Optimal Statistical Design for Phase I Cancer Clinical Trials: A Simulaton Study

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Dose-finding in phase I clinical trials

Doses: $d = \{d_1, \cdots, d_I\}$

Unknown dose toxicity probabilities $\pi = \{\pi_1, \cdots, \pi_I\}$

Target toxicity level (TTL): ϕ

Some design examples –

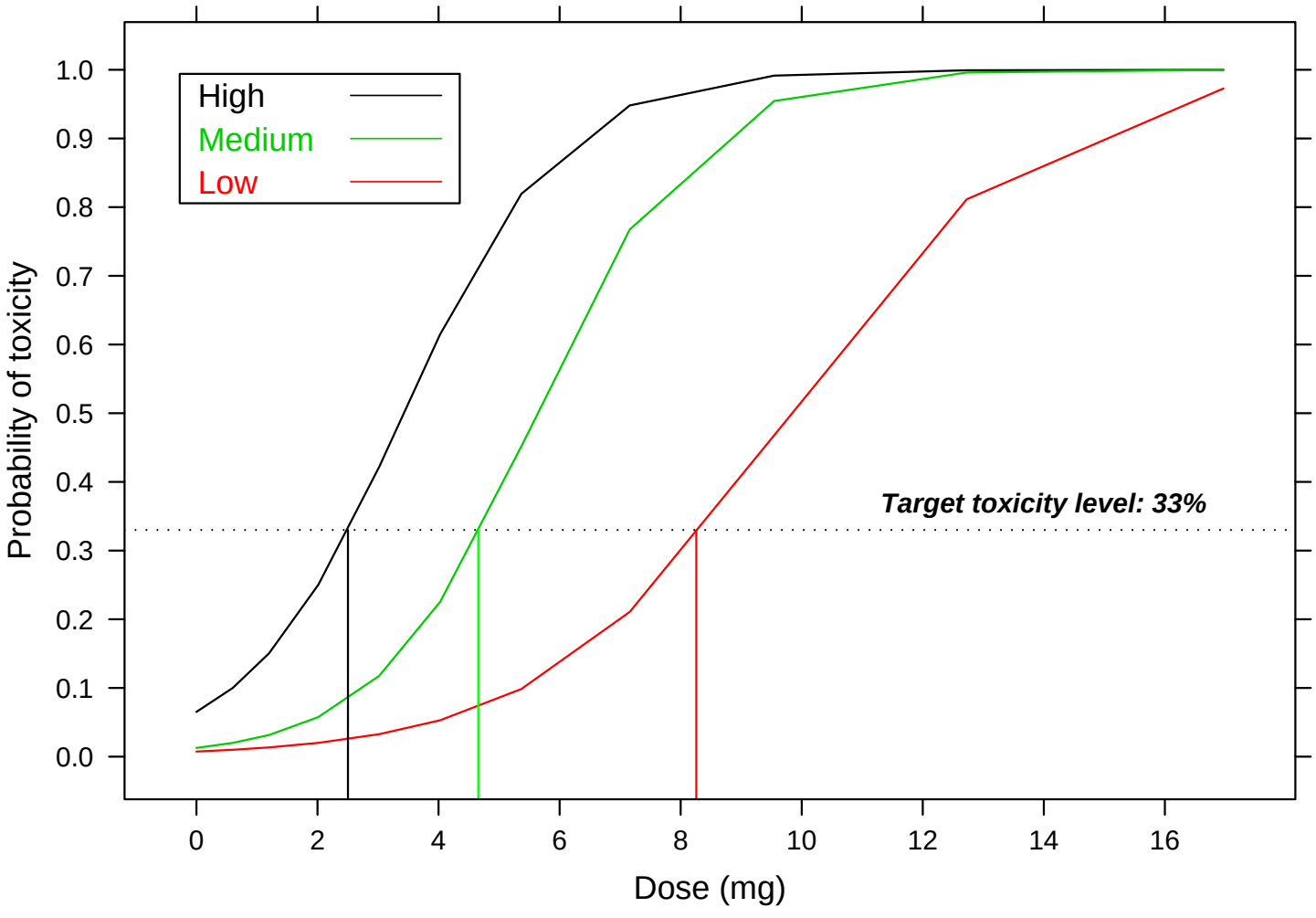
- Algorithm-based:
  - Traditional escalation rule (TER): $3 + 3$
  - Accerlated titration design: allow intra-patient escalation
  - Biased coin design: sequential design
- Model-based:
  - Continual reassessment method (CRM): $\pi_i = p_i^{\exp(\beta)}$ and $\beta \sim N(0, \sigma^2)$; p_i is constant determined from prior toxicity probability, $i = 1, \cdots, I$
  - Beta-binomial design: number of toxicities $\sim Bi(n_i, \pi_i)$, $\pi_i \overset{\text{i.i.d}}{\sim} Beta(a, b)$
  - Bayesian model averaging CRM: allow for multiple prior models
  - Efficacy-toxicity model: dose escalation method accounting for both toxicity and efficacy

Traditional escalation rule (TER)

- Maximum tolerated dose (MTD): dose level with probability of dose limiting toxicity (DLT) less than a pre-specified percentage γ ($\in$ [20%, 35%])
- γ is the target toxicity level (TTL) and typically set $\gamma = 33\%$
- Commonly used TER: 3 + 3 design without dose de-escalation

Maximum tolerated dose

Figure 1: MTD under different scenarios



3 + 3 design: flow chart

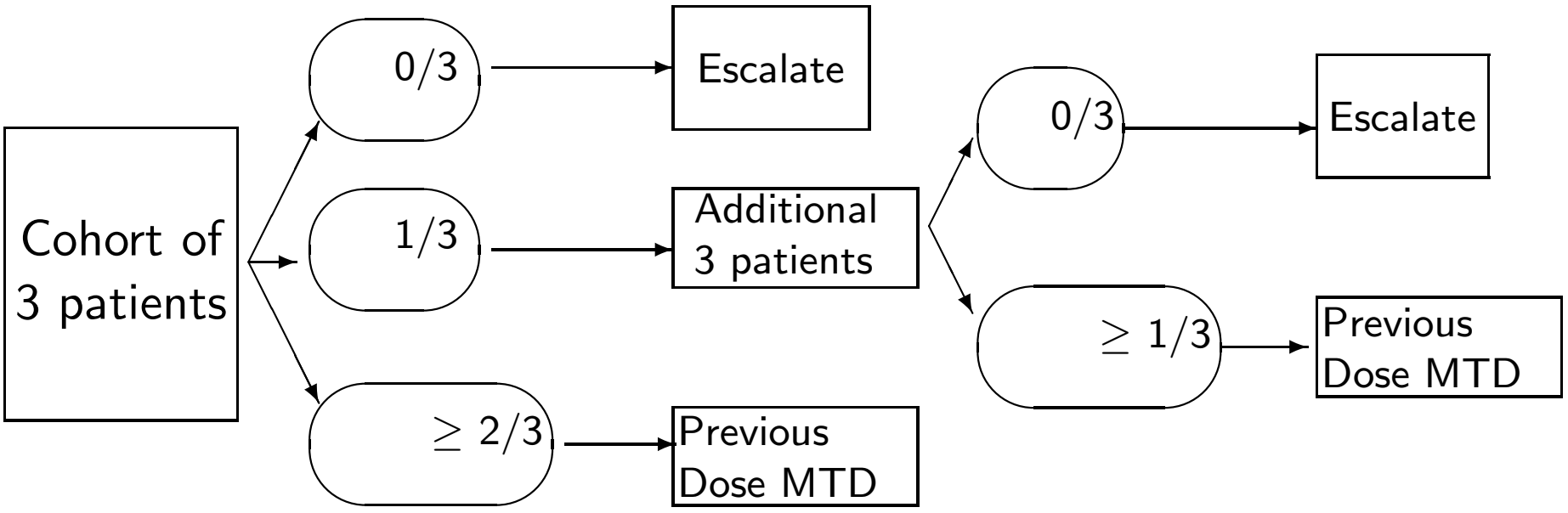


Figure 2: TER flow chart

Does this escalation scheme implies that target toxicity level is 33%?

Target toxicity level (TTL)

TTL is the DLT rate at MTD: not fixed as common perception

Table 1: Prob. of dose level being MTD

Dose level	1	2	3	4	5	6
mg/m^2	60	80	100	120	140	160
First scenario						
P(toxicity)	0.05	0.10	0.15	0.25	0.35	0.5
P(MTD)	0.09	0.16	0.29	0.26	0.14	0.023
Second scenario						
P(toxicity)	0.25	0.30	0.35	0.45	0.55	0.60
P(MTD)	0.30	0.18	0.09	0.02	0.003	0.007
Third scenario						
P(toxicity)	0.05	0.15	0.25	0.35	0.50	0.70
P(MTD)	0.18	0.32	0.29	0.16	0.03	0.001

1st scenario: TTL $= 18.9\%$; 2nd scenario: TTL $= 29.0\%$; 3rd scenario: TTL $= 20.4\%$

Non-fixed TTL

- It is a misconception for some researchers to think that 3 + 3 design has a fixed TTL at 33%
- The TTL depends on the true probability of toxicity at each dose level
- Consider possible scenarios of toxicity rate at each dose level and find out the TTLs
- A survey over 20+ phase I trials by Lee et al. from M.D. Anderson Cancer Center suggests the empirical toxicity rate at MTD is between 23% and 28%

Continual Reassessment Method

- Continual reassessment method (CRM): first adaptation of Bayesian approach to Phase I trial design (O'Quigley, et al., 1990).
- CRM characterizes the dose-toxicity relationship by a simple one-parameter parametric model -
  - Logistic: $p(d) = \frac{\exp(3+\theta d)}{1+\exp(3+\theta d)}$
  - Power: $p(d) = d^{\exp(\theta)}$
  - Hyperbolic tangent: $p(d) = \left[\frac{\exp(d)}{\exp(d)+\exp(-d)}\right]^{\theta}$
- To illustrate how CRM is implemented, assume
  - A working dose-toxicity model $Pr(\text{toxicity at } d_i) = \pi_i = p_i^{\exp\{\beta\}}$, where p_i is constant
  - Prior distribution of β: $\beta \sim f(\beta)$
  - Specify prior mean toxicity probability $S = \{s_1, \cdots, s_I\}$

CRM Algorithm

1. Treat n_i patients at the dose level i
2. Observe toxicity outcome: $D = \{(n_i, y_i), i = 1, \cdots, I\}$, where y_i is the number of pattens who experience DLT
3. The likelihood function based on observed data D is

$$L(D|\beta) = \prod_{i=1}^{I} \left[p_i^{\exp(\beta)}\right]^{y_i} \left[1 - p_i^{\exp(\beta)}\right]^{(n_i - y_i)}.$$

   Using Bayes theorem, the posterior mean of π_i is

$$\hat{\pi}_i = \int p_i^{\exp(\beta)} \frac{L(D|\beta) f(\beta)}{\int L(D|\beta) f(\beta) d\beta} d\beta.$$

4. The next cohort of patients is assigned to dose level i^*, such that

$$i^* = \text{argmin}_{i \in \{1, \cdots, I\}} |\hat{\pi}_i - \phi|.$$

5. Repeat step 1 -4 until the total sample size is exhausted and MTD is the dose with a posterior probability closest to ϕ

CRM: advantages and disadvantages

Continual reassessment method: first adaptation of Bayesian approach to Phase I trial design

- Pros: relatively robust against model misspecification; use all accumulating data; better operating characteristics than 3 + 3
- Issues with CRM:
  - skip intermediate dose levels;
  - lengthening the trial (cohort size of one)
  - excessive experimentation at overly toxic dose levels

Variants of CRM proposed to overcome these problems

Toxicity probability interval approach (1)

Toxicity probability interval (TPI) set up:

- Binomial distribution for the toxicity outcome: $y_i \sim Bi(n_i, \pi_i)$, $i = 1, \cdots, I$
- Beta prior for π_i: $\pi_i \overset{\text{i.i.d}}{\sim} Beta(a, b)$
- Conjugate-prior: posterior of $\pi_i \overset{\text{i.i.d}}{\sim} Beta(a + y_i, n_i + b - y_i)$

A two-components method (Ji, et al. 2007; TPI design):

- Beta-binomial model to compute posterior estimate of dose toxicity probability
- Dose assignment rule that allows escalation (E), stay (S), and de-escalation (D) at current dose based on posterior estimates

Toxicity probability interval approach (2)

To decide which action to take: E, S, or D, denote by σ_i the posterior standard deviation of π_i

- Partition the unit interval $(0, 1)$ into three sub-intervals
  - $(0, \phi - K_1\sigma_i)$: low toxicity
  - $[\phi - K_1\sigma_i, \phi + K_2\sigma_i]$: acceptable toxicity
  - $(\phi + K_2\sigma_i, 1)$: high toxicity

  Here K_1 and K_2 are small positive constants such that $0 < \phi - K_1\sigma_i < \phi + K_2\sigma_i < 1$
- Assume current dose level is i. If
  - posterior distribution of π_i puts most of mass at $(0, \phi - K_1\sigma_i)$, take action E: $i \to i + 1$
  - posterior distribution of π_i puts most of mass at $[\phi - K_1\sigma_i, \phi + K_2\sigma_i]$, take action S: $i \to i$
  - posterior distribution of π_i puts most of mass at $(\phi + K_2\sigma_i, 1)$, take action D: $i \to i - 1$

Toxicity probability interval approach (3)

- For current dose level i, based on the posterior distribution of π_i, compute
  - $q(E, i) = Pr(\pi_i - \phi < -K_1\sigma_i)$
  - $q(S, i) = Pr(-K_1\sigma_i \leq \pi_i - \phi \leq K_2\sigma_i)$
  - $q(D, i) = Pr(\pi_i - \phi > K_2\sigma_i)$
- Define an indicator function for a dose that is highly toxic:

$$\tau_i = I\{Pr(\pi_i > \phi|\text{data}) > \xi\},$$

  where $\xi \in (0, 1)$ is the tolerance threshold, typically takes value 0.95
- Define $q(\tilde{E}, i) = q(E, i)(1 - \tau_i)$
- A dose-assignment rule B_i is defined as

$$B_i = \text{argmax}_{h \in \{\tilde{E}, S, D\}} q(h, i)$$

Trial monitoring table: an example

Table 2: Dose assignment rules: $K_1 = 1, K_2 = 1.5$, prior $Beta(0.005, 0.005), \phi = 0.30$

	Number of patients treated at current dose								
Number of toxicities	1	2	3	4	5	6	7	8	9
0	S	E	E	E	E	E	E	E	E
1	S	S	S	S	S	S	E	E	E
2		DU	D	S	S	S	S	S	S
3			DU	DU	D	D	S	S	S
4				DU	DU	DU	D	D	S
5					DU	DU	DU	DU	D
6						DU	DU	DU	DU
7							DU	DU	DU
8								DU	DU
9									DU

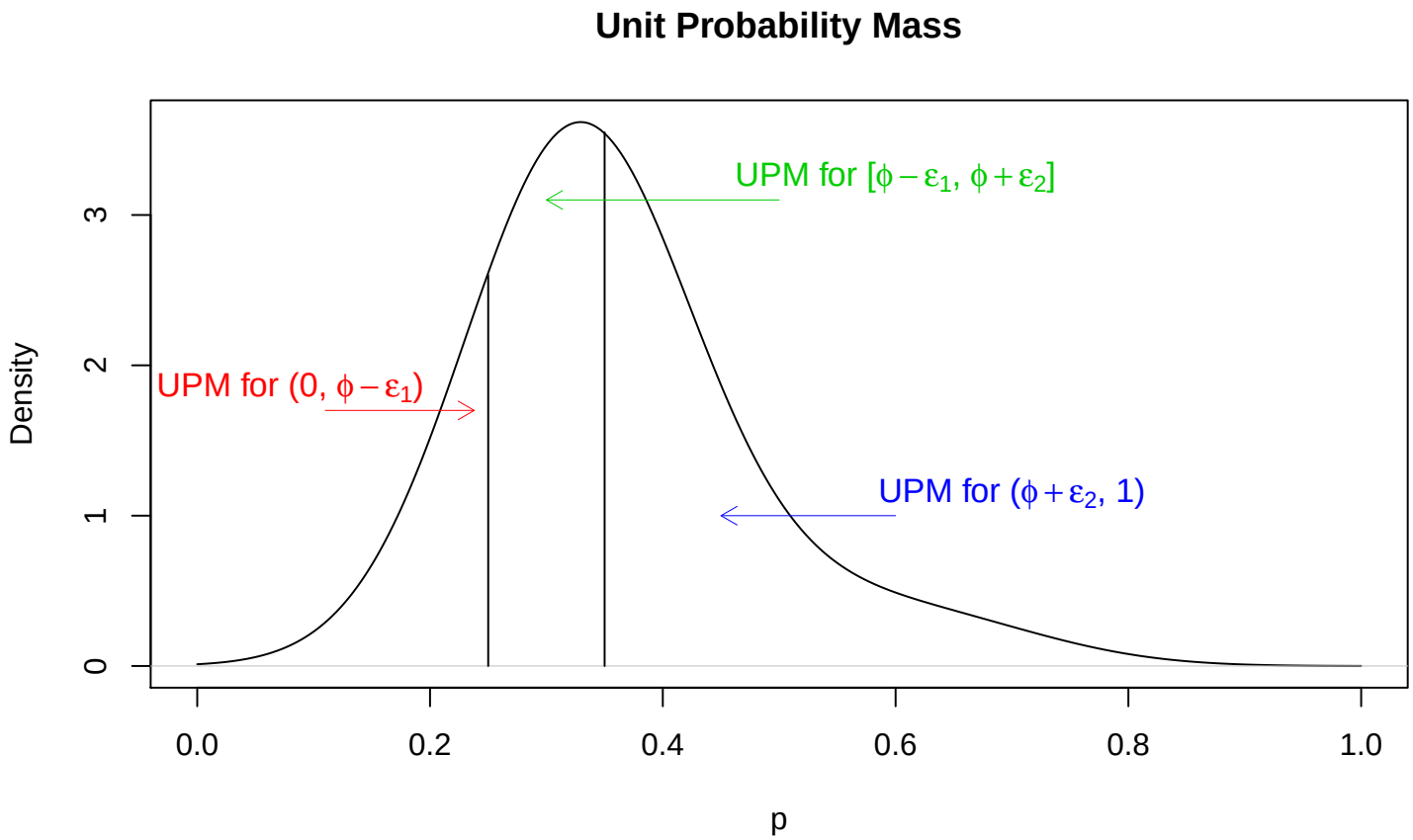
DU: de-escalation and current dose should not be used again

Modified toxicity probability interval (mTPI) dose-finding

- The dose assignment rule based on TPI can be sensitive to (default) tuning parameters K_1 and K_2 (JLB, 2010) - subjectivity issue
- Modified TPI: Calibration-free method:
  - Only define an equivalence interval: $[\phi - \epsilon_1,\ \phi + \epsilon_2]$, $\epsilon_1 > 0, \epsilon_2 > 0$
  - For $X \sim F(x)$ and any interval $(a, b]$ - unit probability mass (UPM) $= [F(b) - F(a)]/(b - a)$
    - In this context: $F(b) - F(a)$ is replaced by the posterior probability of p_i falls into $(a, b]$
  - New dose assignment rule: choose {E, S, D} if the corresponding interval $(0, \phi - \epsilon_1)$, $[\phi - \epsilon_1,\ \phi + \epsilon_2]$, $(\phi + \epsilon_2,\ 1)$ has the largest UPM
- Two safety rules:
  - Early termination: if $Pr(p_1 > \phi|\text{data}) > \xi$
  - Dose exclusion: assume action is E from dose i to $i + 1$. If $Pr(p_{i+1} > \phi|\text{data}) > \xi$, then dose $i + 1$ and higher are excluded and action taken is S

Unit probability mass

Figure 3: Unit probability mass for each interval. Vertical lines define equivalence interval $[\phi - \epsilon_1, \phi + \epsilon_2]$.



Bayesian model averaging CRM

- Despite of its popularity, another major issue with CRM is the need for *pre-specification of toxicity probabilities*
- For a new anti-cancer drug: usually lack information on the toxicity profile in human
- Different physicians likely will give (sometimes substantially) different opinions: multiple guesses on prior toxicity probability
- To implement CRM, however, we must pick one of these prior models

Choose a prior model

- Suppose true toxicity probability
  $\pi = \{0.02, 0.06, 0.08, 0.12, 0.20, 0.30, 0.40, 0.50\}$, and $\phi = 0.30$
- Four different expert guesses on prior mean probabilities (skeletons):
  - $M_1 = \{0.02, 0.06, 0.08, 0.12, 0.20, 0.30, 0.40, 0.50\}$
  - $M_2 = \{0.01, 0.05, 0.09, 0.14, 0.18, 0.22, 0.26, 0.30\}$
  - $M_3 = \{0.10, 0.20, 0.30, 0.40, 0.50, 0.60, 0.70, 0.80\}$
  - $M_4 = \{0.20, 0.30, 0.40, 0.50, 0.60, 0.65, 0.70, 0.75\}$
- Note that:
  - Dose 6 is the true MTD
  - M_1 is the true skeleton

A simple example

Table 3: CRM using different skeletons: $\phi = 0.30$ and 30 patients

Design	Dose recommendation probability								Average toxicity
	1	2	3	4	5	6	7	8	
CRM(M_1)	0.00	0.00	0.00	0.03	0.24	0.44	0.23	0.07	5.9
CRM(M_2)	0.00	0.00	0.01	0.04	0.17	0.28	0.26	0.24	6.5
CRM(M_3)	0.00	0.00	0.00	0.06	0.33	0.41	0.18	0.02	5.2
CRM(M_4)	0.00	0.00	0.01	0.07	0.28	0.35	0.21	0.08	5.5

- Model mis-specification could lead to picking the incorrect dose
- Let $M = \{M_1, \cdots, M_K\}$ denote prior models and $Pr(M_k) = 1/K$ the prior weight for each model
- For k-th model: $\pi_{ik} = p_{ik}^{\exp(\beta_k)}$ and $\beta_k \sim f(\beta_k|M_k)$, $i = 1, \cdots, I$, $k = 1, \cdots, K$

BMA-CRM (Yin and Yuan, 2009)

Given $D = \{(n_i, y_i), i = 1, \cdots, I\}$, for each model M_k:

- Likelihood:

$$L(D|\beta_k, M_k) = \prod_{i=1}^{I} \left[p_{ik}^{\exp(\alpha_k)}\right]^{y_i} \left[1 - p_{ik}^{\exp(\beta_k)}\right]^{n_i - y_i}$$

- Posterior model probability:

$$Pr(M_k|D) = \frac{L(D|M_k)Pr(M_k)}{\sum_{l=1}^{K} L(X|M_l)Pr(M_l)}$$

- Posterior mean of toxicity probability:

$$\hat{\pi}_{ik} = \int p_{ik}^{\exp(\beta_k)} \frac{L(D|\beta_k, M_k)f(\beta_k|M_k)}{\int L(D|\beta_k, M_k)f(\beta_k|M_k)d\beta_k} d\beta_k$$

The posterior estimate of π_i is the weighted average of $\hat{\pi}_{ik}$s, i.e.,

$$\tilde{\pi}_i = \sum_{k=1}^{K} \hat{\pi}_{ik} Pr(M_k|D)$$

Efficacy toxicity dose-finding

- Idea: identify optimal dose by considering both efficacy (E) and toxicity (T) simultaneously (Thall and Cook, 2004)
- Similar to CRM:
  1) Specify the joint dose-response model for E and T and prior distribution for model parameters
  2) Use observed data to update posterior distribution
  3) Dose level with the most desirable efficacy-toxicity trade-off is selected to treat the next cohort of patients
- Let $\underline{\pi}_E$ denote the lower limit of desirable efficacy and $\overline{\pi}_T$ the upper limit of target toxicity
- Given observed data D, a dose d_i is acceptable if

$$Pr(\pi_E(d_i, \beta_E) > \underline{\pi}_E | D) > p_E,$$

and

$$Pr(\pi_T(d_i, \beta_T) < \overline{\pi}_T | D) > p_T,$$

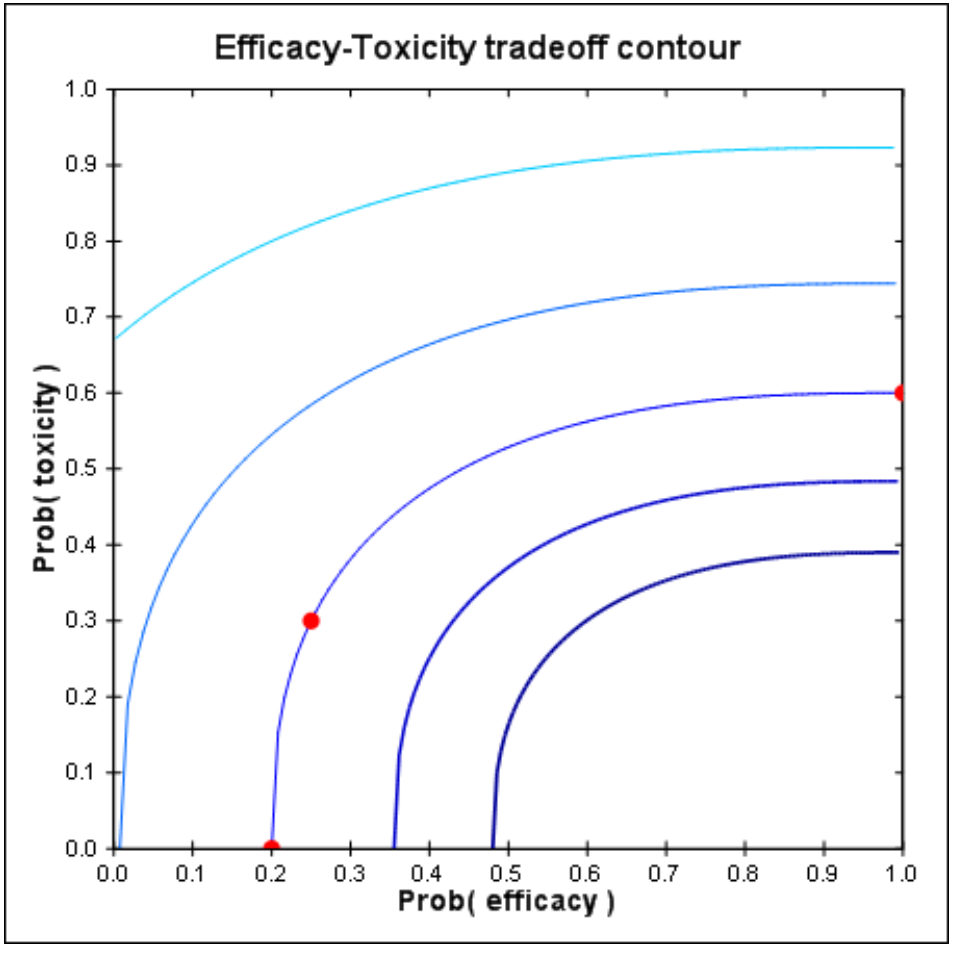
where p_E and p_T are fixed design parameters, often chosen between 5% and 20%

Efficacy toxicity trade-off: desirability measure

- Find the efficacy-toxicity contour C such that all points on contour are equally desirable
- Elicit three design points: $\{\pi_1^*, \pi_2^*, \pi_3^*\}$.
  - $\pi_1^* = (\pi_E^*, 0)$: minimum acceptable efficacy if no toxicity
  - $\pi_2^* = (1, \pi_T^*)$: maximum tolerable toxicity if treatment is 100% effective
  - $\pi_3^* = (\pi_E', \pi_T')$: more realistic but equally desirable as π_1^* and π_2^*
- For any point (π_E, π_T), a desirability measure is $\delta = 1 - r$, with r satisfies

$$\left(\frac{1-\pi_E}{1-\pi_E^*}\right)^\alpha + \left(\frac{\pi_T}{\pi_T^*}\right)^\alpha = r^\alpha$$

Figure 4: Contour plot of desirability measures. Three equally desirable Pr(E) and Pr(T) pairs are given: $(0.2, 0), (1, 0.6), (0.25, 0.3)$.



Simulation setting

- Number of dose levels: 8 and cohort size of 3; $p_T = 30\%$
- CRM and BMA-CRM: 4 skeletons (same as previous example)
- TPI design: $k_1 = 1$, $k_2 = 1.5$, $Beta(0.005, 0.005)$ and $\xi = 0.95$
- mTPI design: $Beat(1, 1)$, $\epsilon_1 = \epsilon_2 = 0.05$ and $\xi = 0.95$
- Hybrid TPI (hTPI) design: start with TER then switch to TPI after identification of preliminary MTD

Table 4: Dose-toxicity probability scenarios

	Dose level							
	1	2	3	4	5	6	7	8
Scenario 1	0.01	0.04	0.06	0.07	0.30	0.50	0.60	0.70
Scenario 2	0.05	0.18	0.30	0.55	0.60	0.65	0.70	0.75
Scenario 3	0.03	0.08	0.12	0.15	0.30	0.40	0.60	0.80
Scenario 4	0.20	0.30	0.40	0.50	0.55	0.60	0.65	0.70
Scenario 5	0.02	0.03	0.05	0.06	0.07	0.09	0.10	0.30
Scenario 6	0.01	0.02	0.10	0.30	0.50	0.65	0.80	0.90

Scenario 1

Table 5: Scenario 1[1]. $\bar{N}$ - average number of patients; $\bar{X}$ - average number of toxicities. Here "1 below" - MTD is one level below the true MTD; "2+ below" - MTD is two levels or more below the true MTD; "1 above" - MTD is one level above the true MTD, "2+ above" - MTD is two levels or more above true MTD.

			Dose recommendation probability					
Design	$\bar{N}$	$\bar{X}$	2+ below	1 below	MTD	1 above	2+ above	None
3 + 3	21.8	3.2	0.12	0.51	0.33	0.04	0.01	0.00
TPI	30.0	5.8	0.01	0.14	0.64	0.19	0.02	0.00
mTPI	30.0	5.8	0.01	0.16	0.66	0.16	0.01	0.00
hTPI	28.4	4.6	0.07	0.27	0.54	0.11	0.01	0.00
CRM (M_1)	30.0	6.1	0.00	0.10	0.73	0.16	0.01	0.00
CRM (M_2)	30.0	6.5	0.02	0.12	0.59	0.24	0.03	0.00
CRM (M_3)	30.0	5.4	0.02	0.17	0.66	0.14	0.01	0.00
CRM (M_4)	30.0	5.6	0.01	0.18	0.64	0.15	0.02	0.00
BMA-CRM	30.0	6.0	0.01	0.14	0.67	0.16	0.01	0.01

[1] True $\pi = (0.01, 0.04, 0.06, 0.07, 0.30, 0.50, 0.60, 0.70)$

Scenario 2

Table 6: Accuracy of different designs: Scenario 2[1].

Design	$\bar{N}$	$\bar{X}$	Dose recommendation probability					
			2+ below	1 below	MTD	1 above	2+ above	None
3 + 3	14.7	3.2	0.28	0.39	0.28	0.02	0.00	0.03
TPI	30.0	7.8	0.02	0.23	0.63	0.11	0.01	0.00
mTPI	30.0	7.7	0.02	0.30	0.59	0.09	0.00	0.00
hTPI	23.7	5.1	0.09	0.41	0.42	0.05	0.00	0.03
CRM (M_1)	30.0	8.6	0.00	0.22	0.64	0.13	0.01	0.00
CRM (M_2)	30.0	8.1	0.01	0.26	0.62	0.10	0.00	0.00
CRM (M_3)	30.0	7.4	0.00	0.29	0.63	0.07	0.00	0.01
CRM (M_4)	30.0	7.5	0.00	0.26	0.66	0.08	0.00	0.00
BMA-CRM	30.0	7.9	0.00	0.25	0.65	0.09	0.00	0.01

[1] True $\pi = (0.05, 0.18, 0.30, 0.55, 0.60, 0.65, 0.70, 0.75)$

Scenario 3

Table 7: Accuracy of different designs: Scenario 3[1].

Design	$\bar{N}$	$\bar{X}$	Dose recommendation probability					
			2+ below	1 below	MTD	1 above	2+ above	None
3 + 3	20.8	3.3	0.36	0.35	0.21	0.07	0.00	0.01
TPI	30.0	5.7	0.04	0.22	0.44	0.26	0.03	0.00
mTPI	30.0	5.6	0.09	0.27	0.40	0.21	0.03	0.00
hTPI	27.1	4.6	0.25	0.30	0.30	0.13	0.01	0.01
CRM (M_1)	30.0	5.7	0.05	0.27	0.53	0.14	0.01	0.00
CRM (M_2)	30.0	6.0	0.12	0.21	0.42	0.21	0.03	0.00
CRM (M_3)	30.0	3.2	0.16	0.32	0.40	0.12	0.00	0.00
CRM (M_4)	30.0	5.1	0.12	0.36	0.37	0.13	0.02	0.00
BMA-CRM	30.0	5.5	0.10	0.30	0.43	0.16	0.01	0.00

[1] True $\pi = 0.03, 0.08, 0.12, 0.15, 0.30, 0.40, 0.60, 0.80)$

Scenario 4

Table 8: Accuracy of different designs: Scenario 4[1].

Design	$\bar{N}$	$\bar{X}$	Dose recommendation probability					
			2+ below	1 below	MTD	1 above	2+ above	None
3 + 3	11.0	3.0	0.00	0.37	0.22	0.07	0.01	0.33
TPI	29.3	8.1	0.00	0.34	0.37	0.20	0.09	0.00
mTPI	29.3	8.2	0.00	0.26	0.45	0.20	0.06	0.03
hTPI	17.7	3.4	0.00	0.19	0.31	0.11	0.02	0.37
CRM (M_1)	30.0	8.7	0.00	0.25	0.48	0.21	0.04	0.02
CRM (M_2)	30.0	8.5	0.00	0.31	0.47	0.18	0.03	0.00
CRM (M_3)	30.0	8.1	0.00	0.26	0.53	0.15	0.02	0.04
CRM (M_4)	30.0	8.1	0.00	0.26	0.51	0.17	0.02	0.04
BMA-CRM	30.0	8.3	0.00	0.26	0.51	0.18	0.02	0.03

[1] True $\pi = (0.20, 0.30, 0.40, 0.50, 0.55, 0.60, 0.65, 0.70)$

Scenario 5

Table 9: Accuracy of different designs: Scenario 5[1].

Design	$\bar{N}$	$\bar{X}$	Dose recommendation probability					
			2+ below	1 below	MTD	1 above	2+ above	None
3 + 3	27.4	2.5	0.26	0.37	0.37	0.00	0.00	0.00
TPI	30.0	2.8	0.10	0.31	0.59	0.00	0.00	0.00
mTPI	30.0	2.8	0.16	0.26	0.57	0.00	0.00	0.01
hTPI	29.3	2.7	0.21	0.26	0.53	0.00	0.00	0.00
CRM (M_1)	30.0	2.6	0.40	0.20	0.40	0.00	0.00	0.00
CRM (M_2)	30.0	3.2	0.17	0.15	0.68	0.00	0.00	0.00
CRM (M_3)	30.0	2.4	0.42	0.25	0.33	0.00	0.00	0.00
CRM (M_4)	30.0	2.8	0.29	0.20	0.51	0.00	0.00	0.00
BMA-CRM	30.0	2.8	0.25	0.22	0.53	0.00	0.00	0.00

[1] True $\pi = (0.02, 0.03, 0.05, 0.06, 0.07, 0.09, 0.10, 0.30)$

Scenario 6

Table 10: Accuracy of different designs: Scenario 6[1].

Design	$\bar{N}$	$\bar{X}$	Dose recommendation probability					
			2+ below	1 below	MTD	1 above	2+ above	None
3 + 3	18.6	3.2	0.11	0.51	0.33	0.05	0.00	0.00
TPI	30.0	6.9	0.03	0.15	0.65	0.19	0.01	0.00
mTPI	30.0	6.7	0.01	0.17	0.63	0.18	0.01	0.00
hTPI	26.7	4.9	0.04	0.32	0.54	0.10	0.00	0.00
CRM (M_1)	30.0	7.8	0.00	0.07	0.70	0.23	0.00	0.00
CRM (M_2)	30.0	7.7	0.00	0.11	0.67	0.20	0.01	0.01
CRM (M_3)	30.0	6.8	0.00	0.11	0.74	0.15	0.00	0.00
CRM (M_4)	30.0	6.8	0.00	0.11	0.75	0.13	0.00	0.01
BMA-CRM	30.0	7.3	0.00	0.11	0.71	0.18	0.00	0.00

[1] True $\pi = (0.01, 0.02, 0.10, 0.30, 0.50, 0.65, 0.80, 0.90)$

Efficacy and toxicity trade-off

Settings for simulation studies on dose-escalation incorporating both toxicity and efficacy:

- Upper limit of toxicity $\overline{\pi}_T = 0.4$ and cut-off $P_T = 0.1$
- Lower limit of efficacy $\underline{\pi}_E = 0.2$ and cut-off $P_E = 0.1$
- $\pi_E^* = 0.2$ and $\pi_T^* = 0.6$, intermediate $\pi_3^* = (\pi'_E, \pi'_T) = (0.25, 0.3)$
- To compute the desirability $\delta = 1 - r$ of each dose, set $r = 1$ in the following equation and replace (π_E, π_T) with (π_E^*, π_T^*). Then solve for α:

$$\left(\frac{1-\pi_E}{1-\pi_E^*}\right)^\alpha + \left(\frac{\pi_T}{\pi_T^*}\right)^\alpha = r^\alpha.$$

- Eight doses are considered; maximum sample size 60 and cohort size of 3

Numerical results

Table 11: Operating characteristics of the EffTox design with eight doses. Here, δ is the desirability measure, $\bar{n}$ is the average number of patients treated at each dose level, Sel.Prob is the probability of dose being selected as the most desirable.

	Doses							
	1	2	3	4	5	6	7	8
Pr(E)	0.05	0.10	0.20	0.45	0.55	0.65	0.75	0.80
Pr(T)	0.02	0.08	0.15	0.30	0.50	0.60	0.65	0.70
Pr(E w/o T)	0.02	0.06	0.10	0.20	0.25	0.30	0.35	0.40
δ	-0.188	-0.126	-0.009	0.214	0.067	-0.040	-0.098	-0.174
$\bar{n}$	4.40	3.26	5.73	**34.03**	10.59	1.08	0.09	0.02
pct ($\bar{n}$/60)	7.43%	5.51%	9.68%	**57.49%**	17.89%	1.82%	0.15%	0.03%
Sel.Prob [1]	0.00	0.00	0.03	**0.79**	0.15	0.01	0.00	0.00

[1] Approximately 2% of 1000 simulations resulted in no acceptable dose found.

Conclusions (1)

- TER is the safest, but the least accurate method - (overshooting, % MTD): b - best, w - worst

Table 12: Summary across six scenarios

	TER	TPI	mTPI	hTPI	CRM.b	CRM.w	BAM-CRM
Overshooting (%)	5	19	16	9	10	19	14
% MTD (%)	29	55	55	44	65	51	58

- TPI design and modified TPI design performs better than TER, comparable to CRM in general
  - Easy to implement
  - Appealing to practitioners since dose-assignment can be pre-specified
  - Modified TPI is calibration-free and slightly safer than TPI in certain scenarios
  - Hybrid TPI provides a integration between 3 + 3 and TPI
- CRM also outperforms TER, and yields higher accuracy than JLB design under certain scenarios

Conclusions (2)

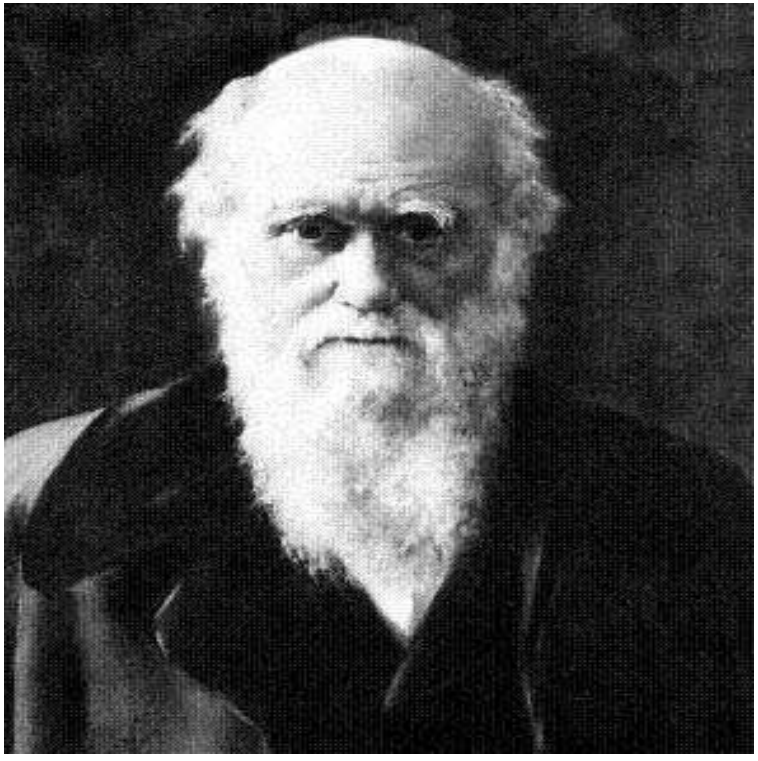
- However, the accuracy of CRM depends heavily on the proper specification of prior model in some scenarios
  - In scenario 5: MTD is the last dose. CRM(M_2) performs the best at 68% while CRM(M_3) the worst at 33%
- Bayesian model averaging CRM can account for model uncertainty.
  - Use multiple skeletons and parallel CRMs
  - BMA-CRM's performance is comparable to correct CRM while much better than mis-specified CRM
  - A valuable tool when the prior information on the toxicity profile is minimal

Conclusions (3)

- EffTox takes into account of both efficacy and toxicity:
  - Dose escalation is based on desirability, not toxicity alone
  - Can be effective by fine-tuning design parameters such as P_E and P_T
  - Assumes efficacy and toxicity outcome are binary: does not take into account when the event occurs
  - Could further delay treatment assignment if efficacy and/or toxicity outcome could not be observed in time

Why do we try different approaches?

"... *It's not the strongest species that survive, nor the most intelligent, but rather the ones most adaptable to change.*"
- Charles Darwin



Statistical properties of TER

- Notation used:
  - π_j: the probability of toxicity at dose level j
  - $P_0^j = \Pr(0/3 \text{ at dose } j) = (1-\pi_j)^3$
  - $P_1^j = \Pr(1/3 \text{ at dose } j) = 3\pi_i(1-\pi_j)^2$
  - $Q_0^j = \Pr(1/3 \text{ and } 0/3 \text{ after expansion at dose } j) = P_1^j P_0^j$
- Probability of dose i $(1 \leq i < n)$ being MTD is then given by

$$Pr(\text{MTD} = \text{Dose } i) = \left(\prod_{j=1}^{i}(P_0^j + Q_0^j)\right)\left[1 - P_0^{(i+1)} - Q_0^{(i+1)}\right]$$

- Similarly $Pr(\text{MTD} < \text{Dose } 1) = 1 - P_0^1 - Q_0^1$ and $Pr(\text{MTD} \geq \text{Dose } I) = \prod_{j=1}^{J}(P_0^j + Q_0^j)$

Toxicity level at MTD

- Target toxicity level (TTL): the expected dose-limiting toxicity rate at the MTD

$$\begin{aligned} \mathrm{TTL} &= P(\text{toxicity at MTD} | \text{dose } 1 \leq \mathrm{MTD} \leq \text{dose } I) \\ &= \frac{\sum_{i=1}^{I} \pi_i Pr(\mathrm{MTD} = \text{Dose } i)}{\sum_{i=1}^{I} Pr(\mathrm{MTD} = \text{Dose } i)}, \end{aligned}$$

where π_i is the probability of observing DLT at dose level i

Find p_i in CRM model

Recall the power model in CRM: $\pi_i = p_i^{\exp(\beta)}$. To determine the constant p_i:

- We need to first specify prior mean probability $S = (s_1, \cdots, s_I)$, $s_1 < \cdots < s_I$.
- Assume prior distribution for β is f. For example, $\beta \sim N(0, \sigma^2)$ with $\sigma^2 = 2$
- Then the value of p_i's are computed through

$$E\left(p_i^{\exp(\beta)}\right) = \int p_i^{\exp(\beta)} f(\beta) d\beta = s_i$$

EffTox joint model

- Assume both dose-response variables are binary:
  - Efficacy (E): $Y = \{0, 1\}$
  - Toxicity (T): $Z = \{0, 1\}$
  - Doses: $X = \{x_1, \cdots, x_k\}$
  - Unknown model parameter: θ
  - Define $\pi_{yz}(x; \theta) = Pr(Y = y, Z = z | X = x; \theta)$
- There are four cell probabilities with dose x and parameter θ:

		T: 1	T: 0	
E	1	$\pi_{11}(x, \theta)$	$\pi_{10}(x, \theta)$	$\pi_E(x, \theta)$
	0	$\pi_{01}(x, \theta)$	$\pi_{00}(x, \theta)$	
		$\pi_T(x, \theta)$		

EffTox model

- Note from the table
  - $\pi_T(x,\theta) = \pi_{01}(x,\theta) + \pi_{11}(x,\theta)$
  - $\pi_E(x,\theta) = \pi_{10}(x,\theta) + \pi_{11}(x,\theta)$
- Marginal probability model for E and T:
  - Logistic model for T: $\text{logit}[\pi_T(x,\theta)] = \mu_T + \beta_T x$
  - Logistic model with quadratic term for E: $\text{logit}[\pi_E(x,\theta)] = \mu_E + \beta_{E,1} x + \beta_{E,2} x^2$
- To model both efficacy and toxicity simultaneously (suppressing x and θ):

$$\pi_{y,z} = \pi_E^y (1-\pi_E)^{1-y} \pi_T^z (1-\pi_T)^{1-z} + (-1)^{y+z} \pi_E (1-\pi_E) \pi_T (1-\pi_T) \frac{e^\psi - 1}{e^\psi + 1}$$

where ψ is the association parameter