Phase I design for locating schedule-specific maximum tolerated doses

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Outline of Talk

- Challenges associated with dose-schedule studies
- Method for locating schedule-specific MTD's
- Operating characteristics
- Conclusions

Dose-schedule Finding

Background

- Dose regimens based on
  1. amount of agent given
  2. frequency with which it is administered
- Each course of therapy is a distinct dose-schedule combination
- Goal is to account for schedule effects in dose-finding design

Dose-schedule Finding

Design Challenges

1. The objective of the trial may be to determine an MTD **in each schedule**.
   - Estimate an MTD equivalence contour
2. DLT probabilities of dose-schedule combinations follow **partial order**
   - If current dose-schedule combo is safe, may not be clear where to go next.
3. Dimension of the problem may be large
   - Many combos to consider

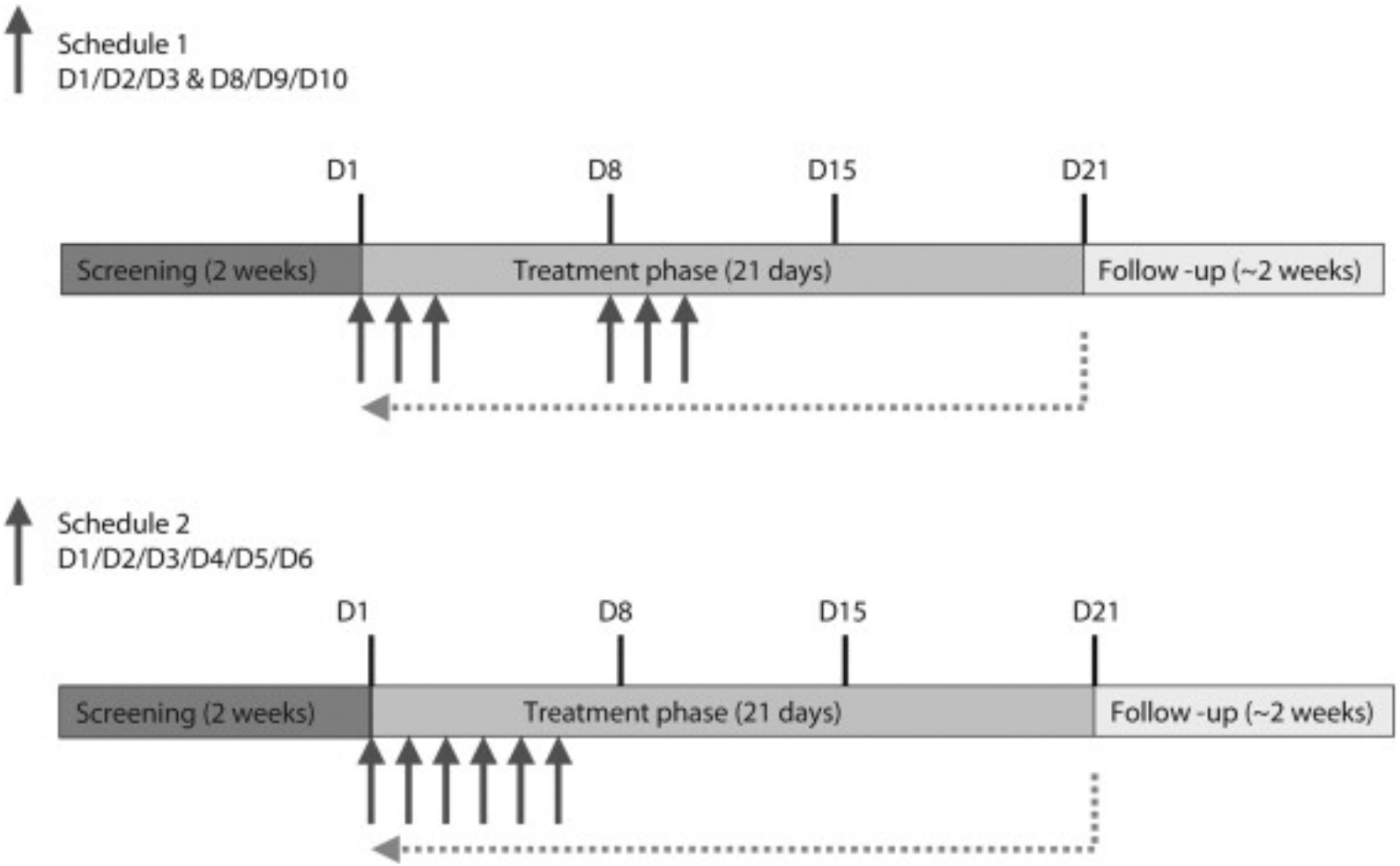
Dose-schedule combinations

General Notation

- Consider a study investigating multiple schedules
  - I ordered schedules: $s_1 < \cdots < s_I$
  - J dose levels of the agent under each schedule: $x_1 < \cdots < x_J$
- $d_{ij} = (s_i, x_j)$ is the combination of schedule s_i and dose level x_j
- Probability of DLT at combination d_{ij} is denoted $R(d_{ij})$

Two schedules

Supplemental Figure 1 Graux *et al.* (2013)



Ordered schedules

Graux *et al.* (2013)

- A phase I dose-escalation study of MSC1992371A, an oral inhibitor of aurora and other kinases, in advanced hematologic malignancies
- Schedule 1 = days 1–3 and 8–10 on 21-day cycle
- Schedule 2 = days 1–6 on 21-day cycle
- Schedule 2 considered "more intense"

Schedule	Doses in $mg/m^2/day$							
2	3	6	10	15	21	28	37	47
1	3	6	10	15	21	28	37	47

Combination-toxicity Relationships

Assumptions

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

		x_1	x_2	$\cdots$	x_8
$\uparrow$	s_2	d_{21}	d_{22}	$\cdots$	d_{28}
$\uparrow$	s_1	d_{11}	d_{12}	$\cdots$	d_{18}
TOXICITY INCREASES		$\longrightarrow$	$\longrightarrow$	$\longrightarrow$	$\longrightarrow$

Primary Objective

Find Multiple MTD's

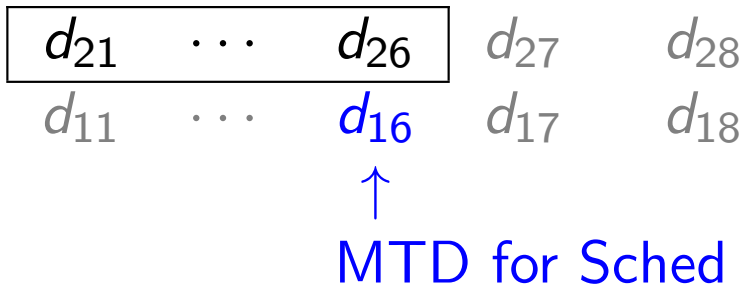
- Goal: find an MTD for each schedule i
- Locate $\nu_i = d_{ij^*}; j^* \in \{1, \ldots, J\}$ such that d_{ij^*} has DLT probability closest to the target rate θ for each $i\,(i = 1, \ldots, I)$
  - i.e. find an MTD in each row i such that

$$\nu_i = \arg\min_j |R(d_{ij}) - \theta|$$

Toxicity Assumptions

Affect on MTD Location

- Schedule 2 is assumed to be more toxic, so its MTD will be at dose lower than or equal to the MTD in Schedule 1
- For instance, suppose MTD in Schedule 1 is estimated to be d_{16}
  - In Schedule 2, MTD level must be lower than or equal to d_{26} (i.e. $d_{21}, \ldots, d_{26}$)



Implemented Trial Design

Graux *et al.* (2013)

- Conducted using parallel 3+3 designs in each schedule.
- Within each schedule, these parallel trials produce an MTD estimate
  - Fail to use ordering information among dose-schedule regimens
- Parallel studies could produce reversals
  - MTD estimates contradict what is known clinically about toxicity
  - **Results in MTD of schedule 2 being at a higher dose than MTD of schedule 1**

Relative Location of MTD's

Shift Model**

- If MTD for s_1 is $\nu_1 = d_{1j^*}$, then the MTD for s_2 is $\nu_2 = \nu_1 - \Delta_2$; $\Delta_2 = 0, 1, 2, \ldots$
- Sensible to restrict Δ_2 to a small set of values
  - MTD's most likely to be $0, 1, 2, 3$ levels away
- Use the data to estimate the relative location of the MTD between rows
- Similar strategy has been used for drug combinations* and patient heterogeneity**

*Wages NA. *Stat in Med* 2016 [epub ahead of print].

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

Relative Location of MTD's

Shifts of 0 or 1

- $\{\Delta_2 = 0\}$

d_{21}	d_{22}	d_{23}	d_{24}	d_{25}	d_{26}	d_{27}	d_{28}
d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}

- $\{\Delta_2 = 1\}$

d_{21}	d_{22}	d_{23}	d_{24}	d_{25}	d_{26}	d_{27}	d_{28}
d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}

Relative Location of MTD's

Shifts of 2 or 3

- $\{\Delta_2 = 2\}$

d_{21}	d_{22}	d_{23}	d_{24}	d_{25}	d_{26}	d_{27}	d_{28}
d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}

- $\{\Delta_2 = 3\}$

d_{21}	d_{22}	d_{23}	d_{24}	d_{25}	d_{26}	d_{27}	d_{28}
d_{11}	d_{12}	d_{13}	d_{14}	d_{15}	d_{16}	d_{17}	d_{18}

Working Models

Targeting $\theta = 0.20$

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

0.03^a	0.07^a	0.13^a	0.20^a	0.29^a	0.38^a	0.48^a	0.55^a
0.03^a	0.07^a	0.13^a	0.20^a	0.29^a	0.38^a	0.48^a	0.55^a

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

0.07^a	0.13^a	0.20^a	0.29^a	0.38^a	0.47^a	0.55^a	0.63^a
0.03^a	0.07^a	0.13^a	0.20^a	0.29^a	0.38^a	0.47^a	0.55^a

Working Models

Targeting $\theta = 0.20$

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

0.07^a	0.20^a	0.29^a	0.38^a	0.47^a	0.55^a	0.63^a	0.70^a
0.03^a	0.07^a	0.13^a	0.20^a	0.29^a	0.38^a	0.47^a	0.55^a

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

0.20^a	0.29^a	0.38^a	0.47^a	0.55^a	0.63^a	0.70^a	0.76^a
0.03^a	0.07^a	0.13^a	0.20^a	0.29^a	0.38^a	0.47^a	0.55^a

Multi-dimensional CRM

Class of Working Models

- Let m index the working models
- Under working model m, the probability of DLT at dose-schedule combination d_{ij} is

$$R(d_{ij}) \approx \psi_m(d_{ij}, a) = \left(\alpha_m(d_{ij})\right)^{\exp(a)}$$

  where $\alpha_m(d_{ij})$ is the skeleton of the model m
- Prior on the working models

$$p = \{p(1), \ldots, p(M)\}$$

Multi-dimensional CRM

Likelihood and Prior

- Data: $\mathcal{D} = \{y_{ij}, n_{ij}\}$, # DLT's and patients at each combo
- Likelihood under model m

$$\mathcal{L}_m(\mathcal{D} \mid a) \propto \prod_{i=1}^{I} \prod_{j=1}^{J} \Big(\psi_m(d_{ij}, a)\Big)^{y_{ij}} \Big(1 - \psi_m(d_{ij}, a)\Big)^{n_{ij} - y_{ij}}$$

- Prior $g(a)$ on a

$$a \sim \mathcal{N}(0, 1.34)$$

Multi-dimensional CRM

Sequential Bayesian Model Choice

- Posterior model probability for m is

$$\pi(m \mid \mathcal{D}) = \frac{p(m) \int \mathcal{L}_m(\mathcal{D} \mid a) g(a) da}{\sum_{m=1}^{M} p(m) \int \mathcal{L}_m(\mathcal{D} \mid a) g(a) da}$$

- After each inclusion, choose model h such that

$$h = \arg\max_m \pi(m \mid \mathcal{D})$$

Multi-dimensional CRM

DLT Probability Estimates

- Estimated DLT probability at each dose-schedule regimen

$$\widetilde{R}(d_{ij}) = \int \psi_h(d_{ij}, a) \frac{\mathcal{L}_h(\mathcal{D} \mid a) g(a)}{\int \mathcal{L}_h(\mathcal{D} \mid a) g(a) da} da$$

- Form a set $\mathcal{S} = \{\widetilde{\nu}_1, \widetilde{\nu}_2\}$ of recommended doses such that

$$\widetilde{\nu}_i = \arg\min_j |\widetilde{R}(d_{ij}) - \theta|$$

- Randomize the next cohort to a treatment in $\mathcal{S}$

Trial Design & Conduct

1. Begin at the lowest dose-schedule combination d_{11}
2. Do not skip doses within a schedule when escalating
3. **At any point**, stop the trial for safety if d_{11} is too toxic

$$\Pr\left(R(d_{11}) > \theta \,|\mathcal{D}\right) > 0.90$$

4. $\mathcal{S}$ is the set of MTD estimates in each schedule after maximum sample size is reached

A Simulation Study

1. Target toxicity rate $\theta = 0.20$
2. 1000 simulated trials
3. Total sample size $n = 60$
   - Compare with a parallel CRM design using $n = 30$ in each schedule

	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
s_2	0.08	0.13	**0.20**	0.29	0.40	0.52	0.63	0.73
s_1	0.06	0.09	0.14	**0.22**	0.31	0.43	0.53	0.65

A Simulation Study

Percent of MTD Selection

- CRM shift model design

	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
s_2	5.7	25.1	**46.4**	21.7	1.1	0.0	0.0	0.0
s_1	0.3	4.6	30.9	**43.7**	17.6	2.8	0.1	0.0

- Parallel CRM designs*

	x_1	x_2	x_3	x_4	x_5	x_6	x_7	x_8
s_2	3.5	24.2	**42.7**	24.8	4.6	0.2	0.0	0.0
s_1	0.8	8.1	33.4	**39.8**	16.2	1.5	0.2	0.0

*Parallel design results in 'reversal' in 18.6% of simulated trials.

Conclusions

- The design presented in this talk
  - can be extended to more than 2 schedules
  - performs well in terms of identifying multiple MTDs
  - allocating a high percentage of patients to doses at and around true MTDs (not shown)
  - protects the study from reversals
- Method compares favorably with alternative methods in the area (not shown)
  - Wang and Ivanova (Stat Med, 2005)
  - Yuan and Yin (Stat Med, 2008)

Thank you!

Questions?

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