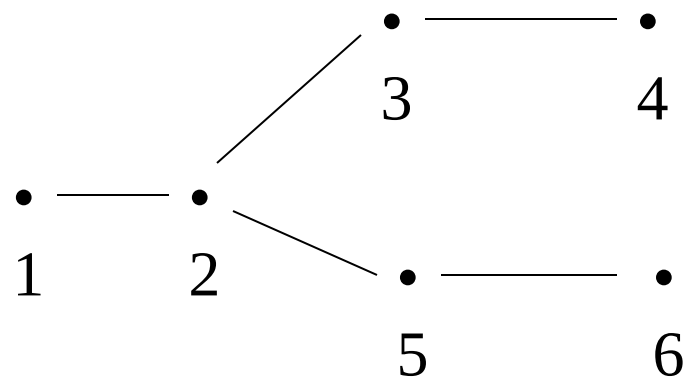
Ordered Restricted and Model-Based Designs for Partial Orders

Examples: Patnaik et al. (JCO, Nov. 2000)

"Combination"	Pacitaxel	Carboplatin
1	54	6
2	67.5	6
3	81	6
4	94.5	6
5	67.5	7.5
6	67.5	9

- Tox probabilities follow a "partial order" : there exist pairs of combinations for which the ordering of toxicity probabilities is not known



Method of CDP (2004, Biometrics)

- Based on a method of estimating parameters subject to a partial order given by Hwang and Peddada (1994, Annals of Statistics)
- Idea:
  - Estimation subject to a simple (complete) order is well worked out
  - There are easy-to-do algorithms to get the estimates

Hwang and Peddada (1994)

- We know all about combinations 1 and 2
  - Tox prob with 1 is less than all the others
  - Tox prob with 2 is more than 1, less than the rest
- Let's guess at the orderings we don't know:
  - Guess order is 1 – 2 – 3 – 4 – 5 – 6
  - Estimate probabilities in this simple order
    - Keep these for 1 and 2, throw away the rest

Hwang and Peddada (1994)

- If we didn't have combinations 5 and 6, we'd have a simple order: 1—2—3—4
  - Hold 1 and 2 at previous estimates, use algorithm for simple order to estimate probabilities for 3 and 4
- If we didn't have combinations 3 and 4, we'd have a simple order: 1—2—5—6
  - Hold 1 and 2 at previous estimates, use algorithm for simple order to estimate probabilities for 5 and 6

Conway, Dunbar, Peddada (2004)

- Compute estimates by taking all possible guesses at the ordering and averaging the results

Possible guesses consistent with the partial order
1 – 2 – 3 – 4 – 5 – 6
1 – 2 – 3 – 5 – 4 – 6
1 – 2 – 3 – 5 – 6 – 4
1 – 2 – 5 – 3 – 4 – 6
1 – 2 – 5 – 3 – 6 – 4
1 – 2 – 5 – 6 – 3 – 4

Dose allocation

- Once the toxicity probabilities have been estimated, allocate next patient to dose level closest to the target

- Had built in stopping rules, etc.

CRM for Partial Orders

Wages, Conaway and O'Quigley (2011)

- Nolan Wages talk will give more detail
- Think of each possible ordering as a "model" within which we can apply usual CRM

"model"	Ordering
M1	1 – 2 – 3 – 4 – 5 – 6
M2	1 – 2 – 3 – 5 – 4 – 6
M3	1 – 2 – 3 – 5 – 6 – 4
M4	1 – 2 – 5 – 3 – 4 – 6
M5	1 – 2 – 5 – 3 – 6 – 4
M6	1 – 2 – 5 – 6 – 3 – 4

Order restricted method is harder to program

- Estimation algorithm should only be applied to subset of dose combinations that have at least one patient on them
  - Depending where you are in the phase I trial, might have a partial order or simple (complete) order
    - If have a partial order, need to be able to generate all simple (complete) orders consistent with the partial order.

CRM for partial orders seems to have better properties

- In terms of identifying the MTD
  - Built on CRM for complete orders
- Intuitive argument: Eventually the data weights the correct ordering and the properties of the usual CRM take over.
  - Not quite as simple as this….
- Is % correctly identifying the MTD the right way to compare?

Different assumptions and diffent goals

- Order restricted: only assumes the partial order is correct
- Gives valid estimates of toxicity probabilities for all combinations?
  - In theory, yes
  - With number of patients in typical phase I?

Multiple MTDs?

- CRM: Goal is to a find a combination that has toxicity probability close to target
  - Not meant to provide estimate of dose-toxicity profile across the combinations

- Should we be looking for one MTD or set of possible MTDs?

Both rely on specification of simple (complete) orders: can be many of these

		Agent 2		
	Level	1	2	3
Agent 1	1	1	2	4
	2	3	5	7
	3	6	8	10
	4	9	11	12

M1) 1-2-3-4-5-6-7-8-9-10-11-12

M2) 1-3-2-4-5-6-7-8-9-10-11-12

M3) 1-2-3-5-4-6-7-8-9-10-11-12

M4) 1-2-3-6-4-5-7-8-9-10-11-12

….

Limiting the number of orders?

- CDP (2004) paper showed that partial order method works well using a subset of all the order
  - As long as the correct order is in the subset
  - Properties decline if correct order is not among the subset chosen.

CRM for partial orders

- Anecdotal evidence suggests that properties may decline as well if correct order is omitted
  - From my experience in simulating properties for a couple of combination agent studies
  - Unknown if this is true in general
- Unknown how the choice of skeleton affects this

Can the order restricted method be used with the CRM method?

- To help reduce the number of complete orders considered
- To help choose one or more skeletons

Choose a subset of complete orders?

- At the end of stage 1:
- Maximize the ln-likelihood under the partial order :
  - This may not be computationally easy, but it can be done
  - Call this L(PO)

Could the order restricted method be used to help choose a subset of complete orders?

- Start with a number (M) of complete orders
- At the end of stage 1, for each complete order, $1 \leq m \leq M$,
  - Compute estimates under the complete order
  - Compute the associated likelihood
  - Call this L(m)

Diagnostics for correct orders

- Prior to beginning partially ordered CRM, drop orderings with small log-likelihoods.
- "Small" relative to either

$$L(PO) \quad \text{or}$$

$$\sum_{i=1}^{M} \mathrm{L(m)}$$

- Could also look at $\sum_{i=1}^{M} \mathrm{L(m)}$ relative to L(PO)

Choosing a complete order subset

- Method does not depend on chosen skeleton values

- Could be viewed in Bayesian framework with priors on the orders or the underlying toxicity probabilities

Choosing a skeleton

- At the end of stage 1, estimate the toxicity probabilities such to the partial order

- Use smoothed versions of this as the skeleton.