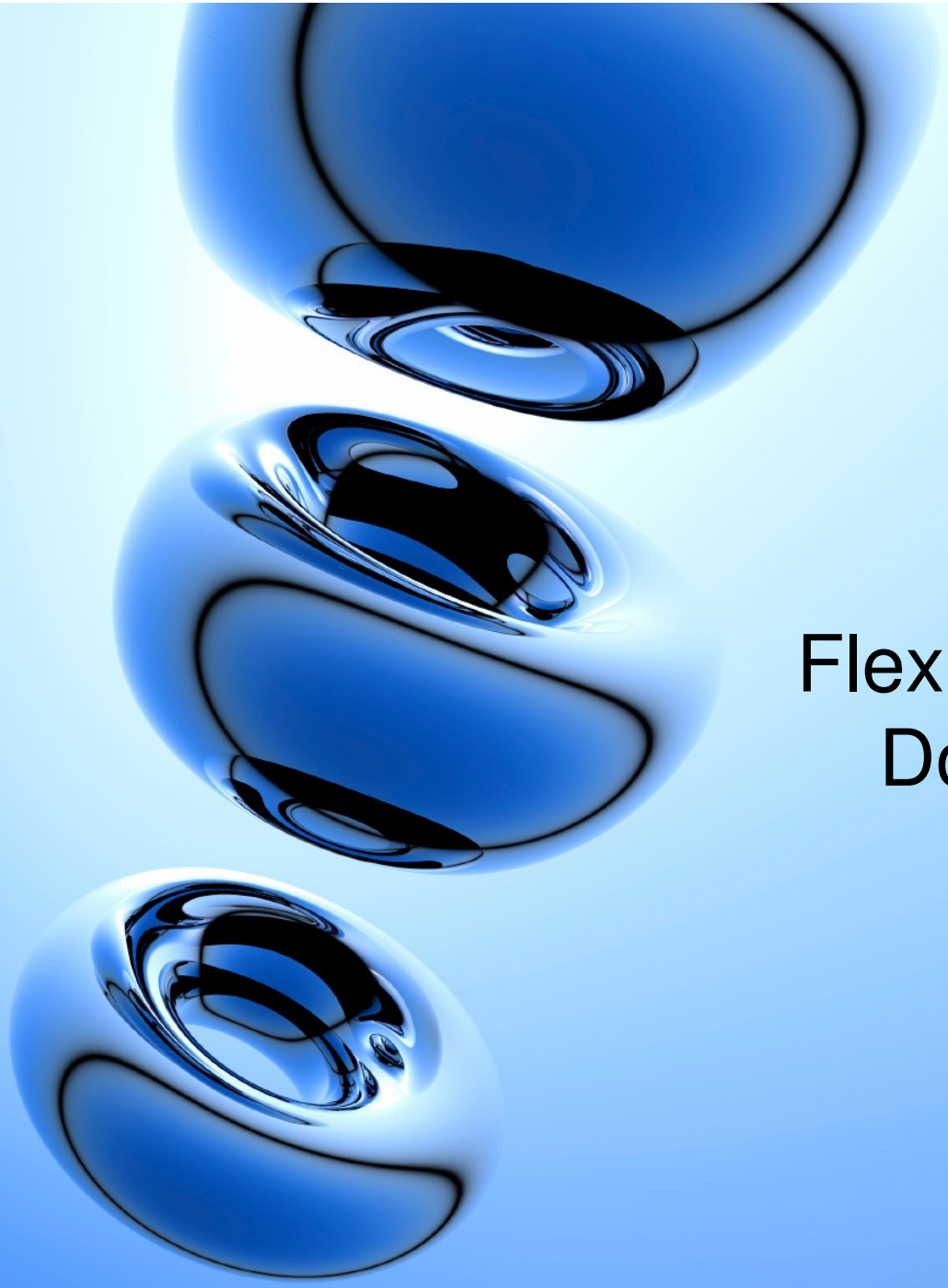

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Shaping the Future of
Drug Development

Flexibility of the BLRM in Dose-Escalation Trials

Ursula Garczarek

Cytel Inc. | Hagen (DE)

Overview

- Bayes logistic regression model (BLRM)
- Why people use **B**LRM
- Application for Dose-Escalation trials and demonstration of flexibility
  - Requirements
  - Prior elicitation
  - Extensions of the basic model

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Bayesian Logistic Regression Model (BLRM) General Model

- Experimental units: n=1,...,N
- Y_n := 0,1 binary outcome,
- X_{n1} ,...,X_{nJ} := predictors per experimental unit
- X_{n1} ,...,X_{nJ} may come from inputs Z_{nk}, k=1,...,K, K<J

$$P(Y = 1|X, ß) = \frac{1}{1 + \exp\left(-\beta_0 - \sum_i ß_i X_i\right)} = \frac{\exp(\beta_0 + \sum_i ß_i X_i)}{1 + \exp\left(+\beta_0 + \sum_i ß_i X_i\right)}$$

$$\log\left(\frac{p}{1-p}\right) = \beta_0 + \sum_i ß_i X_i$$

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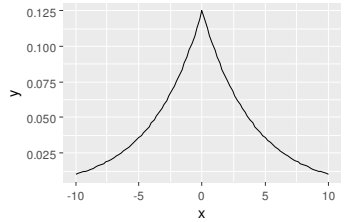
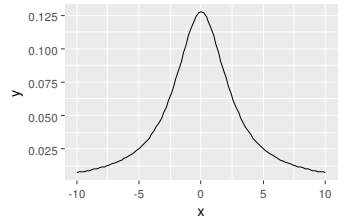
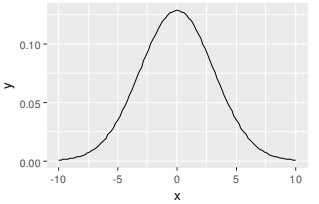
Why do people use BLRM?

- Variable selection
  - E.g. Multimarker diagnostics (Lasso,ML)
- Coping with sparse data
  - E.g. Analysing adverse events (MBLRM), Epidemiology, Genetics,...
- Coping with missing values/information
  - E.g. presence-only data
- Adaptive experimentation
  - Dose escalation ☺







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Dose-Escalation Trials
Phase I

- Assess dose-toxicity relationship
- First-in-human studies
  - Observe Dose limiting toxicities (DLTs)
  - Determine maximum tolerated dose (MTD) or recommended phase II dose (RP2D)
  - MTD := highest dose with toxicity rate lower (or close to) a fixed rate e.g 30%
- Formally:
  - Experimental Units: Patients/Healthy volunteers
  - Binary outcome: experience of a DLT yes/no
  - Other characteristic: controlled drug dose

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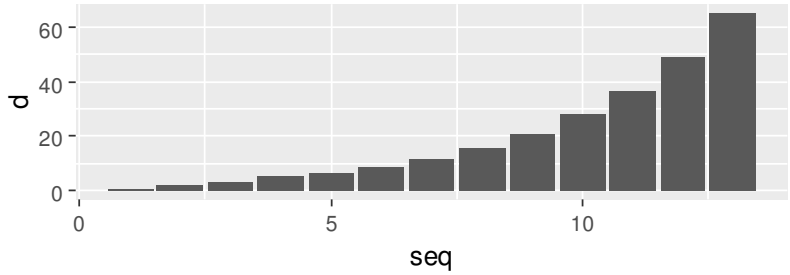
Dose-Escalation Trials
Phase I

- An sequence of increasing doses $d_1, d_2, \ldots, d_J$

  Often: „modified“

  Fibonacci:



- Dose d_j has an unknown toxicity probability π_j
- Monotonicity : $\pi_j < \pi_{j+1}$
- **Goal**: Find MTD
  - $\pi_{MTD} <= 0.3$, $\pi_{D>MTD} > 0.3$

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Design requirements

Challenge	Design Requirement
Untested drug in resistant patients	Escalating dose cohorts with small #s patients (e.g. 3-6 patients)
Primary objective: determine MTD	Accurately estimate MTD
High toxicity potential: safety first	Robustly avoid toxic doses („overdosing“)
Most responses occur 80%-120% of MTD*	Avoid sub-therapeutic doses while controlling overdosing
Find best dose for dose expansion	Enroll more patients at acceptable** active doses (flexible cohort sizes)
Complete trial in timely fashion	Use available information efficiently
High toxicity potential: safety first	Medical experts are in control

Table rows 1-7 from:
Satrajit Roychoudhury, Novartis, https://www.slideshare.net/JamesCahill3/eugm-2014-roychaudhuri-phase-1-combination
* Joffe and Miller 2008 JCO
** Less than or equal to the MTD determined on study

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The 3+3 design (schematic)

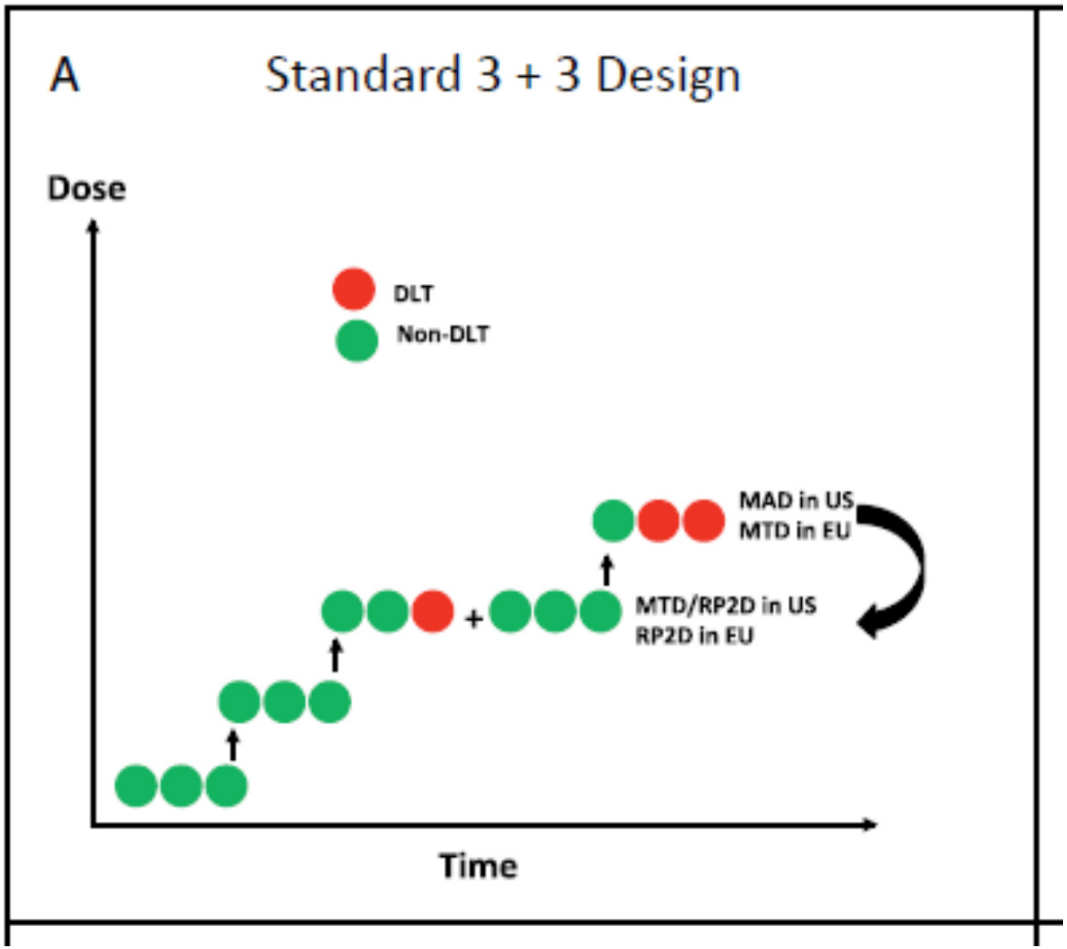

Image from Hansen et al 2014.

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Limitations of 3+3

- Fixed cohort sizes (either 3 or 6)
- Pre-defined dose levels to be potentially tested
- Ignores dosage history other than previous cohort
- Ignores uncertainty:
  - True DLT rate p=0.5 -> 11% chance of 0 or 1 DLT in 6 patients
  - True DLT rate p=0.166, 26% chance of >=2 DLT in 6 patients
- Cannot re-escalate
- Low probability of selecting true MTD (e.g. Thall and Lee. 2003)
- High variability in MTD estimates (Goodman et al. 1995)

Alessandro Matano, Novartis, http://www.smi-online.co.uk/pharmaceuticals/archive/4-2013/conference/adaptive-designs

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** Less than or equal to the MTD determined on study

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Alternatives to 3+3

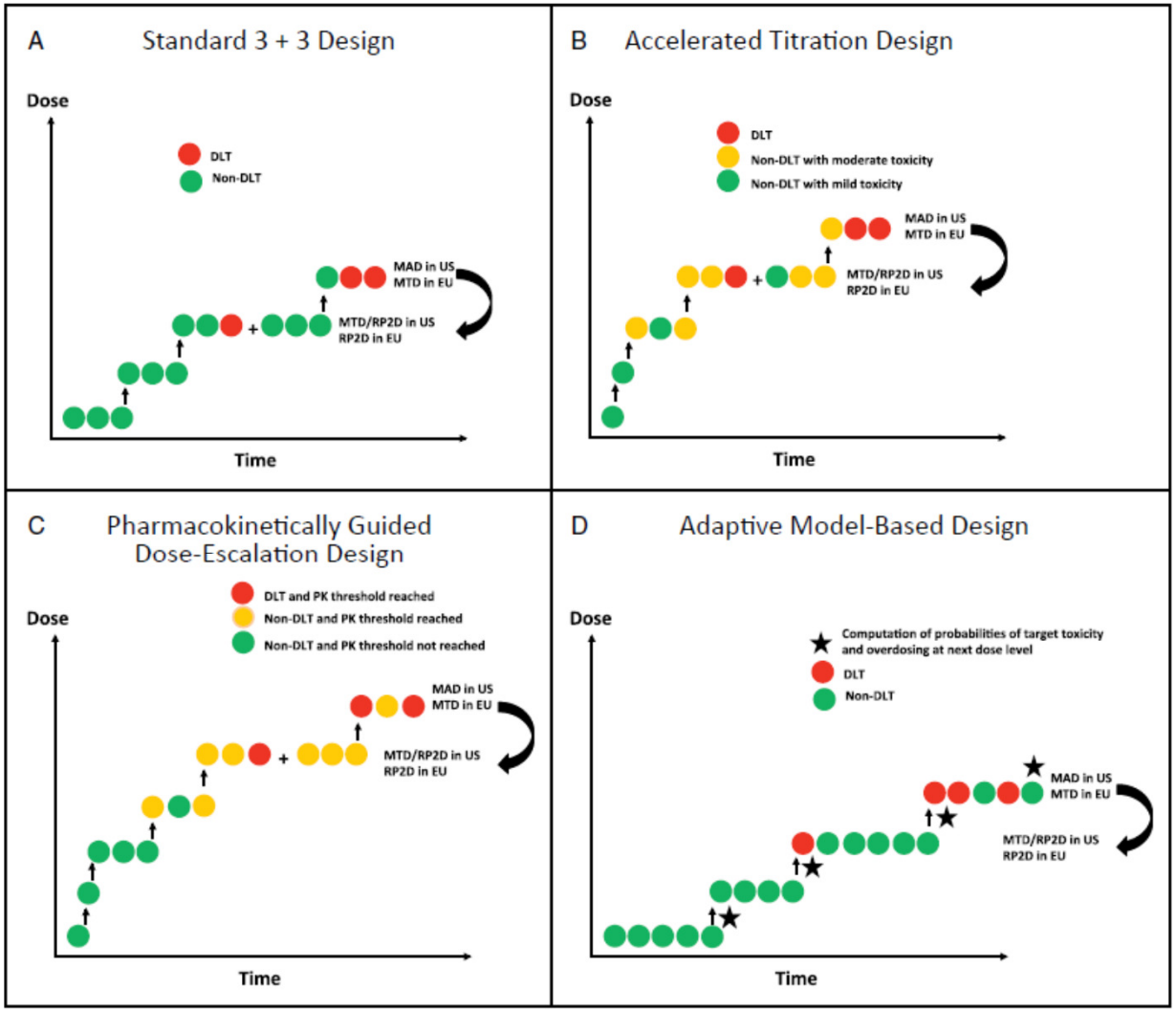

Fig 1. — (A) Schematic of the standard 3 + 3 design. (B) Schematic of the rule-based accelerated titration design. (C) Schematic of the pharmacokinetically guided dose-escalation design. (D) Schematic of an adapative model-based design (eg, escalation with overdose control). DLT = dose-limiting toxicity, EU = European Union, MAD = maximum administered dose, MTD = maximum tolerated dose, PK = pharmacokinetics, RP2D = recommended phase 2 dose, US = United States.

Image from Hansen et al 2014.

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Why Bayesian in Dose-Escalation

Bayesian solution	Design Requirement
Information can be updated for as small and larger groups as one wants	Escalating dose cohorts with small #s patients (e.g. 3-6 patients)
Assessable by posterior	Accurately estimate MTD
Choose next dose based on posterior	Robustly avoid toxic doses („overdosing“)
Choose next dose based on posterior	Avoid sub-therapeutic doses while controlling overdosing
Choose next dose based on posterior	Enroll more patients at acceptable** active doses (flexible cohort sizes)
All information is used + „prior“	Use available information efficiently
High toxicity potential: safety first	Medical experts are in control

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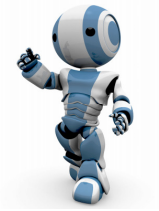
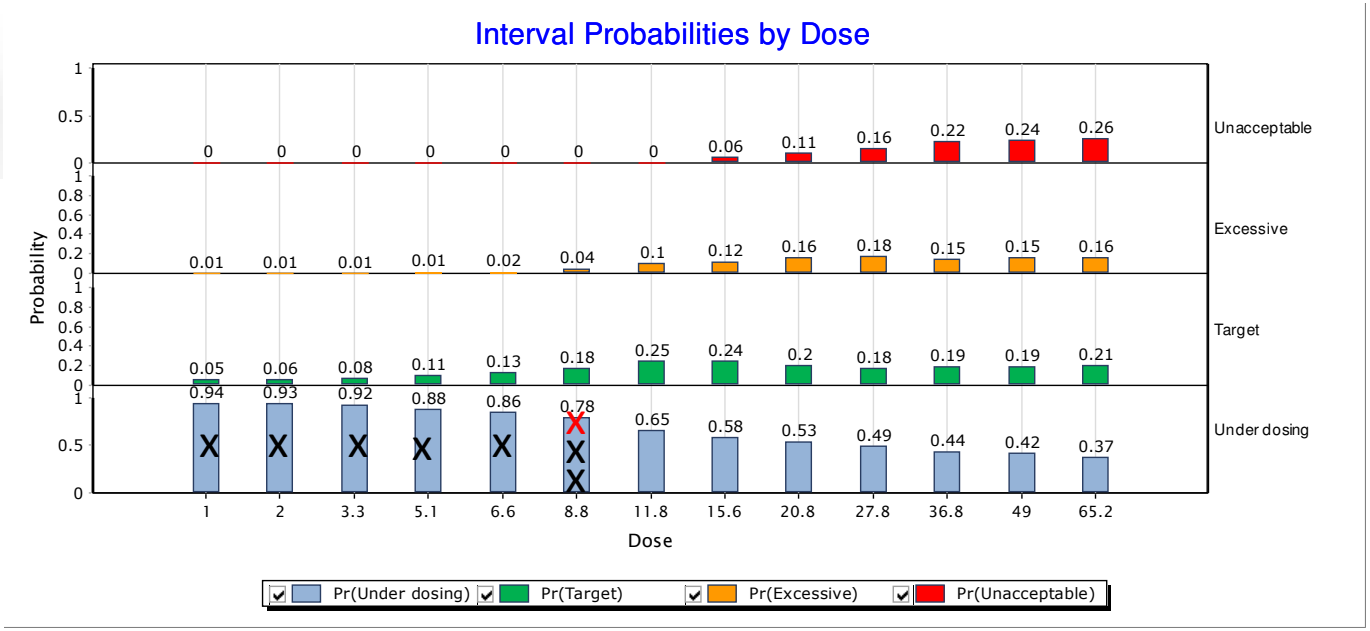
Theoretical and Practical Loss „function“
Dose escalation



Algorithm in control

$$L(\theta, d) = \begin{cases} l_1 = 1 & \pi_{d|\theta} \in (0, 0.2] & under-dosing \\ l_2 = 0 & \pi_{d|\theta} \in (0.2, 0.35] & targeted\ tox \\ l_3 = 1 & \pi_{d|\theta} \in (0.35, 0.6] & excessive\ tox \\ l_4 = 2 & \pi_{d|\theta} \in (0.6, 0.1] & unacceptable\ tox \end{cases}$$

Medical experts in control



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Bayesian Logistic Regression Model
Flex 1: Meaningful parametrization

- Data:
  - #DLT/#Patients: r_d ~Binomial(π_d,n_d)
- Parameter Model:
  - logit(π_d)=log(α)+ß(log(d/d*))
- Prior:
  - (log(α),log(ß)) ~ $\mathcal{N}_2(\mu_1,\mu_2, \sigma_1,\sigma_2, \rho)$

Model parameters α and ß can be interpreted as:

α: odds of a DLT at d*(reference dose)

ß >0: increase log-odds of DLT by unit increase log dose

Satrajit Roychoudhury, Novartis, https://www.slideshare.net/JamesCahill3/eugm-2014-roychaudhuri-phase-1-combination

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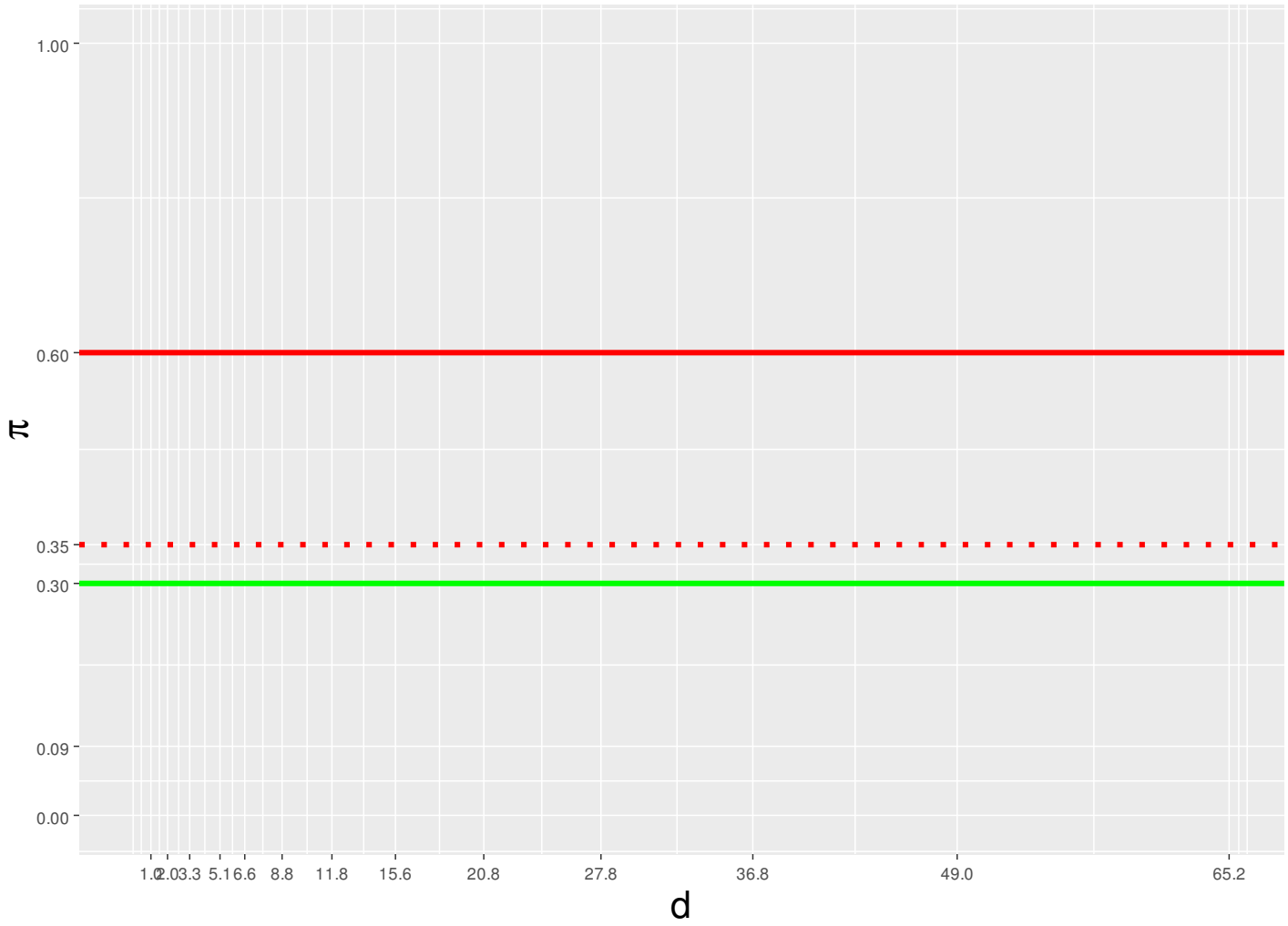
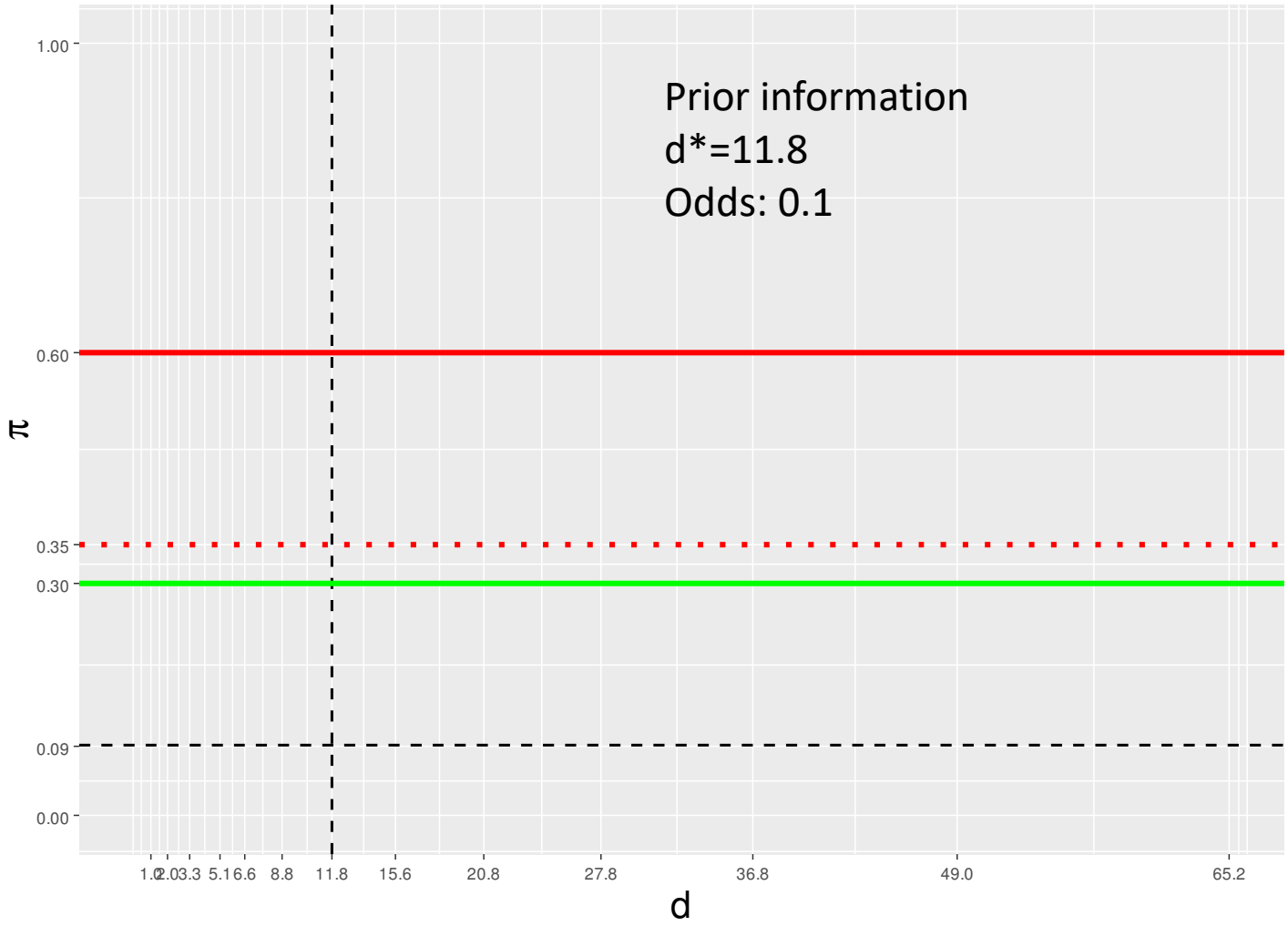
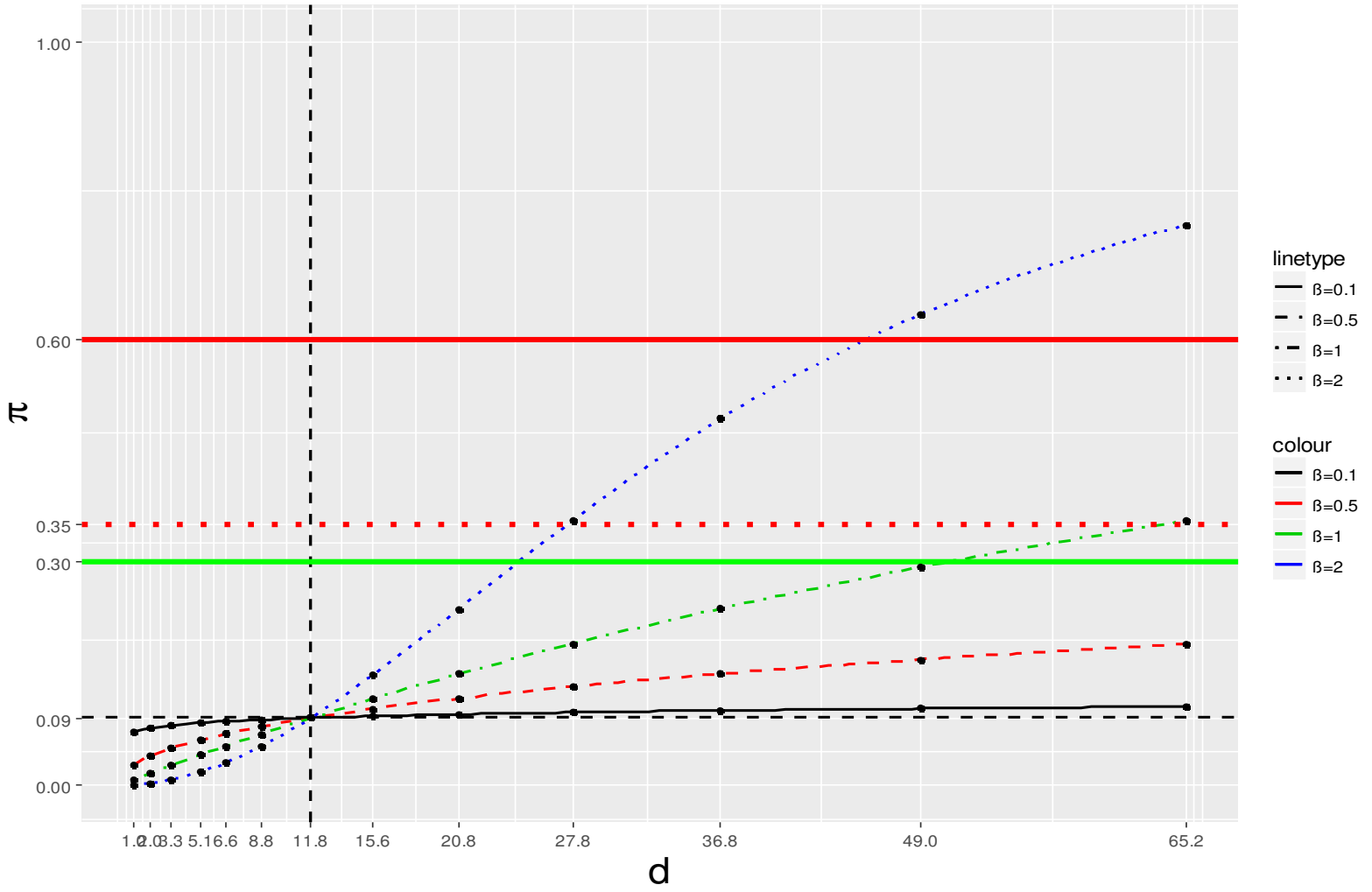
BLRM Flex 2: Plausible functional shapes



BLRM Flex 2: Plausible functional shapes



BLRM Flex 2: Plausible functional shapes



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BLRM Flex 3=1+2: Prior elicitation

There has to be knowledge on lowest dose and on dose range

1. Minimal informative

- $P(\pi_{d1} <= 0.6) = 0.95$
  - $\mathcal{B}(1,\log(0.05/0.4))$
- $P(\pi_{dJ} <= 0.2) = 0.05$
  - $\mathcal{B}(\log(0.05/0.2),1)$

→ Prior medians for the other doses by basic model

- $\mathcal{B}(a,b),j=2,...,J-1$

→ Best approximating $\mathcal{N}_2(\mu_1,\mu_2, \sigma_1,\sigma_2, \rho)$

2. Somewhat informative

- $P(\pi_{d1} <= 0.05) = 0.5$
  - $\mathcal{B}(1,\log(0.05/0.5))$
- $P(\pi_{MTD} <= 0.3) = 0.5$
  - $\mathcal{B}(\log(0.3/0.5),1)$

→ Prior medians for the other doses by basic model

- $\mathcal{B}(a,b),j=2,...,J$ without d=MTD

→ Best approximating $\mathcal{N}_2(\mu_1,\mu_2, \sigma_1,\sigma_2, \rho)$

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Dose-Escalation Trials Phase I

- Assess dose-toxicity relationship
- First-in-human (FIH) studies – single agent
  - Determine maximum tolerated dose (MTD) or recommended phase II dose (RP2D)
  - Observe Dose limiting toxicities (DLTs)
- Combination dose finding studies (Phase Ib)
  - Same primary objective as FIH studies
    - Combination of two (or more) drugs
    - Addition of a new drug to a registered treatment to increase efficacy

http://www.bayes-pharma.org/bayes2014docs/Day1/Jullion.pdf

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Bayesian Logistic Regression Model
Flex 4: Extending

For each single agent we assume:

- $\text{logit}(\pi_i(d_i)) = \log(\alpha_i) + ß_i(\log(d_i))$, i=1,2

Note: „standardized“ d_1 (d_1/d_1^*, agent1) and d_2 (d_2/d_2^* agent2)

With a bit of probability calculus and under independence:

- $\text{odds}^0_{12}(d_1, d_2) = \text{odds}_1(d_1) + \text{odds}_2(d_2) + \text{odds}_1(d_1) * \text{odds}_2(d_2)$

Assign one new parameter η for interaction:

- $\text{odds}_{12}(d_1, d_2) = \text{odds}^0_{12}(d_1, d_2) * \exp(\eta d_1 d_2)$

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BLRM Flex 5: Prior elicitation

There is typically knowledge on at least one agent

Meta-Analytic-Predictive Prior for agent with historical study:

Historical: $\text{logit}(\pi_h(d_h)) = \log(\alpha_h) + \beta_h(\log(d_h))$

Comb trial: $\text{logit}(\pi_1(d_1)) = \log(\alpha_1) + \beta_1(\log(d_1))$

Assumption of similarity:

$\log(\alpha_h), \log(\alpha_1) \sim \mathcal{N}(\mu_\alpha, \tau)$

$\log(\beta_h), \log(\beta_1) \sim \mathcal{N}(\mu_\beta, \tau)$

Choice of τ based on heterogenity (or hyperprior):

τ= 2 (very large), 1 (large), 0.5 (substantial), 0.25 (moderate), 0.125 (small) variability.

Prior on interaction η:

e.g. N(0,1.121): no interaction expected but allowing up to 9-fold increase in 95% increase or decrease in prior interval

All suggestions from Neuenschwandner et al 2016

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