A Decision-Theoretic Bayes Factor approach for Dose Finding in Phase I Oncology Trials

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BASS XXI, November 3, 2014
Rockville, MD

New Drug Development

- Preclinical: Cell-line and Aninal Experiment Studies on Efficacy, Safety, PK/PD
- Phase I: Establish Satety Profile and **Dose-finding**, PK
- Phase II: Pilot Studies on Efficacy
- Phase III: Confirmatory Studies on Efficacy
- Phase IV: Post-Market Surveillance

Oncology Trials

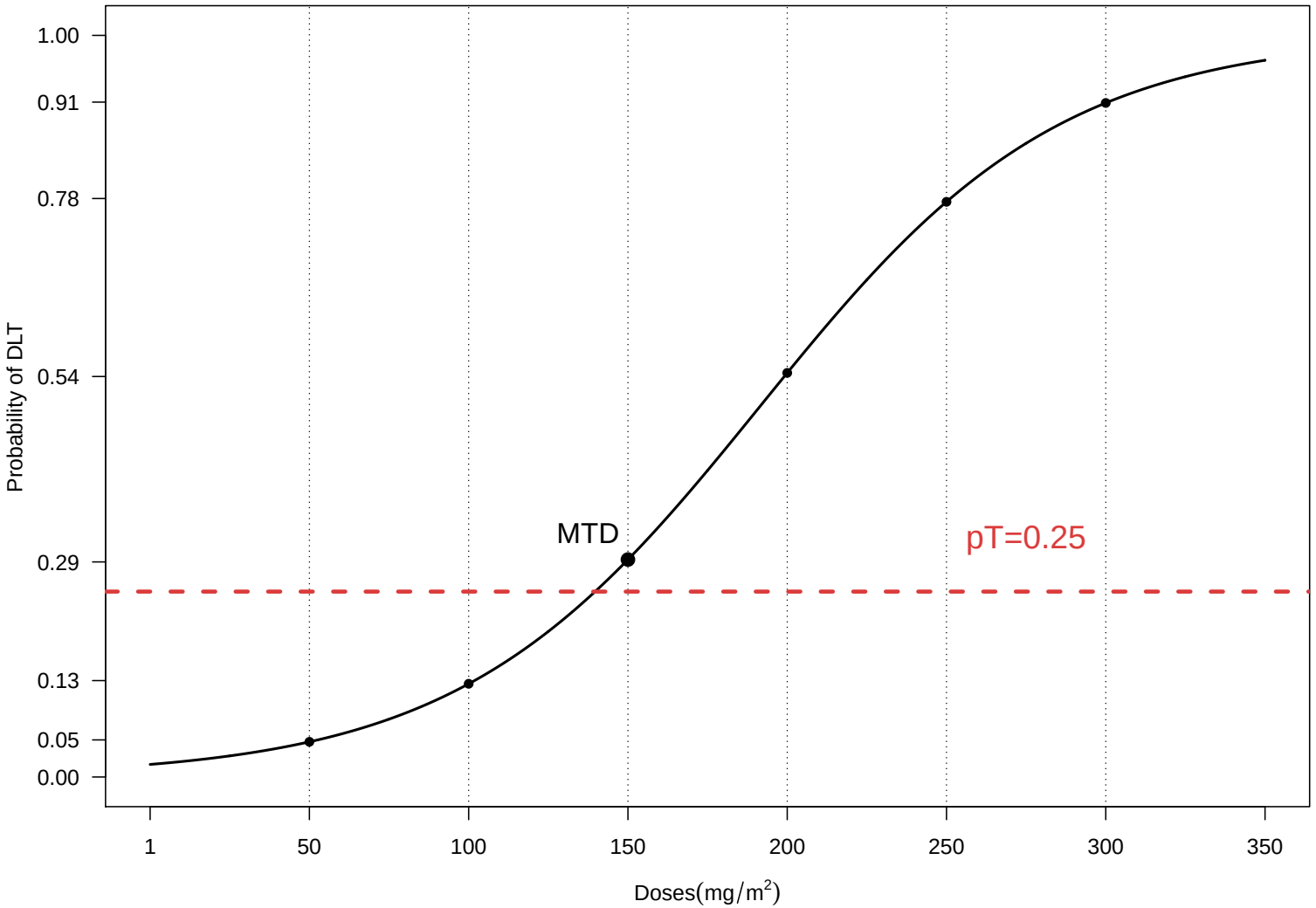
- To verify the treatment effects of cancer therapies for extending and improving a cancer patient' life
- Enroll patients for whom standard treatments have failed; Inclusion Criteria
- Most of Oncology drugs are cytotoxic agents
  - Assumption: both toxicity and efficacy increase with respect to doseage
- Physicians want to find an appropriate dose that is effective and yet not too toxic

Phase I Oncology Trials

- **Goal**: Find the Maximum Tolerated Dose (MTD) with a prespecified target toxicity rate pT
- The Primary Endpoint is Dose Limiting Toxicity (DLT)
  - For cytotoxic agents in oncology trials, DLTs refer to drug-related severe effects such as grade III or worse nonhematologic toxicity and grade IV hematologic toxicity
- Toxicity rate P_i is the probability by which patients receiving *ith* dose will experience DLT; Each patient has a binary outcome
- MTD is defined as the dose with a toxicity rate closest to pT

$$\text{MTD} = \underset{i \in \{1,\ldots,D\}}{argmin} \, |P_i - pT|$$

Dose Response



Phase I Oncology Trials

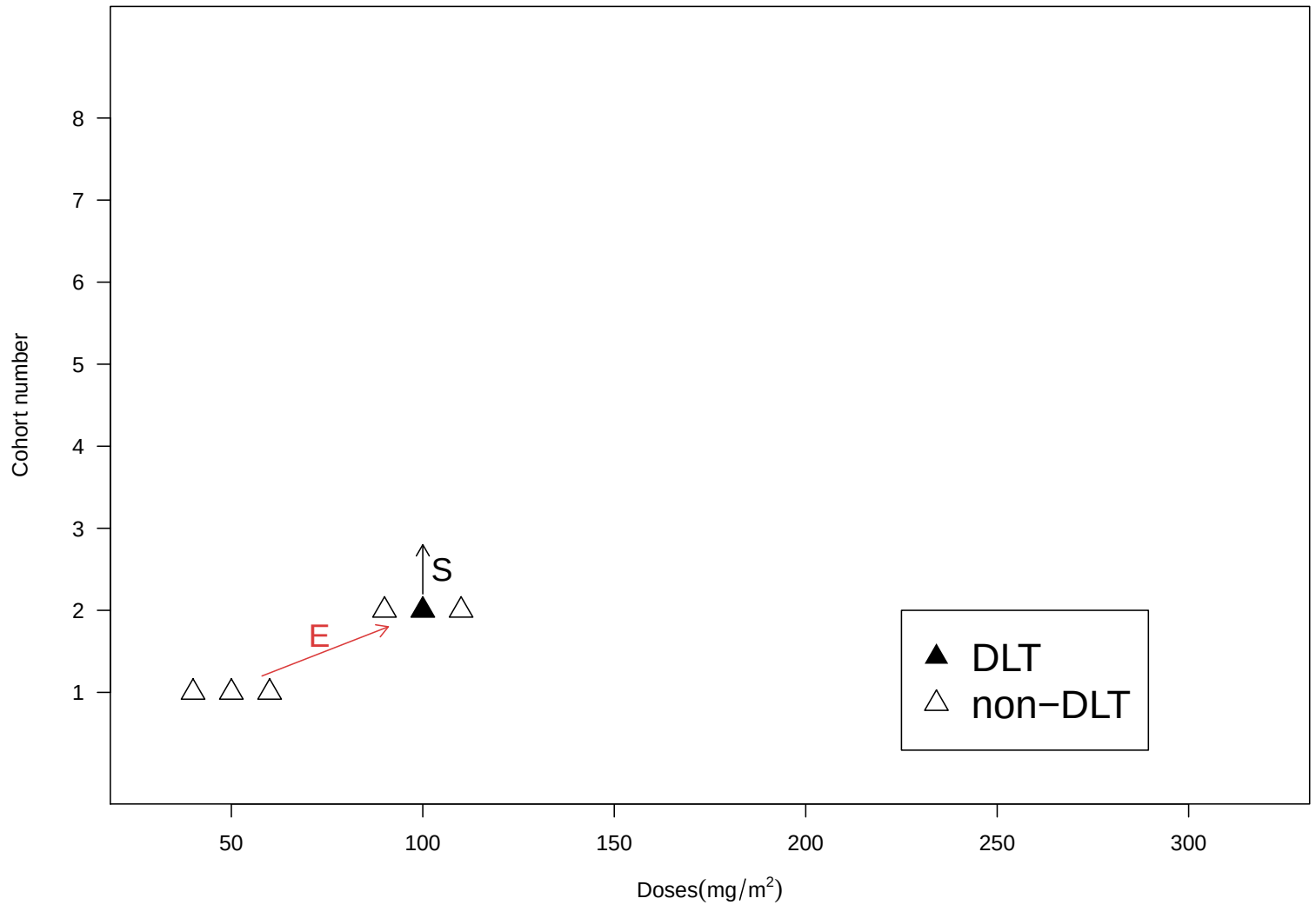
- **Size**: Enrolled by a small cohort $(+3)$ and total is small (< 100)
- **Duration**: Short (eg. up to 1 month)
- **Adaptive**: Use mid-trial data to decide how to treat next cohort
- **Safety**: Limit the number of patients exposed to over-toxic doses
- **Efficacy**: Maximize the number of patients receiving a therapeutic dose (MTD)
  - Benefit both cancer patients and sponsors
  - Statistically efficient: $\hat{\theta}_{MTD} \sim N(\theta, (nI(\theta))^{-1})$

Conducting a Phase I Trial

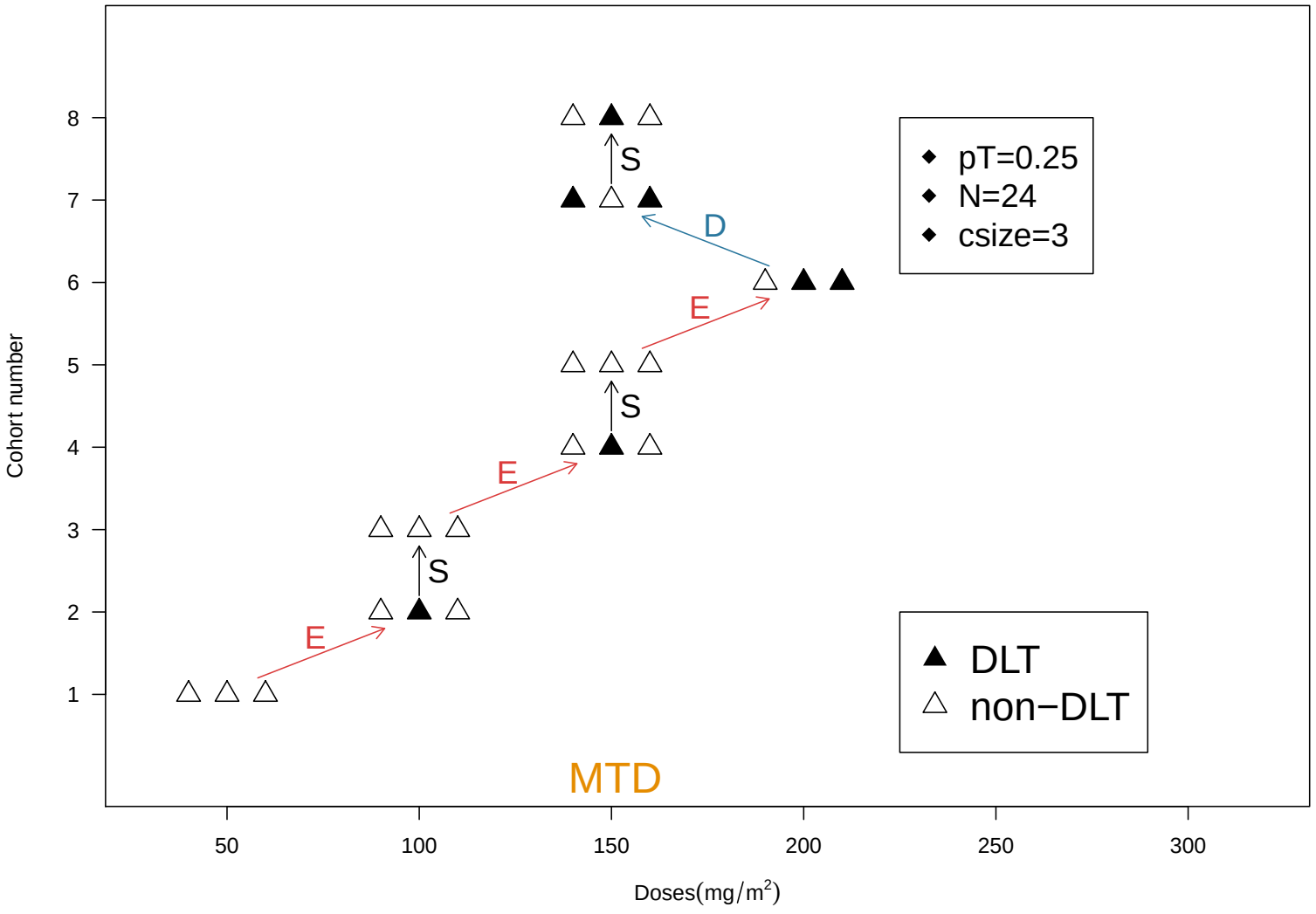
For finding MTD,

1. Physicians first decide the starting dose
2. Enroll, Treat and Follow-up patients
   - If the starting dose is too toxic, stop the trial if it is the lowest dose; otherwise lower the dose to continue
3. Obtain toxicity information, decide the next dose by a rule
4. Repeat step 2 and 3 to the end
5. Determine MTD by a second rule

Conducting a Phase I Trial



Conducting a Phase I Trial



Ideal Design

- Good Operating Performance
  1. Select True MTD
  2. Treat More at MTD
  3. Limit Patients at Over-Toxic
- Efficiency: Fully Utilize Information
- Feasibility
  1. Understandable
  2. Flexible
  3. Transparent
  4. Simple to implement

Dose Finding Design

- Algorithm Based Approach
  - '**3+3**' design : most commonly used
  - Toxicity Probability Interval design (**mTPI**, Ji 2010)
- Model Based Approach
  - Continual Reassessment Model (**CRM**, O'Quiley 1990): need to assume a baseline probability model('Skeleton')

$$P_i = \pi_i^{exp(\alpha)}$$

  - Bayesian Logistic Regression Model (**BLR**)

$$logit(P_i) = log(\alpha) + \beta log(d/d^*)$$

3+3 Design

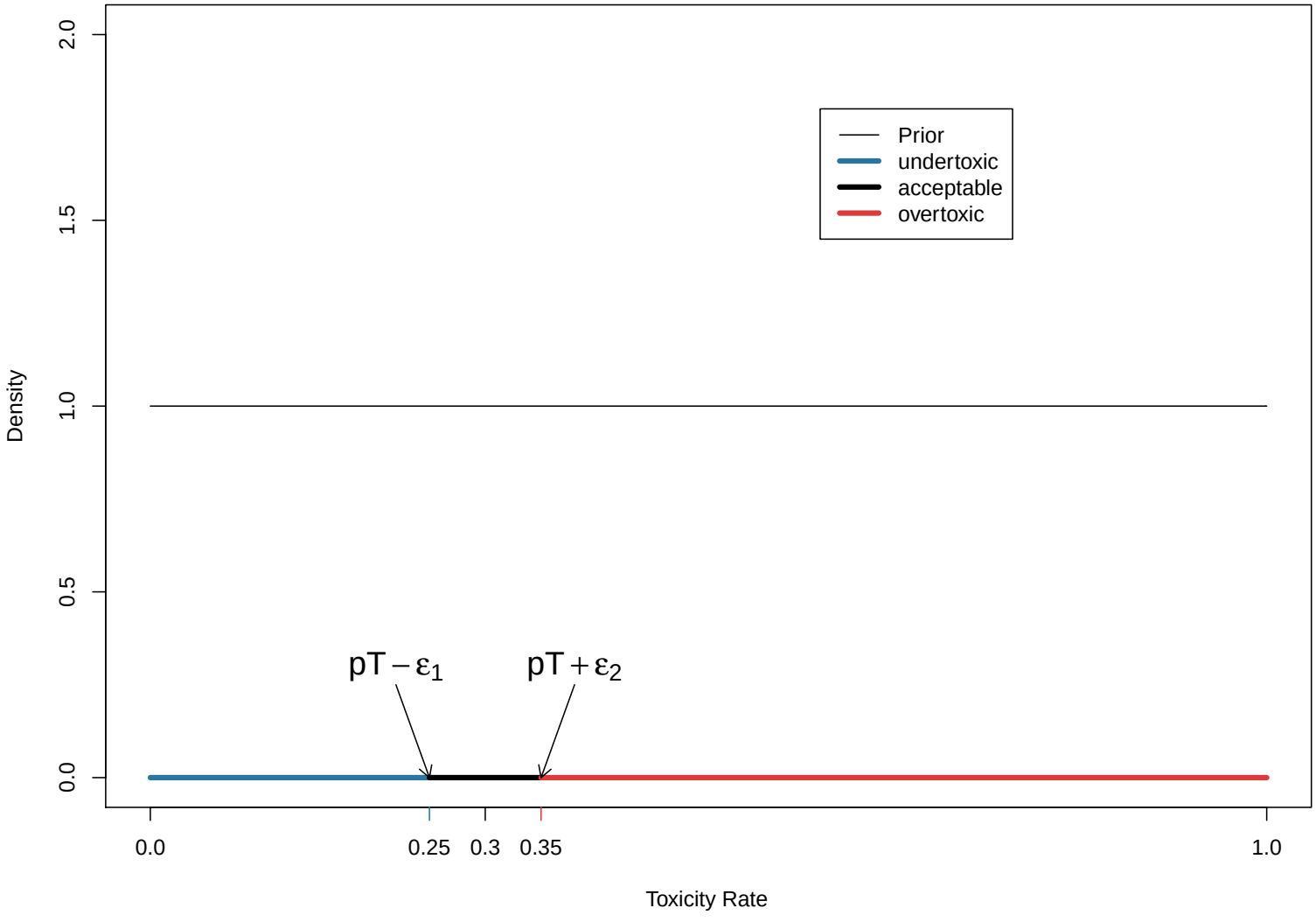
- **Step 1**: Enter first cohort of 3 patients at the lowest dose
- **Step 2**: Observe toxicity outcomes
  - if 0/3 DLT, treat next cohort of 3 patients at next higher dose
  - if 1/3 DLT, treat next cohort of 3 patients at same dose
    - if 1/3 + 0/3 DLT, treat next cohort of 3 patients at next higher dose
    - if 1/3 + 1/3 DLT, define dose as MTD
    - if 1/3 + 2/3 or 3/3 DLT, dose exceeds MTD
  - if 2/3 or 3/3 DLT, dose exceeds MTD
- **Step 3**: Repeat until MTD is reached
- **Step 4**: MTD is definded as a dose with $\leq$ 2/6 DLT

(Berry 2010)

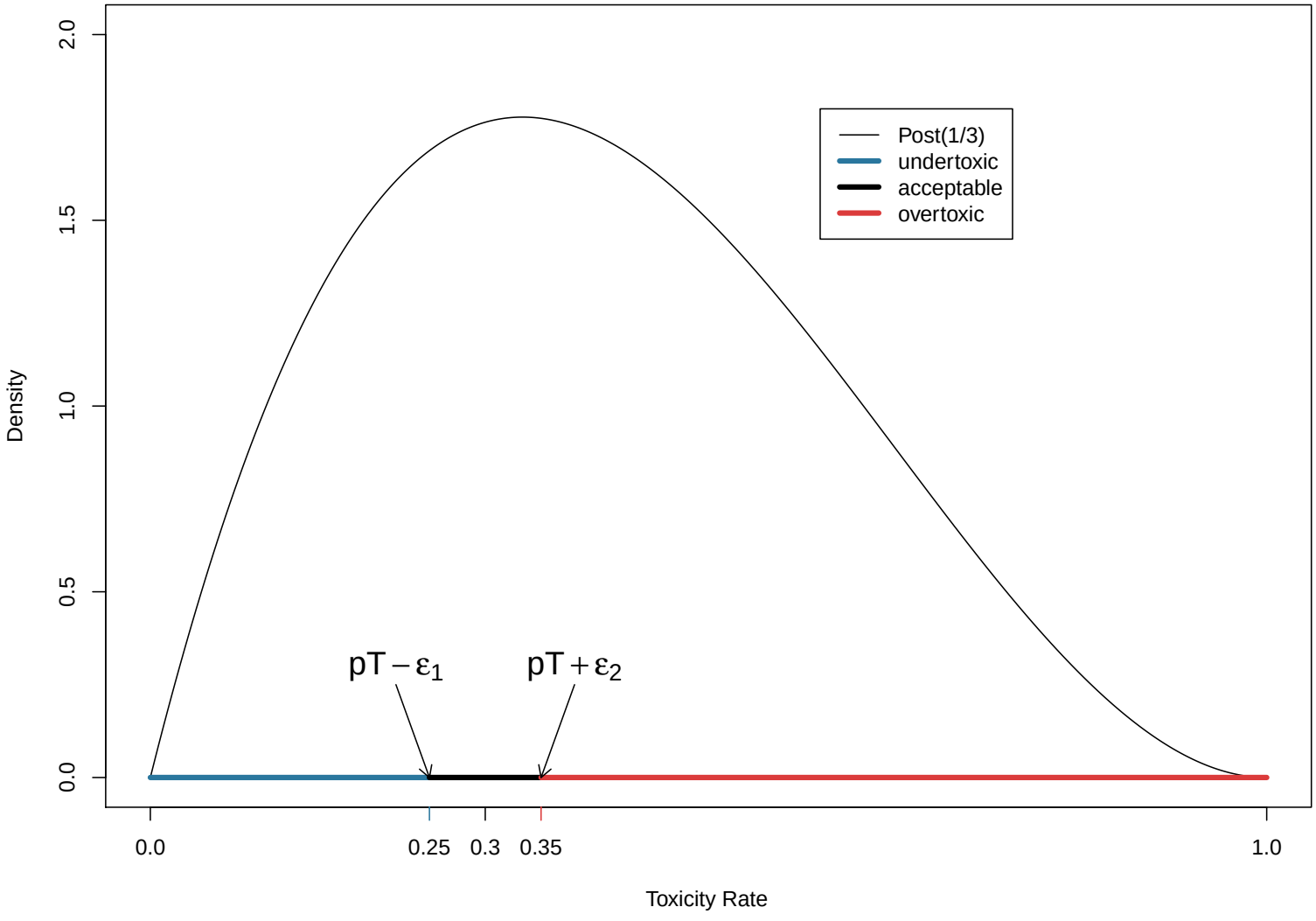
mTPI Design

- Suppose at *ith* dose, x_i out of n_i experience DLT
- Specify an acceptable(tolerance) region $(pT - \epsilon_1, pT + \epsilon_2)$
- The acceptable region boundary distances ϵ_1 and ϵ_2 reflect the minimum toxicity differences we want to distinguish the target toxicity rate from other rates
  - Dose with P_i in this region can be regarded as MTD
  - Investigators and Physicians' perspective
  - Analogous to effect size δ in sample size calculations

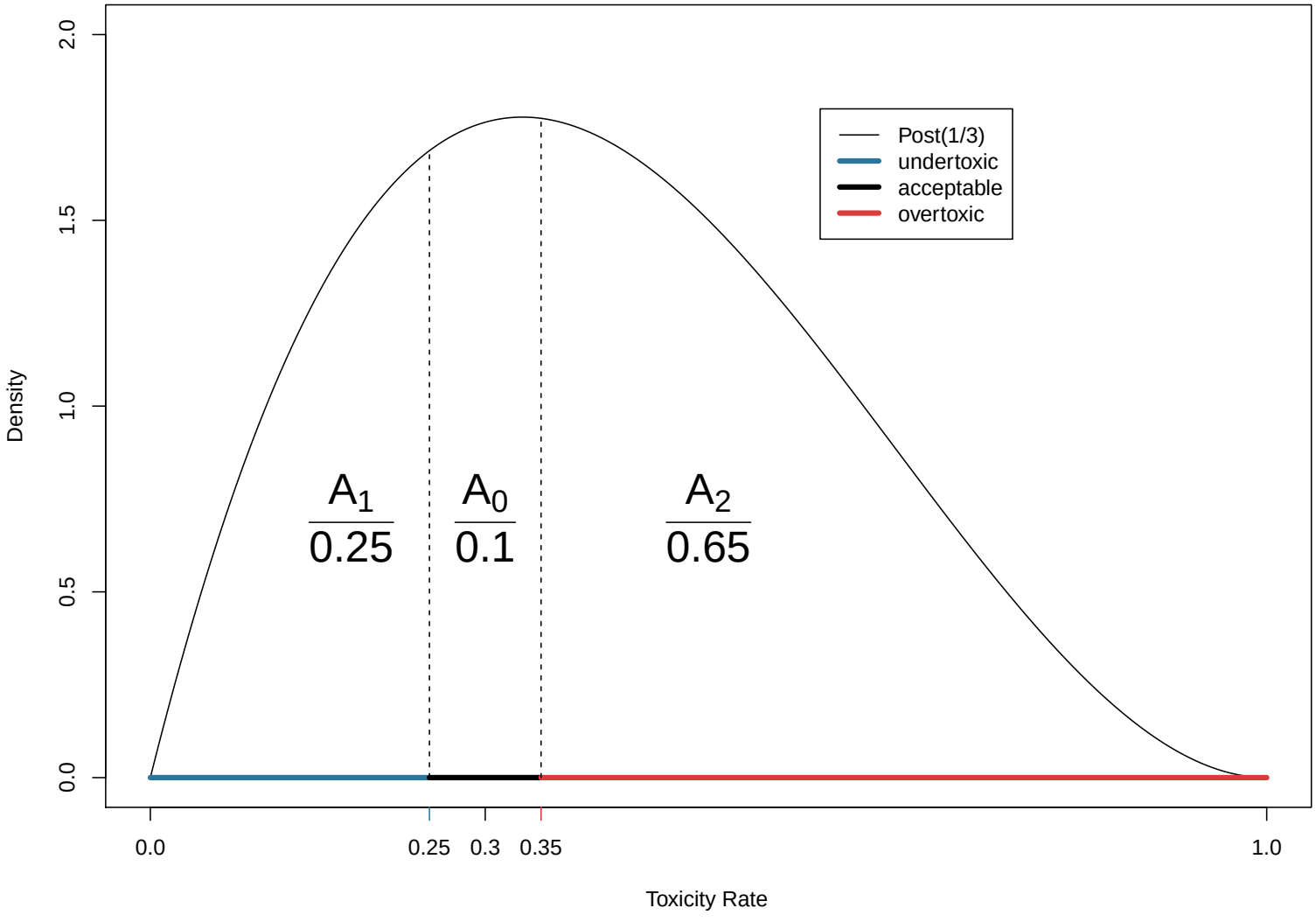
mTPI Design


Prior
undertoxic
acceptable
overtoxic
Density
2.0
1.5
1.0
0.5
0.0
pT − ε1
pT + ε2
0.0
0.25
0.3
0.35
1.0
Toxicity Rate

mTPI Design


Post(1/3)
undertoxic
acceptable
overtoxic
$pT-\varepsilon_1$
$pT+\varepsilon_2$
Density
0.0
0.5
1.0
1.5
2.0
0.0
0.25
0.3
0.35
1.0
Toxicity Rate

mTPI Design


Post(1/3)
undertoxic
acceptable
overtoxic
$\frac{A_1}{0.25}$
$\frac{A_0}{0.1}$
$\frac{A_2}{0.65}$
Density
0.0
0.5
1.0
1.5
2.0
0.0
0.25
0.3
0.35
1.0
Toxicity Rate

CRM Design

- Suppose that we observed x_k DLTs out n_k patients treated at dose k
- The total likelihood function will be

$$f(D|\alpha) = \prod_{k=1}^{D} f(D_k|\alpha)$$

$$f(D_k|\alpha) = (\pi_k^{exp(\alpha)})^{x_k} \times (1 - \pi_k^{exp(\alpha)})^{n_k - x_k}$$

$$f(\alpha|D) = \frac{f(D|\alpha)f(\alpha)}{\int f(D|\alpha)f(\alpha)d\alpha}$$

$$f(\alpha) \sim N(0, \sigma^2)$$

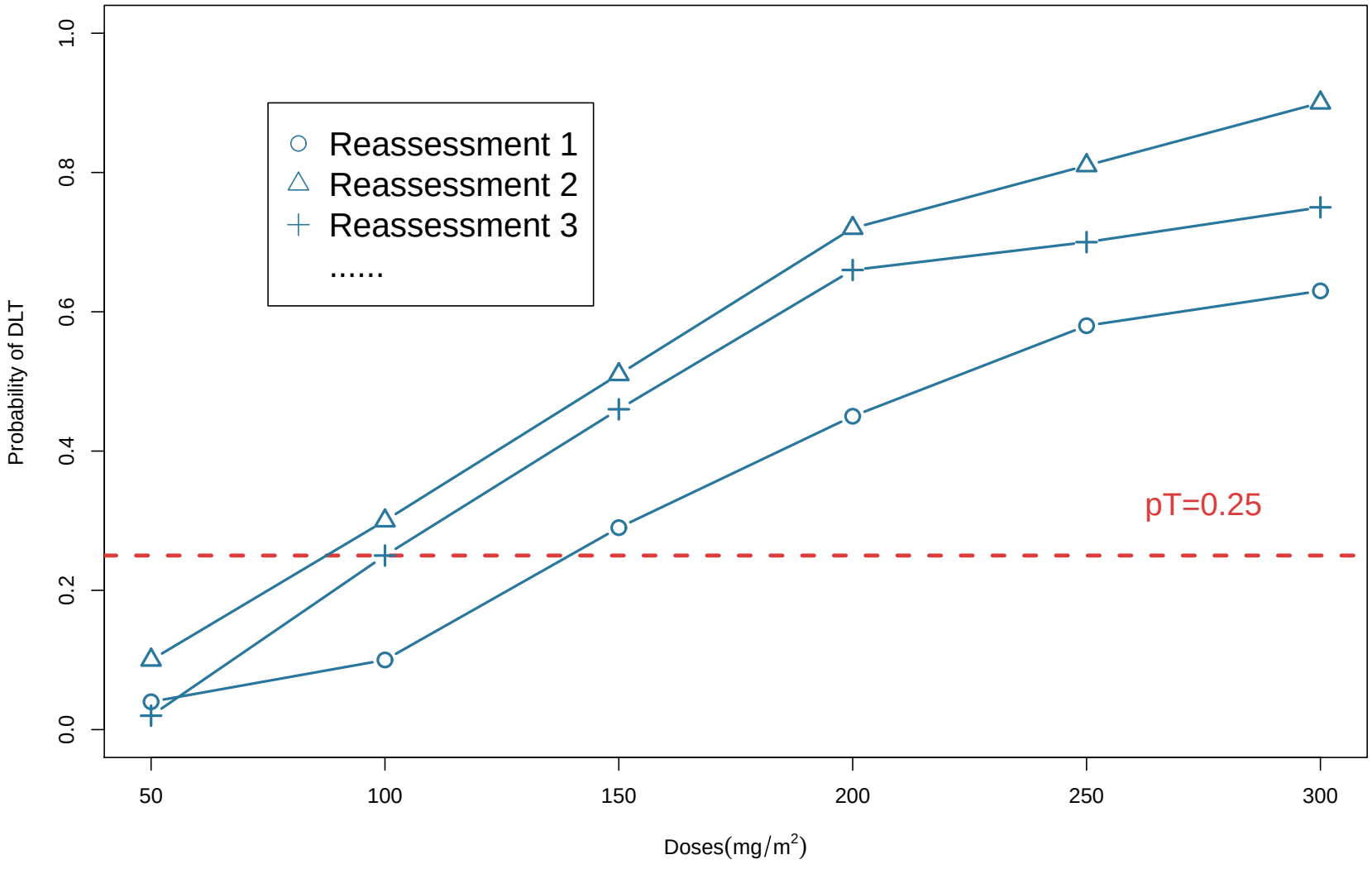
- Then we can calculate the posterior mean of $P_k = \pi_k^{exp(\alpha)}$ with

$$\hat{P}_k = \int \pi_k^{exp(\alpha)} \times f(\alpha|D)d\alpha$$

- Decision rule: A new cohort of patients will be treated at dose level k^*, where

$$k^* = \underset{k \in \{1,\ldots,D\}}{argmin} \; |\hat{P}_k - pT|$$

CRM Design


Reassessment 1
Reassessment 2
Reassessment 3
.....
pT=0.25
Probability of DLT
0.0
0.2
0.4
0.6
0.8
1.0
50
100
150
200
250
300
Doses(mg/m^2)

Pros and Cons

- 3+3
  - Pro: Simple to implement; No Statistics!
  - Con: Only pT=.33; csize=3; Waste data; $\leq$ 6 pts at MTD
- mTPI
  - Pro: No postulated dose toxicity curve π_i; Good performance
  - Con: Single dose information; No explicit justification or proof
- CRM
  - Pro: Borrow data from other doses
  - Con: Mis-specification of skeletons; Aggressive escalation
- BLR

$$logit(P_i) = log(\alpha) + \beta log(d/d^*)$$

  - Pro: Less aggressive than CRM
  - Con: Calibrate the priors (Neuenschwander 2008)

Pros and Cons

- **Our method improves on this!**

- mTPI
  - Pro: No postulated dose toxicity curve π_i; Good performance
  - Con: Single dose information; No explicit justification or proof
- CRM
  - Pro: Borrow data from other doses
  - Con: Mis-specification of skeletons; Aggressive escalation

Model

- First consider modifying the interval design at each **single** dose
- Three interval hypothesis:

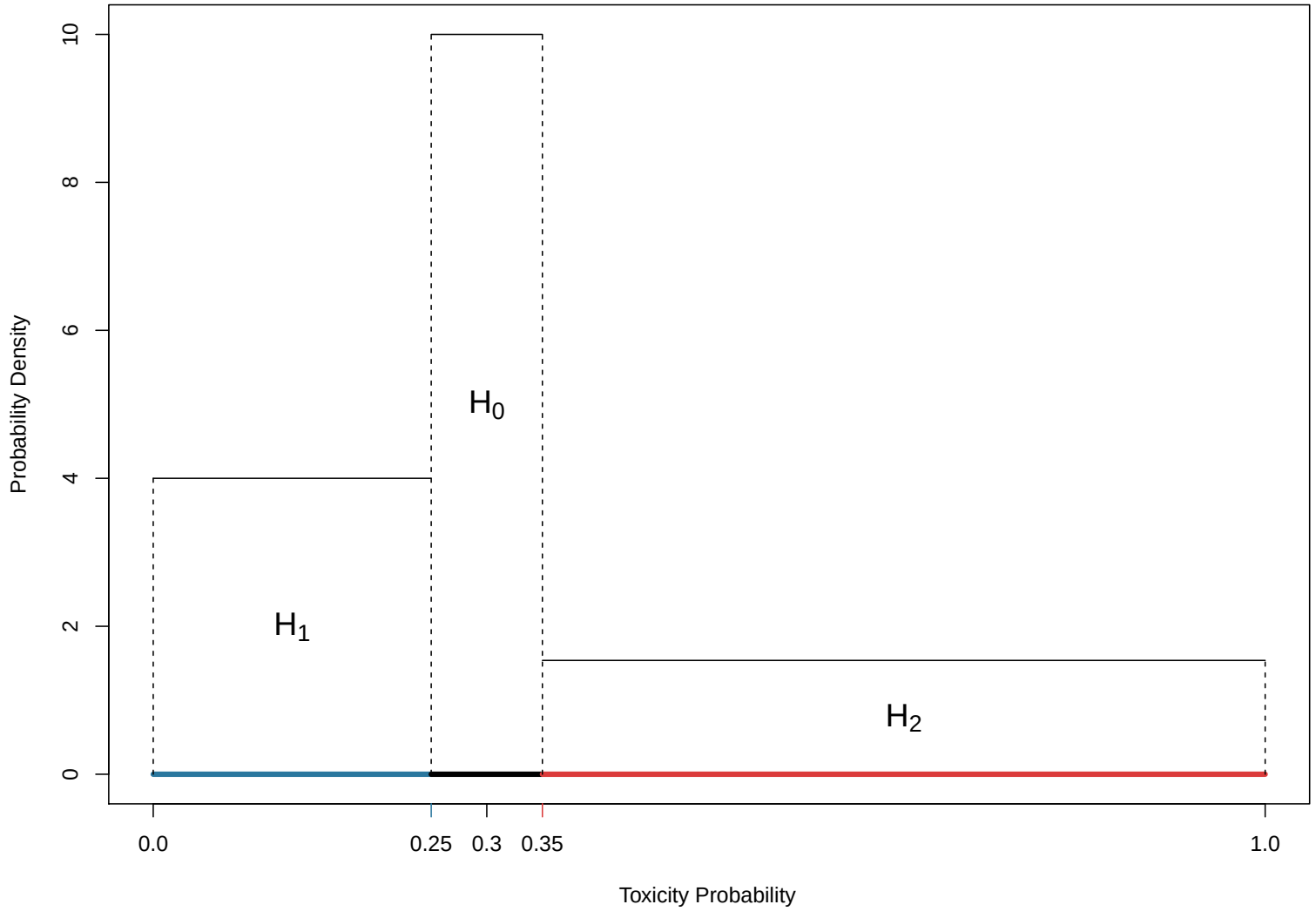
$$H_0 : P_i \sim beta(\alpha_2^{(0)}, \beta_2^{(0)}) I(pT - \epsilon_1, pT + \epsilon_2)$$
$$H_1 : P_i \sim beta(\alpha_2^{(1)}, \beta_2^{(1)}) I(0, pT - \epsilon_1]$$
$$H_2 : P_i \sim beta(\alpha_2^{(2)}, \beta_2^{(2)}) I[pT + \epsilon_2, 1)$$

- Without further information

$$Pr(H_0) = Pr(H_1) = Pr(H_2) = 1/3$$

This is our **fitting prior**

Uniform prior



Posterior

- Posteriors

$$Pr(H_j|D_i) = \frac{Pr(H_j) \times f(D_i|H_j)}{\sum Pr(H_k) \times f(D_i|H_k)} \quad j = 0, 1, 2$$

- where $f(D_i|H_0) = \int f(D_i|P_i, H_0) \times f(P_i|H_0) dP_i$

$$= \frac{F(pT + \epsilon_2; a_i^{(0)} + x_i, b_i^{(0)} + n_i - x_i) - F(pT - \epsilon_1; a_i^{(0)} + x_i, b_i^{(0)} + n_i - x_i)}{F(pT + \epsilon_2; a_i^{(0)}, b_i^{(0)}) - F(pT - \epsilon_1; a_i^{(0)}, b_i^{(0)})}$$

- Also

$$f(D_i|H_1) = \frac{F(pT - \epsilon_1; a_i^{(1)} + x_i, b_i^{(1)} + n_i - x_i)}{F(pT - \epsilon_1; a_i^{(1)}, b_i^{(1)})}$$

$$f(D_i|H_2) = \frac{1 - F(pT + \epsilon_2; a_i^{(2)} + x_i, b_i^{(2)} + n_i - x_i)}{1 - F(pT + \epsilon_2; a_i^{(2)}, b_i^{(2)})}$$

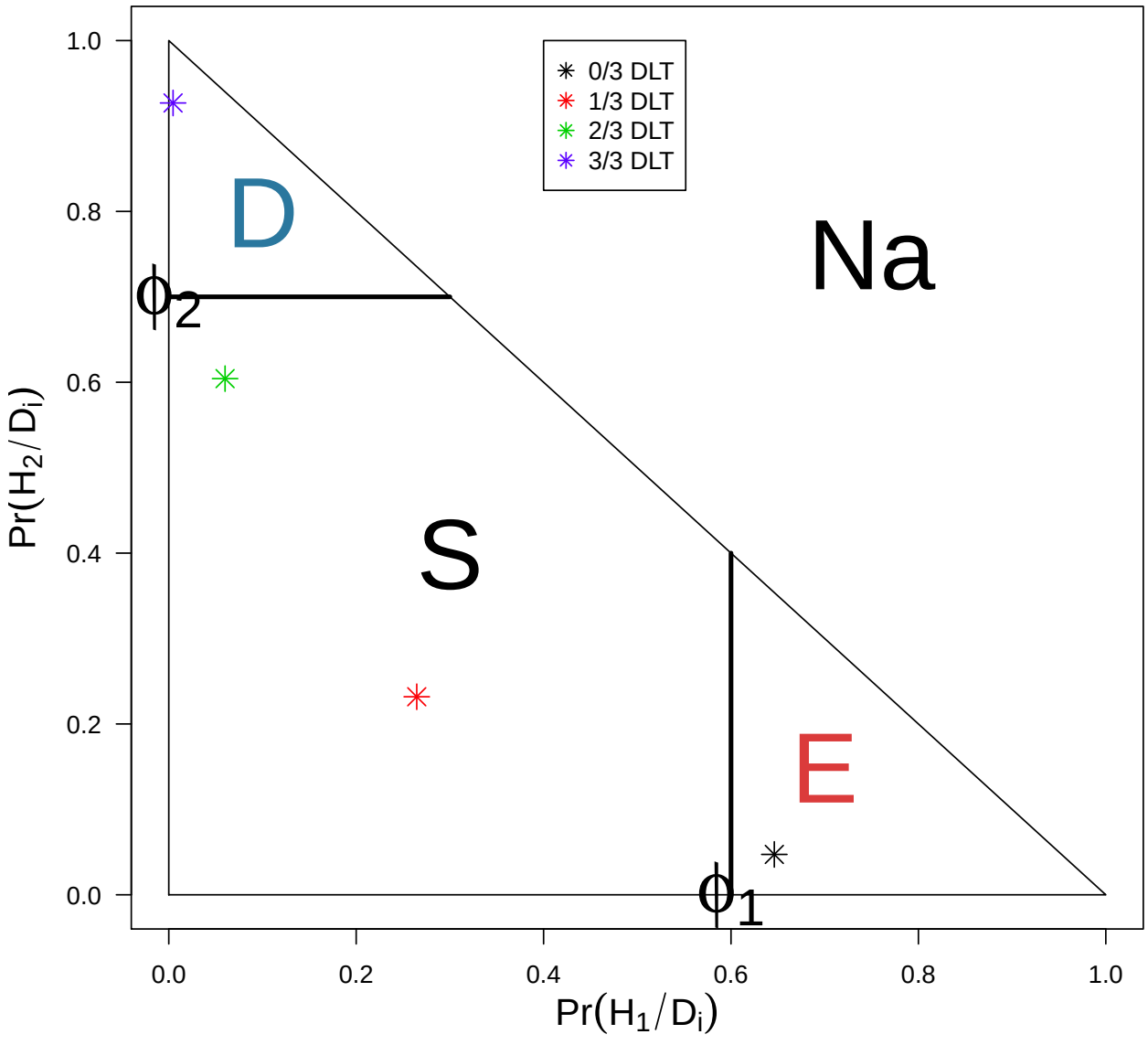
Bayes Factor

- $BF_1 = \frac{f(D_i|H_1)}{f(D_i|\bar{H}_1)}$, where $\bar{H}_1 \in \{H_0, H_2\}$
  relative possibility of *ith* dose being under-toxic
- $BF_2 = \frac{f(D_i|H_2)}{f(D_i|\bar{H}_2)}$, where $\bar{H}_2 \in \{H_0, H_1\}$
  relative possibility of *ith* dose being over-toxic
- Under Bayes Factor criteria λ_1 and λ_2
  - If $BF_1 > \lambda_1$ and $BF_2 \leq \lambda_2$, **Escalate** the dose
  - If $BF_1 \leq \lambda_1$ and $BF_2 > \lambda_2$, **Deescalate** the dose
  - If $BF_1 \leq \lambda_1$ and $BF_2 \leq \lambda_2$, **Stay** at the dose
  - If $BF_1 > \lambda_1$ and $BF_2 > \lambda_2$, the dose's toxicity information not enough for making decision, **Stay** at the dose

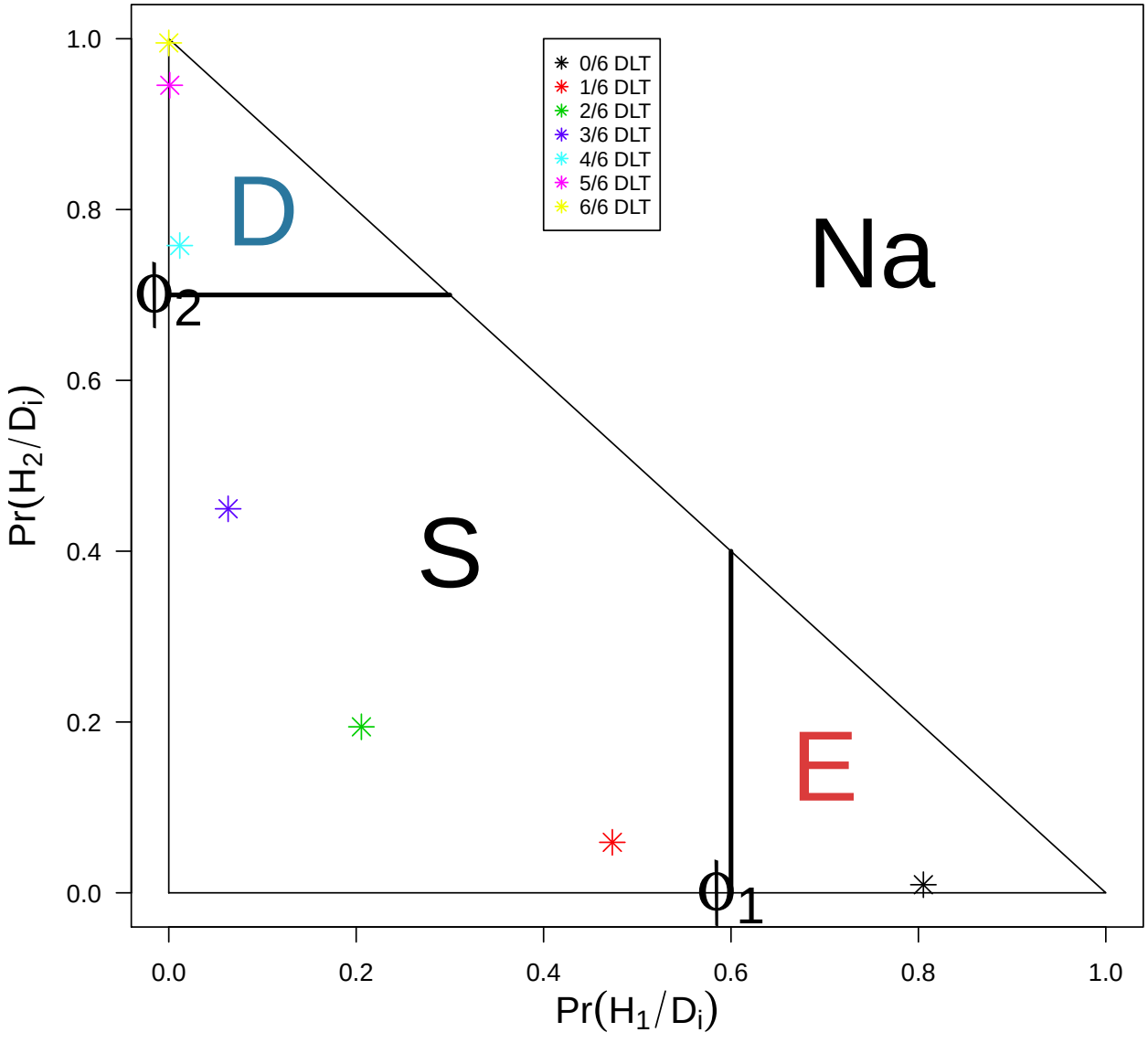
Decision Rule

- $BF_1 = \frac{f(D_i|H_1)}{f(D_i|\bar{H}_1)} = \frac{2Pr(H_1|D_i)}{1-Pr(H_1|D_i)}$
- So $BF_1 > \lambda_1$ is equivalent to set $Pr(H_1|D_i) > \phi_1$, $\phi_1 = \frac{\lambda_1}{2+\lambda_1}$
- Similarly $\phi_2 = \frac{\lambda_2}{2+\lambda_2}$, such that
  - $Pr(H_1|D_i) > \phi_1$ and $Pr(H_2|D_i) \leq \phi_2$, **E**scalate
  - $Pr(H_1|D_i) \leq \phi_1$ and $Pr(H_2|D_i) > \phi_2$, **D**eescalate
  - $Pr(H_1|D_i) \leq \phi_1$ and $Pr(H_2|D_i) \leq \phi_2$, **S**tay
  - $Pr(H_1|D_i) > \phi_1$ and $Pr(H_2|D_i) > \phi_2$, **S**tay
- $0 \leq \phi_1 < 1$ and $0 \leq \phi_2 < 1$

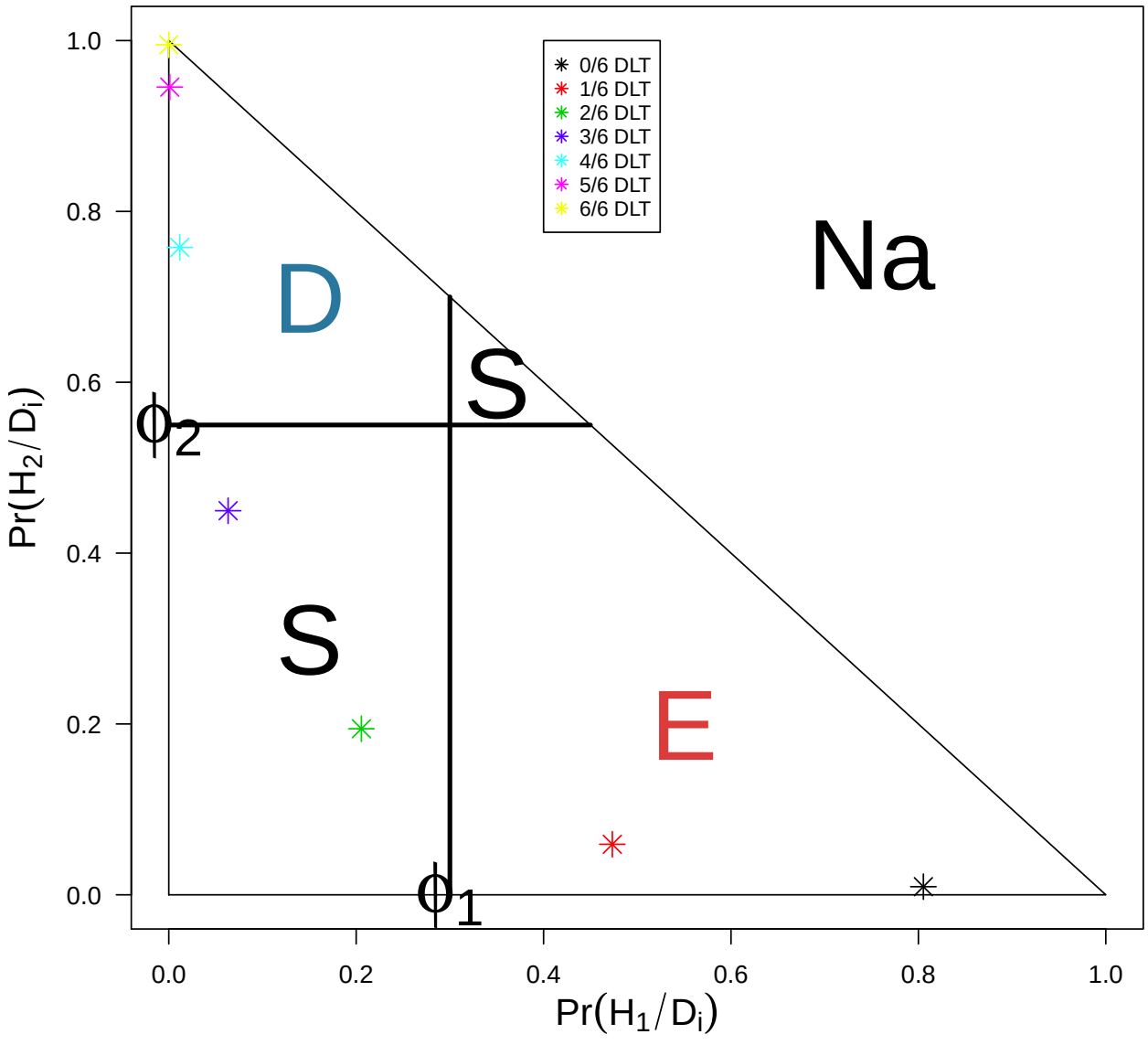
Decision Boundary



Decision Boundary



Decision Boundary



Motivation

- **HOW** to find the optimal criteria ϕ_1 and ϕ_2 ?
- In reality we do not know the true toxicity rate P_i^{tr}. We expect to make correct decision
  - When $P_i^{tr} \leq pT - \epsilon_1$, **E**scalate
  - When $P_i^{tr} \geq pT + \epsilon_2$, **D**eescalate
  - When $pT - \epsilon_1 < P_i^{tr} < pT + \epsilon_2$, **S**tay

Decision-Theoretic model

- Borrow the idea from Bayesian Sample Size Determination to specify our **design prior** of hypothesis for P_i^{tr}
- Three point hypothesis:

$$\begin{aligned}\mathbf{T_0} &: P_i^{tr} = pT \\ \mathbf{T_1} &: P_i^{tr} = pT - \epsilon_1 \\ \mathbf{T_2} &: P_i^{tr} = pT + \epsilon_2\end{aligned}$$

- First assume that

$$Pr(T_0) = Pr(T_1) = Pr(T_2) = 1/3$$

this is our **design prior**

Decision-Theoretic model

- Utility Function:

$$U(\mathbf{T_0}, D_i) = \begin{cases} 1 & \mathbf{S} \\ 0 & \mathrm{E} \\ 0 & \mathrm{D} \end{cases}$$

$$U(\mathbf{T_1}, D_i) = \begin{cases} 0 & \mathrm{S} \\ 1 & \mathbf{E} \\ 0 & \mathrm{D} \end{cases}$$

$$U(\mathbf{T_2}, D_i) = \begin{cases} 0 & \mathrm{S} \\ 0 & \mathrm{E} \\ 1 & \mathbf{D} \end{cases}$$

- Decision Rule:

$$\mathrm{S} : (Pr(H_1|D_i) \leq \phi_1 \wedge Pr(H_2|D_i) \leq \phi_2) \vee (Pr(H_1|D_i) > \phi_1 \wedge Pr(H_2|D_i) > \phi_2)$$
$$\mathrm{E} : Pr(H_1|D_i) > \phi_1 \wedge Pr(H_2|D_i) \leq \phi_2$$
$$\mathrm{D} : Pr(H_1|D_i) \leq \phi_1 \wedge Pr(H_2|D_i) > \phi_2$$

Utility Function

- $U(T_j, D_i)$ $j = 0, 1, 2$ indicate whether we make the correct movement under different values of P_i^{tr}
- Expect to make the overall probability of correct movements as large as possible
- Other utility functions; For example,

$$U(T_1, D_i) = \begin{cases} 0 & \text{S} \\ 0.8 & \mathbf{E} \\ 0 & \text{D} \end{cases}$$

Utility Function

- Given n_i, pT, ϵ_1, ϵ_2, the overal utility function is

$$\mathbf{U}(\phi_1, \phi_2) = E_{D_i}(E_{T_j}(U(T_j, D_i)))$$

$$= \sum_{x_i=0}^{n_i} \Big\{ I(\mathrm{S}|x_i, T_0) \times f(x_i|T_0) \times Pr(T_0) + I(\mathrm{E}|x_i, T_1) \times f(x_i|T_1) \times Pr(T_1)$$

$$+ I(\mathrm{D}|x_i, T_2) \times f(x_i|T_2) \times Pr(T_2) \Big\}$$

- Likelihood

$$f(x_i|T_0) \sim Bin(x_i, pT, n_i)$$

$$f(x_i|T_1) \sim Bin(x_i, pT - \epsilon_1, n_i)$$

$$f(x_i|T_2) \sim Bin(x_i, pT + \epsilon_2, n_i)$$

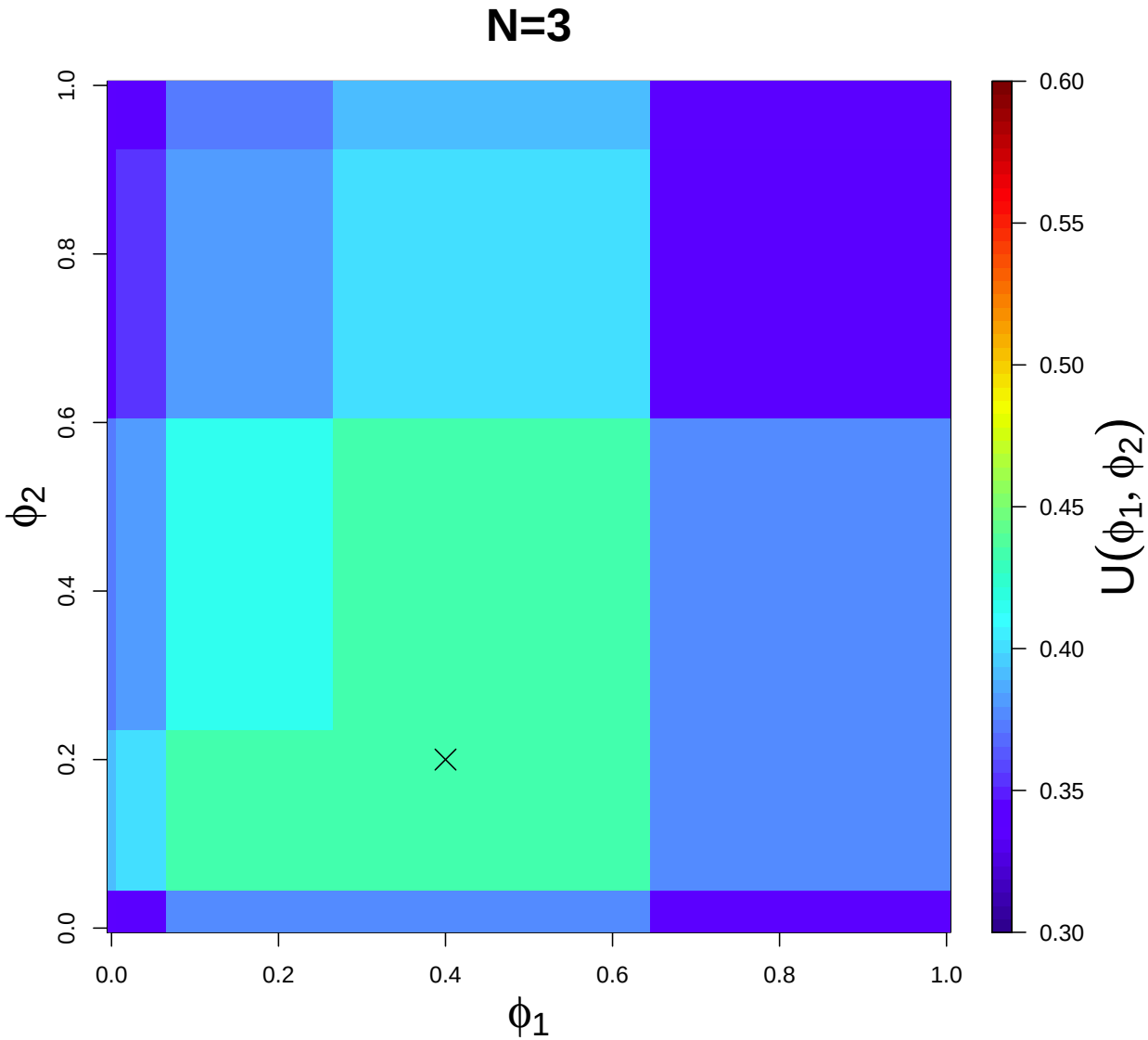
- Decision function

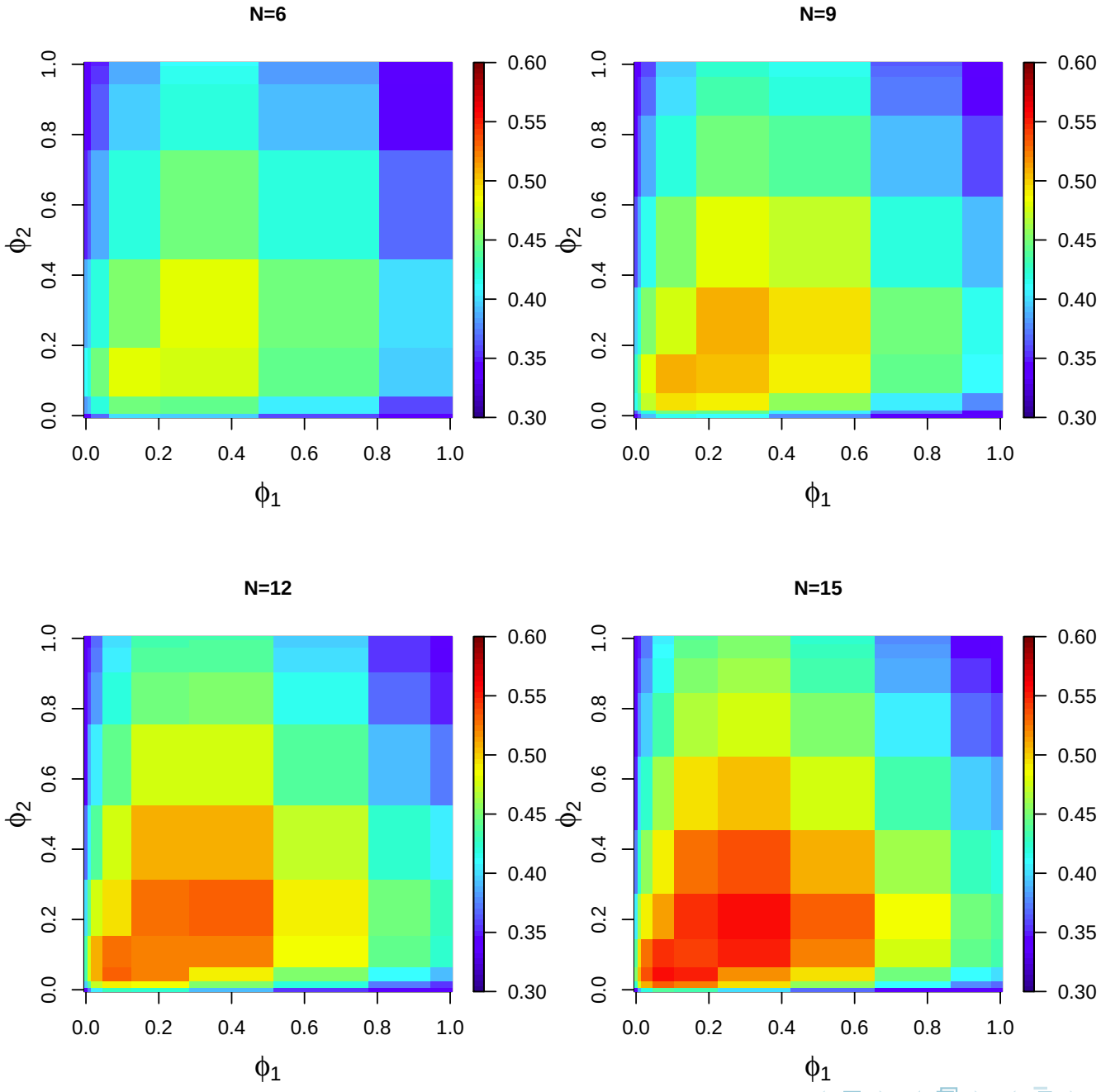
$$I(\mathrm{S}|x_i, T_0) = (Pr(H_1|x_i) \leq \phi_1 \wedge Pr(H_2|x_i) \leq \phi_2) \vee (Pr(H_1|x_i) > \phi_1 \wedge Pr(H_2|x_i) > \phi_2)$$

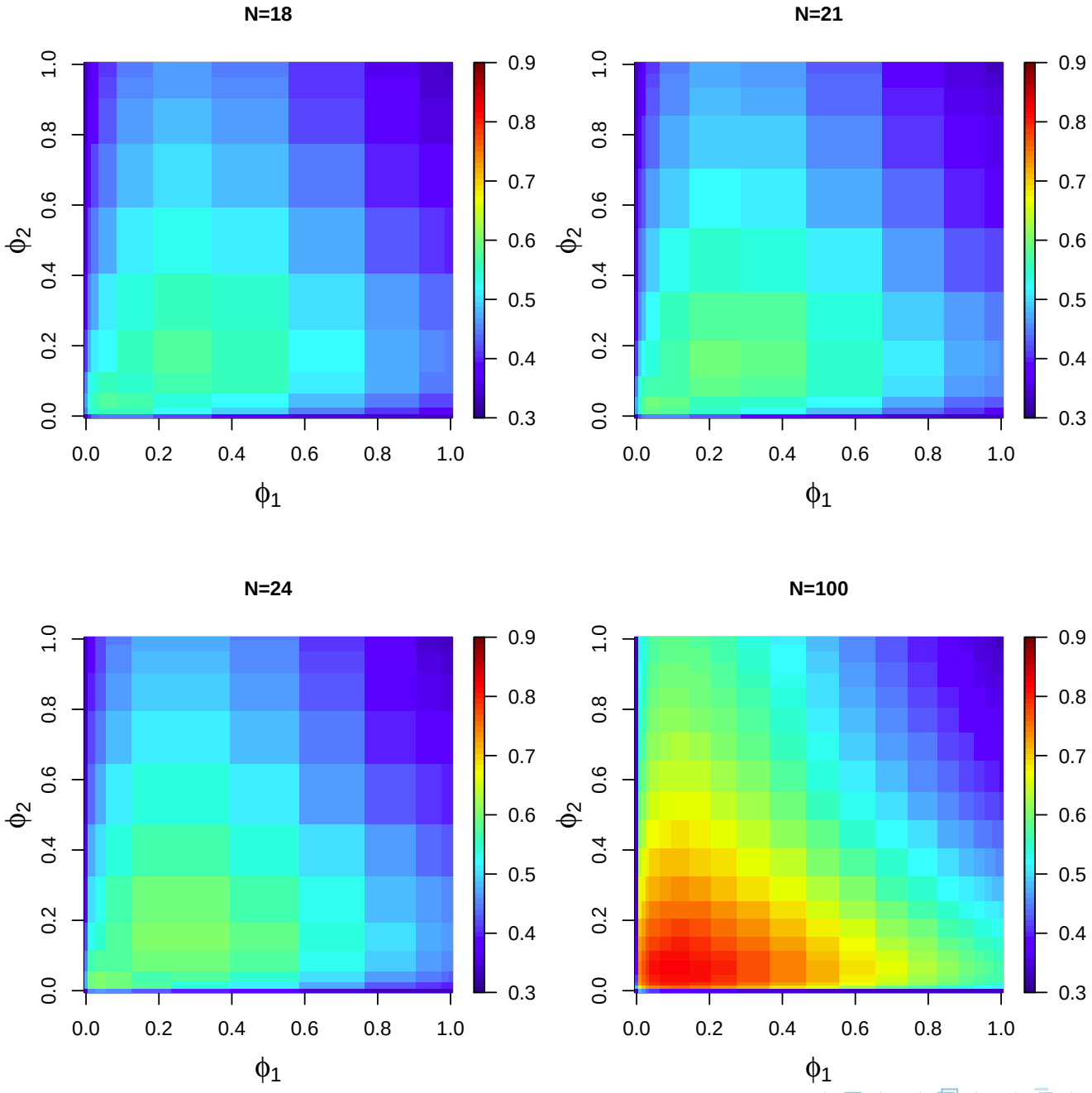
$$I(\mathrm{E}|x_i, T_1) = (Pr(H_1|x_i) > \phi_1 \wedge Pr(H_2|x_i) \leq \phi_2)$$

$$I(\mathrm{D}|x_i, T_2) = (Pr(H_1|x_i) \leq \phi_1 \wedge Pr(H_2|x_i) > \phi_2)$$

Numerical Search




N=6
N=9
N=12
N=15
ϕ_1
ϕ_2
0.0
0.2
0.4
0.6
0.8
1.0
0.30
0.35
0.40
0.45
0.50
0.55
0.60


N=18
N=21
N=24
N=100
ϕ_1
ϕ_2
0.0
0.2
0.4
0.6
0.8
1.0
0.3
0.4
0.5
0.6
0.7
0.8
0.9

Motivation

- The design prior

$$\mathbf{T_0} : P_i^{tr} = pT$$
$$\mathbf{T_1} : P_i^{tr} = pT - \epsilon_1$$
$$\mathbf{T_2} : P_i^{tr} = pT + \epsilon_2$$

$$Pr(T_0) = Pr(T_1) = Pr(T_2) = 1/3$$

- Now we want to measure the posterior probabilities of these hypothesis with all the cumulative toxicity information from doses

$$Pr(T_j | D_i, D_{-i})$$

$$j = 0, 1, 2$$

$$-i = \{1, 2, ..., i-1, i+1, ...D\}$$

Refined Design Prior

- Under Bayes Factor framework

$$Pr(T_j|D_i, D_{-i}) = \frac{f(D_i, D_{-i}|T_j) \times Pr(T_j)}{\sum f(D_i, D_{-i}|T_j) \times Pr(T_j)} \quad j = 0, 1, 2$$

where

$$f(D_i, D_{-i}|T_j) = f(D_i|T_j) \times f(D_{-i}|T_j)$$

- We apply **CRM** to borrow information to refine the design prior

$$f(D_{-i}|T_j) = \int f(D_{-i}|\alpha_j, T_j) \times f(\alpha_j|T_j) d\alpha_j$$

$$f(D_{-i}|\alpha_j, T_j) = \prod_{k=1,\ldots,i-1,i+1,\ldots,D} L(D_k|\alpha_j, T_j)$$

Adjust Parameter

- At current dose level i, $P_{i-1} < P_i < P_{i+1}$
- Under $\mathbf{T_0}$: $P_i^{tr} = pT$

$$\pi_{i-1}^{exp(\alpha_0)} < pT < \pi_{i+1}^{exp(\alpha_0)}$$

$$log\frac{log(pT)}{log(\pi_{i-1})} < \alpha_0 < log\frac{log(pT)}{log(\pi_{i+1})}$$

- Under $\mathbf{T_1}$: $P_i^{tr} = pT - \epsilon_1$ and $\mathbf{T_2}$: $P_i^{tr} = pT + \epsilon_2$

$$log\frac{log(pT-\epsilon_1)}{log(\pi_{i-1})} < \alpha_1 < log\frac{log(pT-\epsilon_1)}{log(\pi_{i+1})}$$

$$log\frac{log(pT+\epsilon_2)}{log(\pi_{i-1})} < \alpha_2 < log\frac{log(pT+\epsilon_2)}{log(\pi_{i+1})}$$

Adjust Parameter

- Propose the priors for the tuning parameter α_j under each hypothesis T_j:

$$f(\alpha_0|T_0) \propto N(0,\sigma^2)I(log\frac{log(pT)}{log(\pi_{i-1})} < \alpha_0 < log\frac{log(pT)}{log(\pi_{i+1})})$$

$$f(\alpha_1|T_1) \propto N(0,\sigma^2)I(log\frac{log(pT-\epsilon_1)}{log(\pi_{i-1})} < \alpha_1 < log\frac{log(pT-\epsilon_1)}{log(\pi_{i+1})})$$

$$f(\alpha_2|T_2) \propto N(0,\sigma^2)I(log\frac{log(pT+\epsilon_2)}{log(\pi_{i-1})} < \alpha_2 < log\frac{log(pT+\epsilon_2)}{log(\pi_{i+1})})$$

- By Monte Carlo integration

$$f(D_{-i}|T_j) = \int f(D_{-i}|\alpha_j, T_j) \times f(\alpha_j|T_j) d\alpha_j$$

which yields the refined design prior $Pr(T_j|D_i, D_{-i})$

Utility Function

- With complete toxicity information,

$$\mathbf{U}(\phi_1, \phi_2) = E_{D_i}(E_{T_j}(U(T_j, D_i, D_{-i})))$$

$$= \sum_{x_i=0}^{n_i} \Big\{ I(\mathrm{S}|x_i, T_0) \times f(x_i|T_0) \times Pr(T_0|D_i, D_{-i})$$

$$+ I(\mathrm{E}|x_i, T_1) \times f(x_i|T_1) \times Pr(T_1|D_i, D_{-i}) + I(\mathrm{D}|x_i, T_2) \times f(x_i|T_2) \times Pr(T_2|D_i, D_{-i}) \Big\}$$

- Find the solution of the optimal criteria ϕ_1 and ϕ_2 for $U(\phi_1, \phi_2)$ by numerical search on $\phi_1 \in [0, 1)$ and $\phi_2 \in [0, 1)$ such that

$$\{\hat{\phi_1}, \hat{\phi_2}\} = argmax\ U(\phi_1, \phi_2)$$

BF Design

1. Treat the first cohort at the lowest dose
2. For safety reasons, an early termination rule is imposed when the first dose is too toxic if
$$Pr(P_i > pT|D_i) > 0.95$$
3. At dose i, find the optimal criteria $\hat{\phi}_1$ and $\hat{\phi}_2$ and make the decision about next dose
4. Repeat step 3 to the end
5. Determine the MTD dose at dose i^* whose estimate of toxicity rate is closest to pT

In Practice

- After solving the optimal criteria $\hat{\phi}_1$ and $\hat{\phi}_2$, we can find the boundaries of the number of DLT for Escalation if $x_i \leq X_e$ and for Deescalation if $x_i \geq X_d$
- Physicians can make decision for dose movement by referring to a decision table. For example,

N	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
X_e	0	1	2	2	3	4	5	5
X_d	2	3	4	5	6	7	8	9

Simulation Study

- Compare our methods:
  - Bayes Factor with $\epsilon_1 = \epsilon_2 = 0.10$
  - Bayes Facotr with $\epsilon_1 = \epsilon_2 = 0.05$
  - With
    1. modified Toxicity Probability Interval
    2. Bayesian Model Averaging CRM (Yin and Yuan 2009)
    3. 'ideal' CRM: $\pi_i = P_i^{tr}$
    4. 3+3
- N=24 and cohort size is 3
- 6 candidate doses for finding the MTD, $pT = 0.30$
- In each scenario, fix the true toxicity rate $P_i^{tr}, \quad i = 1, ..., 6$
- Run 10000 simulations

Bayesian Model Averaging CRM

- BMA-CRM assume multiple skeletons:

$$M_1 : \pi_1^1, ..., \pi_6^1$$

$$M_2 : \pi_1^2, ..., \pi_6^2$$

$$M_3 : \pi_1^3, ..., \pi_6^3$$

- Under each model M_l, the toxicity probability at dose i will be

$$P_k^l = (\pi_k^l)^{exp(\alpha_l)} \quad l = 1, 2, 3$$

- Then the posterior probability of each model will be

$$Pr(M_l|D) = \frac{f(D|M_l)Pr(M_l)}{\sum f(D|M_l)Pr(M_l)}$$

$$f(D|M_l) = \int f(D|\alpha_l, M_l) f(\alpha_l|M_l) d\alpha_l$$

- The posterior mean of toxicity rate will be

$$\hat{P}_k = \sum \hat{P_k^l} \times Pr(M_l|D)$$

Mock-up

Scenario #		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	xx	xx	xx	xx	xx	xx					
$BF_{0.10}$	% MTD	xx	xx	xx	xx	xx	xx	xx	xx	x.x	x.x	xx
	# Pts	x.x	x.x	x.x	x.x	x.x	x.x	x.x				
$BF_{0.05}$	% MTD											
	# Pts											
mTPI	% MTD											
	# Pts											
BMA-CRM	% MTD											
	# Pts											
CRM_{id}	% MTD											
	# Pts											
3+3	% MTD											
	# Pts											

Scenarios

Scenario 1		Dose Level 1	2	3	4	5	6	None	% >*MTD*	# >*MTD*	#T >*MTD*	T% *overal*
	True T%	**30**	44	56	73	81	95					
$BF_{0.10}$	% MTD	58	23	3	0	0	0	16	26	6.7	3.0	34.8
	# Pts	15.0	5.5	1.1	0.1	0.0	0.0	2.3				
$BF_{0.05}$	% MTD	59	22	3	0	0	0	16	25	**6.2**	**2.8**	**34.4**
	# Pts	**15.5**	5.3	0.8	0.1	0.0	0.0	2.3				
mTPI	% MTD	59	22	3	0	0	0	18	25	6.9	3.2	34.9
	# Pts	14.8	5.8	1.0	0.1	0.0	0.0	2.3				
BMA-CRM	% MTD	**64**	19	3	0	0	0	14	**22**	6.3	3.1	35.8
	# Pts	**15.5**	4.6	1.5	0.2	0.0	0.0	2.2				
CRM_{id}	% MTD	64	19	2	0	0	0	15	21	5.7	2.6	34.1
	# Pts	16.0	4.8	0.9	0.0	0.0	0.0	2.3				
3+3	% MTD	46	19	2	0	0	0.0	33	21	3.3	1.5	36.7
	# Pts	4.9	2.6	0.6	0.1	0.0	0.0	15.9				

Scenarios

Scenario 2		Dose Level 1	2	3	4	5	6	None	% >MTD	# >MTD	#T >MTD	T% overal
	True T%	12	**30**	41	52	71	76					
$BF_{0.10}$	% MTD	18	55	22	4	0	0	0	26	5.2	2.2	27.0
	# Pts	7.9	10.7	4.3	0.9	0.0	0.0	0.2				
$BF_{0.05}$	% MTD	17	**56**	22	4	0	0	1	**26**	**4.1**	**1.8**	**24.5**
	# Pts	10.2	9.6	3.3	0.7	0.0	0.0	0.2				
mTPI	% MTD	19	53	23	5	0	0	0	28	5.6	2.4	27.4
	# Pts	7.5	**10.8**	4.5	1.0	0.0	0.0	0.2				
BMA-CRM	% MTD	17	46	28	9	0	0	0	37	7.9	3.6	29.4
	# Pts	7.7	8.2	5.6	2.1	0.2	0.0	0.2				
CRM_{id}	% MTD	14	58	22	5	0	0	1	27	5.3	2.3	27.3
	# Pts	7.8	10.7	3.9	1.4	0.0	0.0	0.2				
3+3	% MTD	31	42	18	4	0	0	7	21	3.0	1.3	26.9
	# Pts	4.5	4.7	2.3	0.6	0.1	0.0	11.8				

Scenarios

Scenario 3		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	10	12	**30**	42	61	83					
$BF_{0.10}$	% MTD	1	22	**54**	22	3	0	1	25	3.5	1.5	23.2
	# Pts	4.6	7.0	**9.0**	3.2	0.3	0.0	0.2				
$BF_{0.05}$	% MTD	1	23	52	22	2	0	1	**24**	**2.8**	**1.2**	**20.3**
	# Pts	6.0	8.6	6.6	2.5	0.3	0.0	0.2				
mTPI	% MTD	3	23	50	21	3	0	0	**24**	3.9	1.7	23.4
	# Pts	5.0	6.6	8.5	3.3	0.6	0.0	0.0				
BMA-CRM	% MTD	2	16	43	34	4	0	0	38	6.	3.1	26.7
	# Pts	4.9	5.2	7.2	5.4	1.2	0.1	0.2				
CRM_{id}	% MTD	1	14	60	24	2	0	1	26	4.7	2.1	25.4
	# Pts	4.6	5.2	9.5	4.1	0.6	0.0	0.2				
3+3	% MTD	8	30	40	17	1	0	4	18	2.6	1.2	22.5
	# Pts	3.8	4.2	4.3	2.1	0.5	0.0	9.1				

Scenarios

Scenario 4		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	5	7	15	**30**	41	55					
$BF_{0.10}$	% MTD	0	2	26	51	17	2	0	19	2.6	1.1	19.1
	# Pts	3.6	4.4	6.8	6.6	2.1	0.5	0.0				
$BF_{0.05}$	% MTD	0	3	28	**52**	14	2	1	**16**	**1.7**	**0.7**	**16.5**
	# Pts	4.3	5.8	6.9	5.4	1.4	0.3	0.2				
mTPI	% MTD	0	3	28	45	20	4	0	24	2.9	1.3	19.5
	# Pts	3.7	4.3	6.6	6.5	2.5	0.5	0.0				
BMA-CRM	% MTD	0	1	13	47	30	9	0	39	5.3	2.3	22.9
	# Pts	3.6	3.5	4.8	**6.9**	4.0	1.3	0.0				
CRM_{id}	% MTD	0	0	20	51	25	4	0	29	4.1	1.9	22.6
	# Pts	3.6	3.3	5.7	7.2	3.3	0.8	0.0				
3+3	% MTD	3	9	35	36	14	1	2	15	2.3	1.0	18.6
	# Pts	3.5	3.7	4.4	3.9	1.9	0.4	6.2				

Scenarios

Scenario 5		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	2	3	6	7	**30**	42					
$BF_{0.10}$	% MTD	0	0	1	18	**57**	24	0	24	2.0	0.9	14.8
	# Pts	3.2	3.4	3.7	4.7	**6.8**	2.0	0.0				
$BF_{0.05}$	% MTD	0	0	2	26	51	21	0	**21**	**1.7**	**0.7**	**12.0**
	# Pts	3.5	4.0	4.3	6.3	4.3	1.7	0.0				
mTPI	% MTD	0	0	2	18	53	27	0	27	2.5	1.1	15.3
	# Pts	3.2	3.4	3.8	4.7	6.3	2.5	0.1				
BMA-CRM	% MTD	0	0	0	10	45	45	0	45	4.9	2.1	18.8
	# Pts	3.2	3.0	3.1	4.0	5.7	4.9	0.1				
CRM_{id}	% MTD	0	0	0	7	62	30	1	30	3.4	1.4	17.9
	# Pts	3.2	3.0	3.0	4.2	7.2	3.4	0.0				
3+3	% MTD	1	2	5	29	44	8	11	8	2.0	0.8	14.1
	# Pts	3.2	3.3	3.5	4.1	4.8	2.0	3.2				

Scenarios

Scenario 6		Dose Level 1	2	3	4	5	6	None	% >*MTD*	# >*MTD*	#T >*MTD*	T% *overal*
	True T%	2	8	12	15	19	**30**					
$BF_{0.10}$	% MTD	0	2	5	17	28	48	0				15.1
	# Pts	3.3	4.2	4.8	4.8	4.1	2.8	0.0				
$BF_{0.05}$	% MTD	0	3	11	33	25	28	0				12.0
	# Pts	4.1	5.4	5.4	4.9	2.6	1.6	0.0				
mTPI	% MTD	0	3	9	21	31	36	0				13.7
	# Pts	3.3	4.3	5.0	4.9	3.8	2.7	0.0				
BMA-CRM	% MTD	0	0	2	12	28	**58**	0				15.8
	# Pts	3.3	3.2	3.7	4.7	4.4	**4.8**	0.0				
CRM_{id}	% MTD	0	0	2	4	21	73	0				16.7
	# Pts	3.2	3.3	3.7	3.3	4.2	6.3	0				
3+3	% MTD	1	9	15	20	25	8	22				13.1
	# Pts	3.2	3.8	3.9	3.5	3.1	1.9	4.6				

Scenarios

Scenario 7		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	50	62	68	73	78	80					
$BF_{0.10}$	% MTD	22	1	0	0	0	0	77	23	13.3	6.8	51.3
	# Pts	12.1	1.1	0.1	0.0	0.0	0.0	10.7				
$BF_{0.05}$	% MTD	22	0	0	0	0	0	78	22	13.3	6.8	51.2
	# Pts	12.2	1.0	0.1	0.0	0.0	0.0	10.7				
mTPI	% MTD	21	1	0	0	0	0	78	22	13.3	6.8	51.3
	# Pts	12.1	1.1	0.1	0.0	0.0	0.0	10.7				
BMA-CRM	% MTD	27	1	0	0	0	0	72	28	13.9	7.1	51.1
	# Pts	12.8	0.9	0.2	0.0	0.0	0.0	10.1				
CRM_{id}	% MTD	25	0	0	0	0	0	75	25	13.0	6.5	50.0
	# Pts	12.0	0.9	0.1	0.0	0.0	0.0	11.0				
3+3	% MTD	28	3	0	0	0	0	69	11	5.3	2.7	51.9
	# Pts	4.4	0.8	0.1	0.0	0.0	0.0	**18.7**				

Scenarios

Scenario 8		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	11	25	**30**	35	51	83					
$BF_{0.10}$	% MTD	8	40	**32**	15	4	0	1	**20**	2.7	1.0	23.4
	# Pts	6.1	9.0	**6.1**	2.2	0.4	0.1	0.1				
$BF_{0.05}$	% MTD	9	41	29	18	3	0	0	21	**2.0**	**0.8**	**21.8**
	# Pts	8.8	8.9	4.3	1.7	0.3	0.0	0.0				
mTPI	% MTD	11	39	29	17	5	0	0	22	2.8	1.1	24.8
	# Pts	6.4	9.2	5.4	2.2	0.6	0.0	0.2				
BMA-CRM	% MTD	7	25	28	32	7	0	1	39	5.7	2.3	26.4
	# Pts	6.2	6.3	5.7	4.2	1.3	0.2	0.1				
CRM_{id}	% MTD	7	33	20	30	9	0	1	39	5.6	2.1	25.4
	# Pts	6.4	6.8	5.2	4.1	1.5	0.0	0.0				
3+3	% MTD	23	35	22	13	2	0	5	15	2.0	0.8	23.9
	# Pts	4.3	4.4	2.7	1.4	0.5	0.3	10.6				

Scenarios

Scenario 9		Dose Level 1	2	3	4	5	6	None	% *>MTD*	# *>MTD*	#T *>MTD*	T% *overal*
	True T%	5	12	**24**	46	53	81					
$BF_{0.10}$	% MTD	0	14	**61**	24	2	0	0	**26**	4.8	2.1	22.3
	# Pts	3.8	6.1	**9.4**	4.3	0.4	0.1	0.1				
$BF_{0.05}$	% MTD	0	15	55	27	2	0	1	29	**3.9**	**1.8**	**19.6**
	# Pts	5.1	7.8	7.2	3.5	0.4	0.0	0.0				
mTPI	% MTD	1	15	56	25	4	0	0	29	5.3	2.5	23.0
	# Pts	3.8	6.2	8.8	4.5	0.7	0.1	0.0				
BMA-CRM	% MTD	0	11	44	39	6	0	0	45	8.1	4.0	27.5
	# Pts	3.8	4.7	7.4	6.4	1.5	0.2	0.0				
CRM_{id}	% MTD	0	8	64	25	3	0	0	28	4.7	2.2	23.9
	# Pts	3.7	4.5	10.9	3.7	1.0	0.0	0.0				
3+3	% MTD	5	24	50	19	2	0	0	21	3.4	1.6	21.6
	# Pts	3.5	4.3	4.6	2.8	0.5	0.0	8.2				

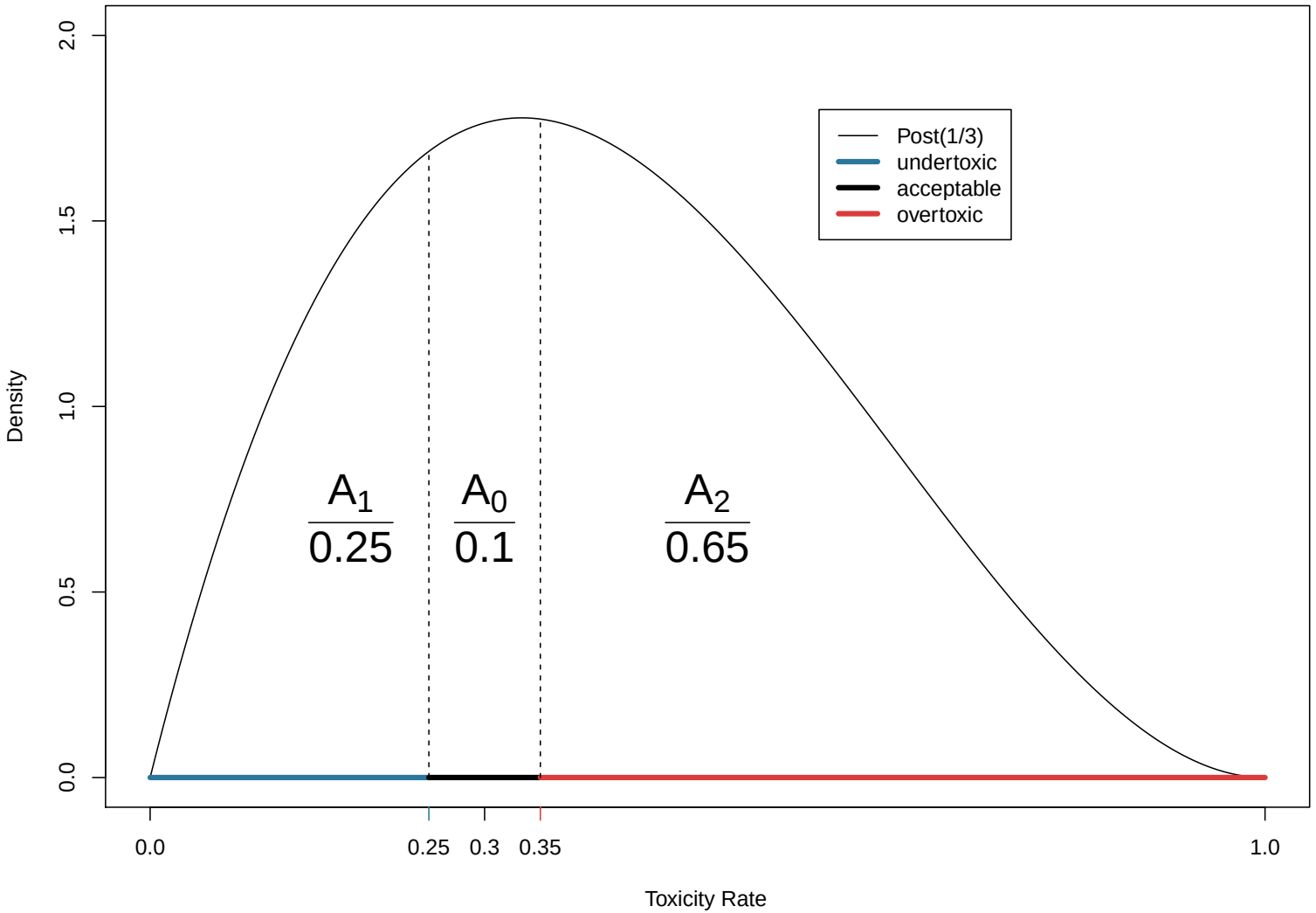
Scenarios

Scenario 10		Dose Level 1	2	3	4	5	6	None	% >MTD	# >MTD	#T >MTD	T% overal
	True T%	10	20	**30**	40	50	60					
$BF_{0.10}$	% MTD	5	31	**46**	15	2	0	0	24	3.2	1.3	23.0
	# Pts	5.5	8.1	**7.2**	2.6	0.5	0.1	0.0				
$BF_{0.05}$	% MTD	5	36	39	18	2	0	0	**20**	**2.3**	**1.0**	**21.2**
	# Pts	7.6	8.9	5.2	2.0	0.3	0.0	0.0				
mTPI	% MTD	6	34	38	18	4	0	0	22	3.4	1.4	23.7
	# Pts	5.5	8.5	6.6	2.7	0.6	0.1	0.0				
BMA-CRM	% MTD	4	23	36	29	6	1	1	36	6.0	2.6	26.3
	# Pts	5.4	6.0	6.6	4.6	1.2	0.2	0.0				
CRM_{id}	% MTD	3	26	42	22	6	1	0	29	4.8	2.1	25.5
	# Pts	5.3	6.5	7.3	3.7	1.0	0.1	0.1				
3+3	% MTD	16	33	31	13	3	0	4	16	2.3	1.0	23.2
	# Pts	4.1	4.4	3.4	1.7	0.5	0.1	9.9				

Simulation Summary

- 3+3: Poor performance
- CRM tends to expose more patients at over-toxic doses
- mTPI and BF perform better than BMA-CRM, except in Scenario 6
- $\mathbf{BF_{0.05}}$ is more conservative than $\mathbf{BF_{0.10}}$ and mTPI, still yields good performance
- $\mathbf{BF_{0.10}}$ outperforms mTPI

mTPI Design


Post(1/3)
undertoxic
acceptable
overtoxic
$\frac{A_1}{0.25}$
$\frac{A_0}{0.1}$
$\frac{A_2}{0.65}$
Density
0.0
0.5
1.0
1.5
2.0
0.0
0.25
0.3
0.35
1.0
Toxicity Rate

mTPI Design

- Decision Rule in mTPI:
  - If $\frac{A_1}{pT-\epsilon_1} > \frac{A_0}{\epsilon_1+\epsilon_2}$ and $\frac{A_1}{pT-\epsilon_1} > \frac{A_2}{1-pT-\epsilon_2}$, Escalate;
  - If $\frac{A_2}{1-pT-\epsilon_2} > \frac{A_0}{\epsilon_1+\epsilon_2}$ and $\frac{A_2}{1-pT-\epsilon_2} > \frac{A_1}{pT-\epsilon_1}$, Deescalate;
  - Otherwise, Stay
- This is a special case of BF model when

$$H_0 : P_i \sim Uniform(pT - \epsilon_1, pT + \epsilon_2)$$
$$H_1 : P_i \sim Uniform(0, pT - \epsilon_1)$$
$$H_2 : P_i \sim Uniform(pT + \epsilon_2, 1)$$

$$Pr(H_0|D_i) = \frac{A_0}{\epsilon_1 + \epsilon_2}$$

$$Pr(H_1|D_i) = \frac{A_1}{pT - \epsilon_1}$$

$$Pr(H_2|D_i) = \frac{A_2}{1 - pT - \epsilon_2}$$

mTPI Design

- Decision Rule in mTPI:
  1. If $Pr(H_1|D_i) > max(Pr(H_0|D_i), Pr(H_2|D_i))$, Escalate;
  2. If $Pr(H_2|D_i) > max(Pr(H_0|D_i), Pr(H_1|D_i))$, Deescalate;
  3. Otherwise, Stay
- Decision Rule in BF:
  1. If $Pr(H_1|D_i) > \hat{\phi}_1$ and $Pr(H_2|D_i) \leq \hat{\phi}_2$, Escalate;
  2. If $Pr(H_1|D_i) \leq \hat{\phi}_1$ and $Pr(H_2|D_i) > \hat{\phi}_2$, Deescalate;
  3. Otherwise, Stay
- Moreover, BF optimizes the decision rule with toxicity informaiton from all doses

In Practice

- Decision Table
  - If $x_i \leq X_e$, Escalate;
  - If $x_i \geq X_d$, Deescalate;
  - Otherwise, Stay

$pT = 0.30$	N	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
$\mathbf{BF_{0.10}}$	X_e	0	1	2	2	3	4	5	5
	X_d	2	3	4	5	6	7	8	9
$\mathbf{BF_{0.05}}$	X_e	0	1	2	3	4	4	5	6
	X_d	1	2	3	4	5	6	7	8
$\mathbf{mTPI_{0.10}}$	X_e	0	1	1	2	2	3	3	4
	X_d	2	4	5	6	8	9	10	12
$\mathbf{mTPI_{0.05}}$	X_e	0	1	1	2	2	3	**4**	4
	X_d	2	4	5	6	8	9	10	**11**

- Based on our studies, we recommend **0.10** as the boundary distance

In Practice

N	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**
X_e	0	1	2	2	3	4	5	5
X_d	2	3	4	5	6	7	8	9
$E(P_c)$	**43.5%**	**47.8%**	**50.7%**	**53.0%**	**55.7%**	**57.7%**	**59.3%**	**60.8%**

Conclusion

- A new dose finding approach with the optimal Bayes Factor framework
- The extensive simulations show the superiority of BF
- Compared with CRM, BF consider the decision uncertainty on each dose level separately
- Compared with mTPI, BF effectively borrow all dose toxicity information

Ideal Design

- Good Operating Performance ✓
  1. Select True MTD
  2. Treat More at MTD
  3. Limit Patients at Over-Toxic
- Efficiency: Fully Utilize Information ✓
- Feasibility
  1. Flexible ✓
  2. Transparent ✓
  3. Understandable ✓ ?
  4. Simple to implement ?

Methodology

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Thank you!