Coherence in early phase dose-finding studies

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Agenda

- Motivation
  - Phase I cancer trials
  - The conventional method ("3+3")
  - Literature: review & critique
- Coherence
  - Example: Coherent designs
  - **Application I: Coherent two-stage CRM**
  - Application II: Combined phase I/II trial (if time)
  - Discussion & resources

Phase I cancer trials

- *Primary objective:*
  - Evaluation of clinical safety
- *Dose-finding:*
  - Maximum tolerated dose (MTD) with respect to dose-limiting toxicity (DLT)
  - A presumed optimal dose
- *Complicated issues:*
  - Trade-off between safety and efficacy

A conventional method

- Specify a set of dose levels for the trial
- Start at the lowest dose level:

#DLT / #Patients	*Action*
0/3	Escalate dose
1/3	Add 3 patients at same level
1/6	Escalate dose / Called MTD
≥ 2/3 or ≥ 2/6	De-escalate

- MTD = Max dose with fewer than 2/6 DLTs

A conventional method

- Disadvantages

1. Quantitative objective is unclear

2. The operating characteristics arbitrarily depend on the underlying dose-toxicity curve

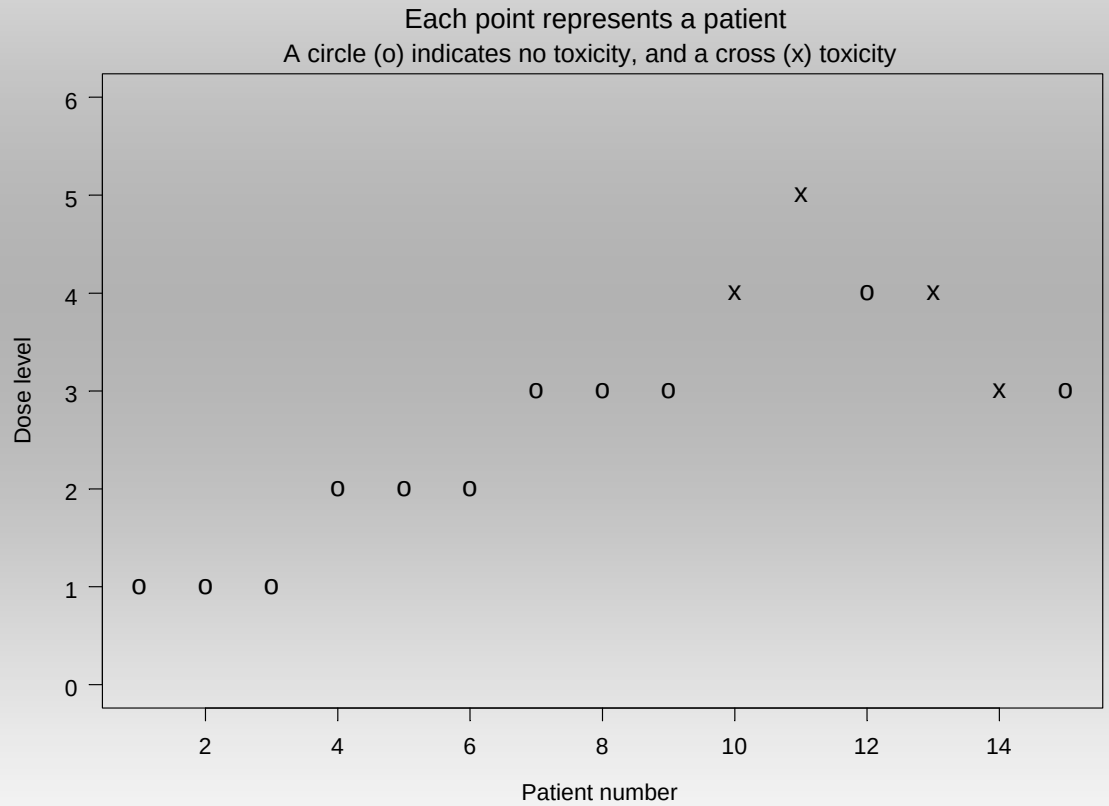
Phase I Methods: Literature

- Proposals
  - Up-and-down designs (Storer, 1989)
  - Continual reassessment method (O'Quigley et al, 1990)
  - Biased coin design (Durham et al, 1997)
  - EWOC (Babb et al, 1998)
  - Curve-free method (Gasparini and Eisele, 2000)
  - …
- MTD = a dose that causes DLT with probability p
- Operating characteristics validated by simulation

Phase I Methods: Critique

- Critiques
  - Is the “conventional wisdom” respected?
    - De-escalate or stay put if toxicity is observed
    - Escalate or stay put if no toxicity is observed
- Consequence: Pathological behaviors of the methods

A pathological outcome sequence



Motivation

- Consequence:
  - Deter clinicians from using the more complicated, outcome-adaptive method, which is supposed to be better but now looks dubious
- Prophylaxis:
  - Study whether a design respects the conventional wisdom – **coherence**

Coherence Principles

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Escalations

- An escalation for the next patient is said to be *in*coherent if the most recent patient experiences some toxic side-effects
- A design is said to be coherent in escalation if

$$\Pr(U_i > 0 \mid Y_{i-1} = 1) = 0 \text{ for all } i \text{ (a.s.)}$$

where U_j is dose level increment from patient j-1 to patient j, and Y_j is the toxicity indicator of patient j.

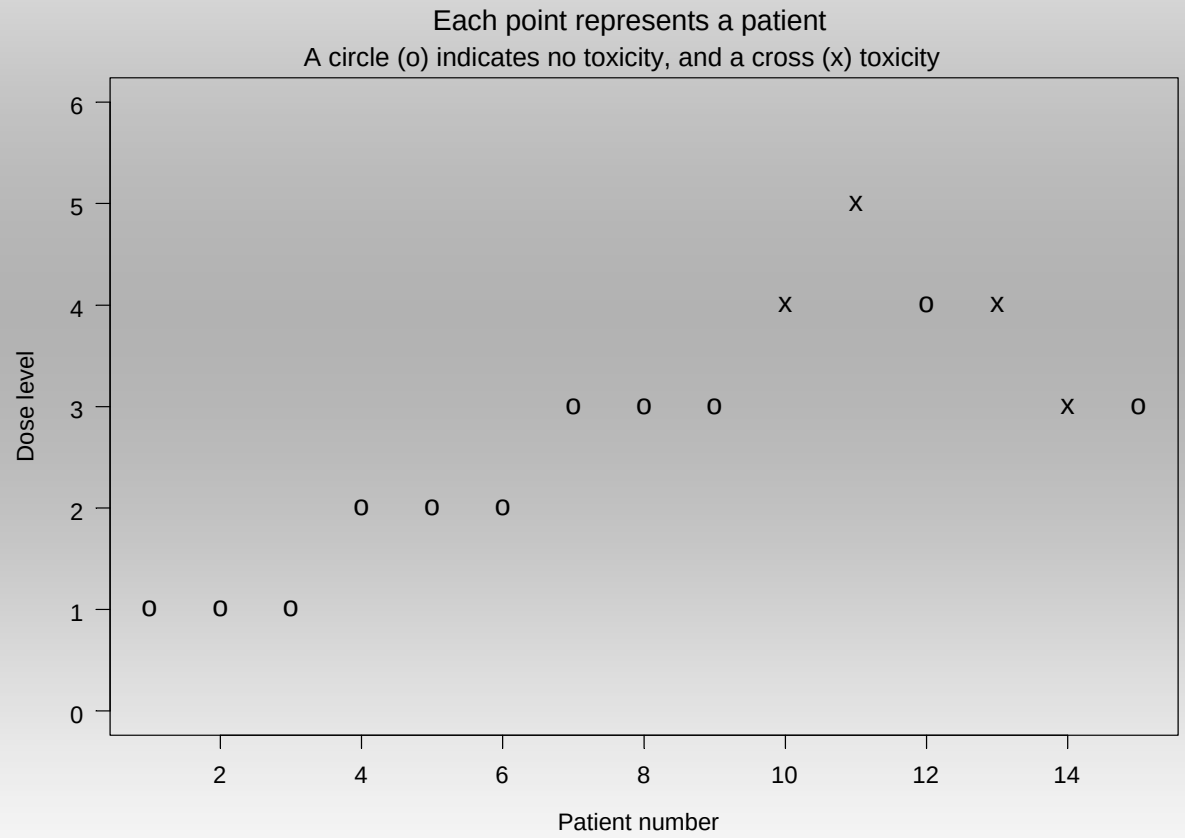
De-escalations

- A de-escalation for the next patient is said to be *in*coherent if the most recent patient shows no sign of toxicity
- A design is said to be coherent in de-escalation if

$$\Pr(U_i < 0 \mid Y_{i-1} = 0) = 0 \text{ for all } i \text{ (a.s.)}$$

where U_j is dose level increment from patient j-1 to patient j, and Y_j is the toxicity indicator of patient j.

Incoherent escalation, Pt 11



Coherent designs

- Algorithm-based designs
  - Coherence by construction
  - Up-and-down (Storer, 1989)
  - Biased coin design (Durham et al., 1997)
- Model-based designs
  - Coherence is not obvious, but can be proved
  - **CRM (O'Quigley et al., 1990)**

One-stage CRM is coherent

- Define the MTD: a dose that causes DLT with probability p
- Assume a dose-toxicity model

$$F(d, \beta) = \text{Prob}(\text{DLT at dose } d)$$

- Treat patient at prior MTD.
- Estimate β based on binary toxic outcomes from first n patients. Denote estimator by b_n.
- Select dose level d* for patient (n+1) such that

$$d^* = \arg\min_k |F(d_k, b_n) - p|$$

Initial design

- Practical considerations
  - "Conservative" initial dose assignments
  - No information about dose-toxicity curve until toxicity is seen (especially, likelihood CRM)
- Initial design D_0
  - A predetermined monotone sequence of dose levels $\{x_{10}, x_{20},..., x_{n0}\}$ such that $x_{i0} \geq x_{i-1,0}$
  - E.g., Groups-of-three:

$$x_{10} = x_{20} = x_{30} = 1,\ x_{40} = x_{50} = x_{60} = 2,\ \ldots$$

Two-stage CRM: definition

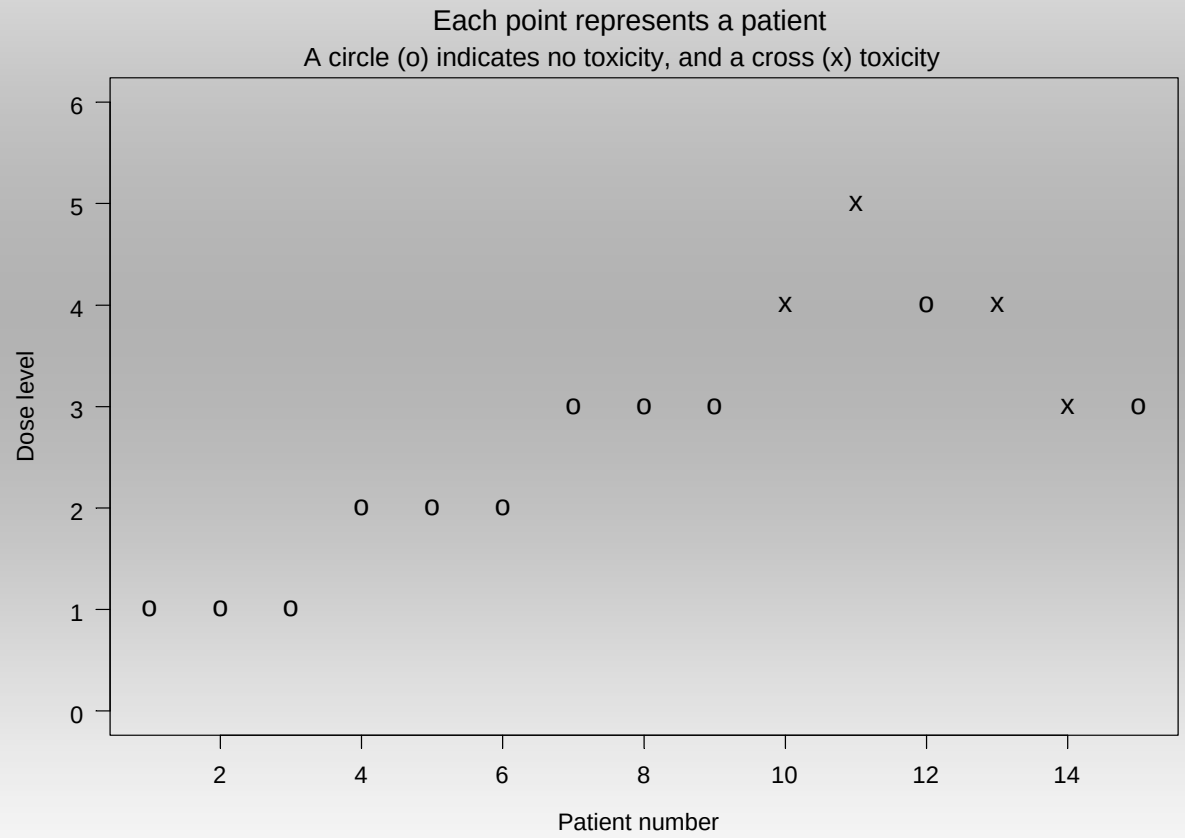
- Let $D_1(H_i)$ be the design point for patient i by the one-stage CRM, where H_i is the information available upon entry of patient i.
- Let $D^*(H_i)$ denote the design point for patient i by a two-stage CRM. Then

$$D^*(H_i) = x_{i0} \quad \text{if } Y_j = 0 \text{ for all } j < i,$$
$$= D_1(H_i) \quad \text{if } Y_j = 1 \text{ for some } j < i.$$

Two-stage CRM: example

- A one-stage CRM is coherent; a two-stage CRM may not be coherent in escalation.
- Consider the following two-stage CRM:
  - $F(d_k, \beta) = d_k^{\beta}$ with d = (0.05,0.10,0.15,0.25,0.35,0.45)
  - log(β) is normal with mean 0 and variance 1.34
  - Initial design: groups of three
  - Target: p = 0.25

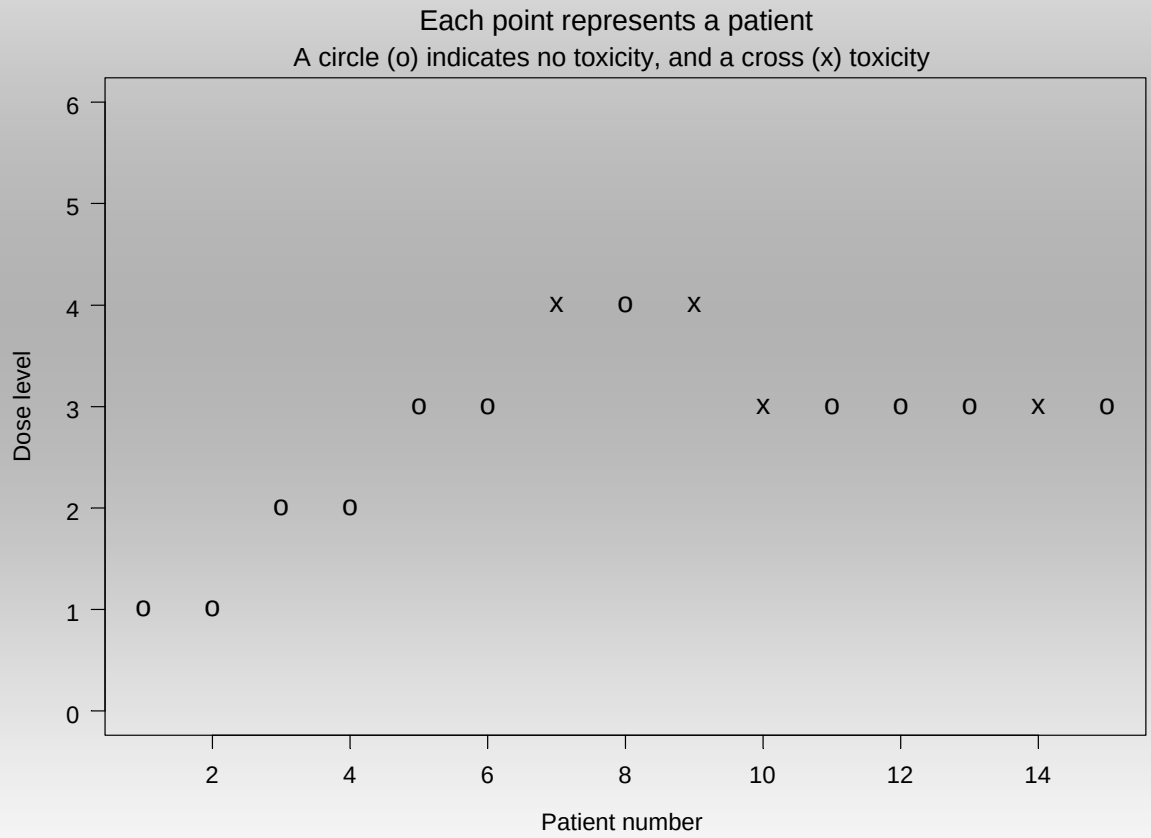
Incoherent escalation, Pt 11



Two-stage CRM: example

- Problem:
  - Nontoxic group size before an escalation is too large: too conservative ***for p = 0.25***
  - Influence estimation at higher doses via parametric extrapolation
- Let's fix it:
  - Decrease group size in the initial design, e.g. groups of two

Coherent two-stage CRM



Two-stage CRM: coherence

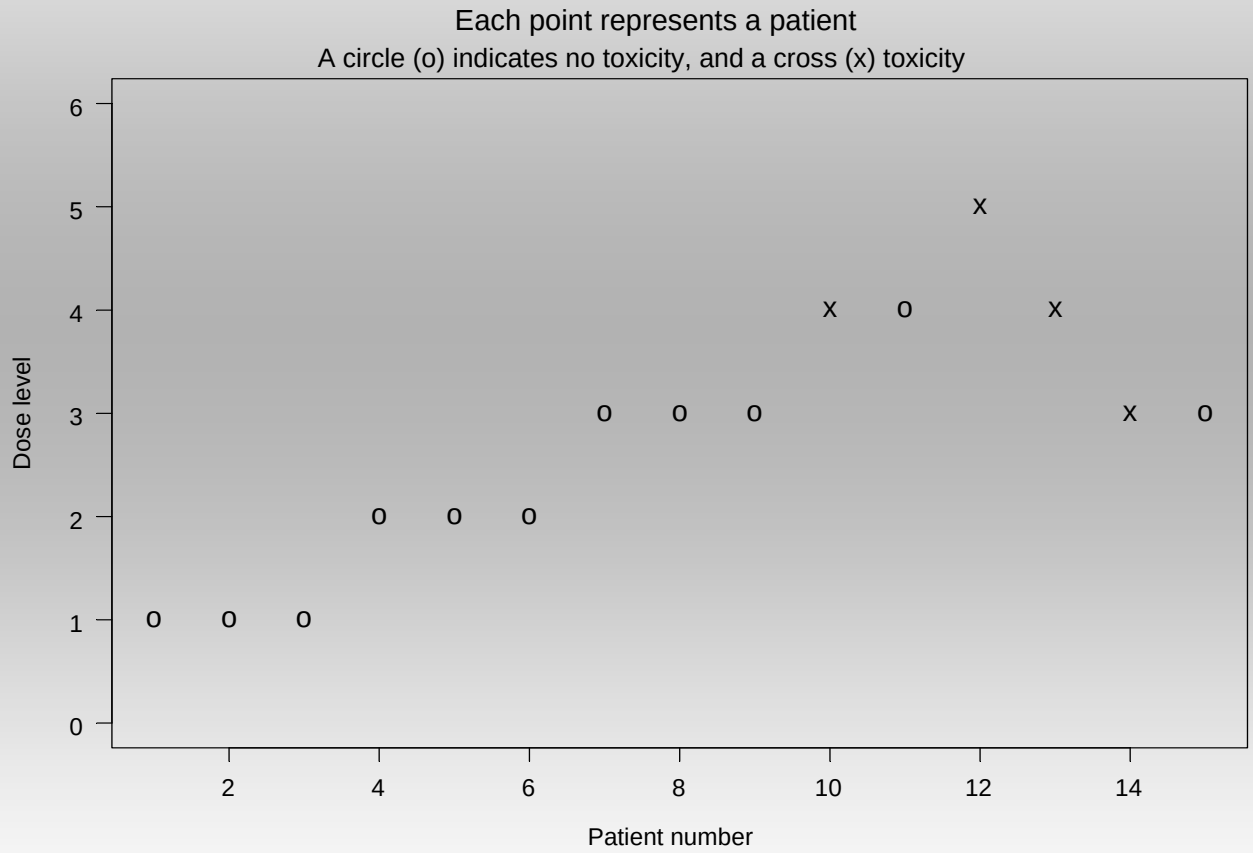
- Let $M_0 = \min\{i: Y_i = 1\}$
- *Theorem 1 – Condition of coherence*

  If $D^*(H_{M0+1}) \leq D^*(H_{M0})$ almost surely, then the (unrestricted) two-stage CRM D* is coherent.
- In words, **coherence at the transition of stages implies coherence.**
- Computational advantage: Examine N-1 sequences instead of 2^{N-1} sequences

Two-stage CRM: coherence

- How about enforcing coherence by restriction? – No escalation for next patient if current patient experiences toxicity
  - Goodman et al. (1995)
  - Faries (1994)
- Consider the previous CRM model with
  - Initial design: Groups of three
  - p = 0.25
  - Enforce coherence by restriction

What is the problem?



Two-stage CRM: compatibility

- *Incompatibility:*
  - Patient 12 receives dose level 5.
  - If patient 10 did not experience toxicity, patient 12 would have received dose level 4 according to the initial design.

Two-stage CRM: compatibility

- Initial design should represent the fastest escalation scheme that takes place when there is no toxicity $\Rightarrow$
- *Definition:* An initial design $\{x_{i0}\}$ is said to be compatible with the CRM component D_1 in an unrestricted two-stage CRM D* with respect to p if $D^*(H_i) \leq x_{i0}$ for all i with probability one.

Two-stage CRM: compatibility

- *Theorem 2:* With some mild conditions on F, if an unrestricted two-stage CRM is coherent in escalation, then its initial design is compatible with its CRM component.

Two-stage CRM: discussion

- Enforce coherence by restriction:
  - Does not enforce compatibility
  - Gives no insight to the choice of initial design
- Enforce coherence by applying Theorem 1
  - Enforce also compatibility
  - Calibrate initial design with respect to p
  - Choose p with respect to an initial design

Application II:

Combined phase I/II trial

Combined phase I/II Trials

- Bivariate binomial outcomes
  - T = indication of Toxicity
  - R = indication of Response
- Monotone dose-toxicity and dose-response
  - P(T = 1 | dose = x) increases in x
  - P(R = 1 | dose = x) increases in x

Combined phase I/II Trials

- Use coherence structure to guide dose assignments:
  - Stuck when (T,R) = (1,0)?
  - Stay or stop

T	R	Escalation	De-escalation
0	0	Ok	X/X
0	1	Ok	X
1	0	X	X
1	1	X	Ok

Summary & resources

- Motivation: Study coherence, whose ethical implication is immediately observed in dose-finding studies.
- Technical details: Cheung (2005). Coherence principles in dose-finding studies. *Biometrika* **92,** 863-873
- Software: An R function “cohere” in the “titecrm” library at CRAN