Cancer Phase I trial design using drug combinations when a fraction of dose limiting toxicities is exclusively attributable to one agent

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Motivation

- Clinician wants to design a phase I cancer trials with drug combinations.

Motivation

- Clinician wants to design a phase I cancer trials with drug combinations.
- She can identify a certain toxicity from one of the drugs.

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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).

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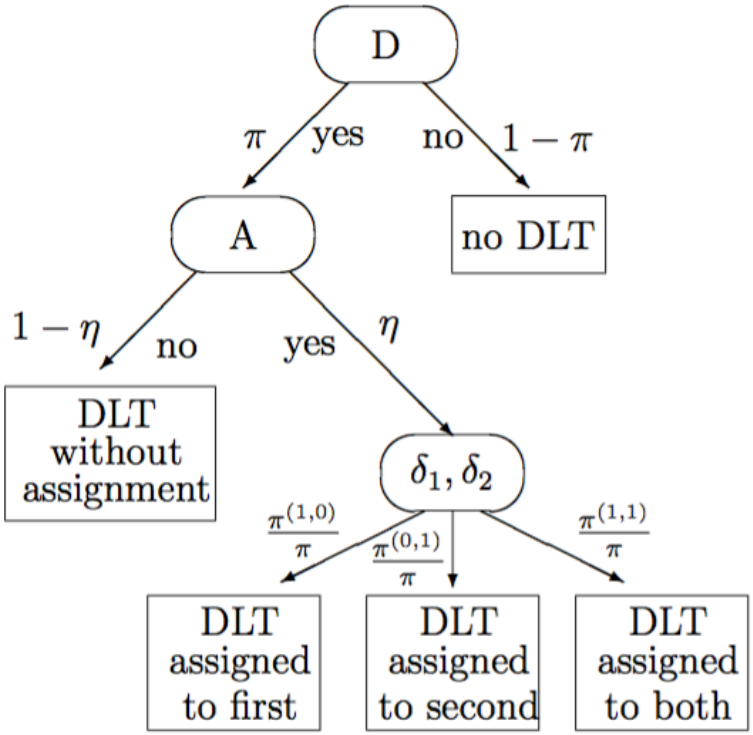
Depending on the outcomes, we have three different types of data.

- Patients with no toxicity.
- Patients with non attributable toxicity.
- Patients with attributable toxicity.

Assumption: When a toxicity is attributed, we assume that we are 100% sure about the attribution.

Dose-toxicity model (II)



- $\Pr(D = 1) = \pi$,
- $\Pr(A = 1|D = 1) = \eta$,
- $\Pr(\delta_1 = 1, \delta_2 = 0|D = 1, A = 1) = \frac{\pi^{(1,0)}}{\pi}$,
- $\Pr(\delta_1 = 0, \delta_2 = 1|D = 1, A = 1) = \frac{\pi^{(0,1)}}{\pi}$,
- $\Pr(\delta_1 = 1, \delta_2 = 1|D = 1, A = 1) = \frac{\pi^{(1,1)}}{\pi}$,

Dose-toxicity model (III)

where

$$\pi^{(\delta_1,\delta_2)} = (x^\alpha)^{\delta_1} (1-x^\alpha)^{1-\delta_1} (y^\beta)^{\delta_2} (1-y^\beta)^{1-\delta_2} + (-1)^{(\delta_1+\delta_2)} x^\alpha (1-x^\alpha) y^\beta (1-y^\beta) \frac{e^{-\gamma}-1}{e^{-\gamma}+1}, \quad (1)$$

and

$$\pi = \pi^{(1,0)} + \pi^{(0,1)} + \pi^{(1,1)}. \quad (2)$$

Dose-toxicity model (IV)

Toxicity (D)	Attribution (A)	δ_1	δ_2	Contribution to the Likelihood
0	-	-	-	$1-\pi = 1-\left[x^{\alpha}+y^{\beta}-x^{\alpha}y^{\beta}- x^{\alpha}\left(1-x^{\alpha}\right)y^{\beta}\left(1-y^{\beta}\right)\frac{e^{-\gamma}-1}{e^{-\gamma}+1}\right]$
1	0	-	-	$\pi\times(1-\eta) = \left[x^{\alpha}+y^{\beta}-x^{\alpha}y^{\beta}- x^{\alpha}\left(1-x^{\alpha}\right)y^{\beta}\left(1-y^{\beta}\right)\frac{e^{-\gamma}-1}{e^{-\gamma}+1}\right]\times(1-\eta)$
1	1	1	0	$\pi\times\eta\times\frac{\pi^{(1,0)}}{\pi} = \eta\left[x^{\alpha}(1-y^{\beta})- x^{\alpha}\left(1-x^{\alpha}\right)y^{\beta}\left(1-y^{\beta}\right)\frac{e^{-\gamma}-1}{e^{-\gamma}+1}\right]$
1	1	0	1	$\pi\times\eta\times\frac{\pi^{(0,1)}}{\pi} = \eta\left[y^{\beta}(1-x^{\alpha})- x^{\alpha}\left(1-x^{\alpha}\right)y^{\beta}\left(1-y^{\beta}\right)\frac{e^{-\gamma}-1}{e^{-\gamma}+1}\right]$
1	1	1	1	$\pi\times\eta\times\frac{\pi^{(1,1)}}{\pi} = \eta\left[x^{\alpha}\times y^{\beta}+ x^{\alpha}\left(1-x^{\alpha}\right)y^{\beta}\left(1-y^{\beta}\right)\frac{e^{-\gamma}-1}{e^{-\gamma}+1}\right]$

Dose-toxicity model (V)

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:

$$\Pr(\alpha, \beta, \gamma \mid \text{data}) \propto$$
$$\Pr(\alpha, \beta, \gamma) \times \prod_{i=1}^{n} \left[\left(\eta \times \pi_i^{(\delta_1, \delta_2)} \right)^{A_i} \left(\pi_i \, (1 - \eta) \right)^{1 - A_i} \right]^{D_i} (1 - \pi_i)^{1 - D_i}. \tag{3}$$

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Dose Escalation Algorithm

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 cause 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 cause by drug B, then y_4 cannot be higher than y_2.
3. Keep adding patients until the maximum sample size is reached.

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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 percent selection.
- Discrete doses:
  1. Percentage of MTD selection.

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Simulation Results (I)

Safety results:

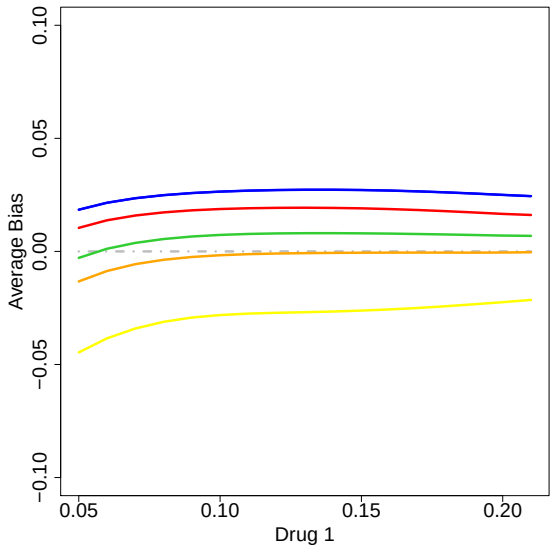
		Average % of toxicities	% of trials with toxicity rate $> \theta + 0.05$	% of trials with toxicity rate $> \theta + 0.10$
Scenario 1	$\eta = 0.00$	33.62	25.90	4.10
	$\eta = 0.10$	32.67	22.60	4.80
	$\eta = 0.25$	31.55	17.60	2.70
	$\eta = 0.40$	30.70	13.30	2.00
	$\eta = 1.00$	27.87	4.70	0.20
Scenario 2	$\eta = 0.00$	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
	$\eta = 1.00$	25.60	1.80	0.10
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
	$\eta = 1.00$	23.57	0.20	0.00

Simulation Results (II)

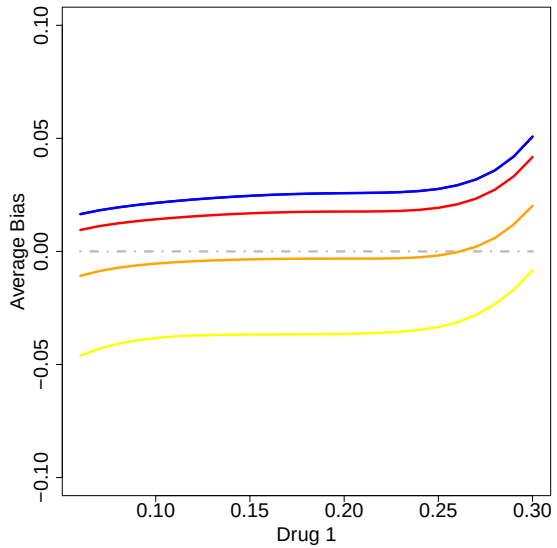
Efficiency results:

Average bias:

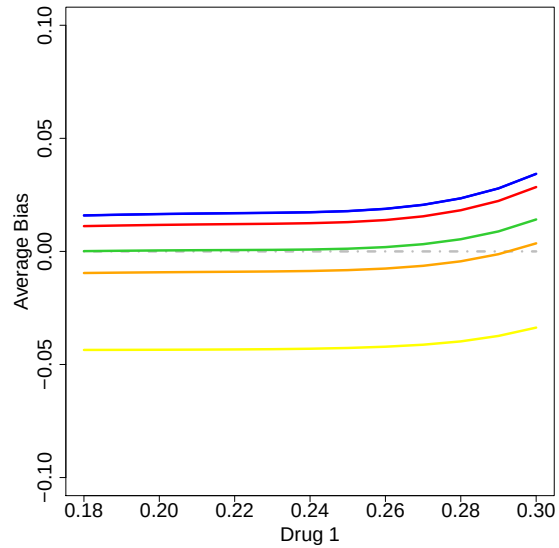
Scenario1



Scenario 2



Scenario 3

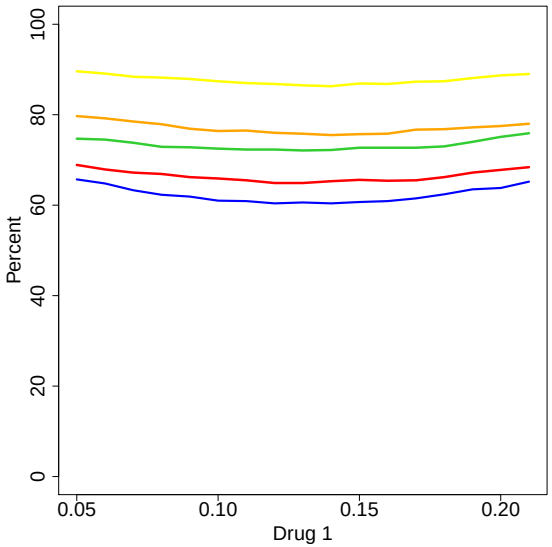


Simulation Results (III)

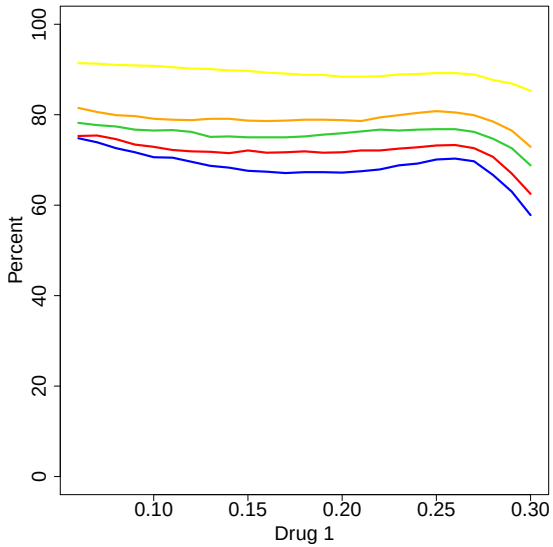
Efficiency results:

Average percent of selection:

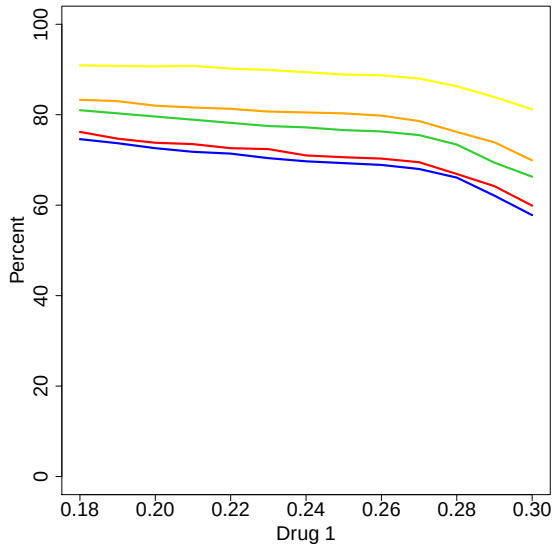
Scenario1



Scenario 2



Scenario 3



Simulation Results (IV)

Discrete dose levels scenarios (dose levels probability of toxicity generated with our own model):

	1	2	3	4		1	2	3	4	5	6
	Scenario 1					Scenario 4					
4	**0.39**	0.46	0.52	0.58		**0.39**	0.43	0.47	0.51	0.55	0.58
3	**0.31**	**0.38**	0.46	0.52		**0.30**	**0.35**	0.40	0.44	0.48	0.52
2	**0.22**	**0.31**	**0.38**	0.46		**0.22**	**0.27**	**0.32**	**0.37**	0.41	0.46
1	0.13	**0.22**	**0.31**	**0.39**		0.13	0.19	**0.24**	**0.29**	**0.34**	**0.39**
	Scenario 2					Scenario 5					
4	**0.30**	**0.36**	0.42	0.48		**0.30**	**0.33**	**0.37**	0.40	0.44	0.48
3	**0.22**	**0.28**	**0.35**	0.42		**0.22**	**0.26**	**0.29**	**0.33**	**0.38**	0.42
2	0.14	**0.21**	**0.28**	**0.36**		0.14	0.18	**0.22**	**0.27**	**0.31**	**0.35**
1	0.07	0.14	**0.22**	**0.30**		0.07	0.11	0.16	0.20	**0.25**	**0.30**
	Scenario 3					Scenario 6					
4	**0.23**	**0.27**	**0.33**	**0.39**		**0.23**	**0.25**	**0.28**	**0.32**	**0.35**	**0.39**
3	0.16	**0.21**	**0.26**	**0.33**		0.16	0.18	**0.22**	**0.25**	**0.29**	**0.33**
2	0.09	0.14	**0.21**	**0.27**		0.09	0.12	0.16	0.19	**0.23**	**0.27**
1	0.04	0.09	0.16	**0.23**		0.04	0.07	0.11	0.14	0.19	**0.23**

Simulation Results (V)

Percentage of MTD selection:

		% of MTD selection for $\theta \pm 0.10$		% of MTD selection for $\theta \pm 0.10$
$\eta = 0.00$	Scenario 1	91.40	Scenario4	90.00
$\eta = 0.10$		92.50		91.30
$\eta = 0.25$		90.90		89.40
$\eta = 0.40$		90.90		89.80
$\eta = 1.00$		84.90		84.40
$\eta = 0.00$	Scenario2	78.10	Scenario 5	82.90
$\eta = 0.10$		79.80		82.80
$\eta = 0.25$		83.00		85.00
$\eta = 0.40$		83.50		85.70
$\eta = 1.00$		80.90		81.90
$\eta = 0.00$	Scenario 3	99.10	Scenario 6	98.80
$\eta = 0.10$		99.30		98.60
$\eta = 0.25$		97.10		96.20
$\eta = 0.40$		95.90		94.00
$\eta = 1.00$		86.90		84.80

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Conclusions

- Bayesian adaptive design for drug combination trials that includes toxicity attributions.
- Improvement of safety results (reduction of average % of toxicities up to 5%) while maintaining high percentage of MTD selection (always $> 78\%$).
- Best overall results obtained when attributing around 40% of the toxicities.

Thanks!

Thanks for your attention! Any questions?

Hope you slept comfortably!