Bayesian Estimation for Dose-Finding Studies

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References

mTPI *v* 3 + 3

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Modified Toxicity Probability Interval Design: A Safer and More Reliable Method Than the 3 + 3 Design for Practical Phase I Trials

Yuan Ji and Sue-Jane Wang

CLINICAL TRIALS *ARTICLE* *Clinical Trials* 2010; **7**: 653–663

A modified toxicity probability interval method for dose-finding trials

Yuan Ji[a], *Ping Liu*[b], *Yisheng Li*[b] *and B Nebiyou Bekele*[b]

CLINICAL TRIALS *ARTICLE* *Clinical Trials* 2007; **4**: 235–244

Dose-finding in phase I clinical trials based on toxicity probability intervals

Yuan Ji[a], *Yisheng Li*[b] *and B. Nebiyou Bekele*[b]

Potential Applications to Behavioral Interventions

Exercise example (health participants; or heart-failure patients):

- Dose levels:
- intensity (low, medium, high) or duration (.5, 1, 2 ,3 hours per week) or some combination of both.
- Toxicity: observe some predetermined SAE, drop out of study, adherence, etc.
- Effectiveness: Assess whether or not the main outcome is achieved (able to walk xx meters, increased stamina etc)

Smoke cessation example:

- Dose levels: (2, 4, 8) messages a day
- Toxicity: Dropouts
- Efficacy: Smoke cessation

Phase I dose-finding

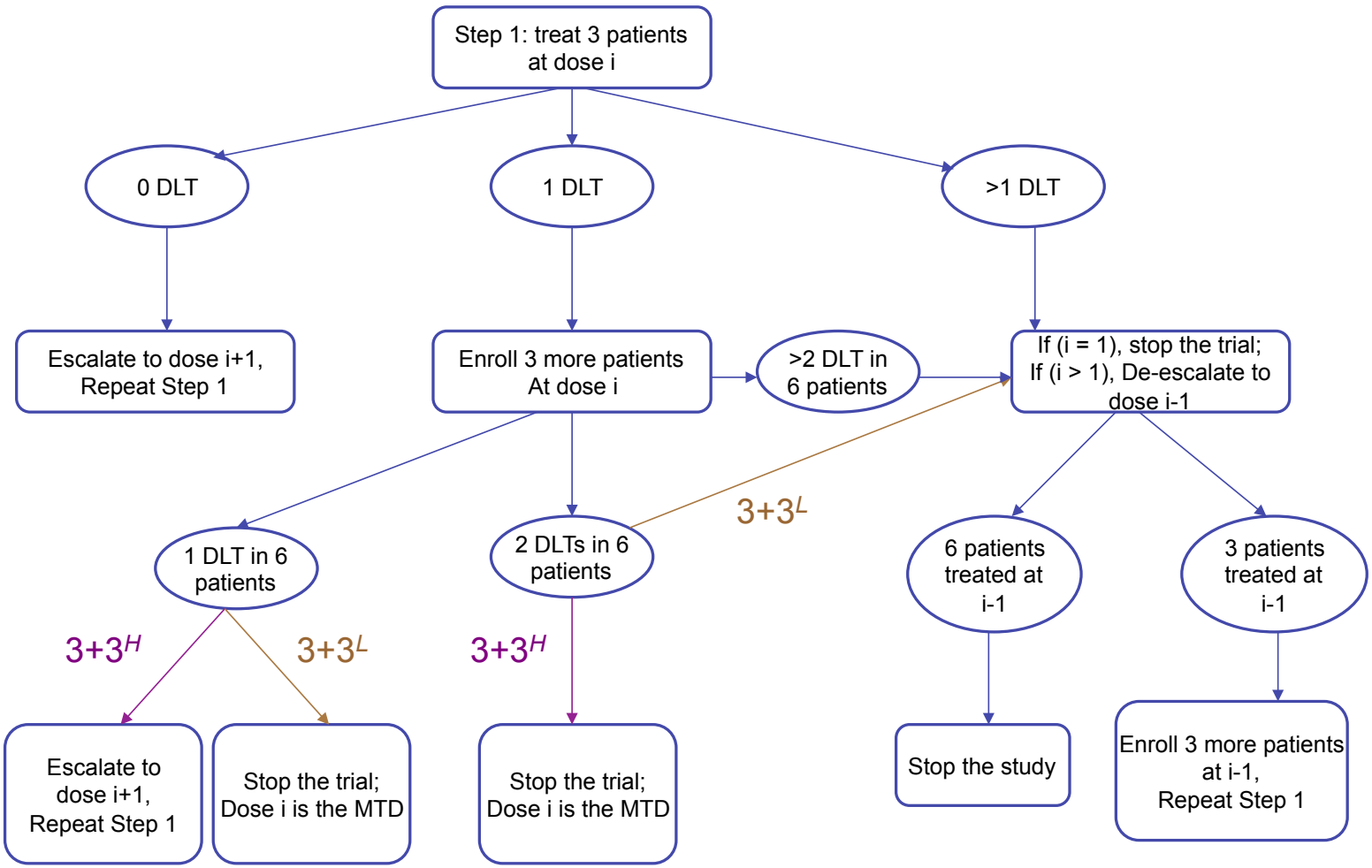
Only consider trials with fixed doses.

A sequence of D doses as candidates.
Dose i has a toxicity probability of p_i (unknown).
Monotonicity : $p_i \leq p_{i+1}$ – higher doses are more toxic
Goal: to find the maximum tolerated dose MTD , defined as the highest dose with toxcity rate lower (or close to) a fixed rate, p_T, e.g., $p_T = 30\%$.
Example: start from 0.5 hours/week for the 1st cohort of patients, and escalate if it is safe; treat future cohorts of patients, and decide on

1. E scalate
2. Stay
3. D e-escalate

The 3+3 Design

Two versions: $3{+}3^H$ and $3{+}3^L$ for high and low maximum toxicity rates p_T, respectively.



The 3+3 Design

Standard in clinical community (simple, transparent, "make sense", perform reasonably well if $p_T \sim 17\%$ or 30%.)

Favorite Target to statisticians

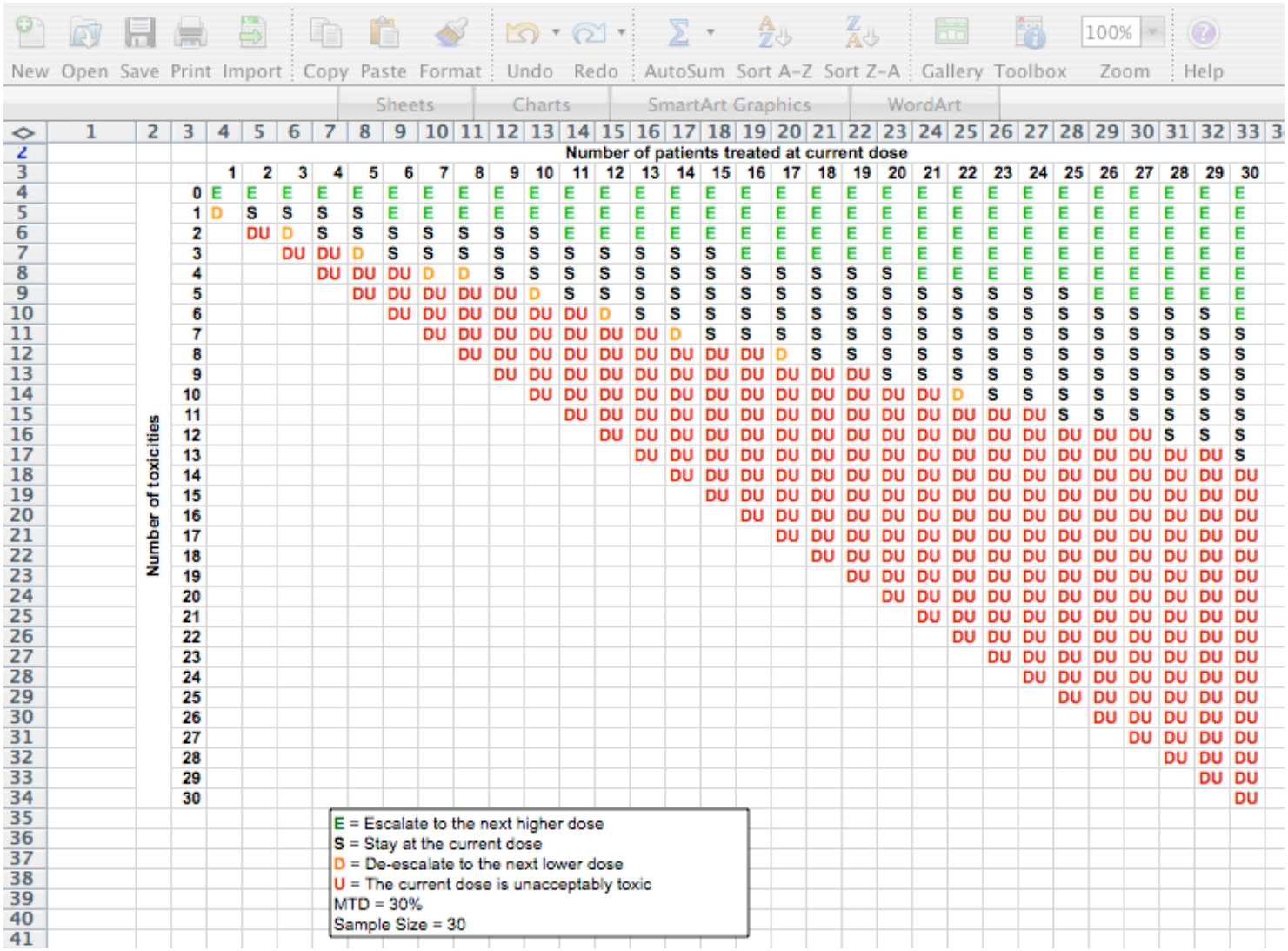
- Not model-based
- No more than 6 patients per dose
- Arbitrary choice of "3"
- Conservative – slow escalation

Dominant in practice (e.g., Rogatko et al. 2007)

- $>98\%$ of all phase I trials between 1991-2006 were based on 3+3 or its variations
- Out of 1,235 trials during the period, 20 were based on CRM; 3 based on EWOC (a variation of CRM)

The mTPI Design

mTPI is a simple, transparant, intuitive and model-based design.



Key Publications to mTPI

Main Publications: Toxicity probability interval (TPI) method: Ji et al. (2007); modified TPI (mTPI) method: Ji et al. (2010); comparison to 3+3: Ji and Wang (2013)

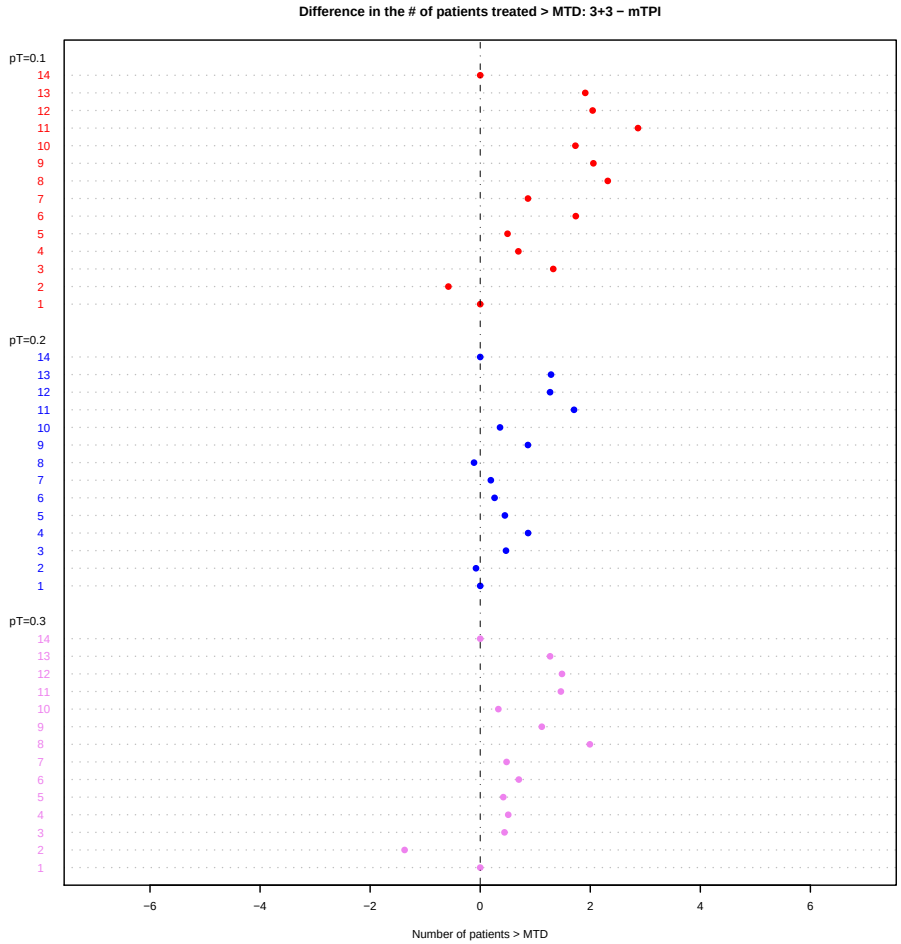
Discussion and Extension by Others: Hather and Mackey (2009); Blanchard and Longmate (2011);

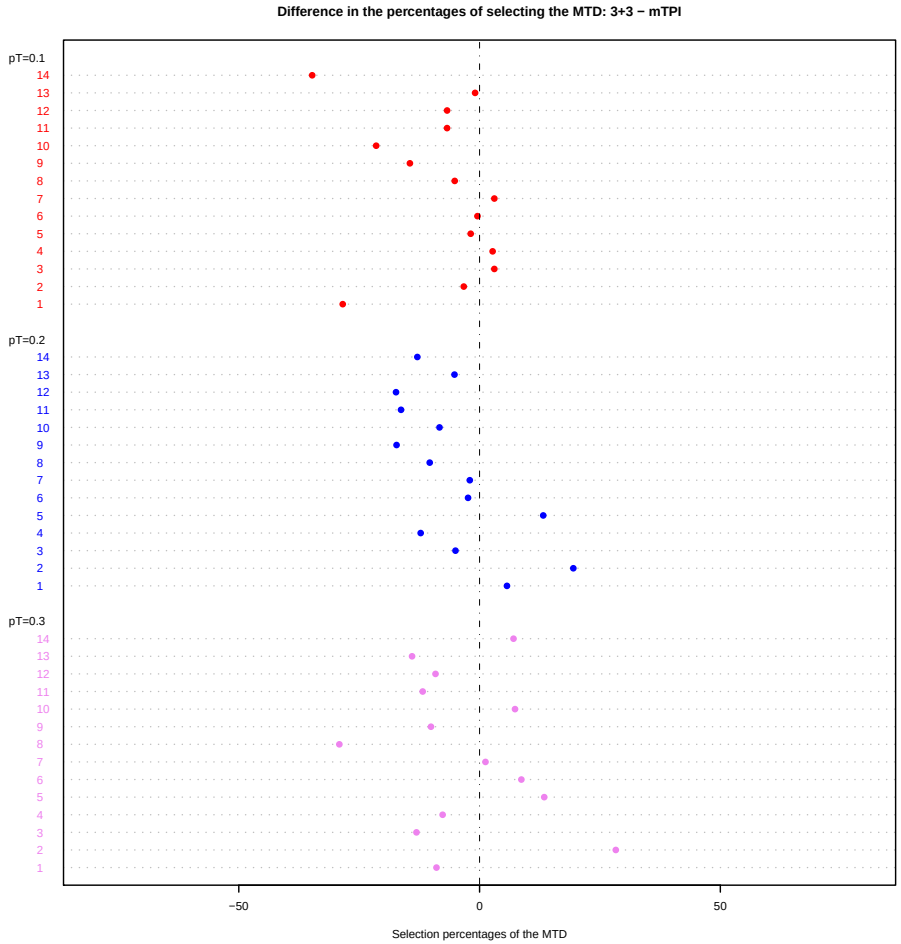
Completed trial: Papers on Brit. J. of Haematology, Lancet Oncology, etc.

Users: Most major pharma companies; Research (e.g., U. Penn); Hospitals and Academic institutions (e.g., MD Anderson; U Penn.)

Comparison between 3+3 (gold standard) vs. mTPI

"% of MTD" and "# pats on doses above the MTD"





Results Summary: 3+3 vs. mTPI

Safety: In 41 out of 42 scenarios, mTPI has smaller overall toxicity than 3+3; In 38 out of 42 scenarios, mTPI puts fewer patients at doses above MTD than 3+3

Power: In 34 out of 42 scenarios, mTPI selects the true MTD with higher frequencies than 3+3

Implementation: mTPI is as easy to implement in practice as 3+3

Next-Generation Dose Finding: Web-TPI

The mTPI method is now fully web-based.

- No hassle in downloading, maintaining, error shooting of local software
- Can be accessed on any browser (caution wit Internet Explorer; try Firefox or Chrom or Safari)
- Work with Tablets and Smart Phones
- Dose finding anywhere and anytime

http://compgenome.org/NGDF/

The rest of the talk demo the NextGen DF.