A Bayesian information theoretic design for Phase I dose finding trials without monotonicity assumption

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February 28th, 2018

PSI One Day Meeting: Bayesian Methods for Dose Finding and Biomarkers

Acknowledgement: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 633567.

Dose escalation

Consider:

- First-in-men clinical trial $\rightarrow$ rough prior knowledge about toxicities for humans.
- Range of m regimens (doses, combinations, schedules)
- n patients

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Goal:

- Find the maximum tolerated regimen that corresponds to a controlled level of toxicity γ, for examples, $\gamma \in (0.20, 0.35)$ for many 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 relation.

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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

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

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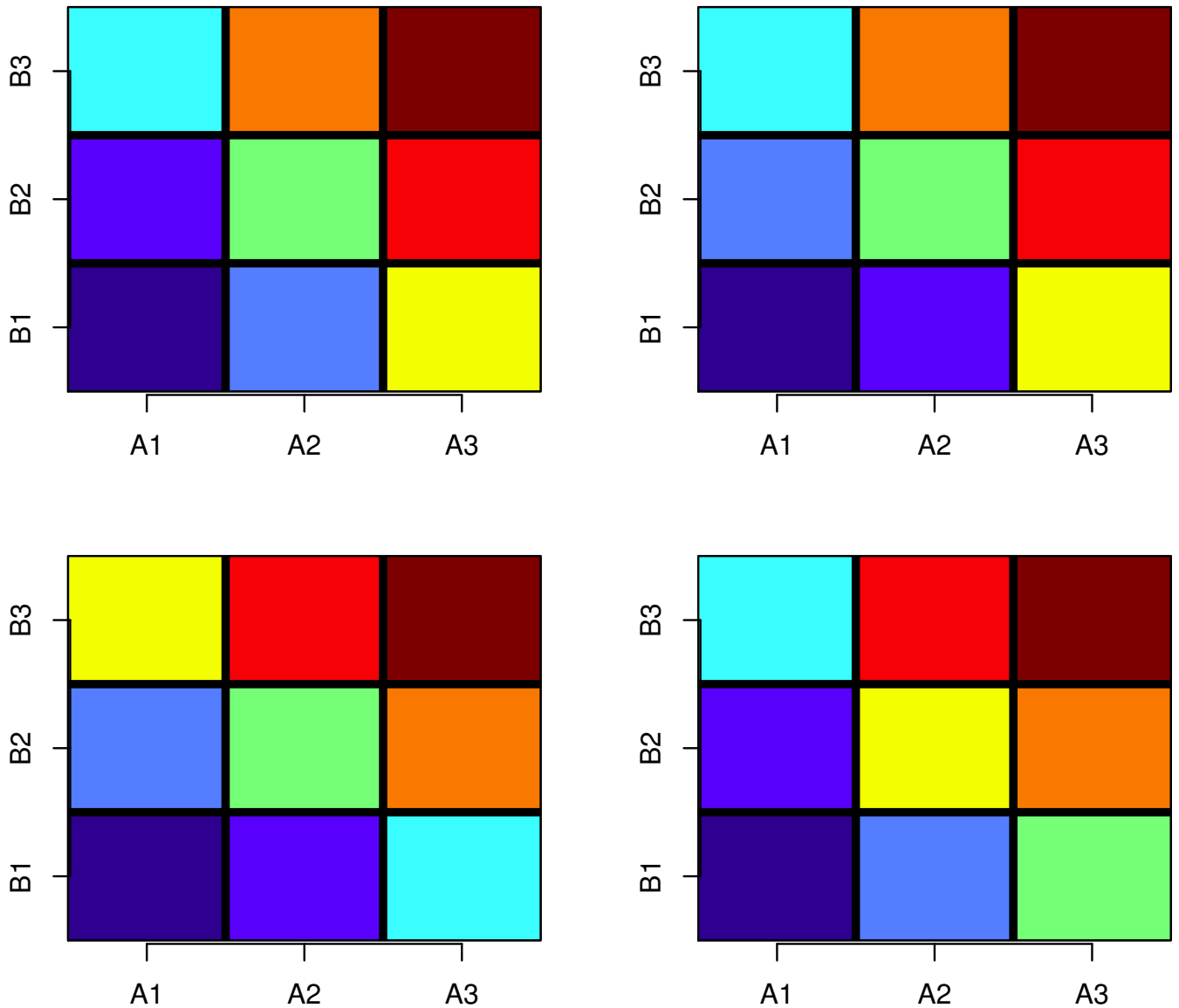
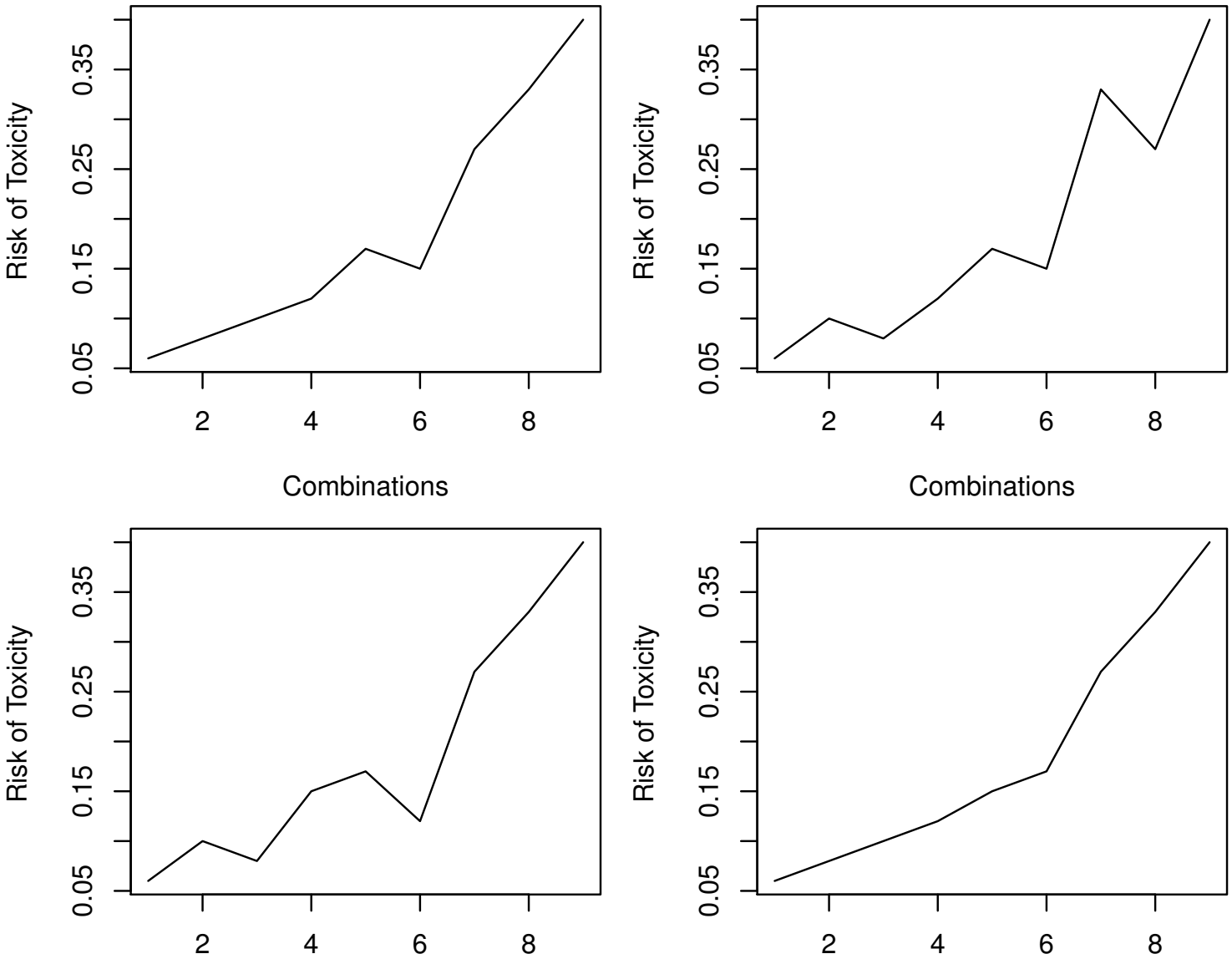
$(A_1; B_1)$	$(A_2; B_1)$	$(A_3; B_1)$

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)



Violation of monotonicity assumption

- Dose-schedule trials

  6 days treatment: *1 pill every day* vs *2 pills every two days*

  What is more toxic?

Violation of monotonicity assumption

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  6 days treatment: *1 pill every day* vs *2 pills every two days*

  What is more toxic?

- Combination-schedule trial

  Various combination are given under different schedules studying both *interaction* and *overlapping* effects

Current methods

Drug combinations

- Six-parameter model *(Thall P. et al, 2003)*
- Copula regression *(G.Yin, Y.Yuan, 2009)*
- POCRM *(N.Wages, M. Conoway, J. O'Quigley, 2011)*

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General restrictions:

- Strong model assumptions are usually needed
- Two combinations might be considered only
- Monotonicity assumption (to various extents)

Goal

To propose a dose-escalation procedure that **does not require any parametric assumptions** (including monotonicity between regimens).

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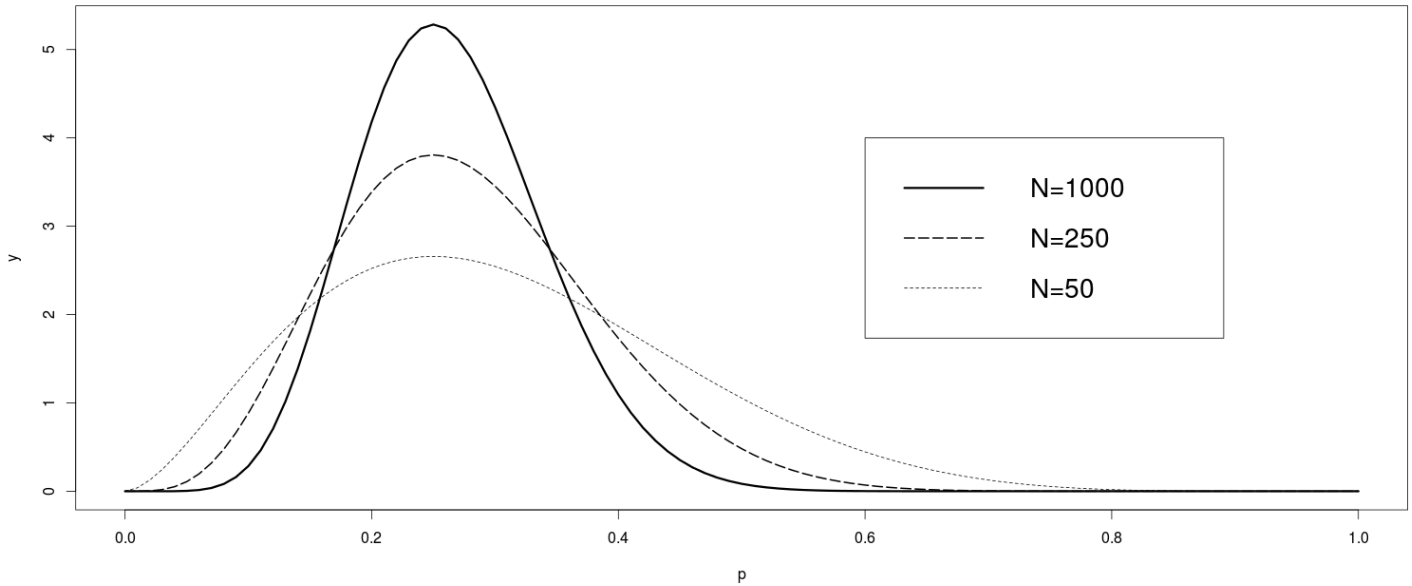
2) A statistical experiment of a sensitive estimation.
The weighted Shannon differential entropy (WDE) , $h^{\phi_n}(f_n)$, of the RV $Z^{(n)}$ with positive weight function $\phi_n(p,\gamma)$ is defined as

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

Weight Function

The Beta-form weight function

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



Regimen-escalation criterion

The Information Gain is the difference of statistical informations in two 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 regimen d_j, $j = 1, \ldots, m$, we obtained that

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

Criterion:

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

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

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

Regimen escalation design

Let $d_j(i)$ be a regimen d_j recommended for patient i.

- The procedure starts from $\hat{\Delta}_j^{(0)}$
- I patients were already assigned.

The $(I+1)^{th}$ patient will be assigned to regimen k such that

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

We adopt regimen $d_j(N+1)$ as the final recommended regimen.

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 $(0, 1)$.

This loss function penalize the values of $\hat{p}_j^{(n)}$ close to 0 to 1 and by that **'pushes' the allocation from bounds** to the neighbourhood of γ.

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This loss function penalize the values of $\hat{p}_j^{(n)}$ close to 0 to 1 and by that **'pushes' the allocation from bounds** to the neighbourhood of γ.

However, this loss function does not include any definition of safety. Thus, safety constraint is needed.

Safety constrain

We propose the following SC for the investigated method. The method considers the regimen d_j as a safe if at the moment n its PDF satisfies the following condition

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

where

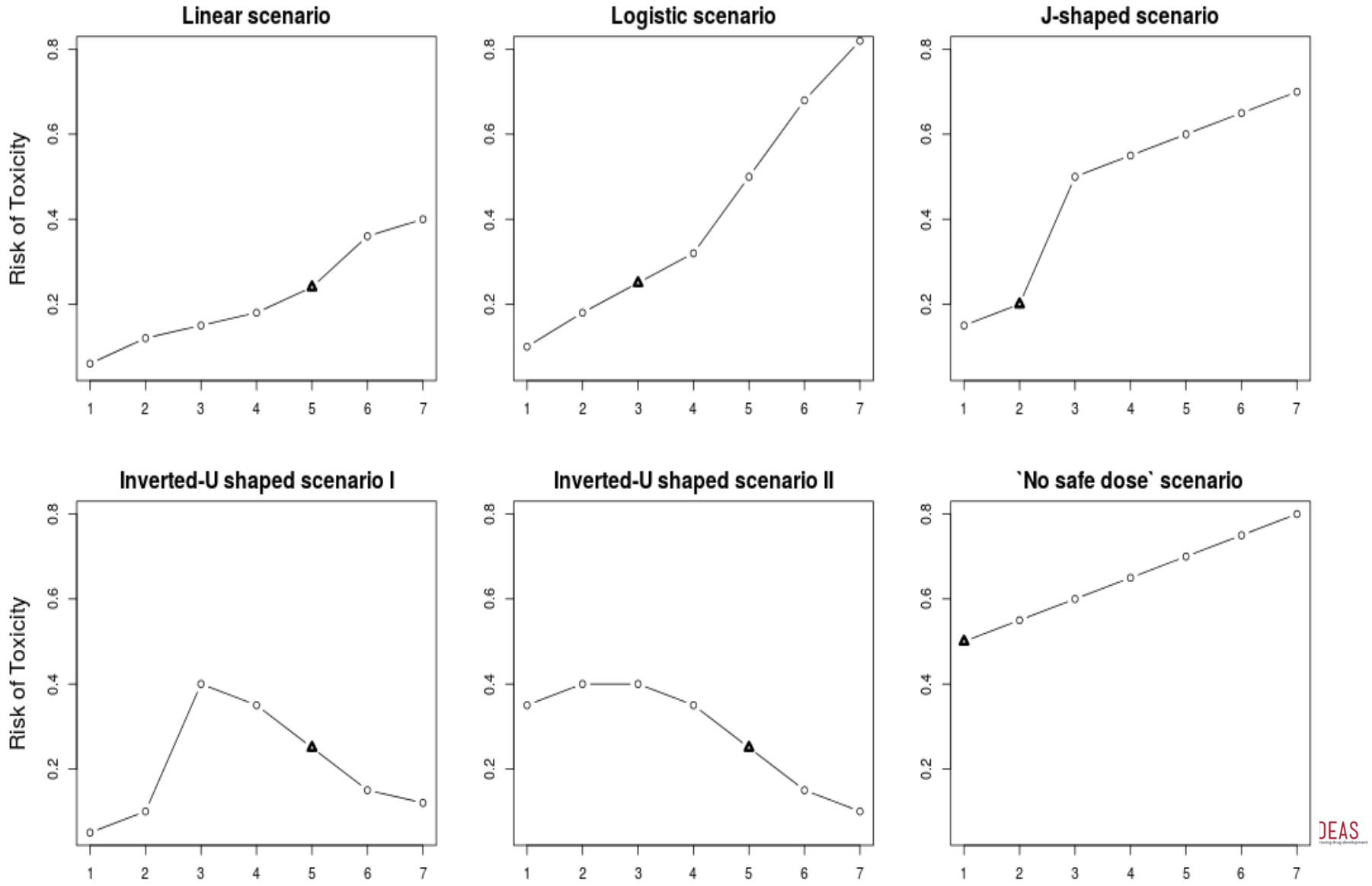
- γ^* is some threshold after which all regimens above are declared as regimens with excessive risk, $\gamma^* = \gamma + 0.2$
- θ_n is the level of probability that controls the overdosing
  - θ_n is a decreasing function of n
  - $\theta_0 = 1$
  - $\theta_N \leq 0.3$

Simulations

For simulations below the following parameters were chosen:

- Cohort size $c = 1$
- Sample size $N = 20$
- Number of regimens $m = 7$
- The target probability $\gamma = 0.25$

Investigated scenarios



Specifying the prior

Assumptions:

- Rough beliefs about toxicity rates
- Prior belief: regimen-response curve is monotonic
- The escalation to be started from d_1

The prior for regimen 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 regimens is defined

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

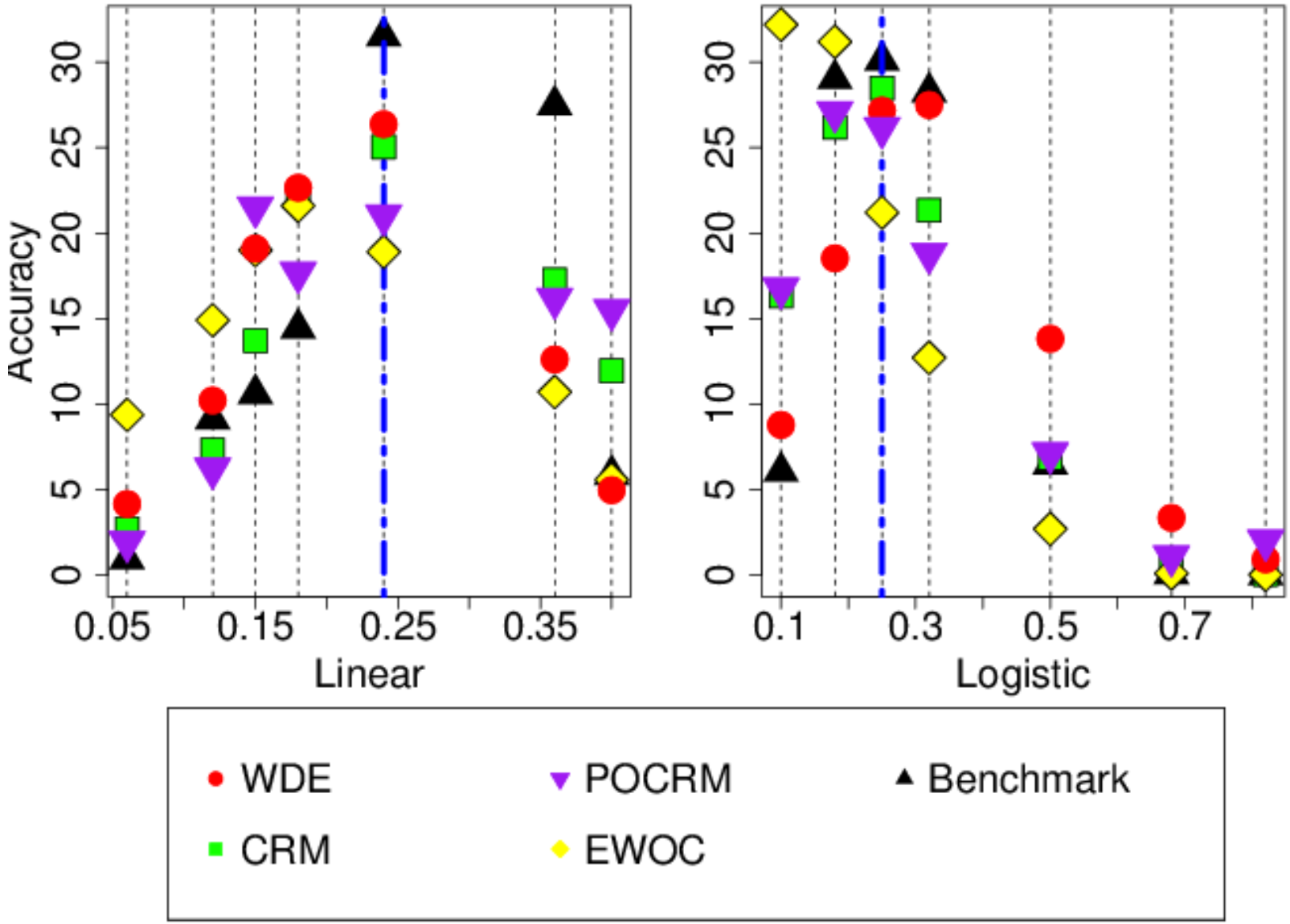
Rough prior $\rightarrow \beta_j = \beta = 1$ for $j = 1, \ldots, m$.

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
- **The time-varying safety constrain** in the proposed form *can overcome overdosing problems* and increase the accuracy of the original method

Extensions

- Phase II design
  (for trials of small populations)
- Phase I/II designs
  (including an activity endpoint; proposed for an ongoing trial)
- Designs with arbitrary number of endpoints and continuous outcomes

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Safety constrain (II)

Why the time-varying SC is needed?

For instance, $\beta = 1$ and $\theta_n = \theta = 0.50$. Then for a regimen with prior mode 0.40 or higher will never be considered by the method, because

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

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

Requirements to the function θ_n

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

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 : Flat and unsafe scenarios for different parameters of the safety constraint. Results based on 10^6 simulations.

Phase I/II design. Motivating trial

Combinations (immunotherapy + chemotherapy) under different schedules:

- 2 days immunotherapy AFTER chemotherapy (S_1)
- 3 days immunotherapy AFTER chemotherapy (S_2)
- 4 days immunotherapy OVERLAP with chemotherapy for 1 days (S_3)
- 4 days immunotherapy OVERLAP with chemotherapy for 2 days (S_4)

Six regimens are considered in the trial:

Regimen	R_1	R_2	$\mathbf{R_3}$	$\mathbf{R_4}$	$\mathbf{R_5}$	R_6
Cycle 1		S_1	S_2	S_3	S_3	S_4
Cycle 2	S_1	S_2	S_2	S_3	S_4	S_4

- 6 toxicity orderings
- 48 efficacy orderings

Choice of prior