Cancer Phase I trial design using drug combinations when a fraction of dose limiting toxicities is attributable to one or more agents

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Motivation

- Design a cancer phase I trial combining a cytotoxic with a biological agent.

- The clinician can attribute certain toxicities to one of the drugs.

Questions:

- Can we incorporate this information?
- How does it affect?

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Dose-toxicity model (I)

Some notation:

- Let D be the dose limiting toxicity (DLT) or toxicity binary indicator.
- Let A be the attribution binary indicator.
- Let (δ_1, δ_2) indicate to which drug the toxicity is attributed (i.e., $(\delta_1 = 1, \delta_2 = 0)$ represents a toxicity attributed to drug 1).
- Let η represent the fraction of toxicity attributions and π the probability of DLT.

Depending on the outcomes, we have three different types of data.

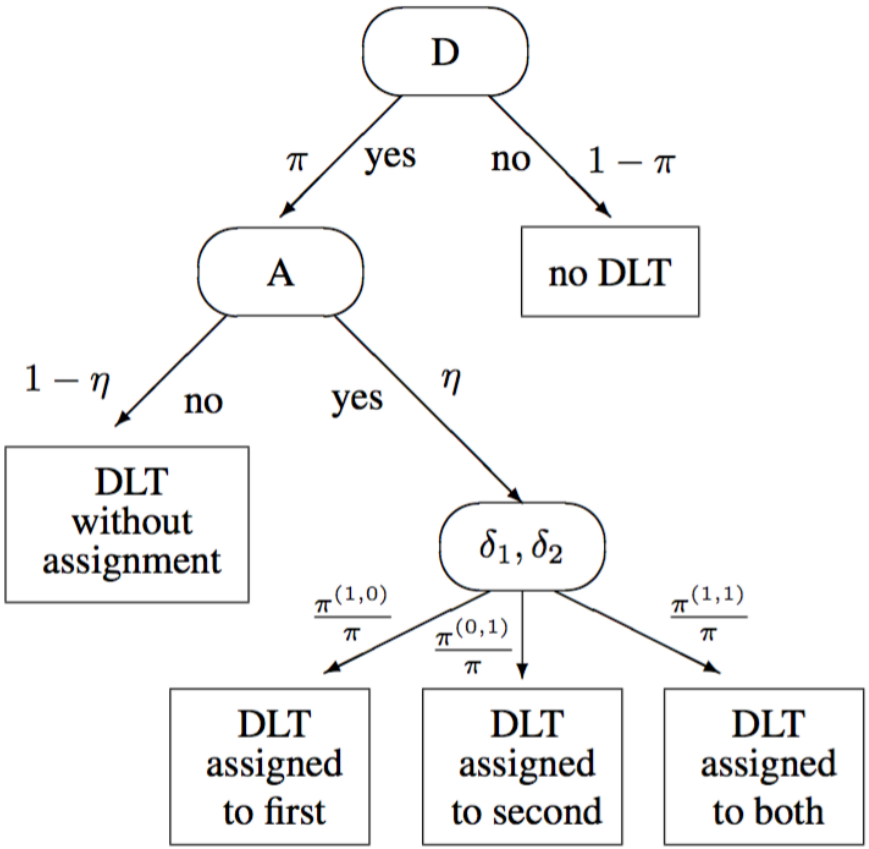
- Patients with no toxicity (D),
- Patients with non attributable toxicity (D, A),
- Patients with attributable toxicity $(D, A, \delta_1, \delta_2)$.

Dose-toxicity model (II)

- $\pi = \pi^{(1,0)} + \pi^{(0,1)} + \pi^{(1,1)}$.
- We employ a copula model known as the Gumbel model [1, 2].

$$\begin{aligned}\pi^{(\delta_1,\delta_2)} &= (x^\alpha)^{\delta_1} (1 - x^\alpha)^{1-\delta_1} (y^\beta)^{\delta_2} (1 - y^\beta)^{1-\delta_2} \\ &+ (-1)^{(\delta_1+\delta_2)} x^\alpha (1 - x^\alpha) y^\beta (1 - y^\beta) \frac{e^{-\gamma} - 1}{e^{-\gamma} + 1}.\end{aligned} \tag{1}$$

Dose-toxicity model (II)



D	A	δ_1	δ_2	Contribution to the Likelihood
0	-	-	-	$1-\pi$
1	0	-	-	$\pi \times (1-\eta)$
1	1	1	0	$\pi \times \eta \times \frac{\pi^{(1,0)}}{\pi}$
1	1	0	1	$\pi \times \eta \times \frac{\pi^{(0,1)}}{\pi}$
1	1	1	1	$\pi \times \eta \times \frac{\pi^{(1,1)}}{\pi}$

Dose-toxicity model (III)

Prior distribution of the model parameters:

- $\Pr(\alpha) = \text{Uniform}(0.2,2)$.
- $\Pr(\beta) = \text{Uniform}(0.2,2)$.
- $\Pr(\gamma) = \text{Gamma}(0.1,0.1)$.

Posterior distribution of the model parameters:

$$\Pr(\alpha, \beta, \gamma \mid \text{data}) \propto$$
$$\Pr(\alpha, \beta, \gamma) \times \prod_{i=1}^{n} \left[\left(\eta_i \times \pi_i^{(\delta_{1_i}, \delta_{2_i})} \right)^{A_i} \left(\pi_i \left(1 - \eta_i \right) \right)^{1-A_i} \right]^{D_i} (1 - \pi_i)^{1-D_i}. \tag{2}$$

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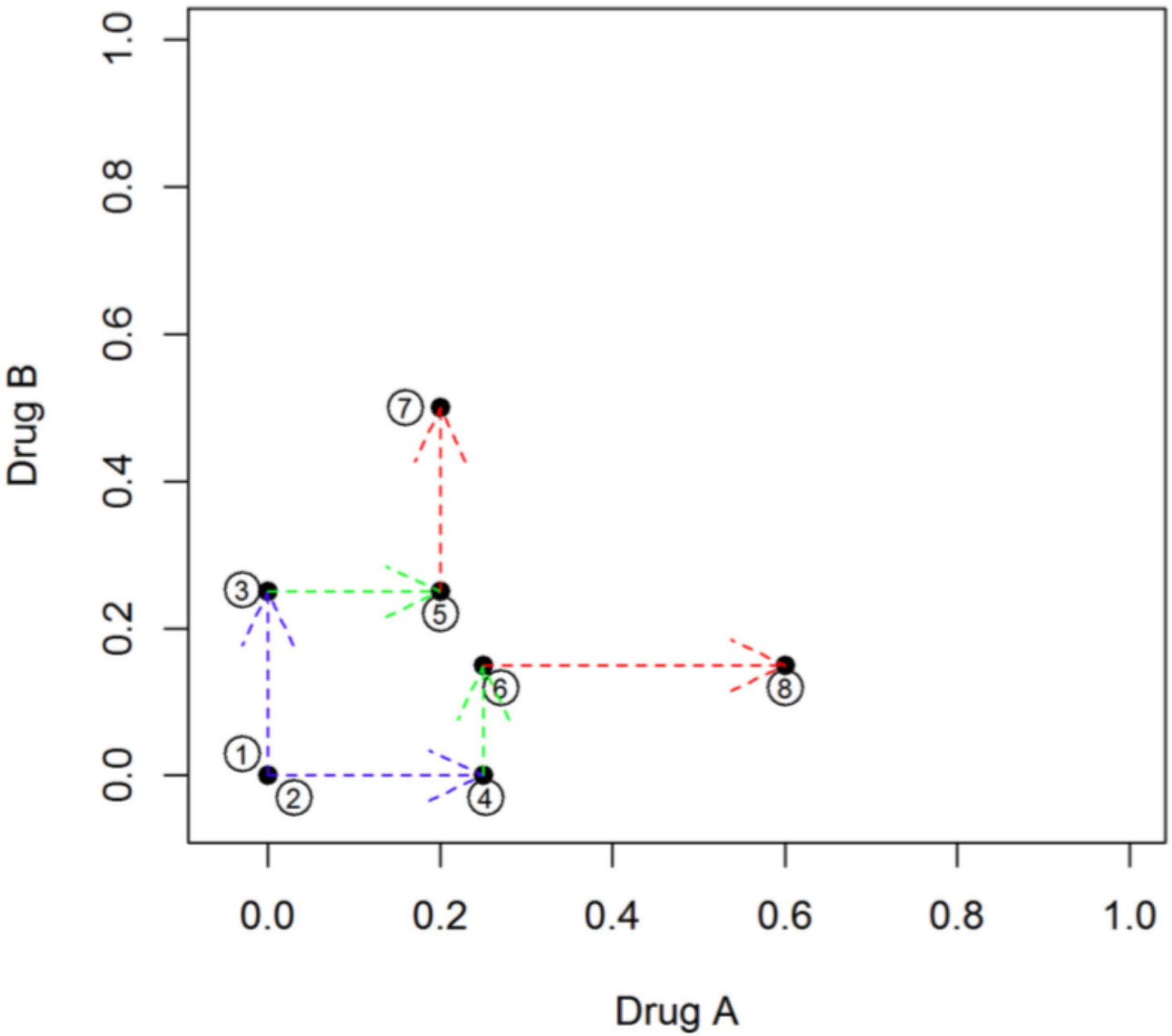
Dose Escalation Algorithm (I)

1. The first cohort in the trials receives the same dose combination. Hence $(x_1, y_1) = (X_{\min}, Y_{\min})$ and $(x_2, y_2) = (X_{\min}, Y_{\min})$.
2. In the second cohort.
   - Patient 3 receives doses (x_3, y_3), where $y_3 = y_1$ and x_3 is equal to the dose $x \in C$ such that
   $$|\text{Prob}(D = 1|x, y = y_1) - \theta|$$
   is closer to zero. If a toxicity was caused by drug A, then x_3 cannot be higher than x_1.
   - Patient 4 receives doses (x_4, y_4) where $x_4 = x_2$ and y_4 is equal to the dose $y \in C$ such that
   $$|\text{Prob}(D = 1|x = x_2, y) - \theta|$$
   is closer to zero. If a toxicity was caused by drug B, then y_4 cannot be higher than y_2.
3. Keep adding patients until the maximum sample size is reached.

Dose Escalation Algorithm (II)



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Design Operations Characteristics

Safety:

- Average % of toxicities.
- % of trials with toxicity rate greater that $\theta + 0.05$ and $\theta + 0.10$.

Efficiency:

- Continuous doses:
  1. Pointwise average relative minimum distance between the true MTD and the estimated MTD curves (average bias).
  2. Pointwise % selection.
- Discrete doses:
  1. % of MTD selection.

MTD = Maximum Tolerated Dose

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Simulation Results (I)

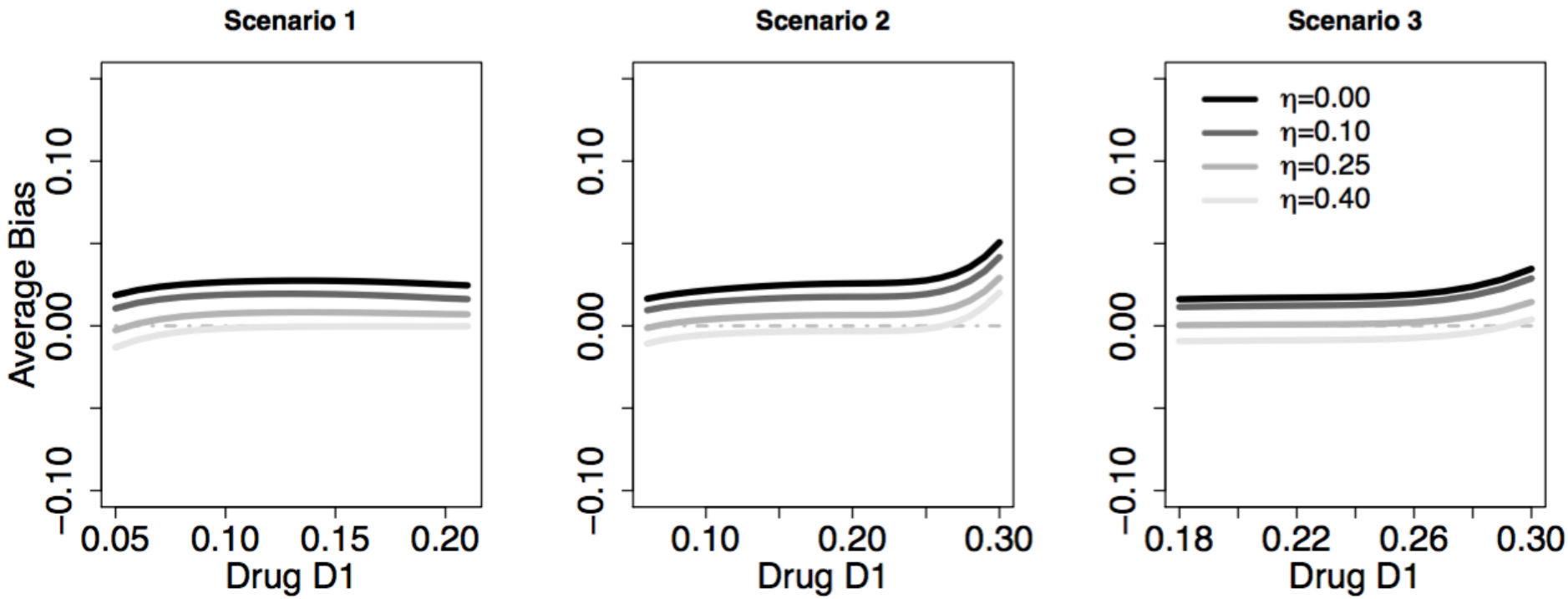
Safety results:

		Average % of toxicities	% of trials with toxicity rate $> \theta + 0.05$	% of trials with toxicity rate $> \theta + 0.10$
Scenario 1	$\eta = 0.00$	33.62	25.90	4.10
	$\eta = 0.10$	32.67	22.60	4.80
	$\eta = 0.25$	31.55	17.60	2.70
	$\eta = 0.40$	30.70	13.30	2.00
Scenario 2	$\eta = 0.00$	30.64	9.40	0.90
	$\eta = 0.10$	29.69	7.30	0.40
	$\eta = 0.25$	28.76	5.00	0.20
	$\eta = 0.40$	28.04	4.10	0.30
Scenario 3	$\eta = 0.00$	27.47	2.00	0.00
	$\eta = 0.10$	26.80	1.80	0.00
	$\eta = 0.25$	25.99	1.30	0.00
	$\eta = 0.40$	25.37	0.70	0.00

Simulation Results (II)

Efficiency results:

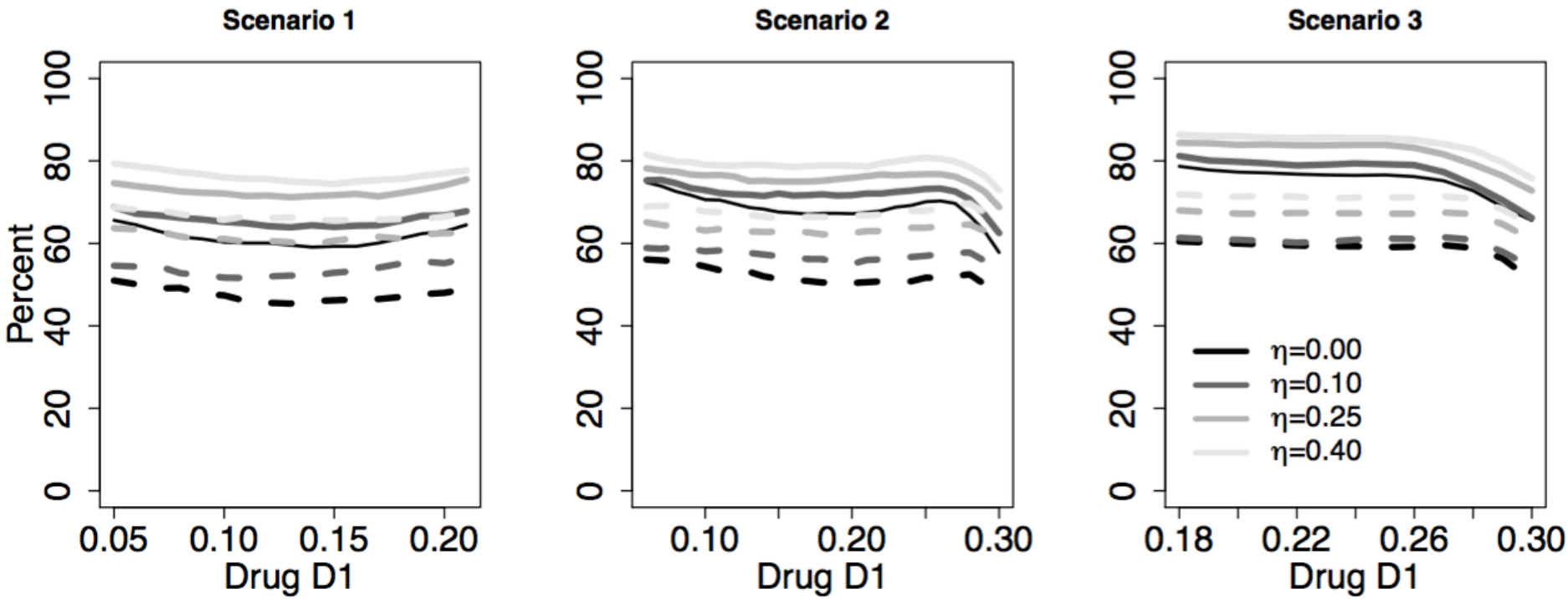
Average bias:



Simulation Results (III)

Efficiency results:

Average percent of selection:



Simulation Results (IV)

% of times a set of recommended MTDs belongs to the true MTD set in a discrete set of doses.

		% of correct MTD recommendation for $\theta \pm 0.10$			
		$\geq 25\%$	$\geq 50\%$	$\geq 75\%$	100%
$\eta = 0.00$		91.40	87.30	83.70	83.70
$\eta = 0.10$		**92.50**	**87.80**	**83.90**	**83.90**
$\eta = 0.25$	Scenario 1	90.90	87.70	83.80	83.80
$\eta = 0.40$		90.90	87.70	83.80	83.80
$\eta = 0.00$		78.10	78.10	73.60	73.60
$\eta = 0.10$		79.80	79.80	73.90	73.90
$\eta = 0.25$	Scenario 2	83.00	83.00	75.50	75.50
$\eta = 0.40$		**83.50**	**83.50**	**76.20**	**76.20**
$\eta = 0.00$		99.10	**99.00**	**97.00**	**97.00**
$\eta = 0.10$		**99.30**	98.60	95.10	95.10
$\eta = 0.25$	Scenario 3	97.10	96.40	91.90	91.90
$\eta = 0.40$		95.90	95.10	89.50	89.50

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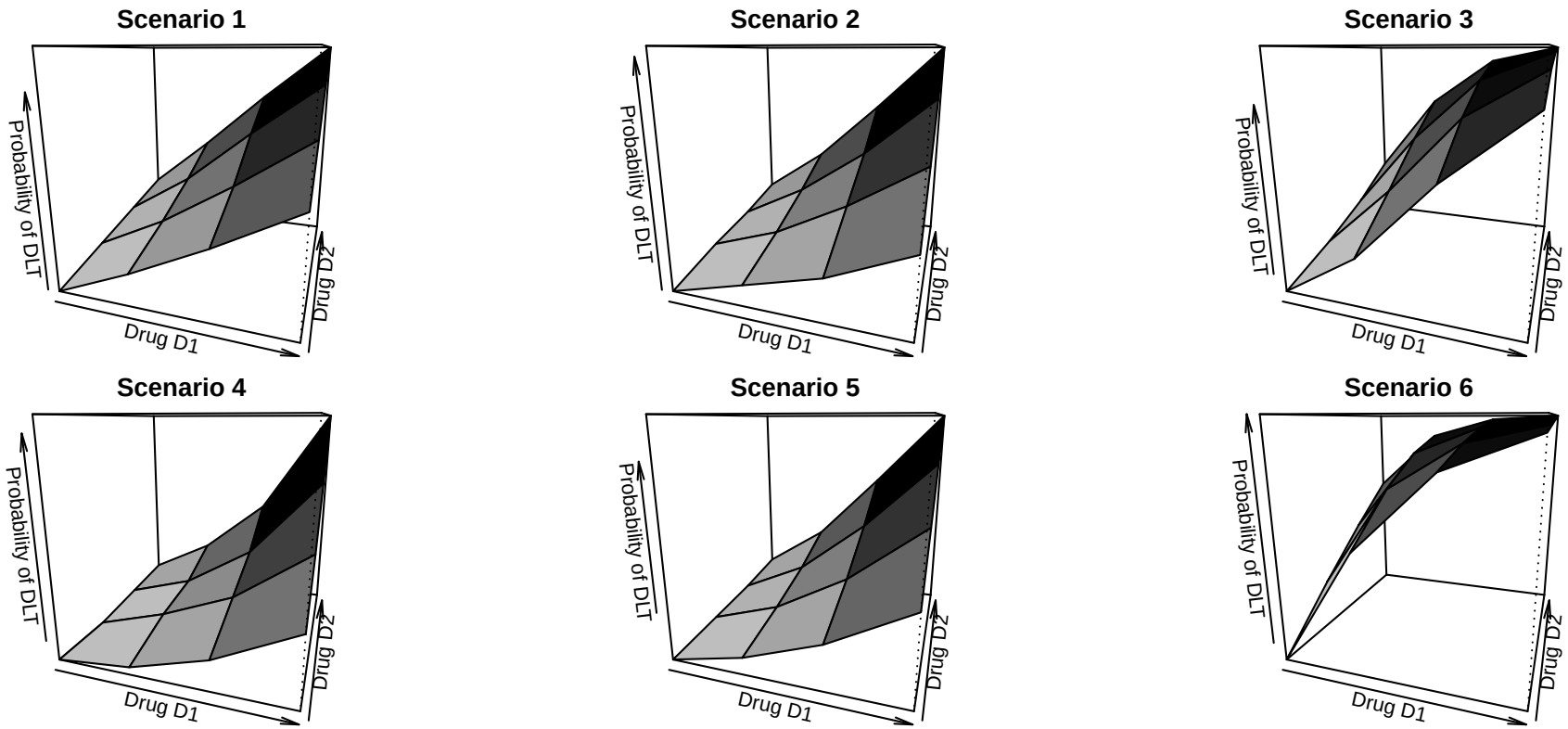
Model Misspecification (I)

Dose level	1	2	3	4	1	2	3	4
	Scenario 1				Scenario 4			
4	**0.28**	0.41	0.55	0.68	0.04	0.09	0.17	**0.32**
3	**0.25**	**0.35**	0.48	0.60	0.03	0.06	0.12	**0.23**
2	**0.22**	**0.30**	**0.40**	0.51	0.02	0.05	0.09	0.16
1	0.19	**0.26**	**0.34**	0.43	0.02	0.03	0.06	0.11
	Scenario 2				Scenario 5			
4	0.17	**0.29**	0.45	0.62	0.12	**0.26**	0.48	0.71
3	0.14	**0.23**	**0.35**	0.50	0.09	0.19	**0.36**	0.57
2	0.12	0.18	**0.27**	**0.38**	0.07	0.14	**0.26**	0.43
1	0.09	0.14	0.19	**0.27**	0.05	0.10	0.18	**0.30**
	Scenario 3				Scenario 6			
4	**0.37**	0.72	0.92	0.98	0.78	0.94	0.99	1.00
3	**0.26**	0.59	0.85	0.96	0.68	0.90	0.97	0.99
2	0.18	0.44	0.74	0.91	0.57	0.83	0.94	0.98
1	0.12	**0.30**	0.59	0.82	0.45	0.73	0.90	0.97

Model Misspecification (II)



Model Misspecification (III)

		% of correct MTD recommendation for $\theta \pm 0.10$			
		$\geq 25\%$	$\geq 50\%$	$\geq 75\%$	100%
$\eta = 0.00$	Scenario 1	82.90	75.60	55.40	55.40
$\eta = 0.10$		82.70	72.70	57.30	57.30
$\eta = 0.25$		**83.30**	**75.80**	**60.40**	**60.40**
$\eta = 0.40$		80.60	73.10	57.60	57.60
$\eta = 0.00$	Scenario 2	74.70	71.00	**58.20**	**45.70**
$\eta = 0.10$		77.00	73.50	53.60	44.60
$\eta = 0.25$		**79.60**	**75.00**	50.00	41.20
$\eta = 0.40$		77.30	73.10	47.90	37.80
$\eta = 0.00$	Scenario 3	**76.90**	**65.30**	**23.30**	**23.30**
$\eta = 0.10$		72.50	61.80	21.90	21.90
$\eta = 0.25$		66.40	57.30	18.60	18.60
$\eta = 0.40$		66.10	54.70	15.70	15.70

Model Misspecification (IV)

		% of correct MTD recommendation for $\theta \pm 0.10$			
		$\geq 25\%$	$\geq 50\%$	$\geq 75\%$	100%
$\eta = 0.00$	Scenario 4	**98.80**	**98.80**	**87.80**	**87.80**
$\eta = 0.10$		97.20	97.20	85.70	85.70
$\eta = 0.25$		95.70	95.70	82.00	82.00
$\eta = 0.40$		95.20	95.20	76.20	76.20
$\eta = 0.00$	Scenario 5	**75.40**	**69.10**	**20.50**	**20.50**
$\eta = 0.10$		71.80	62.80	20.40	20.40
$\eta = 0.25$		70.70	59.40	18.90	18.90
$\eta = 0.40$		71.20	60.50	16.70	16.70
$\eta = 0.00$	Scenario 6	83.60			
$\eta = 0.10$		82.90			
$\eta = 0.25$		84.80			
$\eta = 0.40$		**87.20**			

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Conclusions

- Bayesian adaptive design for drug combination trials that includes toxicity attributions.
- Improvement of safety results and percentage of MTD selection.
- This work was recently published:

  Jimenez, J. L., Tighiouart, M., & Gasparini, M. (2018). Cancer phase I trial design using drug combinations when a fraction of dose limiting toxicities is attributable to one or more agents. *Biometrical Journal*.

- Not very robust when dose-toxicity is very different from a surface generated with the FGM model (further work).

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Thank you for your attention!

Any question?

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