The Problem of Partial Ordering in Phase I Clinical Trials

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Outline

- Background
- Proposed Methods
- Results
- Application to matrix orders
- Conclusions

Partial Order Problems

- Multiple treatment schedules
- Patient heterogeneity
- Combinations of agents

Multiple-agent Trials

- Fundamental assumption in Phase I designs is the monotonicity of the dose-toxicity curve
- Dose-limiting toxicity (DLT) probabilities follow a “complete order”
- In trials combining more than one drug, monotonicity assumption may not hold for every dose
- Toxicity probabilities now follow a “partial order”
- Goal is to find the combination with a DLT probability closest to some pre-specified target toxicity rate.

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
Lexidronam (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. $d_2 \rightarrow d_5$
- The following order relationships between treatments are unknown
  1. $d_2 \; ? \; d_4$
  2. $d_3 \; ? \; d_5$

Partial Ordering of Doses

- This trial requires the investigation of the following *five* complete 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 complete orders

Toxicity Probability Model

- Suppose there are k drug combinations $d_1, d_2, \ldots, d_k$,
- Random variable $Y = 1$ in the case of a toxicity, $Y = 0$ otherwise
- There are M possible orderings of toxicity probabilities
- For a particular ordering, m, $(m = 1, \ldots, M)$, the true probability of toxicity is modeled via a class of working models

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

where $x_j \in \{d_1, \ldots, d_k\}$ is the combination given to the jth patient.

Likelihood Function

- After j inclusions, under ordering m, the log-likelihood of a is given by

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

- For each of the M distinct orderings, $L_{mj}(a)$ can be maximized in order to generate an estimate, $\hat{a}_m$.

Model Selection

- We need some value of m so we weight each of the M candidate orderings as we make progress
- The weight of evidence in favor of model m is given by

$$\pi(m) = \frac{\exp\{L_{mj}(\hat{a}_m)\}}{\sum_{m=1}^{M} \exp\{L_{mj}(\hat{a}_m)\}}$$

- It's possible to put priors on particular orderings.

Toxicity Probability Estimates

- Choose a single ordering, h, with the largest ordering weight $\pi(m)$
- 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, $x_{j+1} = d_i$, with the estimated toxicity probability closest to the target toxicity rate θ; i.e.

$$d_i = \arg\min_i |\hat{R}(d_i) - \theta|$$

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 the example presented earlier, there were five complete orders associated with the partial order.
- 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 complete orders

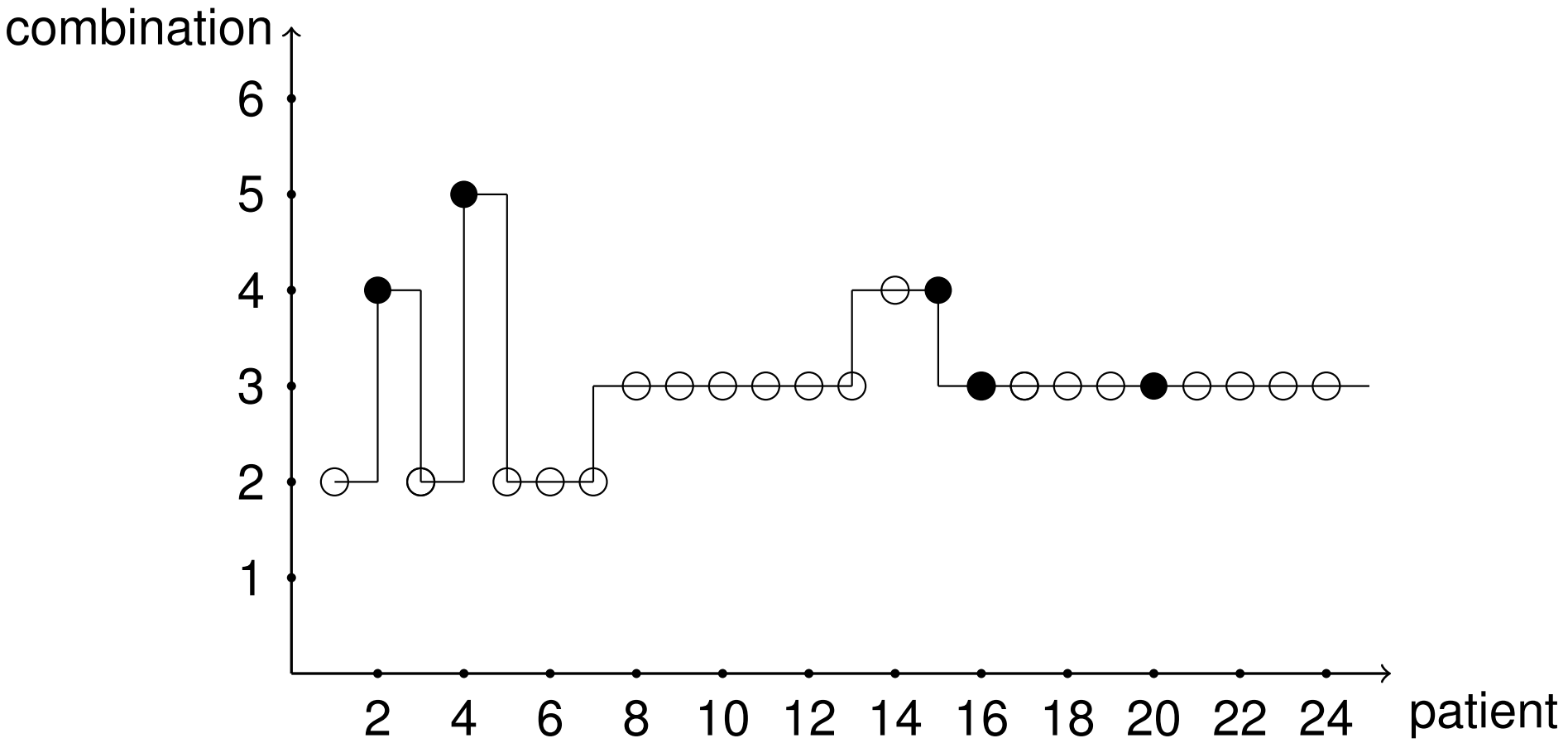
M	Ordering	Combinations 1	2	3	4	5	6
$m = 1$	1-2-3-4-5-6	0.01	0.07	0.20	0.38	0.56	0.71
$m = 2$	1-2-4-3-5-6	0.01	0.07	0.38	0.20	0.56	0.71
$m = 3$	1-2-4-5-3-6	0.01	0.07	0.56	0.20	0.38	0.71
$m = 4$	1-4-2-3-5-6	0.01	0.20	0.38	0.07	0.56	0.71
$m = 5$	1-4-2-5-3-6	0.01	0.20	0.56	0.07	0.38	0.71

Initial Stage

- Partition the combinations into zones of "possible escalation treatments."

Zone	A	B	C	D
dose	d_1	d_2 d_4	d_5 d_3	d_6

Illustration Continued



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	22.6%
% 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	19.7%
% 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	17.4%
% Exp	0.00	0.05	0.17	0.22	**0.36**	0.19	

Matrix Ordering

- Sometimes, it may not be feasible to consider **all** possible orderings
- **Example:** Consider a recent trial run at UVA investigating two agents, A and B. Suppose A has 4 dose levels and B has 3 dose levels.
- Therefore, a total of 12 drug combinations are under consideration and suppose they are labeled as...

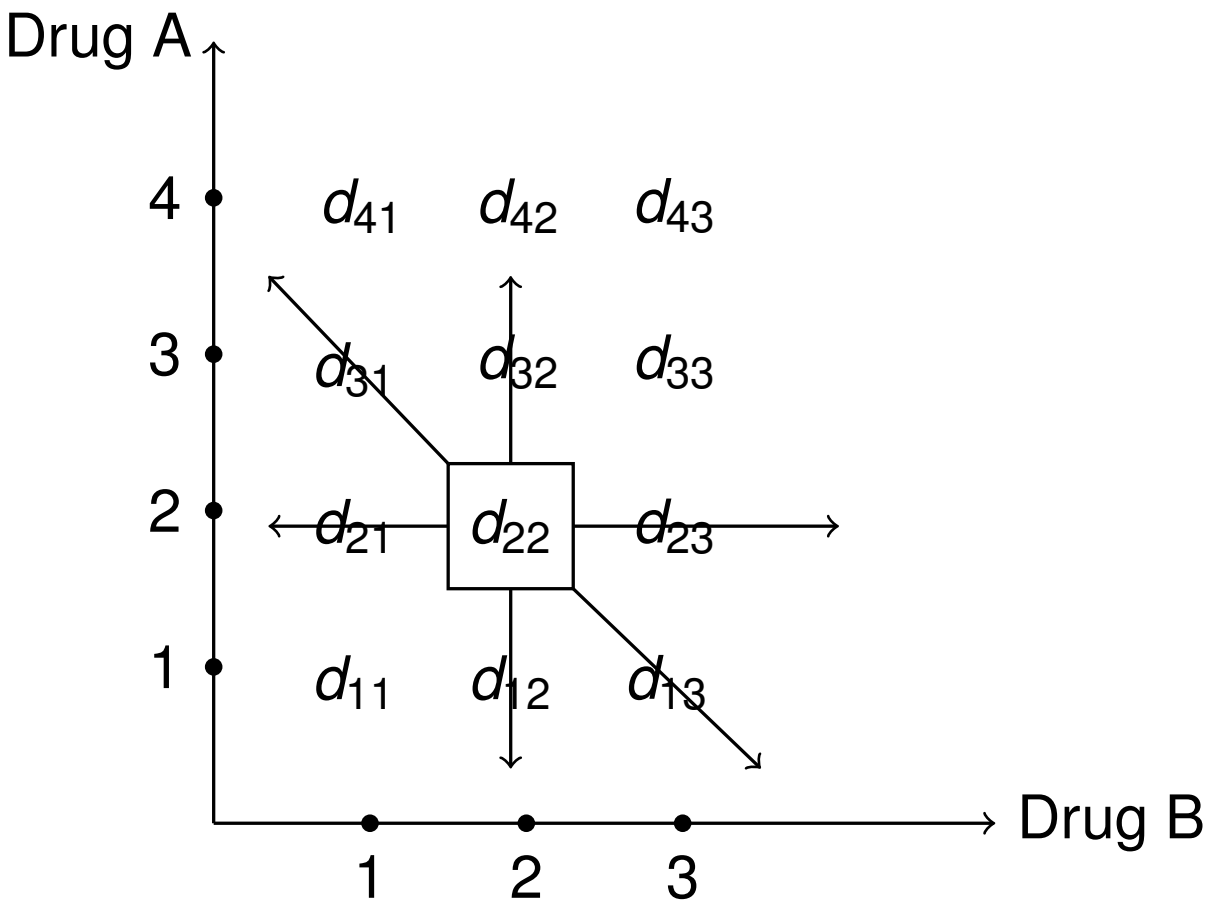
Matrix Ordering Continued

Doses of Drug A	Doses of Drug B 1	2	3
4	d_{41}	d_{42}	d_{43}
3	d_{31}	d_{32}	d_{33}
2	d_{21}	d_{22}	d_{23}
1	d_{11}	d_{12}	d_{13}

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
- Begin by ordering by rows and columns
- Use diagonals as a guide for the selection of other orders
- Recommend using a subset of **six** orderings

Strategy for Matrix Orders



Subset of Possible Orders

$m = 1$ $d_{11} \to d_{12} \to d_{13} \to d_{14} \to \cdots \to d_{41} \to d_{42} \to d_{43}$ (rows)

$m = 2$ $d_{11} \to d_{21} \to d_{31} \to d_{41} \to \cdots \to d_{23} \to d_{33} \to d_{43}$ (columns)

$m = 3$ $d_{11} \to d_{12} \to d_{21} \to d_{13} \to \cdots \to d_{33} \to d_{42} \to d_{43}$ (diag)

$m = 4$ $d_{11} \to d_{21} \to d_{12} \to d_{31} \to \cdots \to d_{42} \to d_{33} \to d_{43}$ (diag)

$m = 5$ $d_{11} \to d_{12} \to d_{21} \to d_{31} \to \cdots \to d_{42} \to d_{33} \to d_{43}$ (diag)

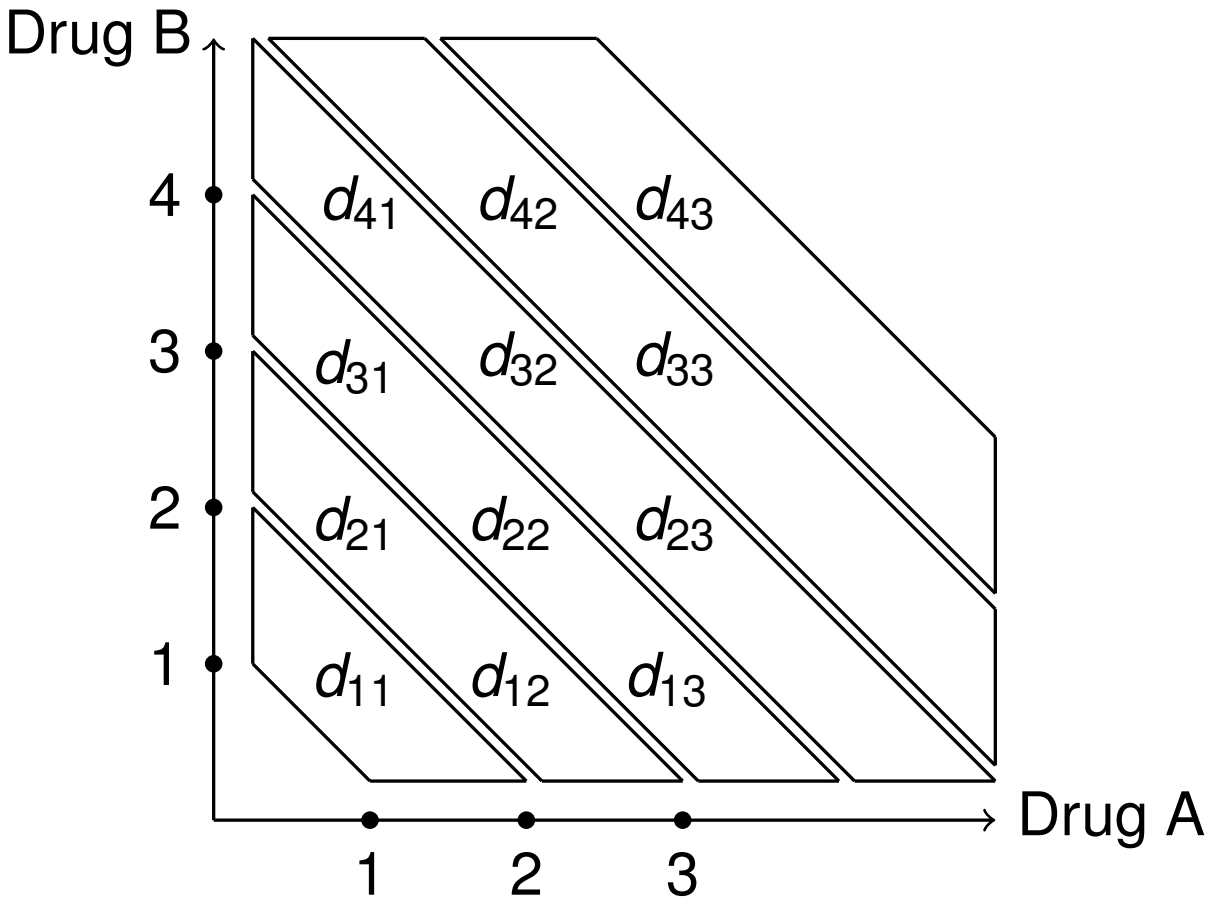
$m = 6$ $d_{11} \to d_{21} \to d_{12} \to d_{13} \to \cdots \to d_{33} \to d_{42} \to d_{43}$ (diag)

Two-stage Design

- The first stage treats single patient cohorts until a DLT is observed
- At observance of first DLT, first stage closes. Second stage (modelling) begins
- Escalation in the first stage is based on grouping combinations into “toxicity zones”

First Stage for Matrix Orders

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



First Stage Continued

- Trial begins in Zone 1. Patient 1 entered on d_{11}
- If no DLT, escalation proceeds to Zone 2. Patient 2 is given d_{12} or d_{21}, chosen at random
- If no DLT, patient 3 is given the combination in Zone 2 that has not yet been tried
- Escalation to a higher zone occurs only when all combinations in the current zone have been tried

Scenario

Doses of Drug A	Doses of Drug B 1	2	3
4	**0.24**	0.30	0.36
3	**0.16**	**0.22**	0.28
2	0.08	0.14	**0.20**
1	0.03	0.06	0.12

% MTD Recommendation

Doses of Drug A	Doses of Drug B 1	2	3
4	**0.11**	0.07	0.09
3	**0.10**	**0.15**	0.11
2	0.02	0.06	**0.17**
1	0.03	0.02	0.06

Summary of Results

% Recommendation within $\pm$ 5% of target	53%
% Stopped after 1st cohort	2.0%
Average trial size	21.7
Average % of DLT's	17.4%

Concluding Remarks

- Overall, the proposed design is competitive with existing methods for dose-finding in multi-agent trials
- Generalization of the CRM
- Good properties when it is possible to write down all possible orderings
- Good properties when a “proper” subset of orderings is used

References

- Berenson, J. R., Yellin, O., Patel, R., et al. (Clinical Cancer Research 2009; 15: 1069 - 1075).
- Wages, Conaway and O'Quigley (Biometrics 2011; 67(4): 1555 - 1563)
- Wages, Conaway and O'Quigley (Clinical Trials 2011; 8(4): 380-389)

Questions?

Thank You!