Bayesian model choice for generalized CRM models

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Bayesian model choice/model selection/model adaptive/assessment/diagnostic

Refs: Kass and Raftery, Gelfand, Gelfand and Ghosh, others

- Model averaging (Yin and Yuan 2009)
- Patient heterogeneity
- Bridging studies
- Multi-drug problem, partial ordering
- Graded toxicities

Continual Reassessment Method

- Typically a unique working model is assumed for the underlying true dose-toxicity relasionship before the start of the trial:

$$\Pr(Y_j = 1 | X_j = x_j) = \psi(d_i, a) = \alpha_i^a.$$

- Model parameter(s) *a* sequentially updated after observations on each subject or group of subjects.
- Subject allocation uses current running esimate of MTD.

Simple patient heterogeneity: 2 groups

- A dose finding study for breast cancer treatment at UVA CC.
- Goal: to determine the MTD of dasatinib.
- Two groups of patients
  - Dasatinib plus capecitabine for paclitaxel-refractory metastatic breast cancer patients ($G1$)
  - Dasatinib plus fulvestrant for hormone-sensitive, progressive metastatic breast cancer patients ($G2$)
- G1 patients are more sensitive to dasatinib and may have a higher probability of toxicity.
- G2 patients may have higher MTD than G1 patients.
- It is believed the difference in MTD would not exceed 2 doses.

A 2-group CRM shift model

Power model for the one-sample CRM model:

$$\psi(x_j, a) = \alpha_i^a \tag{1}$$

Power model for the two-sample CRM shift model:

$$\psi(x_j, a) = \alpha_{\phi(i)}^a, i = 1, ..., k, \phi(i) = i + z_j \Delta(i) \tag{2}$$

where:

- $\Delta(i)$ denotes the doses shifted from dose i and it takes integer value between $-k + 1$ and $k - 1$.
- z_j is an indicator for groups and takes value of 0 or 1.
- $0 < \alpha_m < \alpha_n < 1$ for $m < n$.
- $0 < a < \infty$.

- If the order of the difference is known, the sign of $\Delta(i)$ is known.
- If $z_j = 0$ group is more sensitive to the treatment, $\Delta(i) \leq 0$.
- If $z_j = 0$ group is less sensitive to the treatment, $\Delta(i) \geq 0$.
- We may be able to limit $\Delta(i)$ to very few values.

Particular situations

- Bridging studies
- Several prognostic groups: $\Delta_1, \Delta_2, \Delta_3, \ldots,$
- Several groups, some having known orderings
- Continous prognostic variable broken into classes
- Different treatment schedules
- Schedules $\times$ prognostic groups

Illustration of the 2-group CRM shift model

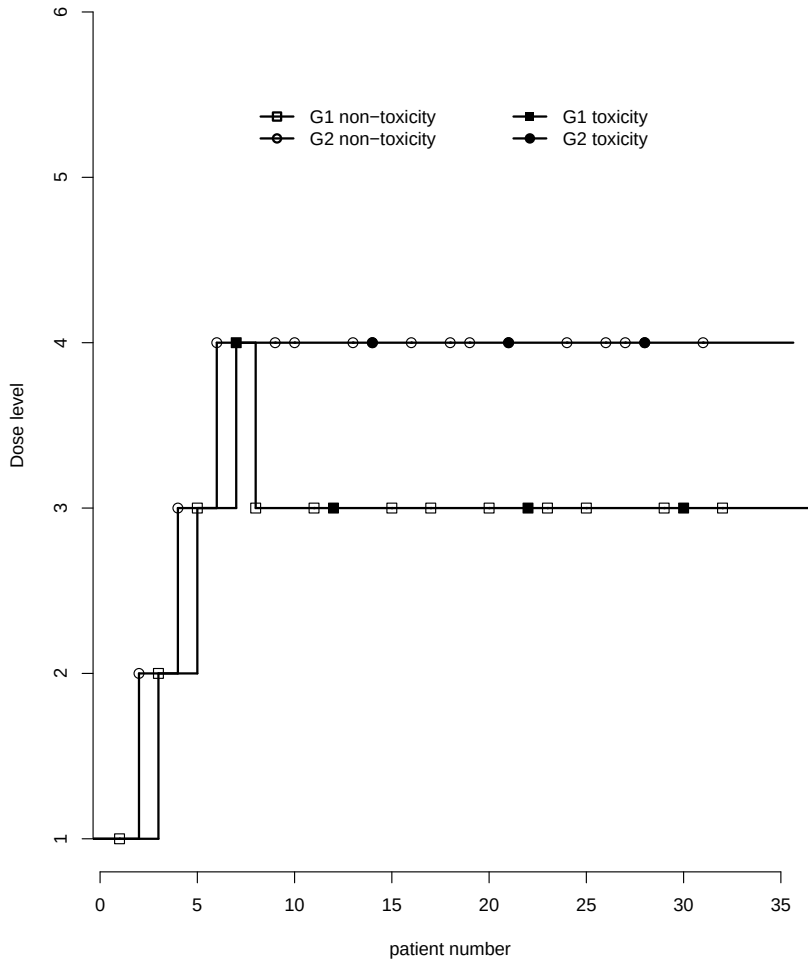
Log-likelihood for power model is:

$$L_j(a)_\Delta = \sum_{i=1}^{6} n_{1i(1)} a \log(\alpha_i) + n_{1i(0)} \log(1-\alpha_i^a) + \sum_{i=1}^{6} n_{2i(1)} a \log(\alpha_{i-\Delta}) + n_{2i(0)} \log(1-\alpha_{i-\Delta}^a) \quad (3)$$

where Δ=0,1 or 2.

$n_{1i(1)}$ = # DLT from $G1$ patients on dose i
$n_{1i(0)}$ = # non-DLT from $G1$ patients on dose i
$n_{2i(1)}$ = # DLT from $G2$ patients on dose i
$n_{2i(0)}$ = # non-DLT from $G2$ patients on dose i

Sample of trial history from the two-group CRM shift design



Four schemes

1. Two-sample CRM shift design
2. Two-group two-parameter CRM design
3. Two separate studies design
4. One single study design, ignoring the group difference

Target rate =0.20
Δ = 0, 1, or 2

Table: Scenarios of probability of toxicity

Scenario	Gr.i	Probability of toxicity $R_i(d_k)$					
A	1	.07	**.23**	.31	.35	.45	.57
	2	.07	**.23**	.31	.35	.45	.57
B	1	.08	**.20**	.35	.50	.70	.80
	2	.01	.05	**.18**	.40	.55	.70
C	1	.02	**.19**	.31	.45	.51	.63
	2	.03	.05	.11	**.21**	.39	.50

Table: MTD recommendation and in-trial allocation for scenario A

	Group 1						Group 2				
	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$	$d1$	$d2$	$d3$	$d4$	$d5$
$R_i(d_k)$	.07	**.23**	.31	.35	.45	.57	.07	**.23**	.31	.35	.45
Proportion of MTD											
Scheme I	.27	**.49**	.19	.04	.00	.00	.12	**.45**	.28	.13	.02
Scheme II	.27	**.47**	.19	.05	.00	.00	.09	**.40**	.29	.16	.04
Scheme III	.22	**.38**	.23	.11	.04	.01	.22	**.39**	.22	.12	.04
Scheme IV	.17	**.51**	.23	.09	.01	.00	.17	**.51**	.23	.09	.01
Proportion of Patients											
Scheme I	.35	**.38**	.19	.06	.02	.00	.19	**.33**	.25	.15	.06
Scheme II	.35	**.33**	.19	.07	.03	.02	.17	**.29**	.26	.15	.08
Scheme III	.31	**.29**	.20	.11	.06	.03	.31	**.29**	.20	.11	.06
Scheme IV	.25	**.37**	.22	.11	.04	.01	.25	**.37**	.22	.11	.04

Table: Recommendation and in-trial allocation for scenario B

	Group 1						Group 2				
	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$	$d1$	$d2$	$d3$	$d4$	$d5$
$R_i(d_k)$	.08	**.20**	.35	.50	.70	.80	.01	.05	**.18**	.40	.55
Proportion of MTD											
Scheme I	.18	**.54**	.27	.01	.00	.00	.00	.19	**.61**	.19	.01
Scheme II	.23	**.49**	.26	.01	.00	.00	.00	.12	**.63**	.21	.03
Scheme III	.22	**.47**	.26	.04	.00	.00	.00	.15	**.62**	.21	.02
Scheme IV	.02	**.43**	.53	.03	.00	.00	.02	.43	**.53**	.03	.00
Proportion of Patients											
Scheme I	.24	**.40**	.29	.06	.01	.00	.07	.22	**.43**	.22	.05
Scheme III	.32	**.35**	.25	.05	.02	.01	.06	.17	**.44**	.23	.08
Scheme II	.30	**.33**	.24	.09	.03	.01	.10	.20	**.41**	.20	.07
Scheme IV	.11	**.35**	.42	.09	.02	.01	.11	.35	**.42**	.09	.02

Table: Recommendation and in-trial allocation for scenario C

	Group 1						Group 2				
	$d1$	$d2$	$d3$	$d4$	$d5$	$d6$	$d1$	$d2$	$d3$	$d4$	$d5$
$R_i(d_k)$	.02	**.19**	.31	.45	.51	.63	.03	.05	.11	**.21**	.39
Proportion of MTD											
Scheme I	.07	**.47**	.39	.07	.01	.00	.00	.07	.32	**.48**	.12
Scheme II	.11	**.47**	.32	.08	.02	.00	.01	.06	.32	**.38**	.20
Scheme III	.11	**.46**	.34	.07	.01	.00	.00	.04	.30	**.43**	.20
Scheme IV	.01	**.23**	.55	.19	.02	.00	.01	.23	.55	**.19**	.02
Proportion of Patients											
Scheme I	.16	**.38**	.34	.09	.03	.00	.05	.13	.29	**.35**	.15
Scheme II	.23	**.34**	.28	.10	.03	.02	.06	.11	.27	**.30**	.18
Scheme II	.24	**.34**	.25	.10	.05	.02	.10	.14	.26	**.26**	.16
Scheme IV	.08	**.24**	.39	.20	.06	.02	.08	.24	.39	**.20**	.06

Table: Simulation results for the shift model with prior probabilities of shifted doses Δ

	Group 1						Group 2					
	d1	d2	d3	d4	d5	d6	d1	d2	d3	d4	d5	d6
$R_i(d_k)$	.08	**.20**	.35	.50	.70	.80	.01	.05	**.18**	.40	.55	.70
						prior = .33, .33, .33						
% of MTD	.18	**.54**	.27	.01	.00	.00	.00	.19	**.61**	.19	.01	.00
% of Patients	.24	**.40**	.29	.06	.01	.00	.07	.22	**.43**	.22	.05	.01
						prior = .25, .50, .25						
% of MTD	.10	**.56**	.32	.01	.00	.00	.00	.12	**.66**	.21	.01	.00
% of Patients	.22	**.44**	.29	.04	.01	.00	.06	.19	**.48**	.22	.04	.01
						prior = .29, .43, .29						
% of MTD	.11	**.57**	.31	.01	.00	.00	.00	.14	**.65**	.20	.01	.00
% of Patients	.21	.43	.30	.04	.01	.00	.06	.21	.45	.22	.05	.01
						prior = .17, .50, .33						
% of MTD	.12	**.62**	.25	.00	.00	.00	.00	.09	**.68**	.22	.01	.00
% of Patients	.24	**.47**	.25	.04	.01	.00	.06	.18	**.47**	.24	.05	.01
						prior = .33, .50, .17						
% of MTD	.09	**.58**	.33	.01	.00	.00	.00	.15	**.65**	.19	.01	.00
% of Patients	.20	**.44**	.31	.04	.01	.00	.06	.22	**.46**	.22	.04	.00

Comparison with optimal design

Table: Simulation results to compare the shift model and the optimal design for Scenario A

	Group 1						Group 2				
d_k	1	2	3	4	5	6	1	2	3	4	5
R_k	0.07	**0.23**	0.31	0.35	0.45	0.57	0.07	**0.23**	0.31	0.35	0.45
$p_k(16)$	0.27	**0.49**	0.19	0.04	0.00	0.00	0.12	**0.45**	0.28	0.13	0.02
$q_k(16)$	0.23	**0.50**	0.14	0.10	0.03	0.00	0.23	**0.50**	0.14	0.10	0.03

Comparison with optimal design

Table: Simulation results to compare the shift model and the optimal design for scenario B

	Group 1						Group 2				
d_k	1	2	3	4	5	6	1	2	3	4	5
R_k	0.08	**0.20**	0.35	0.50	0.70	0.80	0.01	0.05	**0.18**	0.40	0.55
$p_k(16)$	0.18	**0.53**	0.27	0.01	0.00	0.00	0.00	0.19	**0.61**	0.19	0.01
$q_k(16)$	0.24	**0.55**	0.20	0.01	0.00	0.00	0.02	0.13	**0.68**	0.17	0.00

Phase I study of a combination

Table: Drug combinations used in Phase 1 trial of Samarium Lexidronam and Bortezomib DLT defined by as a grade 3+ neutropenia (Berenson et al. 2009)

	Drug Combination					
Agent	d_1	d_2	d_3	d_4	d_5	d_6
Sm (mCi/kg)	0.25	0.5	1.0	0.25	0.5	1.0
Bortezomib (mg/m^2)	1.0	1.0	1.0	1.3	1.3	1.3

Partial Ordering of Doses

- Consider two drugs, A and B, resulting in the treatment combinations.

	Drug Combination					
Agent	d_1	d_2	d_3	d_4	d_5	d_6
A	54	67.5	75	79	84.5	89.5
B	6	6	6	5	7.5	9

- Level d_3 may be more or less toxic than d_4
- There are two possible simple orders (models) consistent with the partial order.
- We index the models by M where M takes value M_h under the h^{th} possible ordering

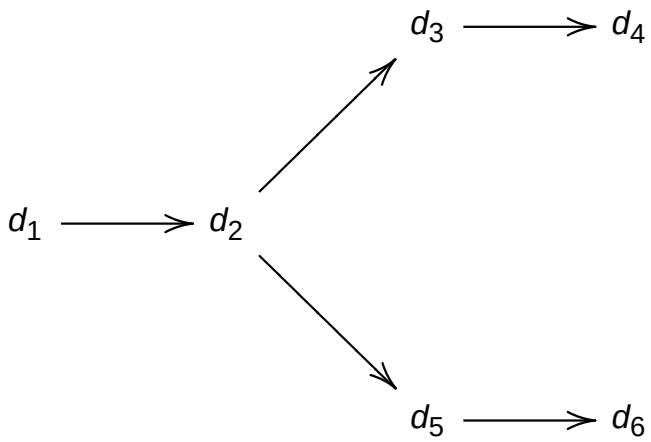
$$M_1 : d_1 \rightarrow d_2 \rightarrow d_3 \rightarrow d_4 \rightarrow d_5 \rightarrow d_6$$
$$M_2 : d_1 \rightarrow d_2 \rightarrow d_4 \rightarrow d_3 \rightarrow d_5 \rightarrow d_6$$

Set of possible orders of toxicity probabilities

Ordering	Simple Order										
M_1	$R(d_1)$	$\leq$	$R(d_2)$	$\leq$	$R(d_3)$	$\leq$	$R(d_4)$	$\leq$	$R(d_5)$	$\leq$	$R(d_6)$
M_2	$R(d_1)$	$\leq$	$R(d_2)$	$\leq$	$R(d_4)$	$\leq$	$R(d_3)$	$\leq$	$R(d_5)$	$\leq$	$R(d_6)$
M_3	$R(d_1)$	$\leq$	$R(d_2)$	$\leq$	$R(d_4)$	$\leq$	$R(d_5)$	$\leq$	$R(d_3)$	$\leq$	$R(d_6)$
M_4	$R(d_1)$	$\leq$	$R(d_4)$	$\leq$	$R(d_2)$	$\leq$	$R(d_3)$	$\leq$	$R(d_5)$	$\leq$	$R(d_6)$
M_5	$R(d_1)$	$\leq$	$R(d_4)$	$\leq$	$R(d_2)$	$\leq$	$R(d_5)$	$\leq$	$R(d_3)$	$\leq$	$R(d_6)$

Escalation rules

	Drug Combination					
Agent	1	2	3	4	5	6
Paclitaxel	54	67.5	81	94.5	67.5	67.5
Carboplatin	6	6	6	6	7.5	9



Probability Model

- Let d_{hi} be the dose combination at level i under ordering h
- We model true probability of toxicity at dose d_{hi}, $d_{hi} \in \{d_1, \ldots, d_k\}$ via

$$R(d_{hi}) = \Pr(Y_j = 1 \mid d_{hi}) = \mathrm{E}(Y_j \mid d_{hi}) = \psi_h(d_{hi}, a_h)$$

- Using simple power model:

$$\psi_h(d_{hi}, a_h) = \alpha_{hi}^{a_h}$$

  where $0 < \alpha_{hi} < 1$ and $0 < a_h < \infty$.
- For each ordering, "model", M_h, find $\hat{a}_h$
- Choose model which maximizes likelihood.
- Can put priors on particular models (orderings).

Inference

Likelihood under ordering M_h is

- $$\phi(\Omega_j \mid M_h, a_h) = \prod_{\ell=1}^{j} \Psi_h^{y_\ell}(x_\ell, a_h)\{1 - \Psi_h(x_\ell, a_h)\}^{(1-y_\ell)}$$
- For each $M_h, h = 1, \ldots, H$, likelihood can be maximized in order to obtain $\hat{a}_h$, for a_h.
- Can use informative priors on M_h or discrete uniform
- $$f(M_h, a_h \mid \Omega_j) \propto \phi(\Omega_j \mid M_h, a_h) g(a_h \mid M_h) p(M_h)$$

  where

  $$C = \sum_{h=1}^{H} \int_{u \in \mathcal{A}} \phi(\Omega_j \mid M_h, u) g(u \mid M_h) p(M_h) d(u)$$

  Marginal posterior distribution of the ordering, M, by integrating out over a_h

  $$f(M_h \mid \Omega_j) = \frac{1}{C} p(M_h) \int_{\mathcal{A}} \phi(\Omega_j \mid M_h, a_h) g(a_h \mid M_h) da_h.$$

- Update in the usual way given Ω_j.
- Can use $f(M_h \mid \Omega_j)$ to sample an ordering (model).

Simulations

Dose	d_1	d_2	d_3	d_4	d_5	d_6	n	tox
$R(d_i)$	0.26	**0.33**	0.51	0.62	0.78	0.86	-	-
Conaway et al.	0.35	**0.52**	0.11	0.02	0.00	0.00	21.3	8.5
POCRM	0.29	**0.50**	0.16	0.04	0.01	0.00	22.0	8.4
CRM	0.27	**0.49**	0.23	0.01	0.00	0.00	22.0	7.9
$R(d_i)$	0.12	0.21	**0.34**	0.50	0.66	0.79	-	-
Conaway et al.	0.07	0.29	**0.42**	0.21	0.01	0.00	25.6	9.0
POCRM	0.02	0.23	**0.55**	0.11	0.10	0.00	26.0	10.0
CRM	0.01	0.18	**0.63**	0.17	0.01	0.00	25.0	7.5
$R(d_i)$	0.04	0.07	0.20	**0.33**	0.55	0.70		-
Conaway et al.	0.00	0.02	0.38	**0.51**	0.08	0.02	28.5	8.8
POCRM	0.00	0.00	0.26	**0.50**	0.23	0.01	29.0	10.8
CRM	0.00	0.01	0.19	**0.67**	0.13	0.00	28.0	8.0
$R(d_i)$	0.01	0.04	0.05	0.17	**0.33**	0.67		-
Conaway et al.	0.00	0.00	0.06	0.25	**0.64**	0.05	29.0	7.8
POCRM	0.00	0.00	0.01	0.29	**0.61**	0.09	29.0	9.4
CRM	0.00	0.00	0.00	0.18	**0.76**	0.06	28.0	6.3
$R(d_i)$	0.01	0.02	0.05	0.15	0.20	**0.33**		-
Conaway et al.	0.00	0.00	0.01	0.04	0.37	**0.59**	26.2	5.8
POCRM	0.00	0.00	0.00	0.20	0.12	**0.68**	27.0	6.4
CRM	0.00	0.00	0.00	0.05	0.26	**0.69**	27.0	4.3

Probability model for grades

- Model $R(d_i)$, the true probability of dose-limiting toxic response for the j^{th} patient via:
$$R(d_i) = \Pr(Y_j = 3|d_i) = \psi(d_i, a) = \alpha_i^a$$
- Model the probability of a grade 2 or grade 3 response by implementing the parameter b:
$$\Pr(Y_j = 2 \text{ or } Y_j = 3|d_i) = \xi(d_i, a, b) = [\alpha_i^a]^b$$
- From which the probability of a grade 2 toxicity is obtained
$$\Pr(Y_j = 2|d_i) = \xi(d_i, a, b) - \psi(d_i, a) = [\alpha_i^a]^b - \alpha_i^a$$
- The probability of a grade 1 toxicity follows:
$$\Pr(Y_j = 1|d_i) = 1 - \xi(d_i, a, b) = 1 - [\alpha_i^a]^b$$

Simulation Results

Table: Compared Frequency of Final Recommendation of a Standard CRM and a Design Using Known Information on Graded Toxicities (θ=0.25, n=25)

	d_1	d_2	d_3	d_4	d_5	d_6
R_k	0.05	0.11	**0.22**	0.35	0.45	0.60
Standard CRM	0.00	0.13	**0.53**	0.30	0.04	0.00
CRM using grades	0.00	0.09	**0.60**	0.29	0.02	0.00