (2)

- Both frequentist and Bayesian methods failed in estimating reliably ED50 (probably due to simulation settings)
- Frequentist methods often failed in estimating E_{max} reliably , whereas no such problems occured for $\boldsymbol{y_d}$ Effect of reparametrization?
- Frequentist method often failed in determining confidence intervals due to technical reasons whereas Bayesian methods did not fail.
- Apparent bias in Bayesian point estimates for the scenarios with high variance (but may be explainable by variability too).

Results / Discussion

Discussion

- Simulation used rather realistic settings for sample size and variability
- Gain in efficacy were seen, but rather small (might be related to assumed sample sizes)
- Bias smaller than to be expected theoretically
- Focus on the situation that new drug shows a high effect
- The proposed approach is
  - still conceptually simple,
  - does not interfere for clear POC rules
  - is generally in line with current drug development paradigms

Results / Conclusions

Further evaluation needed on

- Further evaluation needed:
  - Other types of nonlinear regression,
  - Other sample sizes,
  - Less biased prior.
  - Assess differences in MED estimation

Literature

Literature

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Questions?