Dose-finding for Multi-drug Combinations

Nolan A. Wages, Ph.D.

University of Virginia

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Outline

- Background
- Methods
- Results
- Conclusions

Multiple-agent Trials

- In trials combining more than one drug, monotonicity assumption may not hold for every dose
- The ordering between toxicity probabilities of some combinations is unknown
- Toxicity probabilities now follow a “partial order”

Partial Ordering of Doses

- **Example:** Phase I study of Samarium Lexidronam / Bortezomib combination therapy (Berenson et al., 2009)

	Drug Combination					
Agent	d_1	d_2	d_3	d_4	d_5	d_6
Sm (mCi/kg)	0.25	0.5	1.0	0.25	0.5	1.0
Bortezomib (mg/m^2)	1.0	1.0	1.0	1.3	1.3	1.3

Partial Ordering of Doses

- The following order relationships between treatments are known
  1. $d_1 \rightarrow d_2 \rightarrow d_3 \rightarrow d_6$
  2. $d_1 \rightarrow d_4 \rightarrow d_5 \rightarrow d_6$
  3. $d_2 \rightarrow d_5$

Strategy: specify all possible orderings of doses consistent known with toxicity relationships.

Partial Ordering of Doses

- This trial requires the investigation of the following *five* simple orders
  1. $d_1 \rightarrow d_2 \rightarrow d_3 \rightarrow d_4 \rightarrow d_5 \rightarrow d_6$
  2. $d_1 \rightarrow d_2 \rightarrow d_4 \rightarrow d_3 \rightarrow d_5 \rightarrow d_6$
  3. $d_1 \rightarrow d_2 \rightarrow d_4 \rightarrow d_5 \rightarrow d_3 \rightarrow d_6$
  4. $d_1 \rightarrow d_4 \rightarrow d_2 \rightarrow d_3 \rightarrow d_5 \rightarrow d_6$
  5. $d_1 \rightarrow d_4 \rightarrow d_2 \rightarrow d_5 \rightarrow d_3 \rightarrow d_6$
- A random variable M indexes the set of possible simple orders

Toxicity Probability Model

- For a particular ordering, m, $(m = 1, \ldots, M)$, the true probability of toxicity is modeled via a class of working models

$$R(x_j) = \Pr(Y_j = 1 | X_j = x_j) \approx \psi_m(x_j, a)$$

for $x_j \in \{d_1 \ldots, d_k\}$

Prior Information

- Let $p(m) = \{p(1), \ldots, p(M)\}$ denote a discrete prior over the set of contending models
- Let $g(a)$ represent the prior on the parameter a

Likelihood Function

- Under ordering m, the likelihood of a is given by

$$L_m(a|\Omega_j) = \sum_{\ell=1}^{j} y_\ell \log \psi_m(x_\ell, a) + \sum_{\ell=1}^{j} (1 - y_\ell) \log(1 - \psi_m(x_\ell, a))$$

given the data $\Omega_j = \{x_1, y_1, \ldots, x_j, y_j\}$ for the first j patients.

Model Selection

- The posterior probability of model m is given by

$$\pi(m|\Omega_j) = \frac{p(m)\int_{\mathcal{A}} L_m(a|\Omega_j)g(a)da}{\sum_{m=1}^{M} p(m)\int_{\mathcal{A}} L_m(a|\Omega_j)g(a)da}$$

- Choose a single ordering, h, with the largest posterior model probability $\pi(m|\Omega_j)$

Toxicity Probability Estimates

- Given h, toxicity probabilities estimates are given by

$$\hat{R}(d_i) = \psi_h(d_i, \hat{a}_h); \qquad i = 1, \ldots, k$$

- The next patient is then allocated to the dose combination with the estimated toxicity probability closest to the target.

Illustration

- $R(d_1) = 0.04, R(d_2) = 0.07, R(d_3) = 0.20, R(d_4) = 0.35, R(d_5) = 0.55$ and $R(d_6) = 0.70$.
- Target toxicity rate $\theta = 0.20$.
- The trial will treat $n = 24$ patients.
- For each ordering, we used the power model,

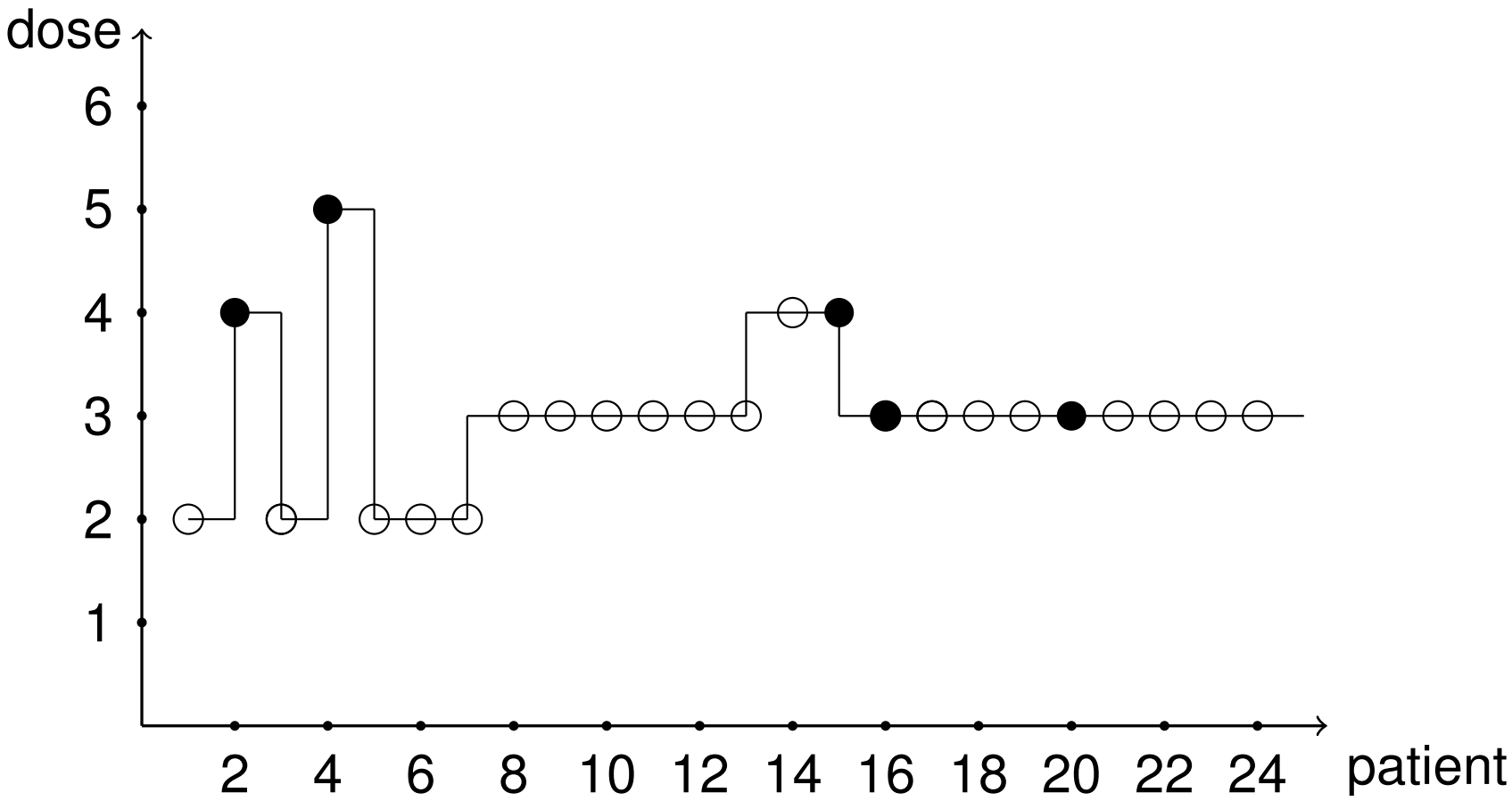
$$\psi_m(d_i, a) = \alpha_{mi}^a; \quad m = 1, \ldots, 5; i = 1, \ldots, 6$$

Working Models

Table: Working model for five simple orders

M	Ordering	Combinations 1	2	3	4	5	6
$m = 1$	1-2-3-4-5-6	0.01	0.07	0.20	0.38	0.56	0.71
$m = 2$	1-2-4-3-5-6	0.01	0.07	0.38	0.20	0.56	0.71
$m = 3$	1-2-4-5-3-6	0.01	0.07	0.56	0.20	0.38	0.71
$m = 4$	1-4-2-3-5-6	0.01	0.20	0.38	0.07	0.56	0.71
$m = 5$	1-4-2-5-3-6	0.01	0.20	0.56	0.07	0.38	0.71

Illustration



Simulation Setup

- 3 different toxicity scenarios.
- Target toxicity rate $\theta = 0.20$.
- The trial will treat $n = 24$ patients.
- Tables present
  1. percentage of MTD recommendation over 2000 simulated trials
  2. percentage of patients that were treated at each combination

Results

Dose	d_1	d_2	d_3	d_4	d_5	d_6	%tox
$R(d_i)$	0.04	0.07	**0.20**	0.35	0.55	0.70	-
% Rec	0.02	0.23	**0.47**	0.26	0.01	0.00	0.23
% Exp	0.07	0.25	**0.34**	0.26	0.07	0.01	
$R(d_i)$	0.01	0.02	0.09	**0.20**	0.40	0.58	-
% Rec	0.00	0.02	0.36	**0.47**	0.14	0.00	0.20
% Exp	0.02	0.10	0.33	**0.33**	0.18	0.05	
$R(d_i)$	0.00	0.00	0.02	0.07	**0.22**	0.41	-
% Rec	0.00	0.00	0.14	0.16	**0.58**	0.12	0.17
% Exp	0.00	0.05	0.17	0.22	**0.36**	0.19	

Matrix Orders

- Sometimes, it may not be feasible to consider **all** possible orderings
- **Example:** Consider a trial investigating two agents, *A* and *B*. Suppose *A* has 4 dose levels and *B* has 4 dose levels.
- Therefore, a total of 16 drug combinations are under consideration

Matrix Orders

Table: *Drug combinations for 4 × 4 matrix order*

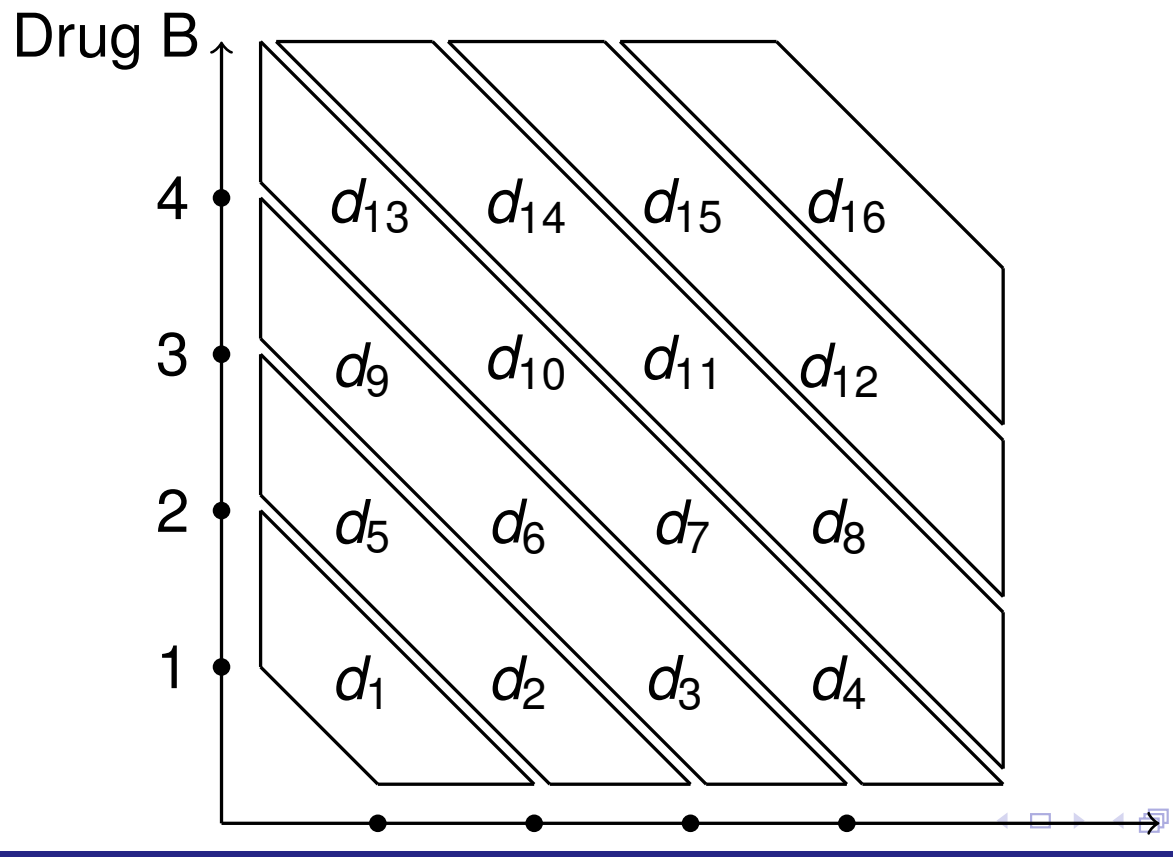
Doses of Drug A	Doses of Drug B 1	2	3	4
4	d_{13}	d_{14}	d_{15}	d_{16}
3	d_9	d_{10}	d_{11}	d_{12}
2	d_5	d_6	d_7	d_8
1	d_1	d_2	d_3	d_4

Strategy for Matrix Orders

- Assume that toxicity increases monotonically for each drug when the other drug is held fixed
- Use known ordering information to choose a “proper” subset of orderings
- Use “toxicity zones” as a guide for order selection

Strategy for Matrix Orders

Figure: *An illustration of zoning a drug combination matrix*



3 Possible Orders

$m = 1$ $d_1 \to d_2 \to d_5 \to d_3 \to d_6 \to d_9 \to d_4 \to d_7 \to d_{10}$
$\to d_{13} \to d_8 \to d_{11} \to d_{14} \to d_{12} \to d_{15} \to d_{16}$

$m = 2$ $d_1 \to d_5 \to d_2 \to d_3 \to d_6 \to d_9 \to d_{13} \to d_{10} \to d_7$
$\to d_4 \to d_8 \to d_{11} \to d_{14} \to d_{15} \to d_{12} \to d_{16}$.

$m = 3$ $d_1 \to d_5 \to d_2 \to d_9 \to d_6 \to d_3 \to d_{13} \to d_{10} \to d_7$
$\to d_4 \to d_{14} \to d_{11} \to d_8 \to d_{15} \to d_{12} \to d_{16}$.

Concluding Remarks

- Overall, the proposed design is competitive with existing methods for dose-finding in multi-agent trials
- When the true ordering is known, the design reduces to the CRM, making it compatible to single-agent trials. Therefore, it can be considered an extension of the CRM

Questions?

Thank You!