Specification of the Bayesian CRM: Model and Sample Size

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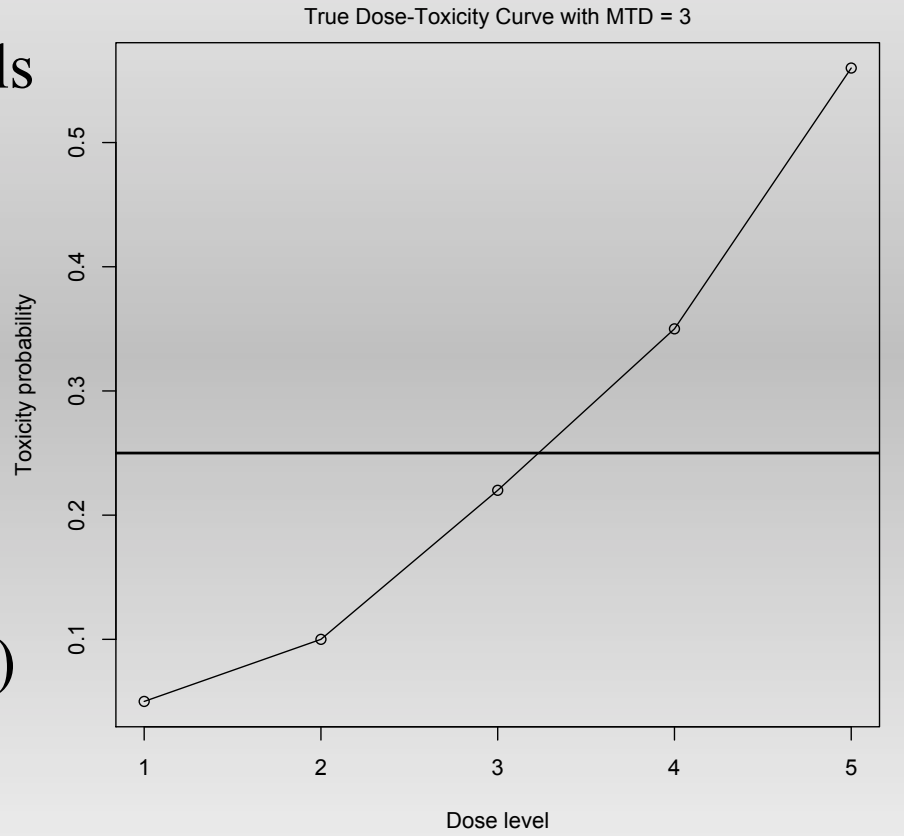
Phase I Dose Finding

- Consider a set of K doses with labels $d_1, d_2, \ldots, d_K$
- Study objective: Find MTD

$$\upsilon = arg\ min_k \mid \pi(d_k) - \theta \mid$$

- $\pi(x)$ is the probability of DLT at dose x
- θ is a pre-specified target (e.g. 0.25)



CRM

- First proposed by O'Quigley et al. (1990)
- Model-based
- Single-parameter model
- Bayesian-flavor
- "Myopic"
- Many variations and extensions
  - Two-parameter or curve free; MLE; Continuous dosage; EWOC

CRM

- This talk focuses specifically on the original version of the Bayesian CRM (1990).
- Treat patients sequentially at dose level

$$\upsilon_n = arg\ min_k \mid F(d_k, b_n) - \theta \mid$$

- The dose-toxicity function F(x, β) is one-parameter, with a prior distribution on β.
- b_n is the posterior mean of β
- Patient 1 gets prior MTD
- Recall study objective – MTD $\upsilon = arg\ min_k \mid \pi(d_k) - \theta \mid$

CRM

- *Model-based*: *For the CRM* to work well:
  - Do not require the model is correct to be consistent, i.e.

$$F(d_k, b) = \pi(d_k) \text{ for some true } b$$

"No model is correct. Some are useful." - George Box

  - Do require model specification is properly calibrated
- *Outcome-adaptive*: *How many patients (N) do we need* – can we determine ahead with respect to some objective criterion?

Objectives of this talk

- Present an approach to specify the Bayesian CRM model in a timely and reproducible manner
- Present a sample size formula for the CRM model obtained via the specification process
- Provide practical guidelines on using the sample size formula

Outline of this talk

- *Calibration* of a Bayesian CRM model
  - Dose-toxicity function
  - **Initial guesses of DLT rates ("Skeleton")**
  - Prior distribution of model parameter
- **Sample size formulae** for a properly calibrated CRM
- **Example:** A PTEN-long trial

CRM model

Three steps to specify a CRM model:

1. Dose-toxicity function $F(x, \beta)$ = P(DLT at dose x)
2. Choose a prior distribution $G(\beta)$ of β.
3. Evaluate the dose labels $\{d_1, d_2, \ldots, d_K\}$ for the K test doses via *backward substitution*:
   - Let p_{i0} denote initial guess of DLT rate for dose i. The dose labels d_i are obtained such that

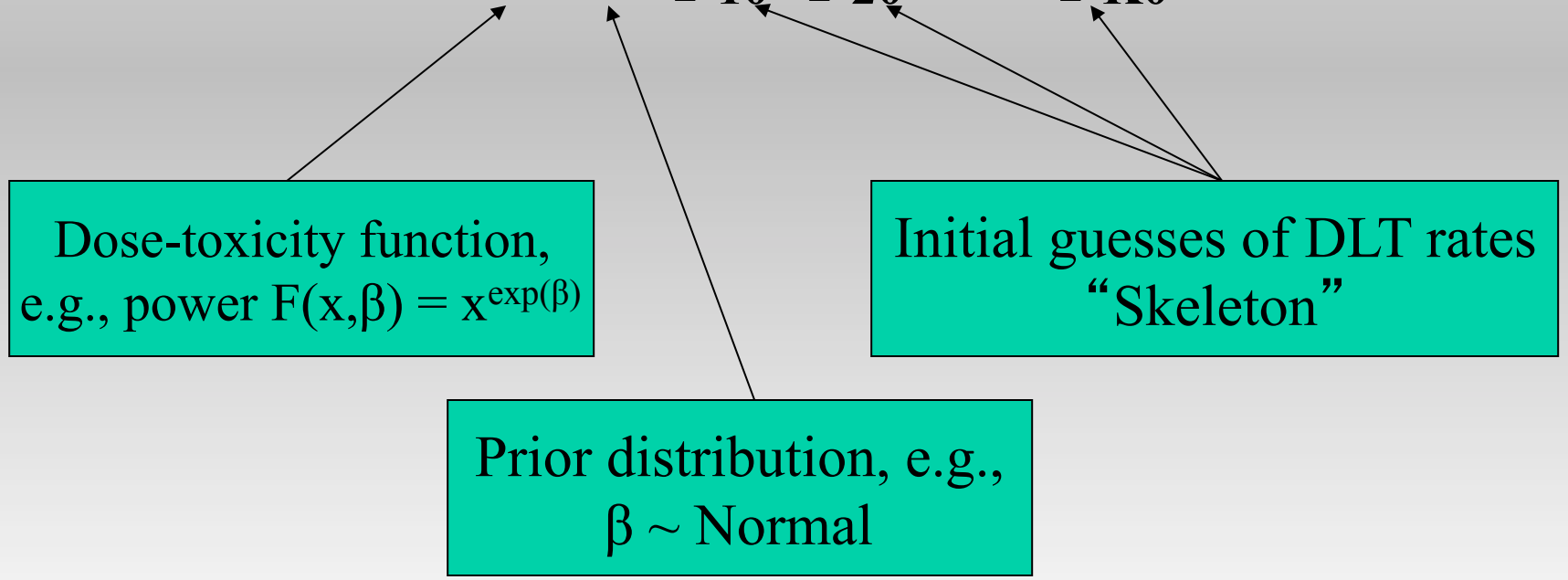
$$F\{d_i, E_G(\beta)\} = p_{i0}$$

   where $E_G(\beta)$ is the prior mean of β.

CRM model

- Thus, the model parameters are

$$(F, G, p_{10}, p_{20}, \ldots, p_{K0})$$

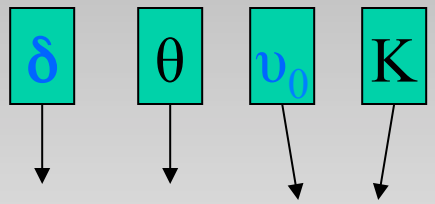


CRM model

- Lee and Cheung (2009): For **any fixed F and G,** we can choose the skeleton $\{p_{10}, p_{20}, \ldots, p_{K0}\}$ to match the operating characteristics
- Approach: Reduce the specification problem of K numbers to 2 meaningful inputs
  - The prior MTD, υ_0 **= Starting dose level**
  - An acceptable range of toxicity rate $\theta \pm \delta$, where θ is the target toxicity rate. E.g., 0.25 ± 0.05

How to choose p_{0k}'s?

- For any given δ, a skeleton can be obtained using the function **`getprior`** in the R package `dfcrm'

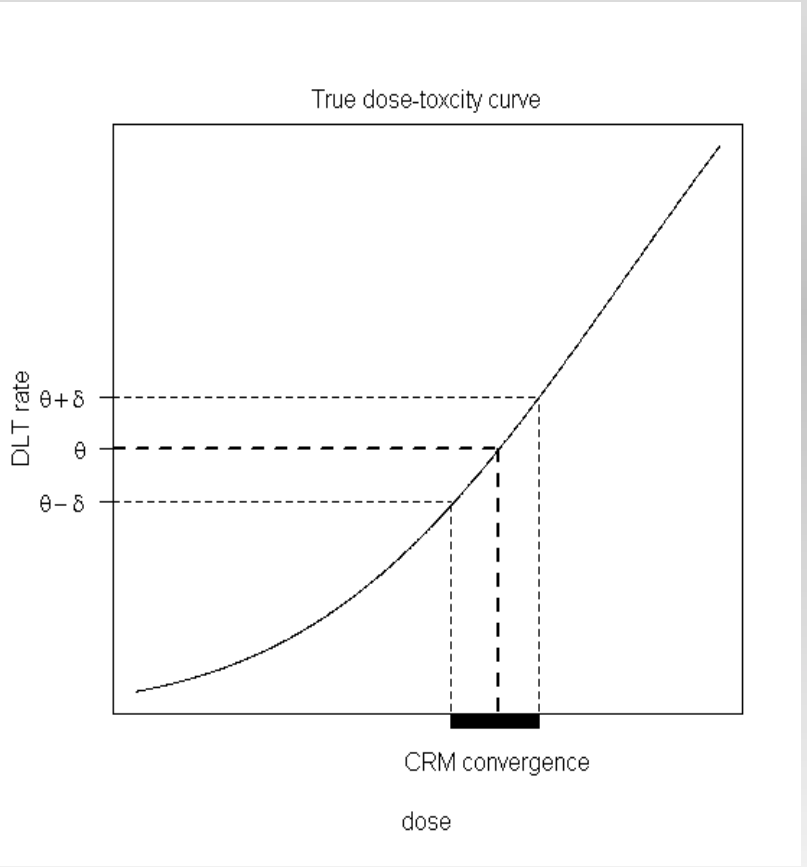



```
> p0 <- getprior(0.05,0.25,3,5,model="logistic")
> round(p0,digits=2)
[1] 0.09 0.16 0.25 0.36 0.46
```

Interpretation of δ

Theoretical basis of p_{0k}'s by the function **`getprior`:**

- The CRM converges to the acceptable range $\theta \pm \delta$ on the probability scale
- Indifference interval (Cheung and Chappell, 2002, *Biometrics*)



How to choose δ?

- Choose δ empirically
  - Asymptotically, a small δ has a small bias.
  - With small-moderate sample size, a small δ has a large variance of selected MTD.
  - Use simulations to obtain a δ that yields competitive operating characteristics over a wide range of scenarios
  - "Optimal" δ tabulated in Lee and Cheung (2009) and Cheung (2011)
- Quick rule of thumb: Setting $\boldsymbol{\delta = 0.25\theta}$

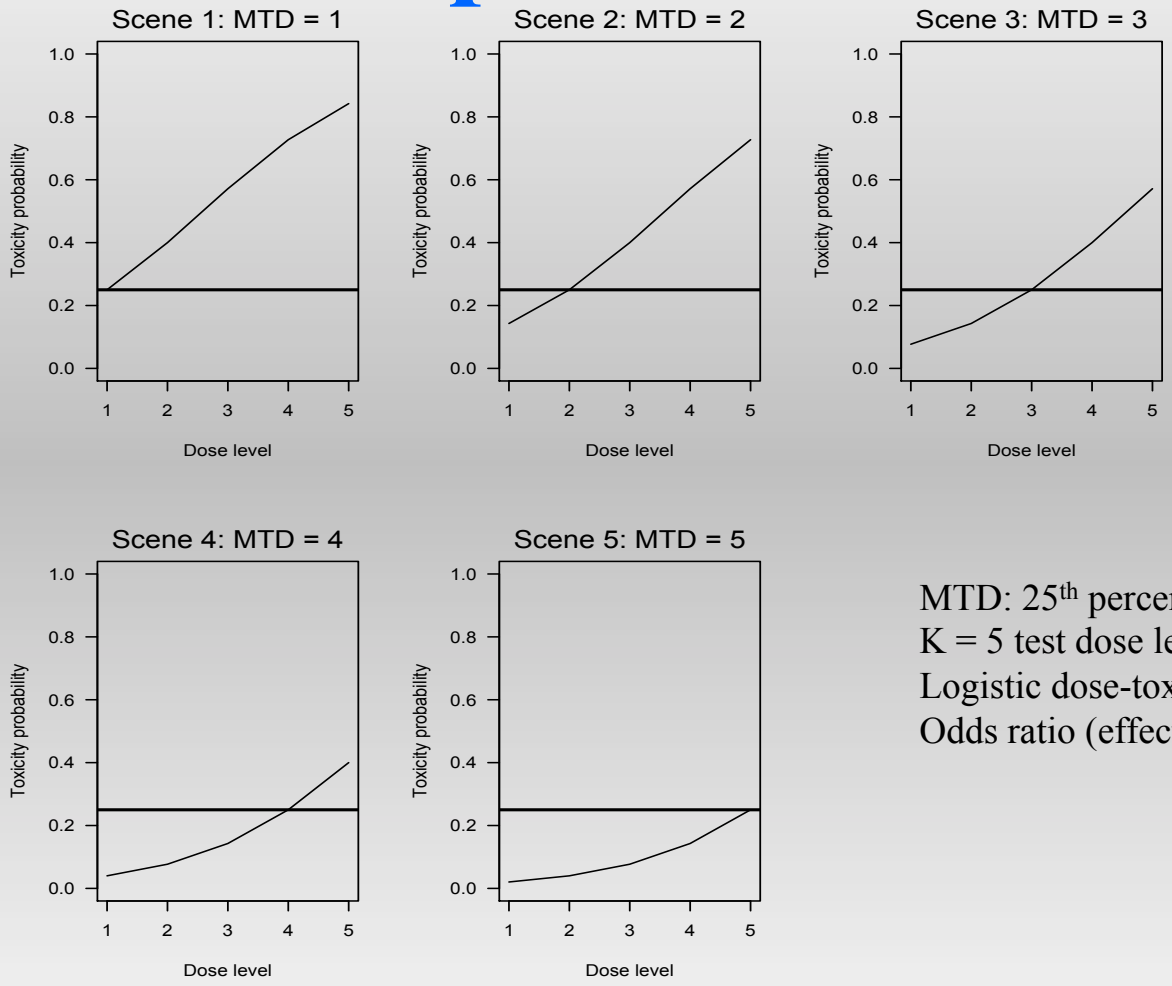
Sample size consideration

- Some underlying difficulties
  - Some methods are highly specific:
    - Phase 1: Specify model, prior, skeleton, N, etc.
    - Phase 2: N
  - The truth lives in a higher dimensional space:
    - Phase 1: dose-toxicity curves
    - Phase 2: effect size
  - Performance metrics
    - Phase 1: accuracy index (?)
    - Phase 2: type I error, power
  - Methods are more complicated:
    - Phase 1: Highly outcome adaptive
    - Phase 2: Central limit theorem → analytical N formula

Sample size consideration

	Two-sample comparison	**Dose finding**
Model assumption	Normal	Logistic dose-toxicity
Effect size (alternative)	A single number: Mean-to-SD ratio	Odds ratio + multiple "alternatives" of true MTD
Performance metrics	Type I error; power	Some sort of average?
Design and analysis	Determine N for t-test	N + model specification

Sample size consideration



MTD: 25th percentile
K = 5 test dose levels
Logistic dose-toxicity relationship
Odds ratio (effect size): 2

Goal: Seek the average of probabilities of correctly selecting MTD as an accuracy index

Sample size consideration

- Assumption: logistic dose-toxicity curves
- Inputs for sample size calculation:
  - Target rate θ
  - Number of dose levels K
  - Effect size (odds ratio) R of the logistic curves
  - Desired accuracy (average PCS): a*
- *Working* models:
  - Power dose toxicity function
  - Starting dose = Prior MTD υ_0 = Median dose level
  - "Skeleton" with sensitivity at 0.25θ (Lee and Cheung, 2009)
  - Normal prior mean 0, variance 1.34 (O'Quigley and Shen, 1996)

Sample size consideration

- N = rounding up $\tilde{n}(b^*)$ where

$$\text{logit}(b^*) = \left\{\text{logit}(a^*) - 2.26 + 0.00235K^2 + 0.7R + 1.903R^{-1}\right\}/0.854$$

$$\tilde{n}(a) = \left\{\Phi^{-1}\left(1 - \frac{K(1-a)}{2(K-1)}\right)\right\}^2 / \bar{\Delta}^2.$$

$\bar{\Delta}$ is a known analytical function of θ and R

Note: *Formulae may not be applicable if calculated N > 60*

How to choose *R*?

- Inputs for sample size calculation:
  - Target rate θ
  - Number of dose levels K
  - Effect size (odds ratio) R of the logistic curves
  - Desired accuracy (average PCS): a*

Table 1. Odds ratio R and steepness of dose-toxicity curve. The pair in each entry indicates the toxicity probabilities associated with the doses adjacent to the MTD, i.e., $(p_{j-1,j}, p_{j+1,j})$.

θ	R					
	1.25	1.50	1.75	2.00	2.25	2.50
0.10	(0.08,0.12)	(0.07,0.14)	(0.06,0.16)	(0.05,0.18)	(0.05,0.20)	(0.04,0.22)
0.15	(0.12,0.18)	(0.11,0.21)	(0.09,0.24)	(0.08,0.26)	(0.07,0.28)	(0.07,0.31)
0.20	(0.17,0.24)	(0.14,0.27)	(0.13,0.30)	(0.11,0.33)	(0.10,0.36)	(0.09,0.38)
0.25	(0.21,0.29)	(0.18,0.33)	(0.16,0.37)	(0.14,0.40)	(0.13,0.43)	(0.12,0.45)
0.30	(0.26,0.35)	(0.22,0.39)	(0.20,0.43)	(0.18,0.46)	(0.16,0.49)	(0.15,0.52)

Example: A PTEN-long trial

- PTEN-long in pancreatic cancer patients
- Trial design: CRM with
  - $\theta = 0.25$, $K = 5$, $\upsilon_0 = 3$
    - → $\delta = 0.0625$
    - → $p_{01} = 0.06$, $p_{02} = 0.14$, $p_{03} = 0.25$, $p_{04} = 0.38$, $p_{05} = 0.51$
  - Power function $F(x, \beta) = x^{\exp(\beta)}$
  - $\beta \sim N(0, 1.34)$

Sample size consideration "getn" in dfcrm

```
> library(dfcrm)
> a = 0.6
> theta = 0.25
> K = 5
> oddsRatio = 1.8
> obj = getn(a, theta, K, oddsRatio)
> obj
 Target rate:                    0.25
 Number of dose levels:          5
 Effect size (odds ratio):       1.8
 Required accuracy:              0.6
 Calculated sample size:         32
```

Sample size consideration Simulation

CRM model	Probability selecting MTD under Scene					Ave PCS
	1	2	3	4	5	
Assumed working model $\delta = 0.25\theta$, $\nu_0 = 3$	.77	.56	.52	.52	.65	.604
Optimal δ for $\nu_0 = 3$	.78	.56	.53	.52	.66	.610
Optimal δ for $\nu_0 = 2$	.80	.53	.52	.51	.64	.600

Optimal δ is obtained the algorithm in Cheung 2011.

Target = 0.6

Practical Guidelines

- Calibration & Sample size formulae
  - Reduce the dimension of the specification problem
  - Provide a reproducible approach to specify a CRM model
  - *Facilitate sample size calculation*
  - Quick N formula is useful in consultation setting and for initial budgeting purposes
  - Like in other N calculation settings, simplifying assumptions are needed and desirable
  - Intended to be starting point

Practical Guidelines

- Simulation is essential after initial N calculation
  - *Refinement:* To improve upon the working model – or use other methods
  - *Robustness:* To assess impact of model violation
  - *Rollout:* To examine other metrics of operating characteristics and report performance under a variety of scenarios

Useful Resources

- "dfcrm" library in R
  - Version 0.2-2 [update if you have 0.2-1]
- Main references
  - Lee and Cheung (2009): Model calibration in the CRM. *Clinical Trials* **6:**227—238.
  - Cheung (2011). *Dose Finding by the Continual Reassessment Method.* CRC Press/Taylor & Francis Group
  - Cheung (2013): Sample size formulae for the Bayesian CRM. *Clinical Trials* in press.