Bayesian Continuous Reassessment Method

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Introduction

- Aim: Use prespecified model to find the Maximum Tolerable Dose (MTD).
- Requires Target Toxicity Level (TTL) to determine what is an acceptable level of toxicity.
- Existing knowledge can be incorporated through prior distribution
- Steps for the CRM:
  1. Specify prior distribution with expert knowledge.
  2. Run first cohort based on available information.
  3. Compute the posterior distribution using $f(\theta|y_1, \ldots, y_n) \propto f(\theta)L(\theta; y_1, \ldots, y_n)$.
  4. Are the stopping rules satisfied?
     - If yes, stop the trial.
     - If no, return to Step 2 with the posterior distribution as the new prior.

1. **Theory:** Neuenschwander, B., Branson, M. and Gsponer, T., 2008. Critical aspects of the Bayesian approach to phase I cancer trials. *Statistics in medicine*, 27(13), pp.2420-2439.
   - More realistic approach to modelling dose-toxicity.
   - Maintain benefits of Bayesian framework.
   - Comparison of one-parameter and two-parameter models.
   - Oversimplified implementation of models and summaries leads to inadequecies in one-parameter model.
2. **Applied:** Sweeting M., Mander A., Sabin T., 2013. bcrm: Bayesian Continual Reassessment Method Designs for Phase I Dose-Finding Trials. *Journal of Statistical Software*
   - Bring methods into practice.
   - Creation of R package with step-by-step guidance.

Continuous Reassessment Method

- $\mathscr{D}$ is set of J available doses.
- $\pi_\theta(d_i)$ is the probability of toxicity at dose d with parameter θ.

$$\textbf{Power Model: } \pi_\theta(d_i) = c_{d_i}^{\theta},\ \theta > 0,$$

where c_d are monotonically increasing skeleton probabilities corresponding to a dose, $d_i \in \mathscr{D}$.

- Skeleton probabilities are structural and constant throughout a trial. Often set as equal to the prior estimates of DLT.

$$\textbf{Two-parameter Logistic Model: } \text{logit}[\pi_\theta(d_i)] = \log\alpha + \beta \log\left(\frac{d_i}{d^*}\right),$$

with $\alpha, \beta > 0$, $\theta = (\log\alpha, \log\beta)$, and d^* is some predefined reference dose.

Prior Specification

- Aim to incorporate external information (e.g. similar or previous studies).
- Flat priors are not favourable.
- No formal analysis can be made without any observed DLTs, i.e. formal methods for dose recommendation cannot be used.
- The following is proposed:
  1. Formulate prior information on the scale of interest, i.e. the probabilities of toxicity, $\pi_\theta(d)$ s.t. $d \in \mathscr{D}$.
  2. To define the prior of θ so that its implied information on the π-scale is in agreement with the information in 1.

Formal process of prior specification:

1. Prior information is defined on K quantiles

$$q_d = \{q_d(p_1), \ldots, q_d(p_k)\},$$

$$\Rightarrow \Pr[\pi_\theta(d_i) \leq q_d(p_k)] = p_k, \quad k = 1, \ldots, K$$

   Priors are defined by $J \times K$ quantiles, i.e. K quantiles for each dose.

2. Minimise difference between prespecified quantiles Q and fitted quantiles $Q^{'}$,

$$C(Q, Q^{'}) = \max_{j,k} |q_{jk} - q^{'}_{jk}| \quad j = 1, \ldots, J, k = 1, \ldots, K.$$

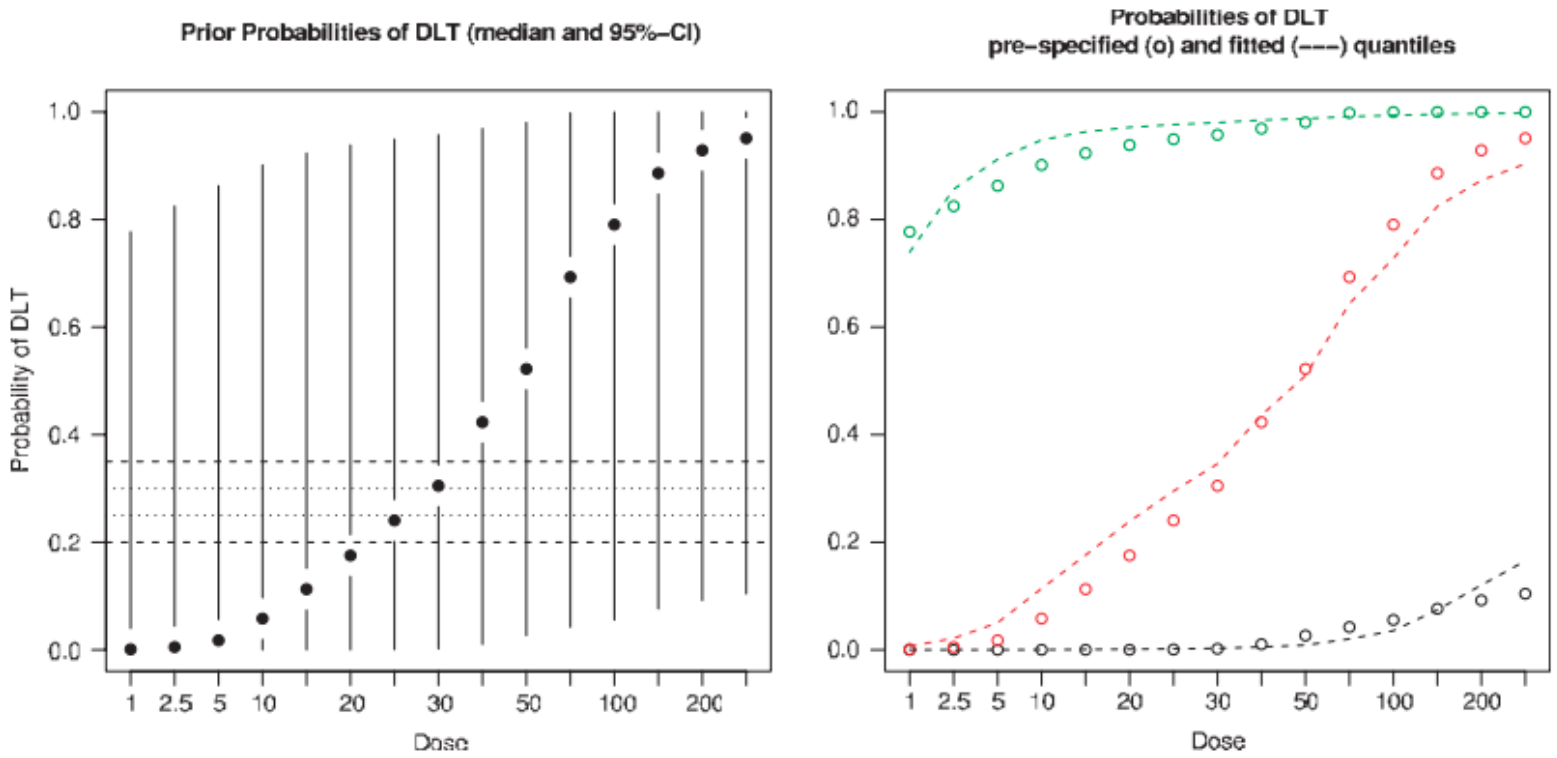

Figure: Left panel shows an uninformative prior. Right panel shows quantiles as dots and fitted quantiles as dotted lines [1].

Dose Recommendation

1. Power Model:
   - Information obtained from posterior distribution.
   - Mean posterior probability of DLT is used.

   Plug-in mean:

$$\mu_1(d_i; y_1, \ldots, y_n) = \pi\left(d_i; \int_0^\infty \alpha f(\alpha | y_1, \ldots, y_n) d\alpha\right)$$

   Posterior mean:

$$\mu_2(d_i; y_1, \ldots, y_n) = \int_0^\infty \pi(d_i; \alpha) f(\alpha | y_1, \ldots, y_n) d\alpha$$

   - Dose with posterior mean closest to the Target Toxicity Level (TTL) is chosen as the next dose
   - Approach does not take into account uncertainties about the posterior means.

2. Two-parameter Logistic Model:
   - One approach is to use posterior mean as described for one-parameter model.
   - Another approach is to use a Bayesian analytic approach with toxicity intervals.

   Loss function:

$$\text{Loss}(\beta_1, \beta_2; d_i) = \begin{cases} \ell_1 & \text{if } \pi_\theta(d_i; \beta_1, \beta_2) \in (p_0, p_1] \\ \vdots & \vdots \\ \ell_m & \text{if } \pi_\theta(d_i; \beta_1, \beta_2) \in (p_{m-1}, p_m] \end{cases}$$

   Bayes Risk:

$$B(d_i) = \int_0^\infty \int_0^\infty \text{Loss}(\beta_1, \beta_2; d_i) f(\beta_1, \beta_2 | y_1, \ldots, y_n) d\beta_1 d\beta_2$$

- Example loss function:

$$\text{Loss}(\beta_1, \beta_2; d_i) = \begin{cases} \ell_1 = 1 & \text{if } \pi_\theta(d_i; \beta_1, \beta_2) \in (0, 0.2] \\ \ell_2 = 0 & \text{if } \pi_\theta(d_i; \beta_1, \beta_2) \in (0.2, 0.35] \\ \ell_3 = 1 & \text{if } \pi_\theta(d_i; \beta_1, \beta_2) \in (0.35, 0.6] \\ \ell_4 = 2 & \text{if } \pi_\theta(d_i; \beta_1, \beta_2) \in (0.6, 0.1] \end{cases}$$

- Assume known posterior distributions.
- Simplified Bayes Risk

$$\begin{aligned} &= \ell_1 \Pr\{\pi_\theta(d_i) \in (0, 0.2]\} + \ell_2 \Pr\{\pi_\theta(d_i) \in (0.2, 0.35]\} \\ &+ \ell_3 \Pr\{\pi_\theta(d_i) \in (0.35, 0.6]\} + \ell_4 \Pr\{\pi_\theta(d_i) \in (0.6, 1.00]\} \end{aligned}$$

- Conservative and aggressive loss functions.
- Uncertainty is taken into account.

	Doses									
	1	2.5	5	10	15	**20**	25	30	40	50
No. of patients	3	4	5	4	—	—	2	—	—	—
No. of DLTs	0	0	0	0	—	—	2	—	—	—
(A) Posterior summaries (prior similar to CRM prior)										
Under-dosing	1.000	0.996	0.970	0.809	0.581	**0.377**	0.234	0.140	0.050	0.017
Target	0.000	0.004	0.029	0.170	0.324	**0.401**	0.393	0.343	0.212	0.117
Excessive	0.000	0.000	0.001	0.021	0.094	**0.216**	0.352	0.464	0.574	0.544
Unacceptable	0.000	0.000	0.000	0.000	0.001	**0.006**	0.021	0.052	0.164	0.322
Risk 1-0-1-1	1.000	0.996	0.971	0.830	0.676	**0.599**	0.607	0.657	0.788	0.883
Risk 1-0-1-2	1.000	0.996	0.971	0.830	0.677	**0.605**	0.628	0.710	0.952	1.205
Risk 1-0-2-4	1.000	0.996	0.972	0.852	**0.773**	0.833	1.021	1.279	1.855	2.393
Mean	0.011	0.029	0.061	0.127	0.191	0.252	**0.309**	0.360	0.449	0.522
Std. dev.	0.018	0.034	0.056	0.088	0.111	0.126	0.136	0.142	0.148	0.147
(B) Posterior summaries (non-informative default prior)										
Under-dosing	1.000	0.998	0.968	0.740	**0.476**	0.287	0.173	0.110	0.051	0.027
Target	0.000	0.002	0.030	0.215	**0.337**	0.350	0.305	0.247	0.148	0.093
Excessive	0.000	0.000	0.001	0.044	**0.179**	0.319	0.413	0.450	0.432	0.357
Unacceptable	0.000	0.000	0.000	0.000	**0.009**	0.043	0.109	0.193	0.369	0.523
Risk 1-0-1-1	1.000	0.998	0.970	0.785	0.663	**0.650**	0.695	0.753	0.852	0.907
Risk 1-0-1-2	1.000	0.998	0.970	0.785	**0.672**	0.693	0.804	0.946	1.222	1.430
Risk 1-0-2-4	1.000	0.998	0.971	**0.830**	0.869	1.099	1.436	1.782	2.392	2.832
Mean	0.010	0.028	0.065	0.148	0.230	**0.305**	0.372	0.429	0.523	0.593
Std. dev.	0.014	0.030	0.056	0.099	0.132	0.155	0.171	0.180	0.189	0.189

Figure: Table of posterior probabilities of DLT [1].

Simulations: One-parameter Power Model

– Key to determining operating characteristics of various approaches to dose-finding.

Dose	5mg	10mg	15mg	25mg	40mg	50mg	60mg
Prior guess of risk	0.05	0.10	0.20	0.30	0.35	0.40	0.45
Scenario 1 (Toxicity as expected)	0.05	0.10	0.20	0.30	0.35	0.40	0.45
Scenario 2 (20% greater than expected)	0.06	0.12	0.24	0.36	0.42	0.48	0.54
Scenario 3 (20% less than expected)	0.04	0.08	0.16	0.24	0.28	0.32	0.36
Scenario 4 (greater rate of DLT increase)	0.05	0.11	0.24	0.39	0.49	0.60	0.72
Scenario 5 (lesser rate of DLT increase)	0.05	0.09	0.16	0.21	0.23	0.24	0.25

Figure: True toxicity values under each scenario in the simulation study [2].

	True risk DLT			
Scenario	[0, 0.2]	(0.2, 0.4]	(0.4, 0.6]	(0.6, 0.8]
Experimentation proportions				
Scenario 1	0.398	0.539	0.064	0.000
Scenario 2	0.192	0.617	0.191	0.000
Scenario 3	0.301	0.699	0.000	0.000
Scenario 4	0.184	0.675	0.136	0.004
Scenario 5	0.294	0.706	0.000	0.000
Recommendation proportions				
Scenario 1	0.204	0.737	0.059	0.000
Scenario 2	0.022	0.837	0.141	0.000
Scenario 3	0.051	0.949	0.000	0.000
Scenario 4	0.019	0.926	0.054	0.001
Scenario 5	0.033	0.967	0.000	0.000

Figure: Simulation results for one-parameter model with non-informative Gamma(1,1) prior [2].

Scenario	True risk DLT [0, 0.2]	(0.2, 0.4]	(0.4, 0.6]	(0.6, 0.8]
Experimentation proportions				
Scenario 1	0.280	0.719	0.000	0.000
Scenario 2	0.143	0.743	0.113	0.000
Scenario 3	0.236	0.764	0.000	0.000
Scenario 4	0.143	0.775	0.082	0.000
Scenario 5	0.234	0.766	0.000	0.000
Recommendation proportions				
Scenario 1	0.082	0.916	0.002	0.000
Scenario 2	0.000	0.904	0.096	0.000
Scenario 3	0.012	0.988	0.000	0.000
Scenario 4	0.000	0.954	0.046	0.000
Scenario 5	0.005	0.995	0.000	0.000

Figure: Simulation results for one-parameter model with informative Gamma(20,0.05) prior [2].

Simulations: Two-parameter Logistic Model

		True risk DLT		
Scenario	Model	[0, 0.2]	(0.2, 0.4]	(0.4, 0.6]
	Experimentation proportions			
Scenario 1	Two-parameter	0.395	0.566	0.039
	EWOC $q = 0.25$	0.532	0.462	0.007
	Toxicity intervals	0.415	0.573	0.012
Scenario 2	Two-parameter	0.193	0.714	0.093
	EWOC $q = 0.25$	0.288	0.687	0.025
	Toxicity intervals	0.190	0.766	0.044
	Recommendation proportions			
Scenario 1	Two-parameter	0.202	0.747	0.051
	EWOC $q = 0.25$	0.324	0.662	0.014
	Toxicity intervals	0.200	0.784	0.016
Scenario 2	Two-parameter	0.020	0.894	0.086
	EWOC $q = 0.25$	0.055	0.916	0.029
	Toxicity intervals	0.020	0.925	0.055

Figure: Simulation results for two-parameter logistic model.

Key Points

- Use of uncertainty.
- Priors are important in determining how a method reacts to toxicities.
- Similar operating characteristics.
- Comparisons can be very dependent on the choice of doses, model,
- Trade-off between conservatism and finding MTD.