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Shaping the Future of Drug Development

Alternative dose escalation rules for dual agent designs

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PIPE design

Research Article

Statistics in Medicine

Received 12 September 2014, Accepted 9 January 2015 Published online 29 January 2015 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.6434

A product of independent beta probabilities dose escalation design for dual-agent phase I trials

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Dual-agent trials are now increasingly common in oncology research, and many proposed dose-escalation designs are available in the statistical literature. Despite this, the translation from statistical design to practical application is slow, as has been highlighted in single-agent phase I trials, where a 3 + 3 rule-based design is often still used. To expedite this process, new dose-escalation designs need to be not only scientifically beneficial but also easy to understand and implement by clinicians. In this paper, we propose a curve-free (nonparametric) design for a dual-agent trial in which the model parameters are the probabilities of toxicity at each of the dose combinations. We show that it is relatively trivial for a clinician's prior beliefs or historical information to be incorporated in the model and updating is fast and computationally simple through the use of conjugate Bayesian inference. Monotonicity is ensured by considering only a set of monotonic contours for the distribution of the maximum tolerated contour, which defines the dose-escalation decision process. Varied experimentation around the contour is achievable, and multiple dose combinations can be recommended to take forward to phase II. Code for `R`, `Stata` and Excel are available for implementation. © 2015 The Authors. *Statistics in Medicine* Published by John Wiley & Sons Ltd.

Keywords: adaptive design; dual-agent trial; nonparametric; phase I clinical trial; dose escalation

- 'Model-free' approach to avoid complexities of model-based designs
- Conjugate Bayesian methods, similar to mTPI

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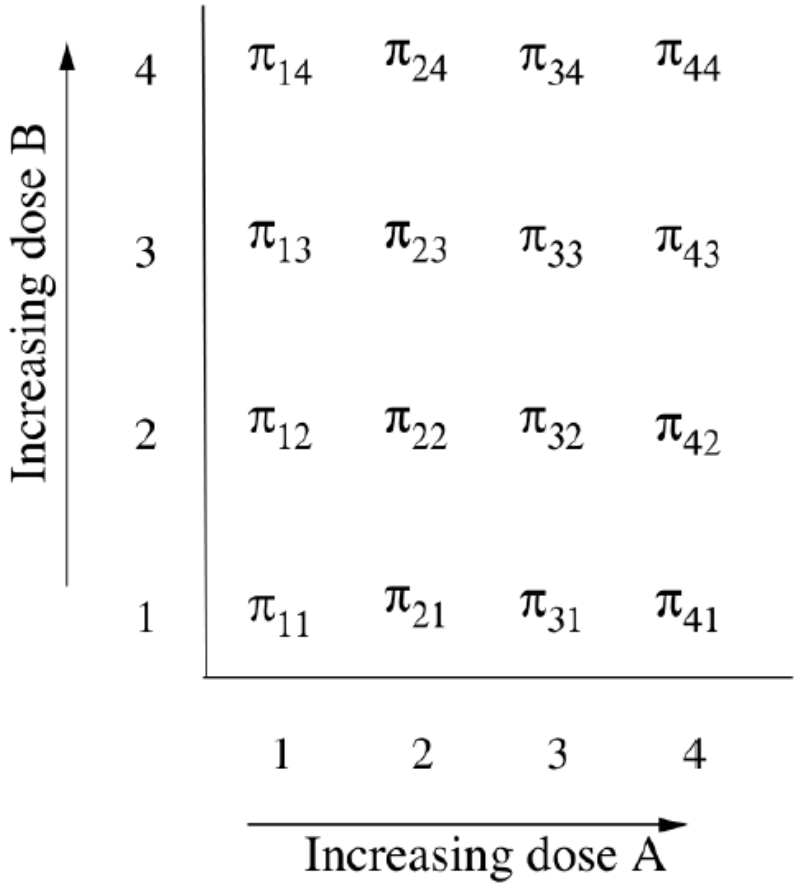
Dose Combination Space



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Independent beta prior distributions

4	$Be(a_{14},b_{14})$	$Be(a_{24},b_{24})$	$Be(a_{34},b_{34})$	$Be(a_{44},b_{44})$
3	$Be(a_{13},b_{13})$	$Be(a_{23},b_{23})$	$Be(a_{33},b_{33})$	$Be(a_{43},b_{43})$
2	$Be(a_{12},b_{12})$	$Be(a_{22},b_{22})$	$Be(a_{32},b_{32})$	$Be(a_{42},b_{42})$
1	$Be(a_{11},b_{11})$	$Be(a_{21},b_{21})$	$Be(a_{31},b_{31})$	$Be(a_{41},b_{41})$
	1	2	3	4

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Uniform prior?

Specify Prior Using: Prior P(DLT) and Prior SS

Prior Specification

Prior P(DLT):

Agent1 \ Agent2	D1	D2	D3	D4
D1	0.5	0.5	0.5	0.5
D2	0.5	0.5	0.5	0.5
D3	0.5	0.5	0.5	0.5
D4	0.5	0.5	0.5	0.5

Prior Sample Size:

Agent1 \ Agent2	D1	D2	D3	D4
D1	2	2	2	2
D2	2	2	2	2
D3	2	2	2	2
D4	2	2	2	2

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“Weak” prior

Specify Prior Using: Prior P(DLT) and Prior SS

Prior Specification

Prior P(DLT):

Agent2

Agent1 \ Doses	D1	D2	D3	D4
D1	0.04	0.08	0.12	0.16
D2	0.12	0.16	0.2	0.24
D3	0.16	0.2	0.24	0.28
D4	0.2	0.24	0.28	0.32

Prior Sample Size:

Agent2

Agent1 \ Doses	D1	D2	D3	D4
D1	0.0625	0.0625	0.0625	0.0625
D2	0.0625	0.0625	0.0625	0.0625
D3	0.0625	0.0625	0.0625	0.0625
D4	0.0625	0.0625	0.0625	0.0625

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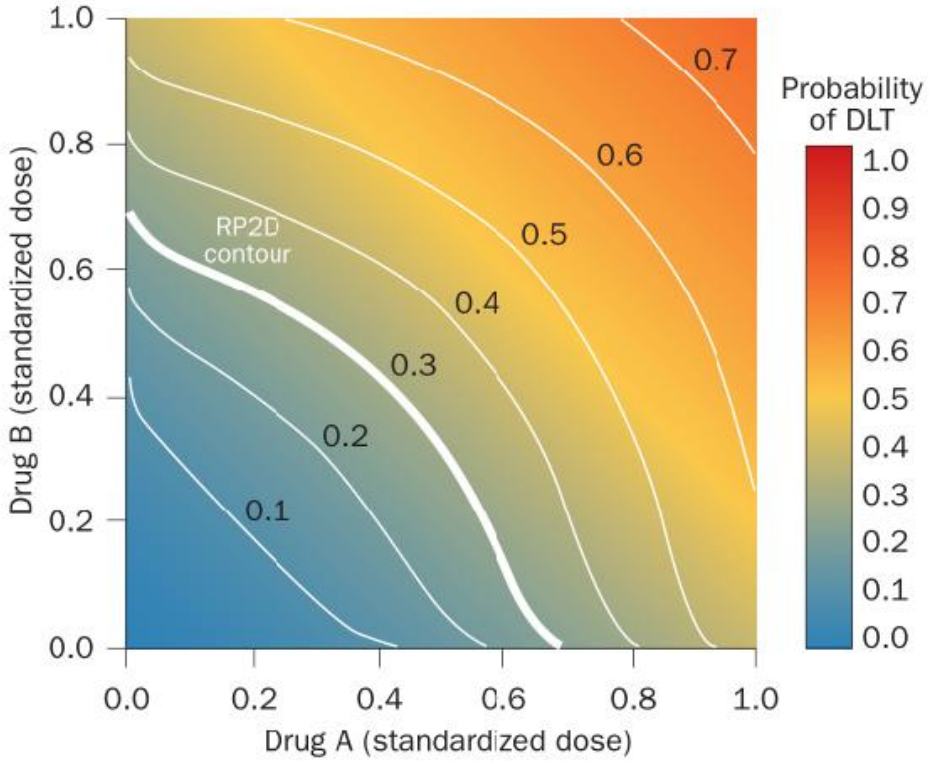
2D Dose Surface



(Harrington et al., 2013)

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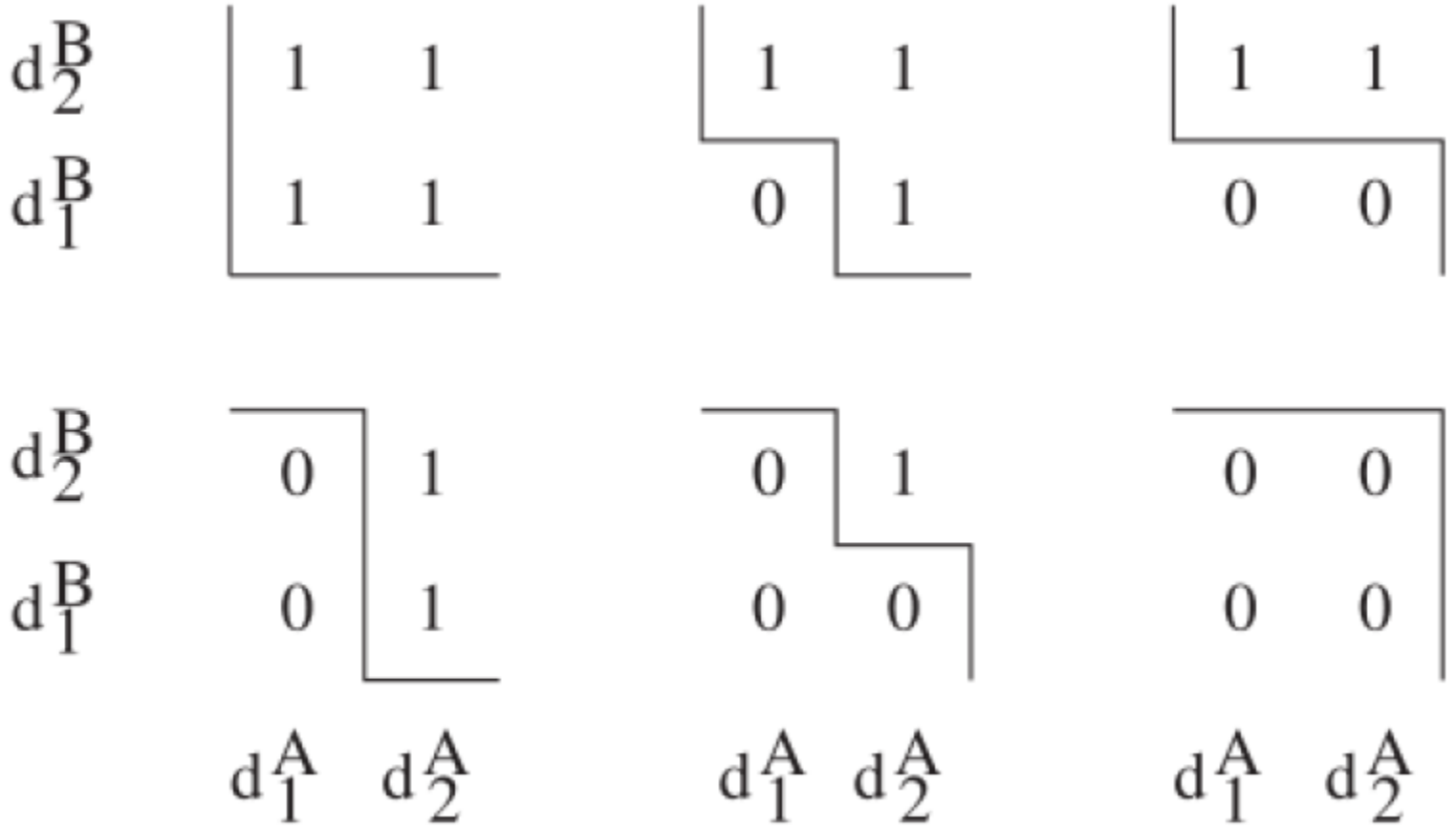
Monotonic Contours



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Product of Beta Tail Probabilities

- Bayesian update:
  - $(\pi_{ij}|Y, a_{ij}, b_{ij}) \sim \text{Beta}\,(a_{ij} + r_{ij}, b_{ij} + n_{ij} - r_{ij})$, for dose combination d_{ij}.
- Define tail probability:
  - $p_{ij}(p_T|Y) = F(p_T; r_{ij}, n_{ij}, a_{ij}, b_{ij})$ where $F()$ is the cdf of beta.
- Product of tail probabilities:
  - $P(MTC = C_s|Y) = \prod_{i,j} \left(1 - p_{ij}^{C_s[i,j]}\right) p_{ij}^{1-C_s[i,j]}$.

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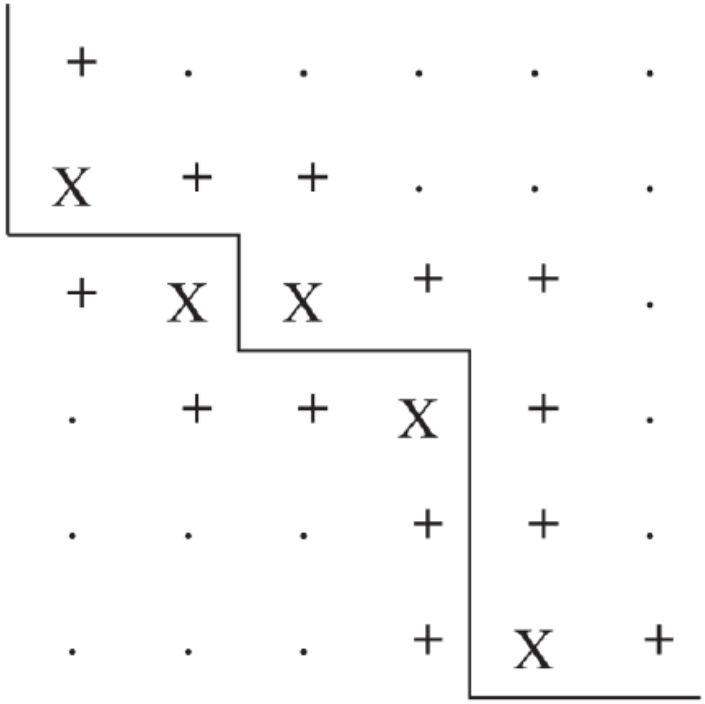
Closest & Adjacent Doses



- Admissible dose set: (X) or (+) = "Adjacent", (X) only = "Closest"

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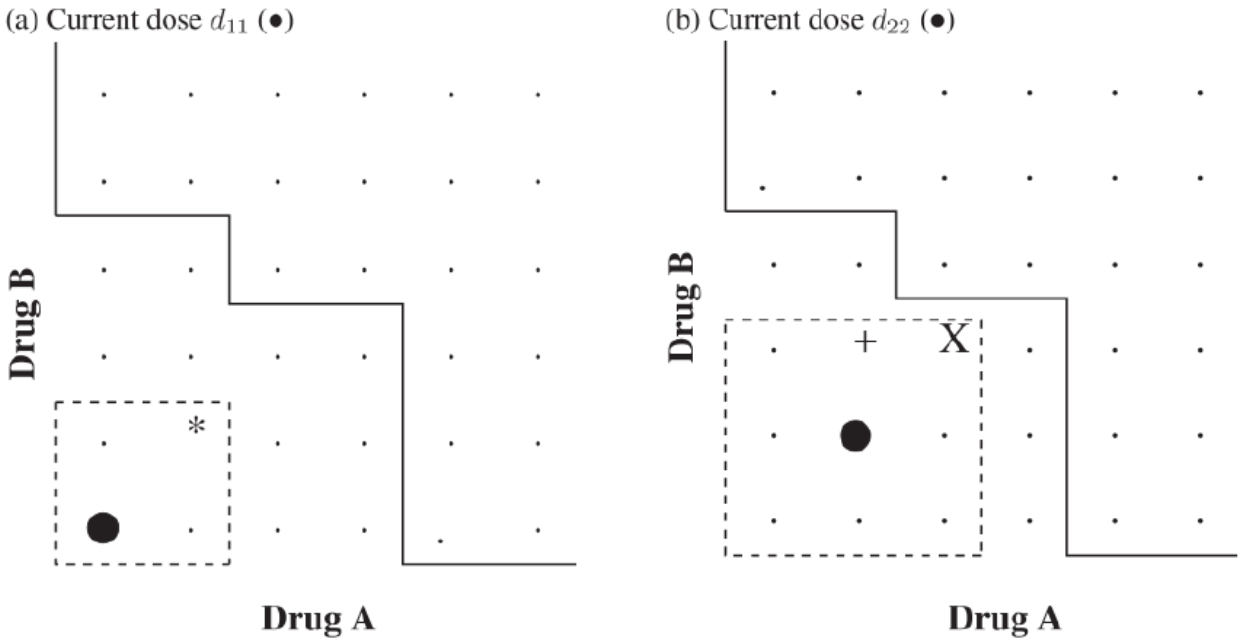
Dose Skipping: Neighborhood



- Cannot selected doses outside dashed line (* = highest combination)
- Neighborhood constraint: Not more than one dose level higher than current dose combination.

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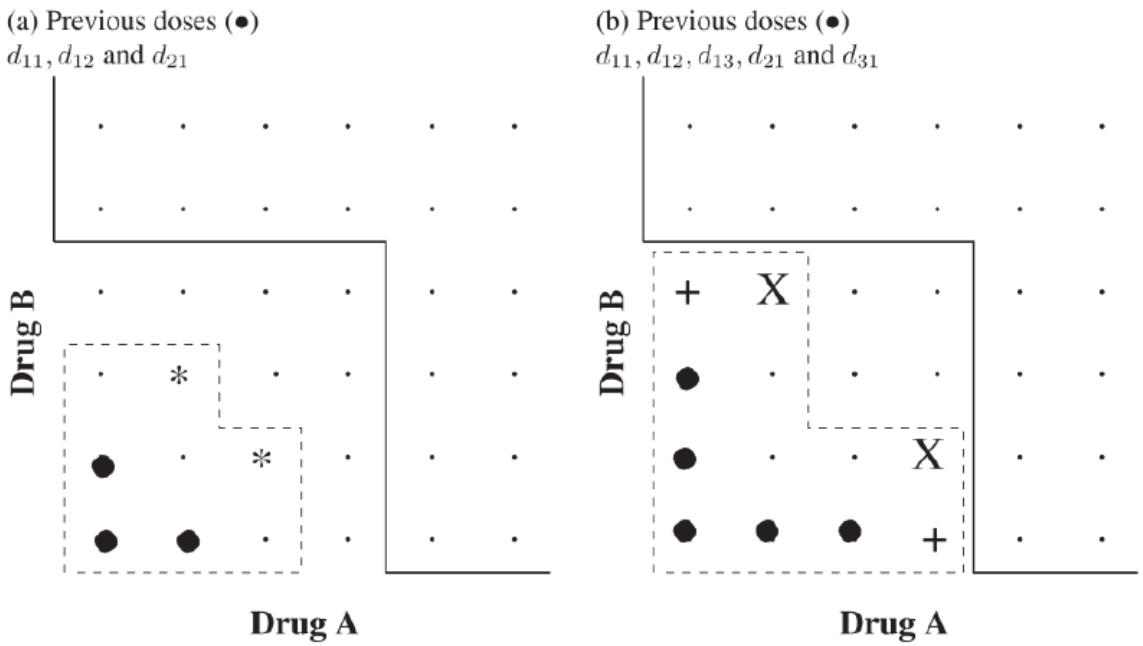
Dose Skipping: Non-neighborhood



- Cannot selected doses outside dashed line (* = highest combinations)
- Non-Neighborhood constraint: Not more than one dose level higher than *any previously* visited combination.

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Dose Selection Method

- Given admissible dose set (closest or adjacent) and dose skipping constraint (neighborhood or non-neighborhood), select combination with:
  - minimum sample size (observed + prior)
  - or weighted randomization, to encourage experimentation

Problem: Overly aggressive escalation

Solution: Incorporate mTPI decision rules

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Number of patients treated at current dose

Number of Toxicities

r\n	1	2	3	4	5	6	7	8	9
0	E	E	E	E	E	E	E	E	E
1	DU	S	E	E	E	E	E	E	E
2		DU	D	S	S	S	S	S	E
3			DU	DU	D	S	S	S	S
4				DU	DU	DU	D	D	S
5					DU	DU	DU	DU	D
6						DU	DU	DU	DU
7							DU	DU	DU
8								DU	DU
9									DU

E = Escalate

S = Stay

D = De-escalate

DU = The current dose is unacceptably toxic

Target Toxicity (%) = 30%

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Simulation Details

- 2 doses of Agent1 (levels 1 and 2)
- 6 doses of Agent2 (levels 1 to 6)
- Start at lowest dose (1, 1)
- Cohort size = 3 patients
- No diagonal dose escalation

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Stay

- If mTPI step = **Stay**, then next recommended dose combination is current dose combination.
- Skip PIPE dose selection.

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Escalate

- If mTPI step = **Escalate**, then admissible dose combinations ≤ 1 dose level above any previously visited dose levels of Agent 1 or Agent 2.

- PIPE step: among admissible doses, recommended dose combination is one closest to current MTC.

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De-escalate

- If mTPI step = **De-escalate**, then the admissible dose combinations are 1 dose level below in one agent, and ≤ 1 dose level above in other agent.
- Increasing the dose of an agent is admissible only if current dose level already visited in combination with the next lower dose of the other agent.

- PIPE step: among admissible doses, recommended dose combination is one closest to current MTC.

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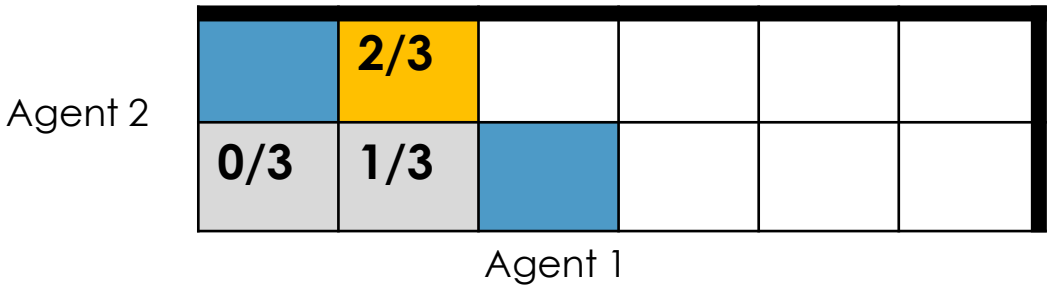
Illustration (De-escalate)

Modified PIPE



Current

Visited

Recommended

PIPE

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Stop for over-dosing

- A dose combination (and all higher doses) excluded from further consideration if:
  - at least 6 subjects have been evaluated at that dose combination, and
  - posterior probability > 0.95 of exceeding the target toxicity of 0.3.
- Trial stops if the lowest dose combination excluded

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Stop for under-dosing

- Trial stops if:
  - at least 6 subjects have been evaluated at the highest dose combination, and
  - highest dose combination has posterior probability > 0.9 of being below the target toxicity of 0.3.

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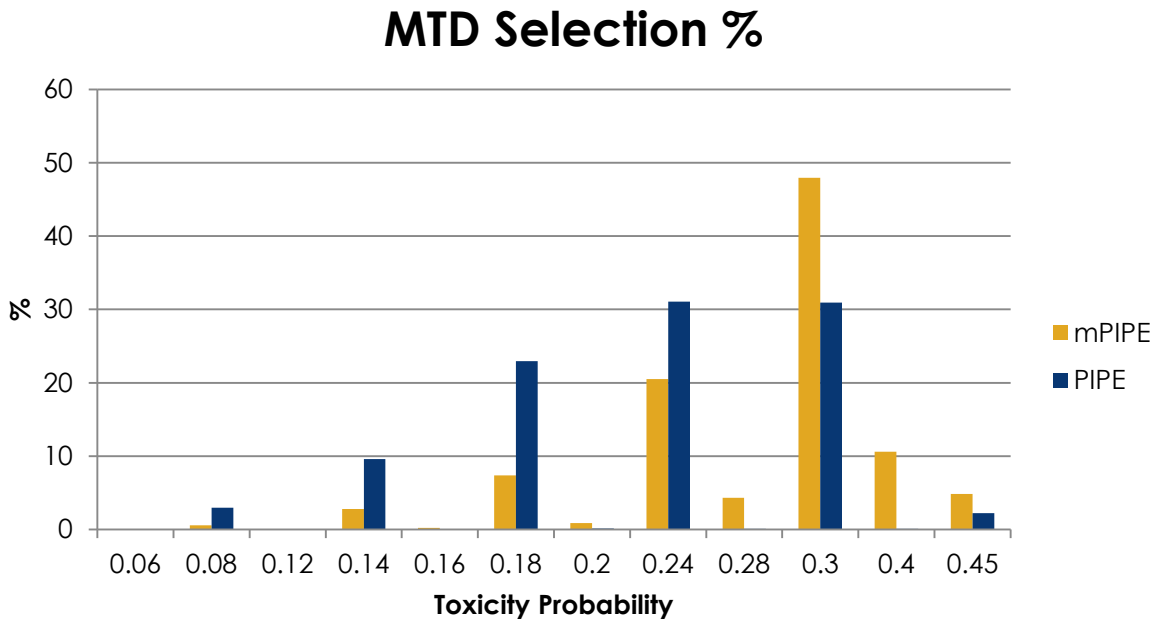
Compare operating characteristics



Toxicity Probability

Agent 2

.08	.14	.18	.24	.3	.45
.06	.12	.16	.2	.28	.4

Agent 1

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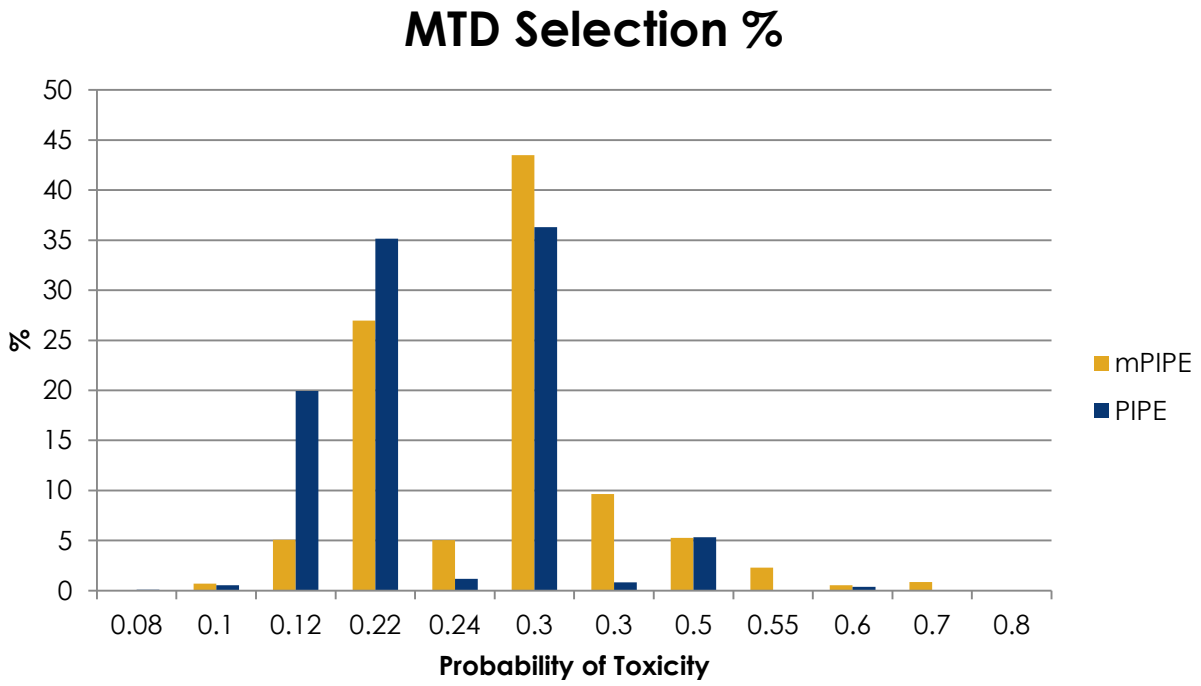
Compare operating characteristics



Toxicity Probability

Agent 2						
	.12	.22	.30	.50	.60	.80
	.08	.10	.24	.30	.55	.70

Agent 1

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Discussion / Summary

- Using mTPI decision rule allows safer escalation
- Still use PIPE strategy of moving toward MTC (when safe)
- Similar MTD selection profile

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Questions?

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