Phase I Design for Multiple Treatment Schedules

The Problem of Partial Ordering in Dose-finding

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Outline

- Background
- Proposed Methods
- Results
- Conclusions

The Problem of Partial Ordering

- Multiple treatment schedules
- Combinations of agents
  - Wages, Conaway and O'Quigley, 2011
  - Wages and Conaway, 2013

The Problem of Partial Ordering

- Fundamental assumption in Phase I designs is the monotonicity of the dose-toxicity curve
- Toxicity probabilities follow a “complete order”
- In dose-finding problems above, monotonicity assumption may not hold for every dose
- Toxicity probabilities now follow a “partial order”

Multiple Treatment Schedules

- Doses based on
  1. amount of agent given
  2. frequency with which it is administered
- Each course of therapy is a distinct dose-schdule combination
- Goal: find a dose-schedule combination with acceptable toxicity

Example

- Dose-and-schedule dependent Phase I study of Everolimus (Tabernero et al., 2008)
- Patients were assigned to one of the following courses of therapy: everolimus at 20, 50 or 70 mg weekly or 5 and 10 mg daily.

	Doses in mg				
Schedule	5	10	20	50	70
Daily	1	2			
Weekly			3	4	5

Partial Orders

- Monotonoicity with dose within each schedule
- Complete order: $3 - 4 - 5$
- Ordering along diagonals is not fully known
- Going from 2 to 3 is an increase in dose but a “decrease” in schedule
- Partial order: $2 - 3$ or $3 - 2$

Overall Strategy for Partial Orders

- Determine between which combinations order relationships are completely known
  - Known: $1 - 2$ and $3 - 4 - 5$
- Begin by ordering by rows and columns
- Use diagonals as a guide for determining other orders
- **Goal:** specify all (or a reasonable subset of) possible orderings of combinations consistent w/ completely known toxicity relationships.

Partial Ordering of Combinations

- There are a total of 10 possible complete orderings, five of which are:
  1. $1 - 2 - 3 - 4 - 5$ (columns)
  2. $3 - 4 - 5 - 1 - 2$ (rows)
  3. $1 - 3 - 2 - 4 - 5$ (diag)
  4. $3 - 1 - 2 - 4 - 5$ (diag)
  5. $1 - 3 - 4 - 2 - 5$ (diag)
- In general, a random variable M indexes the set of possible complete orders

Overall Strategy

- "Two-parameter" version of continual reassessment method
  1. Estimate the correct ordering of toxicity probabilities
  2. Within the estimated ordering, use CRM to estimate toxicity probabilities

Models and Inference

- Working model for probability of toxicity for dose-schedule combination i under ordering m is $p_{im}^{\theta_m}$
- The p_i are standardized units representing the discrete dose levels (i.e. skeleton of the model)

Example of Working Model

Table : *Working model consistent with each ordering*

Ordering (M)	1	2	3	4	5
1	$(0.10)^{\theta_1}$	$(0.20)^{\theta_1}$	$(0.30)^{\theta_1}$	$(0.40)^{\theta_1}$	$(0.50)^{\theta_1}$
2	$(0.40)^{\theta_2}$	$(0.50)^{\theta_2}$	$(0.10)^{\theta_2}$	$(0.20)^{\theta_2}$	$(0.30)^{\theta_2}$
3	$(0.10)^{\theta_3}$	$(0.30)^{\theta_3}$	$(0.20)^{\theta_3}$	$(0.40)^{\theta_3}$	$(0.50)^{\theta_3}$
$\vdots$			$\vdots$		

Allocation of Dose-schedule Combinations

- As data accumulates, estimate θ_m for each ordering by maximum likelihood estimation
- Choose the ordering that the data indicates to be the most likely
- Update estimates of toxicity probabilities for combinations within that ordering
- Next patient goes on dose combination with estimated toxicity probability closest to a target toxicity rate

Illustration

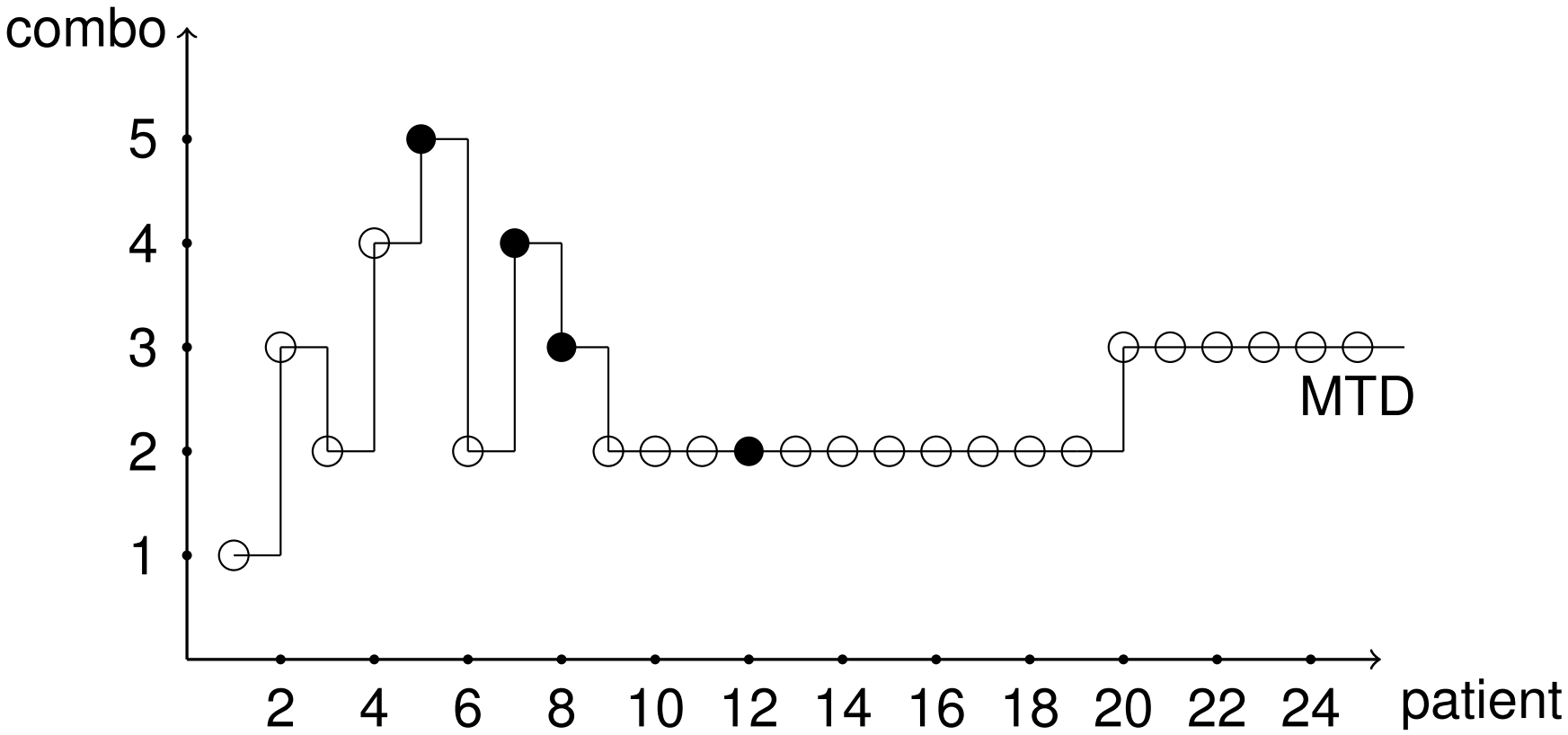
- Target toxicity rate is 20%
- The trial will treat $n = 24$ patients
- 10 possible complete orderings of toxicity probabilities

	Combinations				
	1	2	**3**	4	5
True DLT prob.	0.05	0.10	**0.20**	0.33	0.45

Initial Stage

- Partition the combinations into zones of “possible escalation treatments.”
- Zone 1: lowest dose for each schedule (1 and 3)
- Zone 2: 2nd lowest dose for each schedule (2 and 4)
- Zone 3: remaining dose (5)
- Randomize pts within zones until DLT is observed or until zones are exhausted

Illustration Continued



Simulated Results

- Each trial will treat $n = 36$ patients; Target rate is 20%
- Percent MTD selection over 2000 simulated trials; benchmark is CRM with known ordering
- `R` package `pocrm`

Simulated Results

True DLT prob.	0.09	**0.20**	0.30	0.46	0.60
PO-CRM	0.22	**0.43**	0.31	0.03	0.00
CRM	0.20	**0.54**	0.24	0.02	0.00
True DLT prob.	0.05	0.10	**0.20**	0.33	0.45
PO-CRM	0.04	0.28	**0.44**	0.21	0.03
CRM	0.01	0.24	**0.54**	0.20	0.01
True DLT prob.	0.01	0.05	0.11	**0.22**	0.32
PO-CRM	0.01	0.15	0.16	**0.48**	0.19
CRM	0.00	0.01	0.29	**0.52**	0.18

Concluding Remarks

- Generalization of the CRM
- “Partial order” CRM can applied to trials of
  - Multiple-drug combinations
  - Multiple treatment schedules
- Good properties in terms of recommending correct MTD combinations and allocating patients to desirable combinations (results not shown).

References

- Tabernero et al. Journal of Clinical Oncology 2008; 26: 1603–1610.
- Wages, Conaway and O'Quigley. Biometrics 2011; 67(4): 1555 - 1563.
- Wages, Conaway and O'Quigley. Clinical Trials 2011; 8(4): 380-389.
- Wages and Conaway. Pharmaceutical Statistics 2013; *in press*.

Questions?

Thank You!