Identifying multiple MTD combinations in two-dimensional dose-finding

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Outline of Talk

- Challenges associated with Drug combination studies
- Method for locating multiple MTD combinations
- Operating characteristics
- Conclusions
  - Extension to other two-dimensional problems

Drug combinations

Notation

- Consider a two-drug combination study
  - Agent A has I dose levels: $A_1 < \cdots < A_I$
  - Agent B has J dose levels: $B_1 < \cdots < B_J$
- (A_j, B_k) is the combination of Agent A at dose level j and Agent B at dose level j
- Probability of DLT at combination (A_i, B_j) is denoted π_{ij}
- **Goal:** find maximum tolerated dose combinations (MTDC's)

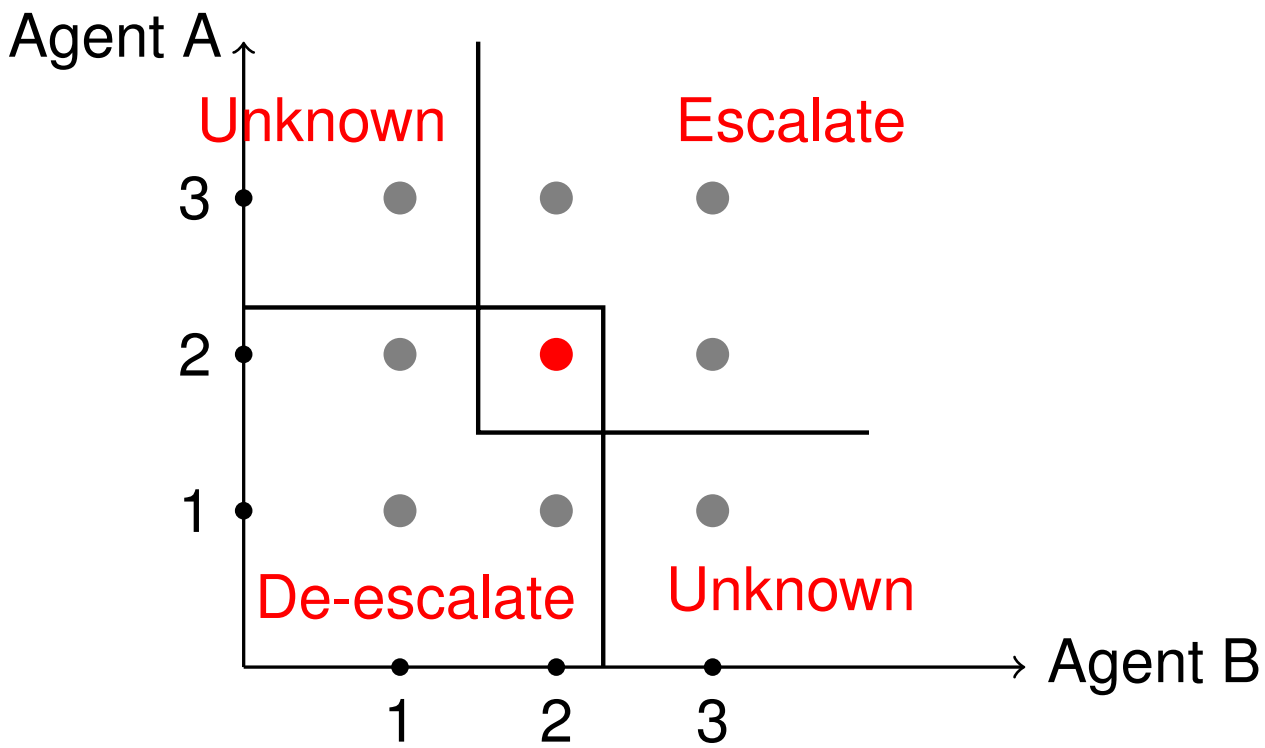
Drug Combination Studies

Challenges

1. Toxicity order of the dose combinations is only **partially** known
   - If current combination is safe, may not be clear where to go next.
2. Dimension of the problem may be large
   - Many combinations to consider
3. Multiple MTD combinations may exist in the two-dimensional space
   - MTD equivalence contour

Drug Combination Studies

Challenges



Drug Combination Studies

Design Considerations

- Is the objective of the trial to find a...
  1. single MTDC?
  2. MTD equivalence contour containing multiple combinations?

Recent Methods

Single MTD Combination

- Hirakawa, Hamada, Matsui (*Stat Med*, 2013)
- Braun and Jia (*Stat Biopharm Res*, 2013)
- Jin, Huo, Yin, Yuan (*Pharm Stat*, 2015)
- Mander and Sweeting (*Stat Med*, 2015)

Existing Methods

Multiple MTD Combinations

- Thall, Millikan, Mueller, Lee (*Biometrics*, 2003)
- Ivanova and Wang (*Stat Med*, 2004)
- Wang and Ivanova (*Biometrics*, 2005)
- Yuan and Yin (*Stat Med*, 2008)
- Tighiouart, Piantidosi, Rogatko (*Stat Med*, 2014)

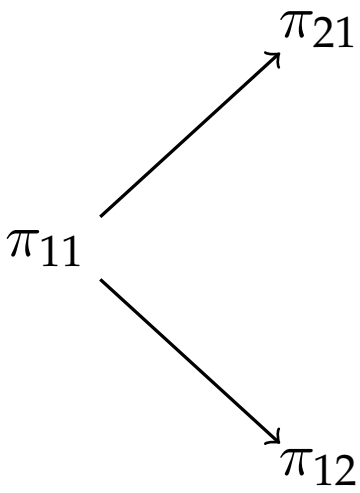
Review of Harrington *et al.*, 2013

Table 1 | Summary of features for various dual-agent dose escalation study designs

Study	Number of model parameters	Stages	Outcomes	Response values	Number of RP2D combinations
Model-based designs					
Wang and Ivanova (2005)[60]	3	2	Toxicity	Binary	Minimum number of doses of drug A or drug B
Yin and Yuan (2009)[62]	3	2	Toxicity	Binary	1
Yin and Yuan (2009)[63]	3	2	Toxicity	Binary	1
Kramar *et al.* (1999)[61]	2	2	Toxicity	Binary	1
Su (2010)[64]	1	3	Toxicity	Binary	1
Thall *et al.* (2003)[31]	6	2	Toxicity	Binary	3
Conaway *et al.* (2004)[68]	*K*	2	Toxicity	Binary	1
Wages *et al.* (2011)[70]	*M*‡	2	Toxicity	Binary	1
Wages *et al.* (2011)[69]	*M*‡	1	Toxicity	Binary	1
Braun and Wang (2010)[80]	6	1	Toxicity	Binary	1
Bailey *et al.* (2009)[67]	≥3§	1	Toxicity	Binary	1

Partial Order Continual Reassessment Method

Wages, Conaway, O'Quigley (2011)



$$\pi_{11} < \pi_{12} < \pi_{21}$$

or

$$\pi_{11} < \pi_{21} < \pi_{12}$$

- POCRM has been applied in several ongoing/completed studies*
- Question: Can POCRM select more than one MTD combination?

* Wages, Conaway, Slingluff, Williams, Portell, Hwu, Petroni. *Ann Oncol* 2015; [epub ahead of print].

Example

Two agents A and B

- Phase I trial of two small molecule inhibitors in patients in relapsed/refractory mantle cell lymphoma.
- Agent A has 2 dose levels: $A_1 < A_2$
- Agent B has 4 dose levels: $B_1 < B_2 < B_3 < B_4$

		Doses of B			
		B_1	B_2	B_3	B_4
Doses of A	A_2	(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
	A_1	(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)

Primary Objective

Find Multiple MTD's

- Goal: find an MTDC for each dose of Agent A
- Locate $j^* \in \{1, \ldots, 4\}$ such that (A_i, B_{j^*}) has DLT probability closest to the target rate ϕ for each $i\,(i = 1, 2)$
  - i.e. find an MTD combination in each row i such that

$$(A_i, B_{j^*}) = \arg\min |\pi_{ij} - \phi|$$

Combination-toxicity Relationships

Assumptions

- Toxicity increases with increasing dose of each agent, holding the other agent fixed
- DLT probabilities increase up rows and across columns of matrix

		B_1	B_2	B_3	B_4
$\uparrow$	A_2	(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
$\uparrow$	A_1	(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)
TOXICITY INCREASES		$\longrightarrow$	$\longrightarrow$	$\longrightarrow$	$\longrightarrow$

Combination-toxicity Relationships

Affect on MTD Location

- Row 1 is at least the most toxic MTDC (i.e. the MTDC in row 1 will contain at least the largest dose of Agent B)
- For instance, suppose MTDC in row 1 is estimated to be (A_1, B_3)
  - If dose of A is fixed at A_2, MTD level of drug B must be lower than or equal to 3 (i.e. B_1, B_2, or B_3)

(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)

↑
MTD for A_1

Relative Location of MTD's

Shift Model*

- If MTD for A_1 is (A_1, B_{j^*}), then MTD for A_2 is $(A_2, B_{j^*-\Delta_2})$; $\Delta_2 \in \{0, 1, 2, 3\}$
- The truth could be any one of the four possible values for Δ_2
  - Use the data to estimate the relative location of the MTD between rows
- Similar strategy has been used for patient heterogeneity**

* O'Quigley J, Conaway MR. *Stat Science* 2010; 25: 202–16.

** O'Quigley J, Iasonos A. *Stat Biopharm Res* 2014; **6**: 185–197

Relative Location of MTD's

Shifts of 0 or 1

- $\{\Delta_2 = 0\}$

(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)

- $\{\Delta_2 = 1\}$

(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)

Relative Location of MTD's

Shifts of 2 or 3

- $\{\Delta_2 = 2\}$

(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)

- $\{\Delta_2 = 3\}$

(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)
(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)

Working Models

Targeting $\phi = 0.30$

- Model $m = 1 : \{\Delta_2 = 0\}$

0.06^{θ_1}	0.16^{θ_1}	0.30^{θ_1}	0.45^{θ_1}
0.06^{θ_1}	0.16^{θ_1}	0.30^{θ_1}	0.45^{θ_1}

- Model $m = 2 : \{\Delta_2 = 1\}$

0.16^{θ_2}	0.30^{θ_2}	0.45^{θ_2}	0.59^{θ_2}
0.06^{θ_2}	0.16^{θ_2}	0.30^{θ_2}	0.45^{θ_2}

Skeleton 1 = getprior(0.075,0.30,3,4)

Skeleton 2 = getprior(0.075,0.30,2,4)

Working Models

Targeting $\phi = 0.30$

- Model $m = 3 : \{\Delta_2 = 2\}$

0.30^{θ_3}	0.45^{θ_3}	0.59^{θ_3}	0.71^{θ_3}
0.06^{θ_3}	0.16^{θ_3}	0.30^{θ_3}	0.45^{θ_3}

- Model $m = 4 : \{\Delta_2 = 3\}$

0.30^{θ_4}	0.45^{θ_4}	0.59^{θ_4}	0.71^{θ_4}
0.01^{θ_4}	0.06^{θ_4}	0.16^{θ_4}	0.30^{θ_4}

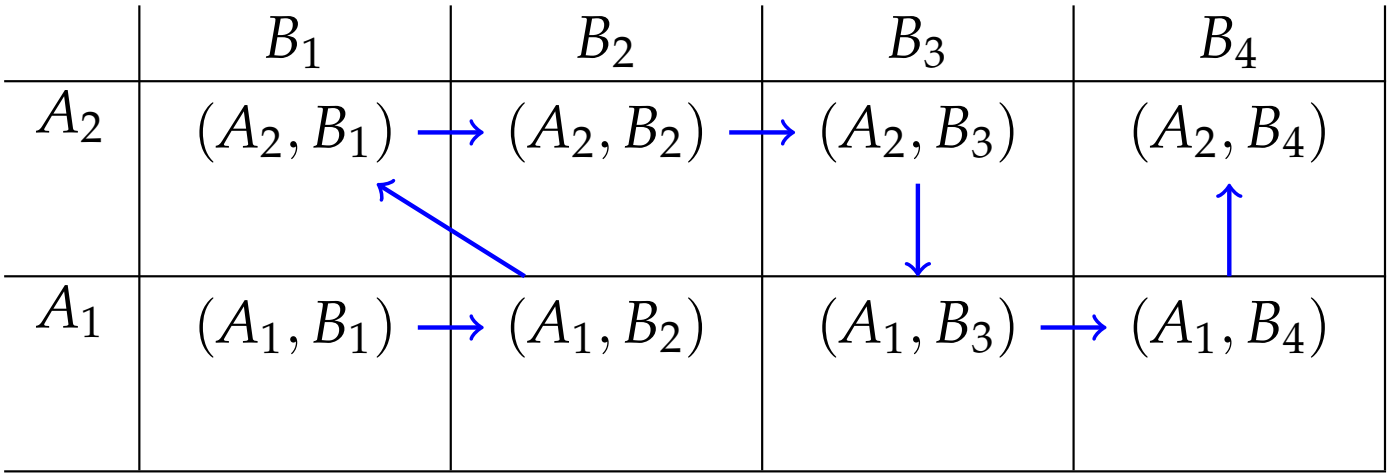
Skeleton 1 = getprior(0.075,0.30,1,4)

Skeleton 2 = getprior(0.075,0.30,4,4)

Getting Trial Underway

Initial Escalation Scheme

- Choose a path for initial escalation scheme
- Follow path in the absence of DLT's, until first DLT is observed



Modeling Stage

After each cohort inclusion...

1. Use adaptive model selection to choose working model most consistent with data
2. Update estimates of DLT probabilities, $\widehat{\pi}_{ij}$, for each combination
3. Recommend a combination in each row with $\widehat{\pi}_{ij}$ closest to target rate ϕ

$$S = \{(A_1, B_{j_1^*}), (A_2, B_{j_2^*})\}$$

4. Randomize next patient to treatment in S

Extension To More Than 2 Rows

- If MTD for A_1 is (A_1, B_{j^*}), then MTD for A_i is $(A_i, B_{j^*-\Delta_i})$
- Each model m consists of multiple Δ values $\{\Delta_2, \Delta_3, \ldots, \Delta_I\}$, where $\Delta_2 \leq \Delta_3 \leq \cdots \leq \Delta_I$
- For instance, m : $\{\Delta_2 = 2, \Delta_3 = 3\}$

(A_3, B_1)	(A_3, B_2)	(A_3, B_3)	(A_3, B_4)	(A_3, B_5)	(A_3, B_6)
(A_2, B_1)	(A_2, B_2)	(A_2, B_3)	(A_2, B_4)	(A_2, B_5)	(A_2, B_6)
(A_1, B_1)	(A_1, B_2)	(A_1, B_3)	(A_1, B_4)	(A_1, B_5)	(A_1, B_6)

Simulation Studies

- Evaluated performance over four 3×6 combination-toxicity scenarios in Wang and Ivanova (2005)
- Sample size $N = 60$; Target DLT rate; $\phi = 0.20$
- Compared to Wang and Ivanova (2005), Yuan and Yin (2008).

Scenarios in Wang and Ivanova (2005)

	s_1	s_2	s_3	s_4	s_5	s_6
			Scenario 1			
Level 3	0.08	0.13	**0.20**	0.29	0.40	0.53
Level 2	0.05	0.08	0.13	**0.20**	0.29	0.40
Level 1	0.03	0.05	0.08	0.13	**0.20**	0.29
			Scenario 2			
Level 3	0.05	0.08	0.11	0.15	**0.21**	0.29
Level 2	0.04	0.06	0.09	0.13	**0.18**	0.25
Level 1	0.04	0.05	0.08	0.11	0.15	**0.21**
			Scenario 3			
Level 3	**0.20**	0.30	0.41	0.53	0.65	0.70
Level 2	0.10	**0.20**	0.25	0.32	0.41	0.50
Level 1	0.03	0.05	0.13	**0.20**	0.27	0.35
			Scenario 4			
Level 3	**0.20**	0.40	0.47	0.56	0.65	0.76
Level 2	0.08	0.13	**0.20**	0.32	0.41	0.50
Level 1	0.03	0.05	0.08	0.13	0.17	**0.20**

Assessing Performance

Combined PCS

- In each row of the matrix, we are interested in how often each dose of Agent B is selected as the MTD
- Use the combined proportion of correct selection (CPCS) for each row i

Results in Scenario 1 of WI (2005)

0.25	0.23	**0.33**	0.18	0.02	0.00
0.00	0.04	0.26	**0.54**	0.14	0.01
0.00	0.03	0.13	0.53	**0.27**	0.04

CPCS = 0.33 + 0.54 + 0.27 = 1.14

Some Results

	Scenario			
Method	1	2	3	4
Proposed	1.31	1.62	1.73	1.36
WI (2005)	1.14	1.54	1.32	0.99
YY (2008)	1.03	1.25	1.46	1.04

Concluding Remarks

- **R** package **pocrm** can be used to implement design
  - in the process of updating simulation functions
- Method has good properties in identifying multiple MTDCs
  - compares favorably with alternative methods in the area (WI, 2005; YY, 2008)
- Method could be applied to other two-dimensional dose-finding problems
  - rows could represent different treatment schedules or prognosis groups