Dose-escalation trials without monotonicity assumption: A weighted differential entropy approach

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Dose escalation

- Limited prior knowledge about toxicities in humans
- Range of m regimes (doses, combinations, schedules)
- n patients

Goal:

- Find the maximum tolerated regime that corresponds to a controlled level of toxicity, usually $\gamma \in (0.2, 0.35)$ in oncology trials

Single agent dose-escalation designs

Model-based methods

- CRM
- EWOC

Algorithm based methods

- '3+3' design
- Biased Coin Design

Fundamental assumption: a **monotonic** dose-response relationship

Cannot be applied to:

- Combination trials with many treatments
- Scheduling of drugs
- Non-monotonic dose-toxicity relations

Unknown ordering problem. Example (I)

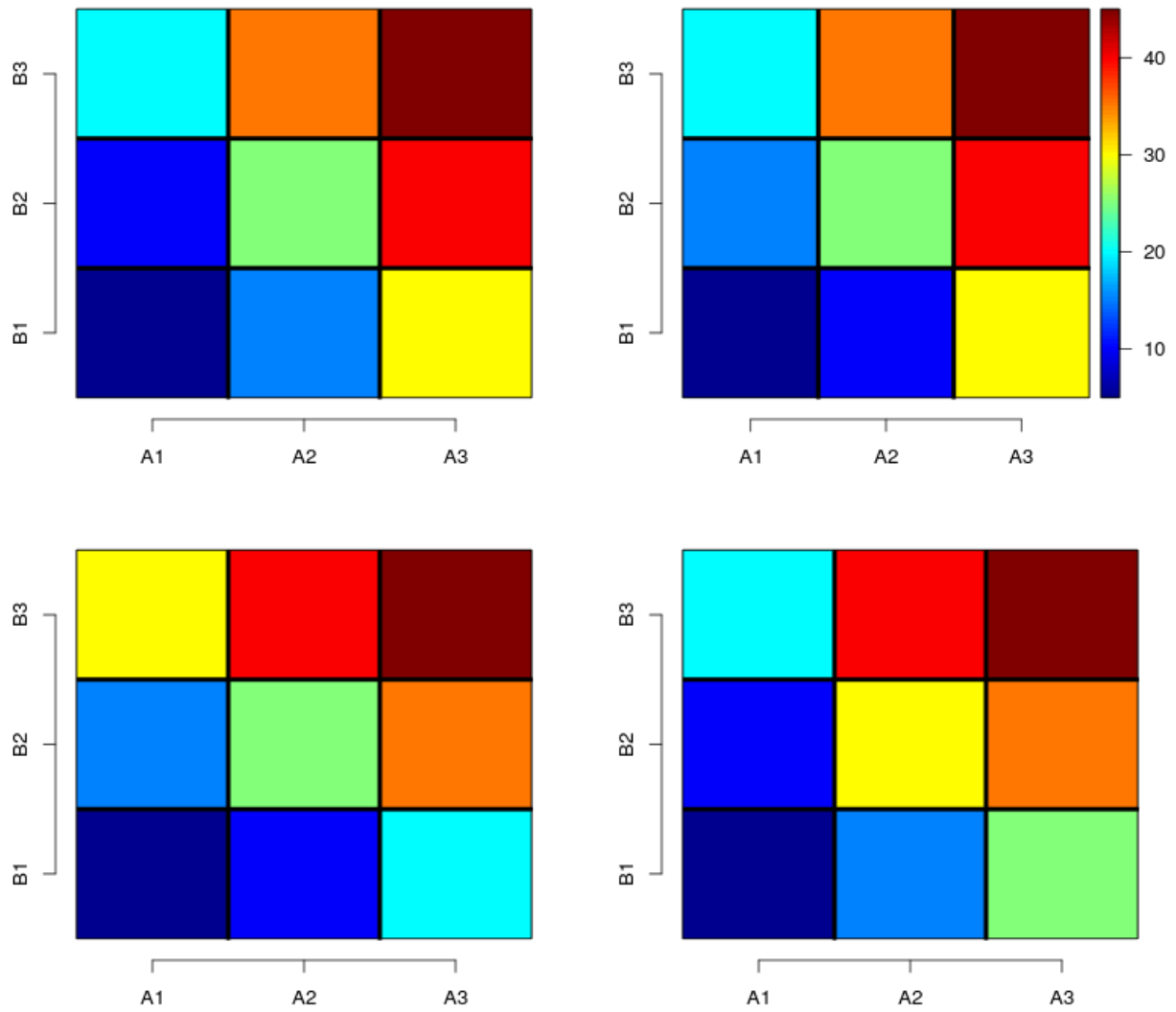
Let us consider drugs combination dose-escalation trial with

- 3 dose levels of drug A: A_1, A_2, A_3
- 3 dose levels of drug B: B_1, B_2, B_3

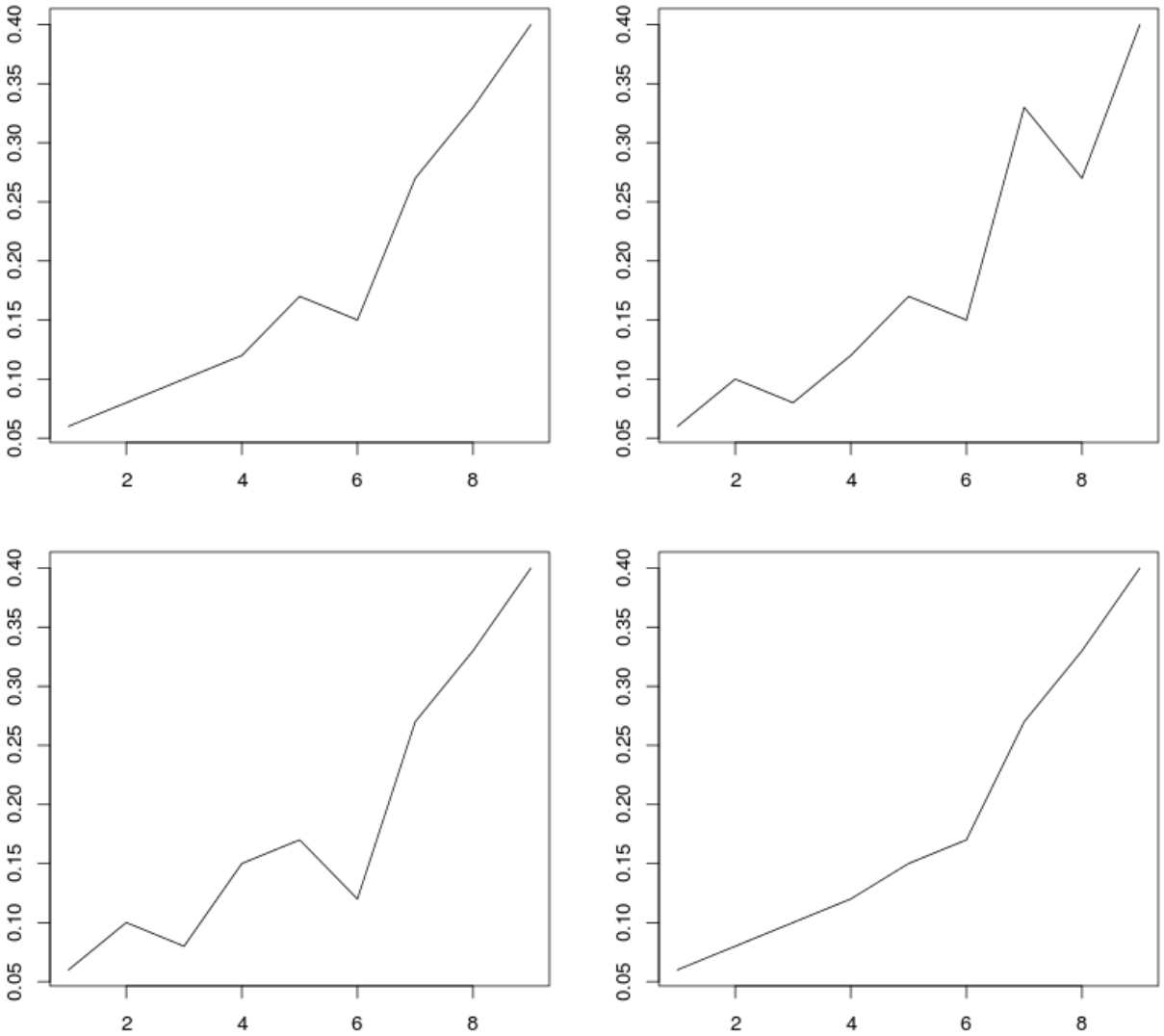
$(A_1; B_3)$	$(A_2; B_3)$	$(A_3; B_3)$
$(A_1; B_2)$	$(A_2; B_2)$	$(A_3; B_2)$
$(A_1; B_1)$	$(A_2; B_1)$	$(A_3; B_1)$

Even assuming monotonicity one drug being fixed, we cannot order
$(A_1; B_2)$ and $(A_2; B_1)$;
$(A_1; B_3)$ and $(A_2; B_1)$;
$(A_1; B_3)$ and $(A_3; B_1)$ and so on...

Unknown ordering problem. Example (II)



Unknown ordering problem. Example (III)



Method for drug combinations

- **Six-parameter model** *(Thall P. et al, 2003)*
- **Up-and-down design** *(Ivanova A, Kim S., 2009)*
  Using the T -statistic
- **Copula regression** *(G.Yin, Y.Yuan, 2009)*
  Parametrization of drug-drug interactive effect
- **POCRM** *(N.Wages, M. Conoway, J. O'Quigley, 2011)*
  Choose several ordering and randomize between them during the trial

General restrictions:

- Strong model assumptions are usually needed
- No diagonal switching is allowed
- Synergistic effect is usually assumed
- Two combinations might be considered only

Goal

To propose an escalation procedure that **does not require any parametric assumptions** (including monotonicity between regimes).

Problem formulation

- Toxicity probabilities $Z_1, \ldots, Z_m$ are random variables with Beta prior $\mathrm{B}(\nu_j + 1, \beta_j - \nu_j + 1)$, $\nu_j > 0, \beta_j > 0$
- n_j patients assigned to the regime j and x_j toxicities observed
- Beta posterior f_{n_j} $\mathrm{B}(x_j + \nu_j + 1, n_j - x_j + \beta_j - \nu_j + 1)$
- Let $0 < \alpha_j < 1$ be the unknown parameter in the neighbourhood of which the probability of toxicity is concentrated
- Target toxicity γ

Information theory concepts

1) A statistical experiment of estimation of a toxicity probability.
The Shannon differential entropy (DE) $h(f_n)$ of the PDF f_n is defined as

$$h(f_n) = -\int_0^1 f_n(p)\log f_n(p)\mathrm{d}p \tag{1}$$

with the convention $0\log 0 = 0$.

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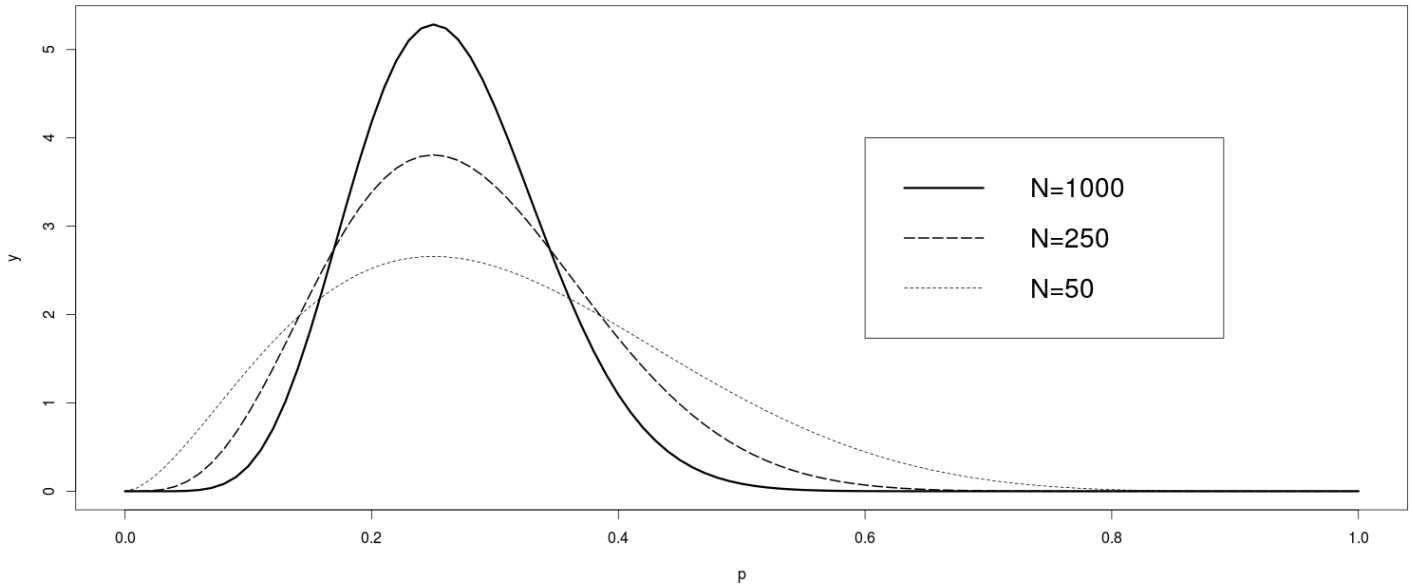
2) A statistical experiment of a sensitive estimation.
The weighted Shannon differential entropy (WDE) , $h^{\phi_n}(f_n)$, of the RV $Z^{(n)}$ with positive weight function $\phi_n(p) \equiv \phi_n(p, \alpha, \gamma)$ is defined as

$$h^{\phi_n}(f_n) = -\int_0^1 \phi_n(p) f_n(p)\log f_n(p)\mathrm{d}p. \tag{2}$$

Weight Function

The Beta-form weight function

$$\phi_n(p) = \Lambda(\gamma, x, n) p^{\gamma\sqrt{n}} (1-p)^{(1-\gamma)\sqrt{n}}. \tag{3}$$



Escalation criteria

The difference of informations in two statistical experiments:

Theorem

Let $h(f_n)$ and $h^{\phi_n}(f_n)$ be the DE and WDE corresponding to PDF f_n when $x \sim \alpha n$ with the weight function ϕ_n given in (3). Then

$$\lim_{n\to\infty} \left(h^{\phi_n}(f_n) - h(f_n)\right) = \frac{(\alpha-\gamma)^2}{2\alpha(1-\alpha)} \equiv \Delta. \tag{4}$$

Therefore, for a regime d_j, $j = 1, \ldots, m$, we obtained that

$$\Delta_j \equiv \frac{(\alpha_j-\gamma)^2}{2\alpha_j(1-\alpha_j)}.$$

Criteria:

$$\Delta_j = \inf_{i=1,\ldots,m} \Delta_i.$$

Estimation

Consider the mode of the posterior distribution f_{n_j}

$$\hat{p}_j^{(n)} = \frac{x_j + \nu_j}{n_j + \beta_j}.$$

Then the following "plug-in" estimator $\hat{\Delta}_j^{(n)}$ may be used

$$\hat{\Delta}_j^{(n)} = \frac{(\hat{p}_j^{(n)} - \gamma)^2}{\hat{p}_j^{(n)}(1 - \hat{p}_j^{(n)})}. \tag{5}$$

Escalation design

Let $d_j(i)$ be a regime d_j recommended for cohort i.

- The procedure starts from $\hat{\Delta}_j^{(0)}$
- l cohorts were already assigned

The $(l+1)^{th}$ cohort of patients will be assigned to regime k such that

$$d_j(l+1): \ \hat{\Delta}_k^{(l)} = \inf_{i=1,\ldots,m} \hat{\Delta}_i^{(l)}, \ l = 0, 1, 2, \ldots, C.$$

We adopt regime $d_j(C+1)$ as the final recommended regime.

Alternative angle

One can consider

$$\hat{\Delta}_j^{(n)} = \frac{(\hat{p}_j^{(n)} - \gamma)^2}{\hat{p}_j^{(n)}(1 - \hat{p}_j^{(n)})}$$

as a **loss function** for a parameter defined on $(0, 1)$.

- Loss function penalize $\hat{p}_j^{(n)}$ close to 0 to 1 and **'pushes' the allocation away from bounds** to the neighbourhood of γ
- Does not include any definition of safety $\rightarrow$ safety constraint is needed

Safety constrain (I)

Considers regime d_j as safe if at the moment n its PDF satisfies

$$\int_{\gamma^*}^{1} f_{n_j}(p)\mathrm{d}p \leq \theta_n \tag{6}$$

where

- γ^* is some threshold after which all regimes above are declared to have excessive risk, $\gamma^* = \gamma + 0.2$
- θ_n is the level of probability that controls the overdosing
  - Note that this depends on n

Why is a time-varying SC is needed?

If $\beta = 1$ and $\theta_n = \theta = 0.50$ then regimes with prior mode ≥ 0.40 will never be considered since

$$\int_{0.45}^{1} f_0(p|x = 0)\mathrm{d}p = 0.5107 > 0.50$$

Requirements to the function θ_n

- θ_n is a decreasing function of n
- $\theta_0 = 1$
- $\theta_N \leq 0.3$
- $\rightarrow \theta_n = 1 - rn$

Choice of SC parameters

	r							
	0.010	0.015	0.020	0.025	0.030	0.035	0.040	0.045
$\gamma^* = 0.55$	0.00	0.32	4.32	18.47	36.15	49.06	61.49	75.70
	26.47	26.65	26.40	26.05	26.85	25.03	24.10	20.23
$\gamma^* = 0.50$	0.15	2.50	17.76	38.75	52.74	63.06	74.94	87.22
	26.27	26.22	26.53	27.24	25.46	23.30	19.35	17.10
$\gamma^* = 0.45$	1.13	12.72	35.72	56.49	67.16	**77.55**	86.53	93.49
	26.15	26.02	26.81	25.18	22.26	**21.75**	15.16	11.05
$\gamma^* = 0.40$	7.47	37.95	59.49	70.52	80.53	88.32	94.18	97.63
	26.04	25.91	24.90	21.98	17.66	14.47	8.05	3.51
$\gamma^* = 0.35$	33.98	58.22	74.42	84.14	90.52	94.86	97.90	99.20
	25.65	24.54	20.45	15.55	13.77	7.21	3.25	0.70
$\gamma^* = 0.30$	55.51	77.02	87.21	92.99	96.50	98.55	99.37	99.83
	24.21	18.09	14.40	11.42	7.13	0.95	0.08	0.04

Table: Top row: Proportion of no recommendations for toxic scenario. Bottom row: Proportion of correct recommendations. 10^6 simulations.

Simulations

For simulations below the following parameters were chosen:

- The cohort size $c = 1$
- Total sample size $N = 20$
- Number of regimes $m = 7$
- The target probability $\gamma = 0.25$
- Safety constraint

$$\theta_n = \begin{cases} 1 - 0.035n, \ \textit{if} \ 0.035 \times n \leq 0.7; \\ 0.3, \ \textit{otherwise}. \end{cases}$$

Investigated scenarios

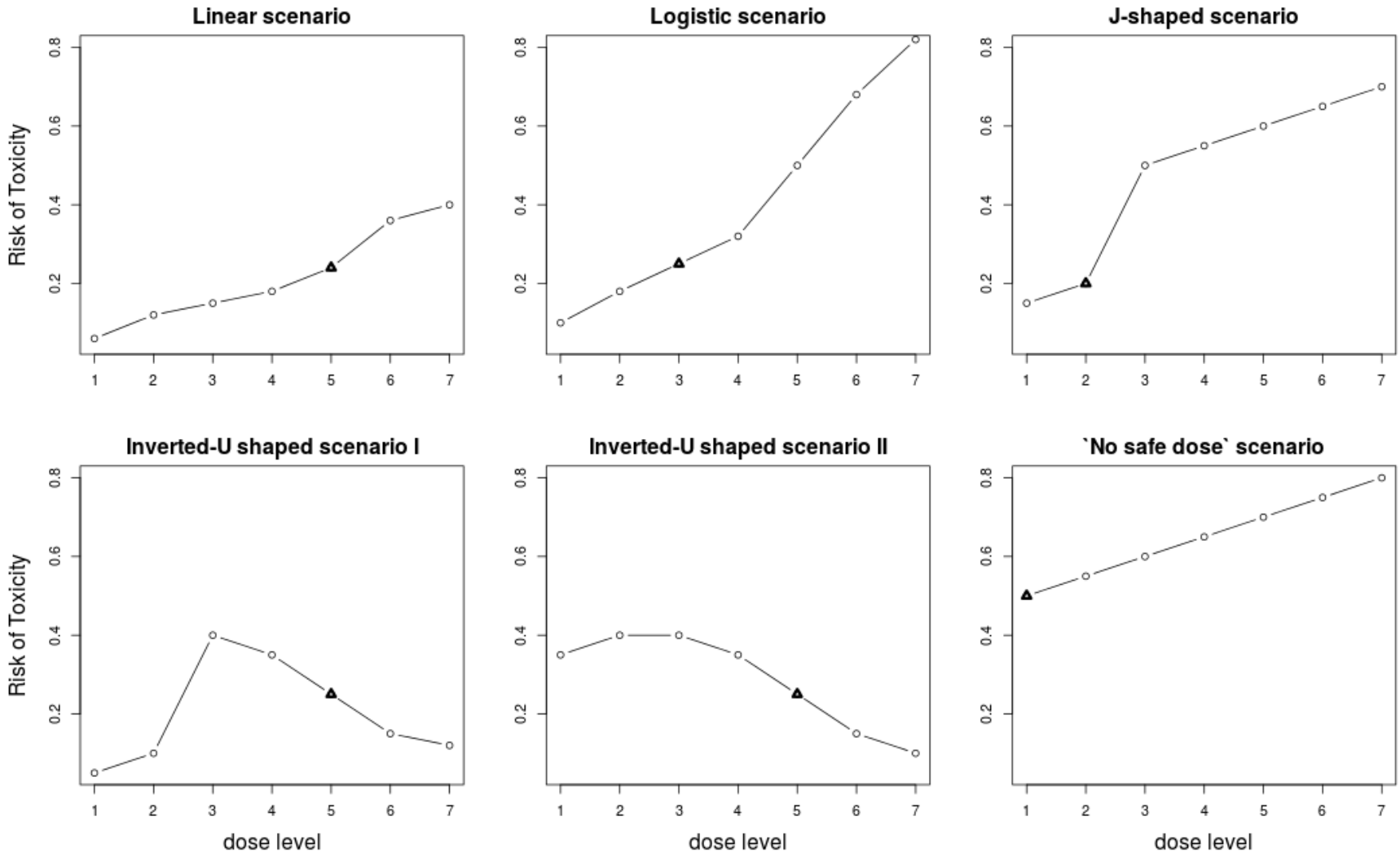


Figure: Considering response shapes. The TD is marked as triangle.

Specifying the prior

Assumptions:

- Vague beliefs about toxicity risk
- Prior belief: regimes have been correctly ordered monotonically
- A escalation to be started from d_1

The prior for regime d_j $(1 \leq j \leq 7)$ is specified thought the mode $\hat{p}_j^{(0)} = \frac{\nu_j}{\beta_j}$.
Starting from the bottom: $\hat{p}_1^{(0)} = \gamma$.
The vector of modes $\hat{\mathbf{p}}$ for all regimes is defined

$$\hat{\mathbf{p}} = [0.25, 0.3, 0.35, 0.4, 0.45, 0.5, 0.55]^{\mathrm{T}}.$$

Vague prior $\rightarrow \beta_j = \beta = 1$ for $j = 1, \ldots, m$.

Is there a unique set of prior parameters that lead to the equivalent performance?

Choice of prior

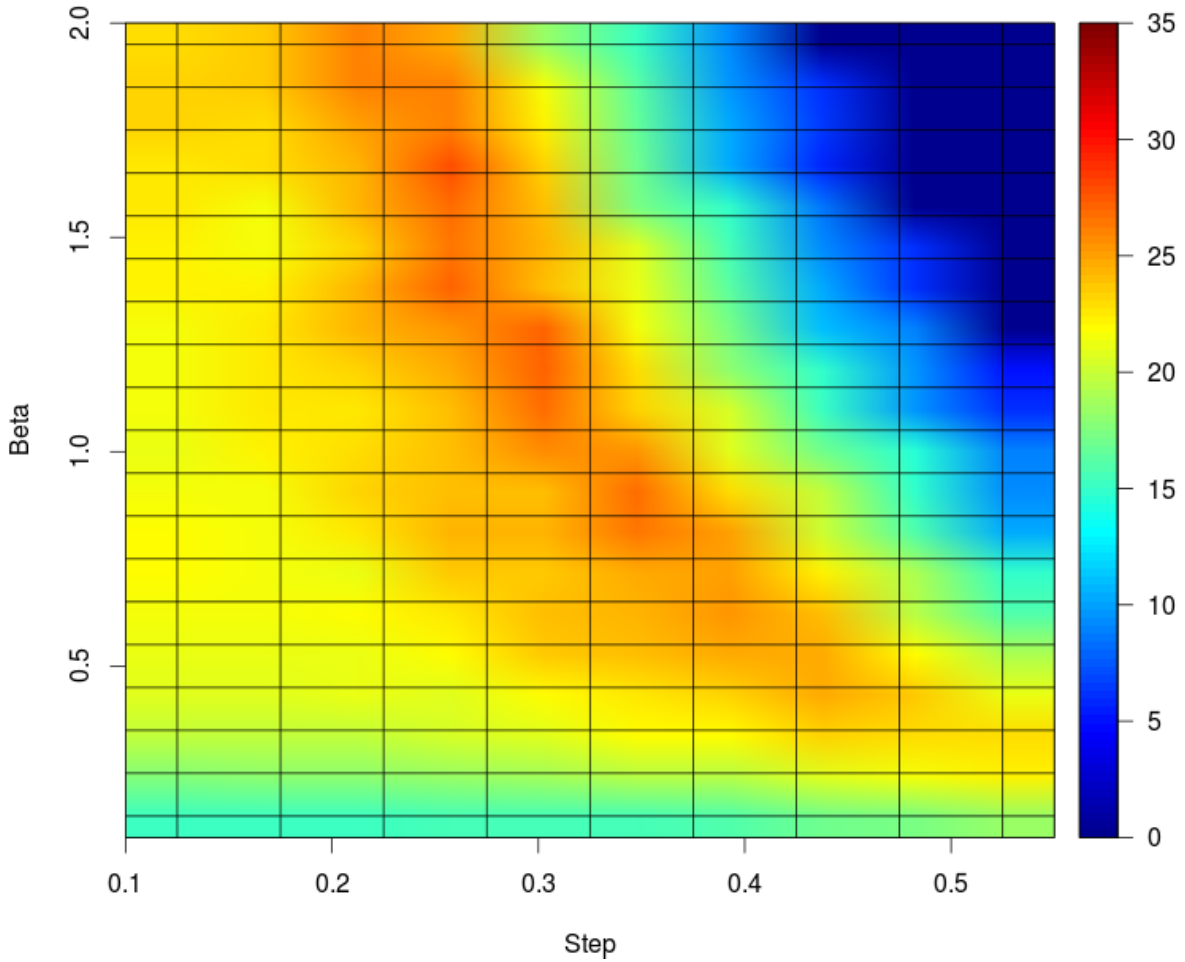


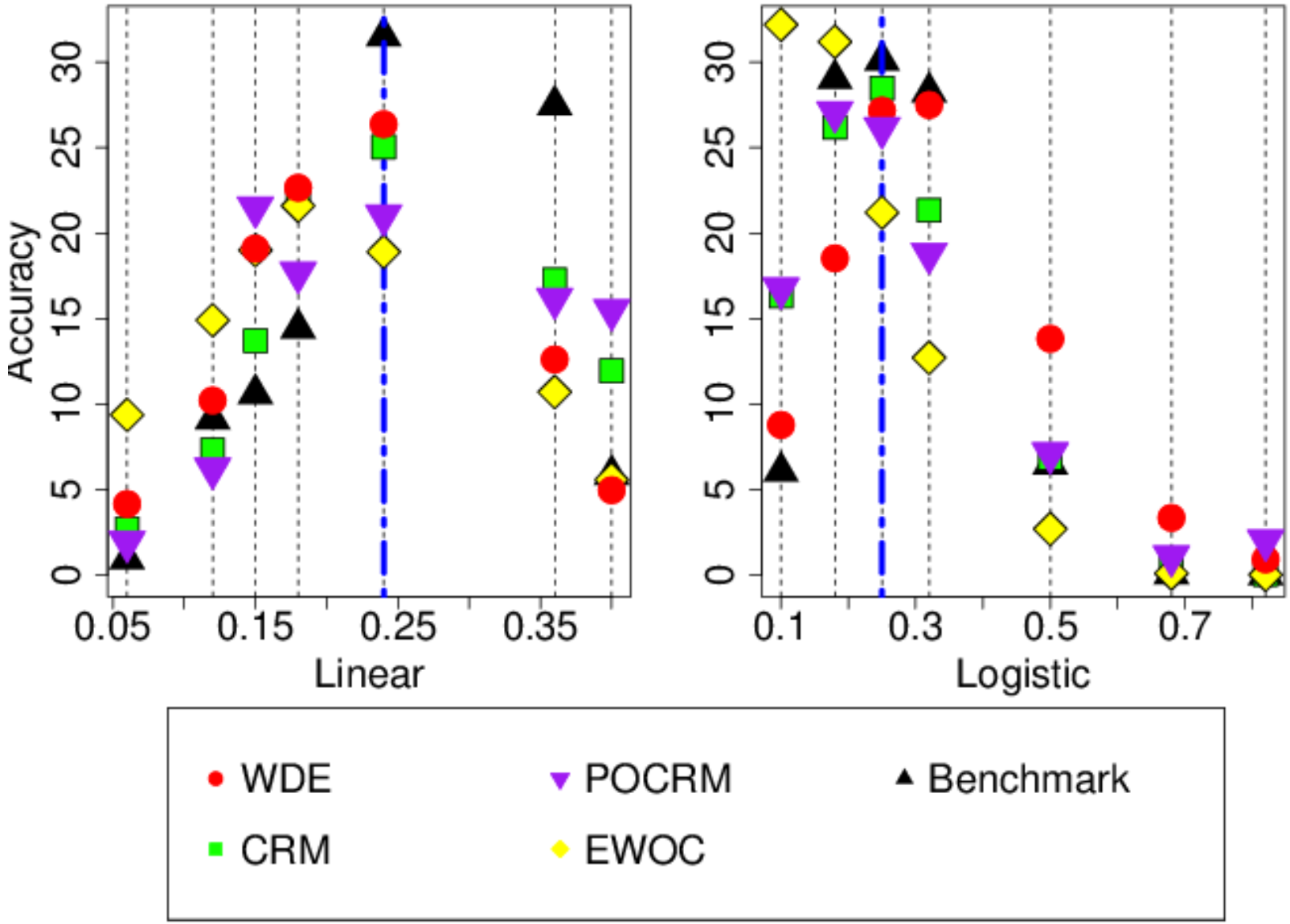
Figure: Proportion of correct recommendations: $\beta =$ number of patients and difference between the risk of toxicity on lowest and highest dose across six scenarios.

Alternative methods

We have also investigated

- Continual reassessment method (CRM)
- Partial ordering continual reassessment method (POCRM)
  All correct orderings used in simulation are incorporated in the model.
- Escalation with overdose control (EWOC)
  A target 25^{th} *percentile is used.*
- Non-parametric optimal benchmark

Simulation results. Ordering is correctly specified



Simulation results. Ordering is wrongly specified.

	d_1	d_2	d_3	d_4	d_5	d_6	d_7	No	TR	$\bar{N}$
True	0.05	0.10	0.40	0.35	**0.25**	0.15	0.12			
WDE_{SC}	14.11	19.13	11.77	18.27	**27.90**	8.50	0.23	0.15	**4.26**	19.99
CRM_{SC}	4.26	**19.90**	17.70	6.31	**2.84**	3.00	**46.10**	0.31	**3.26**	19.92
POCRM_{SC}	2.87	11.39	11.75	9.32	**19.11**	33.94	11.62	0.24	**4.29**	19.99
EWOC_{SC}	7.18	**24.90**	18.60	3.79	**2.52**	3.79	**30.60**	6.62	**2.73**	18.89

	d_1	d_2	d_3	d_4	d_5	d_6	d_7	No	TR	$\bar{N}$
True	0.35	0.40	0.40	0.35	**0.25**	0.15	0.10			
WDE_{SC}	15.57	12.65	13.31	18.27	**27.92**	8.90	0.58	9.96	**5.81**	19.73
CRM_{SC}	**47.41**	2.51	0.97	0.48	**0.72**	0.40	**30.10**	27.30	**4.27**	15.96
POCRM_{SC}	16.81	5.98	5.66	12.42	**20.10**	**23.13**	10.23	9.67	**5.14**	19.46
EWOC_{SC}	**30.75**	1.26	0.78	0.47	**0.47**	0.31	9.78	**56.15**	**3.30**	11.02

Simulation results. Highly toxic scenarios.

	d_1	d_2	d_3	d_4	d_5	d_6	d_7	No	TR	$\bar{N}$
True	0.15	**0.20**	0.50	0.55	0.60	0.65	0.70			
WDE_{SC}	38.07	**44.65**	6.59	3.44	1.48	0.28	0.02	5.47	**5.94**	19.77
CRM_{SC}	37.47	**37.85**	17.41	2.92	0.36	0.07	0.00	3.92	**5.10**	19.41
POCRM_{SC}	33.57	**37.76**	13.27	2.55	0.54	1.33	6.04	4.95	**6.06**	19.82
EWOC_{SC}	**51.00**	**26.11**	11.01	0.88	0.13	0.00	0.00	10.87	**3.60**	16.82
True	**0.50**	0.55	0.60	0.65	0.70	0.75	0.80	**No**		
WDE_{SC}	13.63	5.53	2.45	0.88	0.27	0.06	0.00	**77.17**	**8.02**	14.28
CRM_{SC}	**32.24**	0.32	0.08	0.00	0.00	0.00	0.00	**67.36**	**5.33**	10.30
POCRM_{SC}	15.18	0.57	0.12	0.04	0.01	3.06	0.08	**80.94**	**7.12**	12.59
EWOC_{SC}	16.17	0.00	0.12	0.00	0.00	0.00	0.00	**83.71**	**3.07**	6.05

Conclusions

The WDE-based method

- **performs comparably** to the model-based methods **when the ordering is specified correctly** scenarios
- **outperform** them in **wrongly specified** setting

However, WDE-based method

- **experience problems** in scenarios with **no safe doses** or with sharp jump in toxicity probability at the bottom.
- **The time-varying safety constrain** in the proposed form *can overcome overdosing problems* and increase the accuracy of the original method

Further development

- Phase II
- Generalized weight function
- Consistency conditions

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