Comprehensive evaluation of CRM, mTPI, and 3+3 relative to a benchmark

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Outline of Talk

- Methods compared
- Summary estimates used to compare methods
- Simulation study

Methods compared

- Continual reassessment method (CRM)
- Modified toxicity probability interval (mTPI)
- 3+3
- Benchmark

CRM

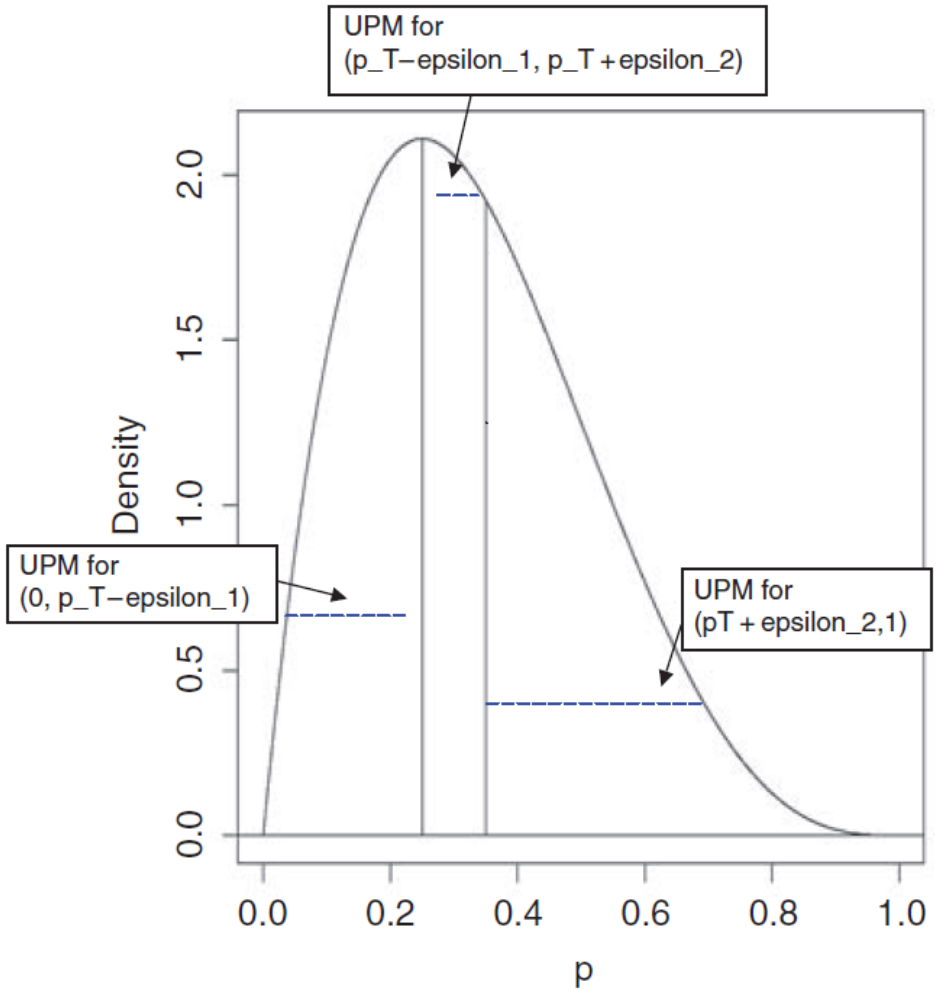
- 2-stage design
- Stage 1
  - Cohort size of 1
  - Increase until heterogeneity is observed responses
- Stage 2
  - dfcrm package used to make dose recommendations specifying a power model to model DLT probabilities
  - Skeleton generated with the getprior function from dfcrm
    - getprior(0.06,0.2,2,# of dose levels)
  - Trial terminated if at dose 1 and the lower bound of 90% confidence interval of the probability of toxicity is greater than the target toxicity

mTPI

- Decisions are based on an equivalence interval
  - $[p_T - \epsilon_1, p_T + \epsilon_2]$
- Safety stopping measures
  - Terminate early if probability of toxicity, given data, too high
  - Exclude doses in future if probability of toxicity too high
- http://compgenome.org/NGDF/
  - Specifying a cohort size of 3 and $\epsilon_1 = \epsilon_2 = 0.05$
- Next dose chosen by maximum unit probability mass (UPM)

mTPI

Posterior probability distribution



Ji, Liu, Li, and Bekele (2010)

Benchmark

- Suppose we know each patient's toxicity tolerance
  - tolerance generated from uniform (0,1) distribution
- For a specified toxicity curve, know when each patient would have a DLT
- Example:
  - 4 dose levels
  - Toxicity curve: (0.1, 0.19, 0.30, 0.39)

O'Quigley, Paoletti, and Maccario (2002)

Benchmark

True toxicity curve: (0.1, 0.19, 0.30, 0.39)

Patient	Tolerance	Toxicity at dose level i			
		1	2	3	4
1	0.349	0	0	0	1
2	0.462	0	0	0	0
3	0.222	0	0	1	1
4	0.517	0	0	0	0
⋮	⋮	⋮	⋮	⋮	⋮
23	0.074	1	1	1	1
24	0.382	0	0	0	1
Est. Tox. Rate		0.06	0.22	0.27	0.40

Benchmark

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Summary estimates used to compare methods

- Percent correct selection (PCS)
- Accuracy index
- Other basic statistics:
  - Proportion of toxicities observed
  - Average number of subjects allocated to a dose

Percent correct selection (PCS)

- The probability of selecting the true MTD
- Percent of dose selection within 5% and 10% of the target toxicity rate

Accuracy Index

- For dose selection:
  - $A_N = 1 - K \times \frac{\sum_{k=1}^{K} \rho_k \times \text{Probability of selecting dose k}}{\sum_{k=1}^{K} \rho_k}$
  - K is the number of doses
  - $\rho_k = |p_k - \theta|$, where p_k is the true toxicity probability at dose k and θ is the target toxicity

- Also used for subject allocation

Cheung (2011)

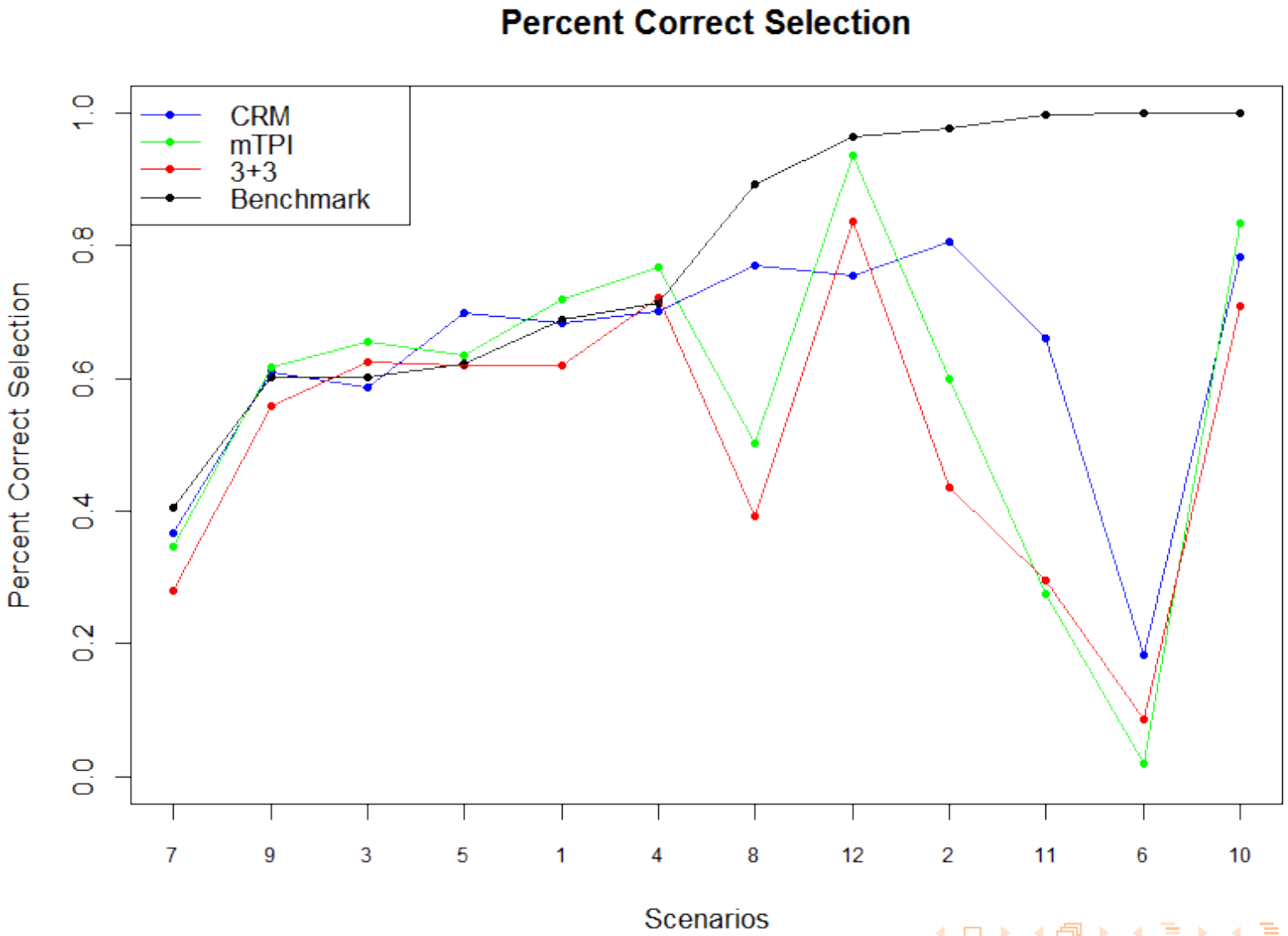
Dose curve selection

- 10,000 curves were simulated using order statistics from a Beta distribution (8 dose levels)
- K-means clustering used to partition these curves into 12 groups
- Curves within groups were averaged to create the 12 curves used in the simulations

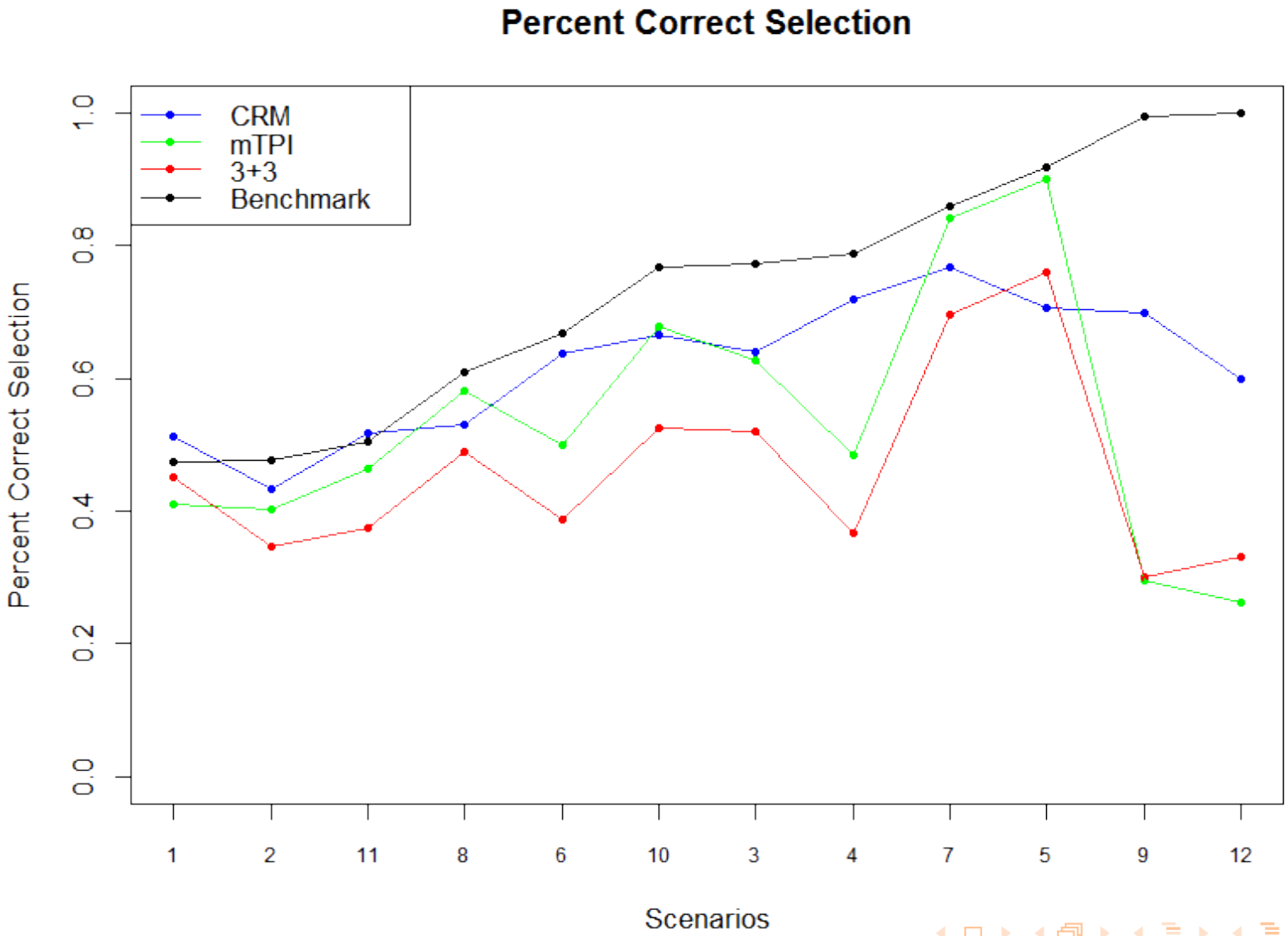
Simulation setup

- 2,000 simulations
- Target toxicity rate $\theta = 0.2$
- Varying number of dose levels
  - 3 dose levels $\rightarrow$ n=18
  - 4 dose levels $\rightarrow$ n=24
  - 6 dose levels $\rightarrow$ n=36
  - 8 dose levels $\rightarrow$ n=48
- dfcrm package in R used for CRM
- http://compgenome.org/NGDF/ used for mTPI

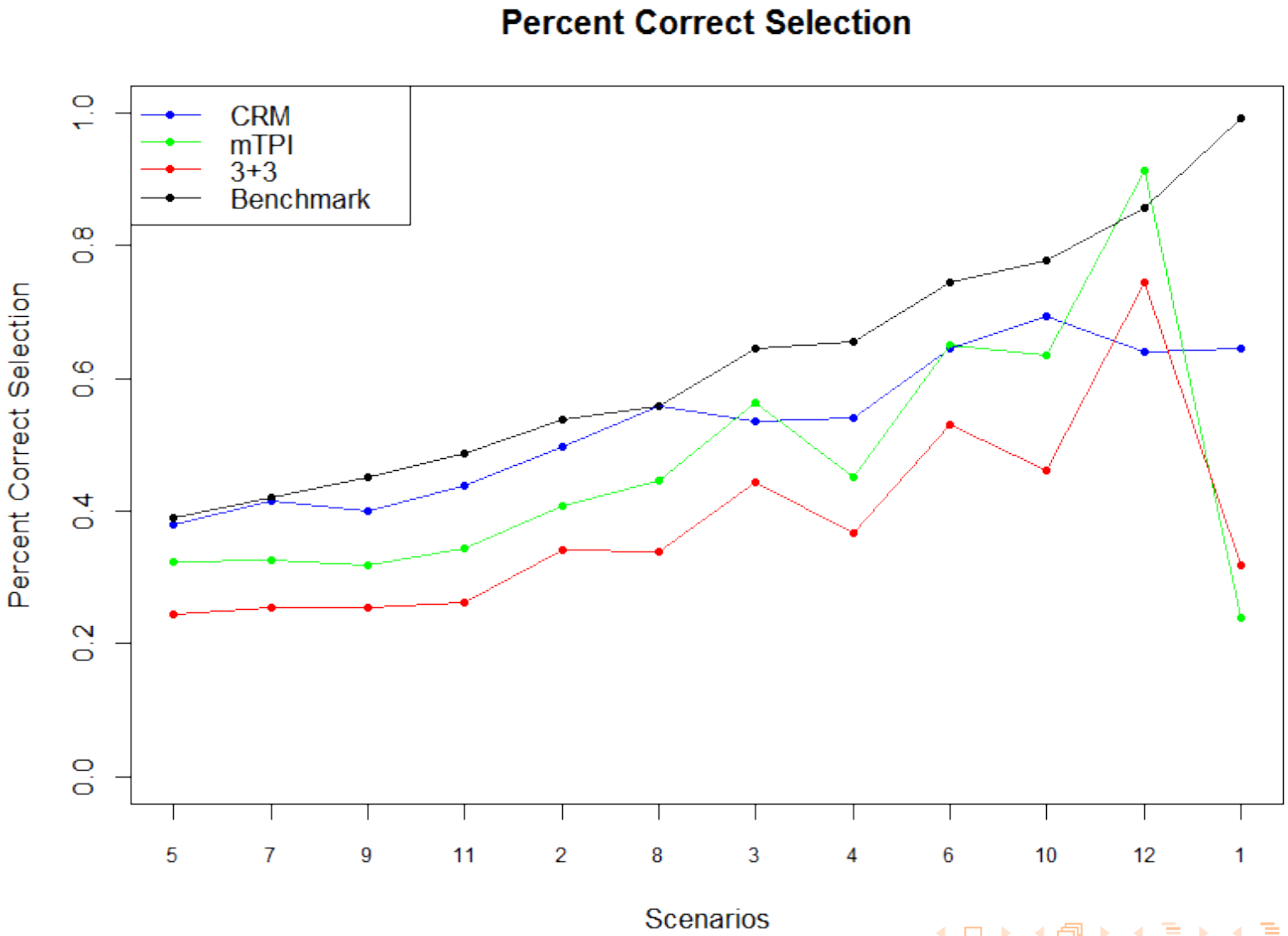
3 Dose levels



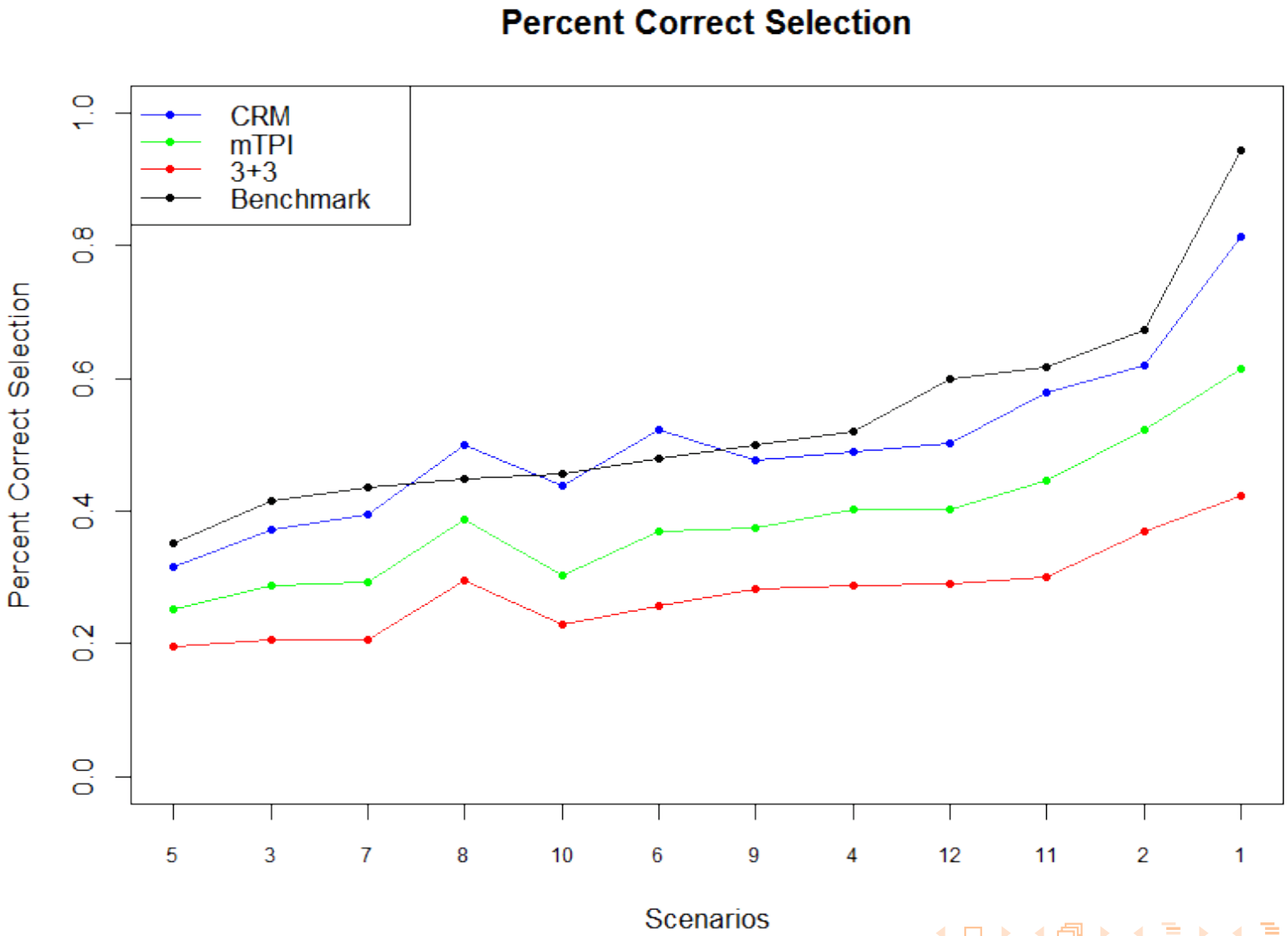
4 Dose levels



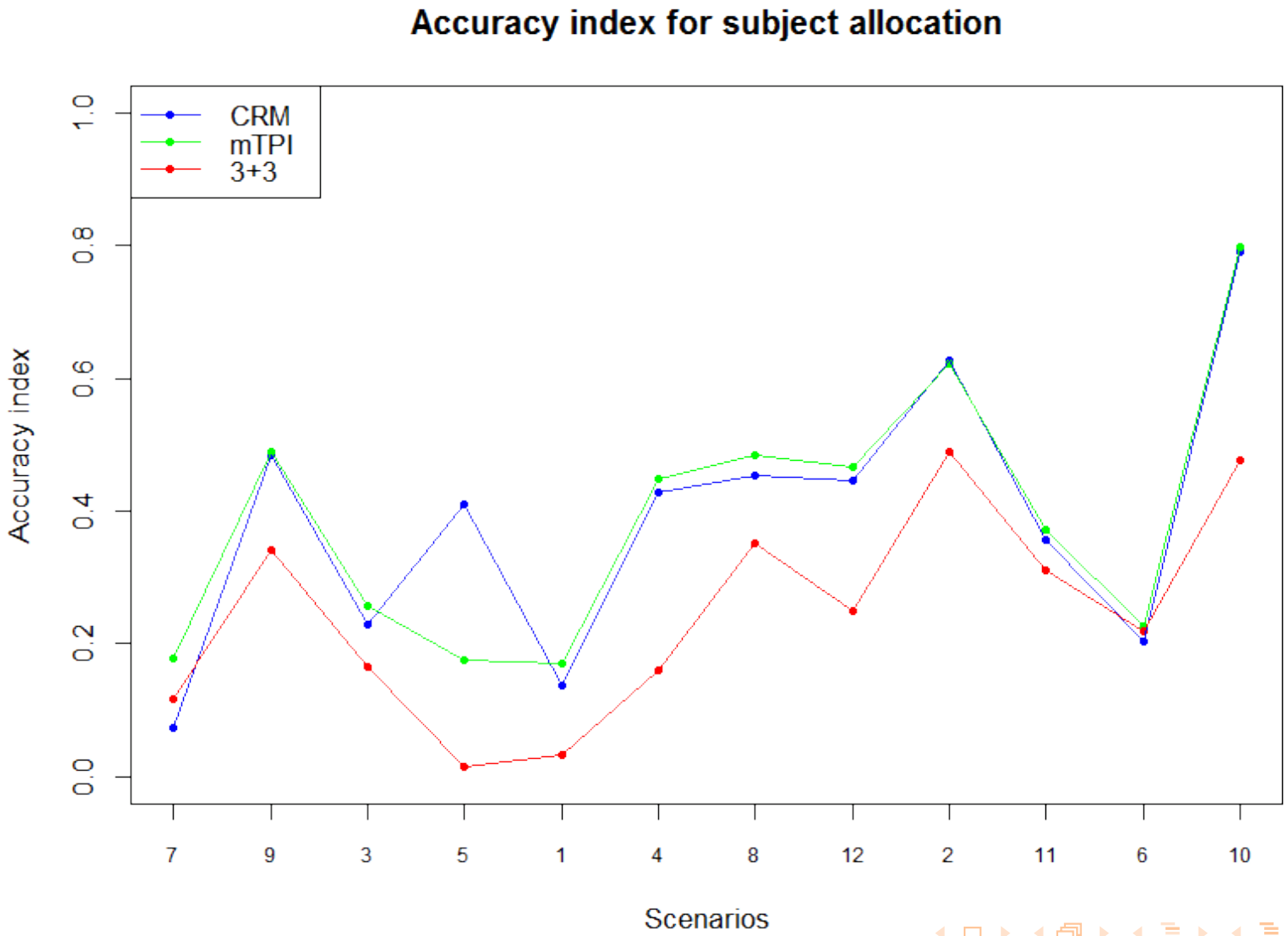
6 Dose levels



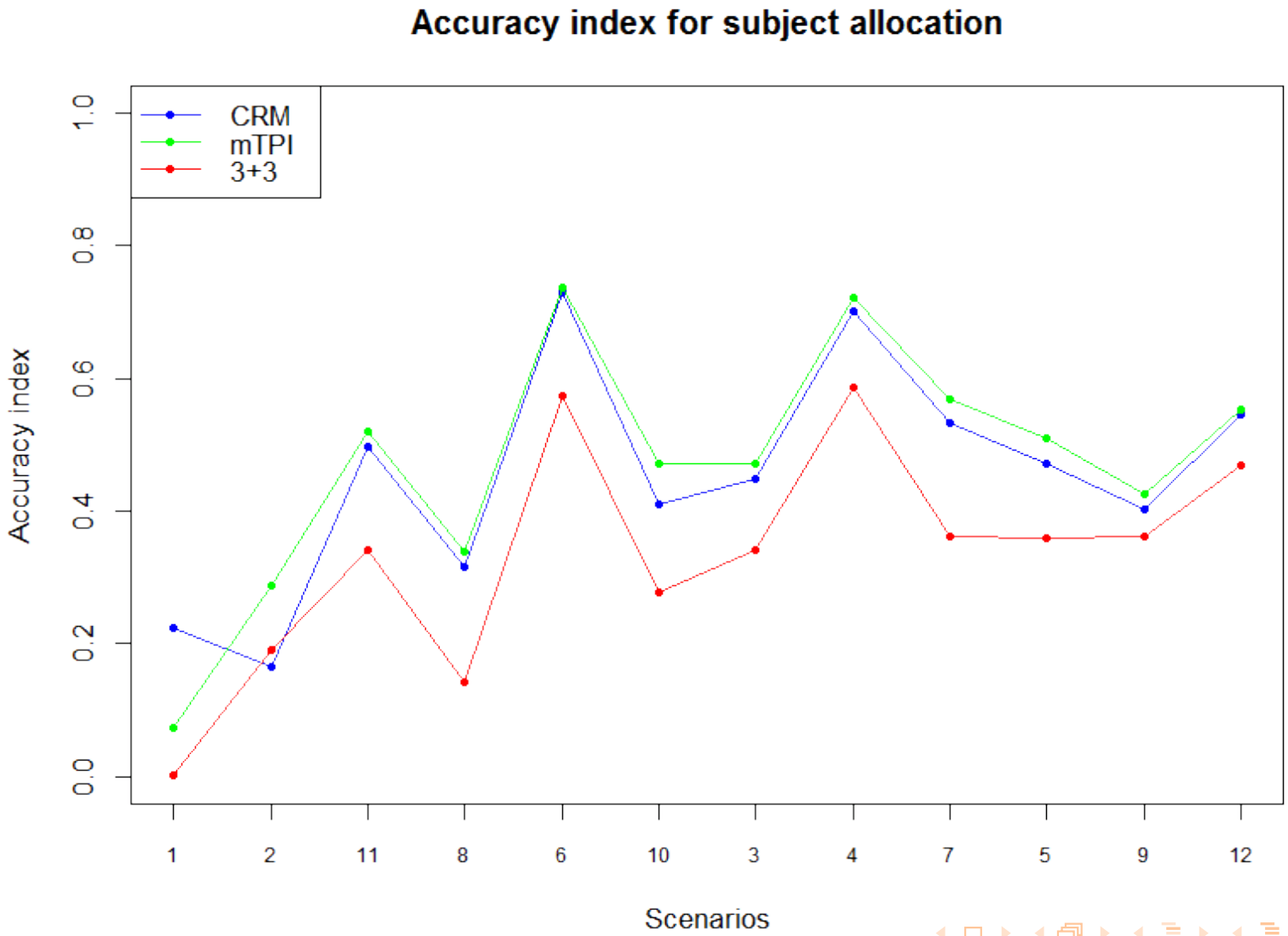
8 Dose levels



3 Dose levels



4 Dose levels



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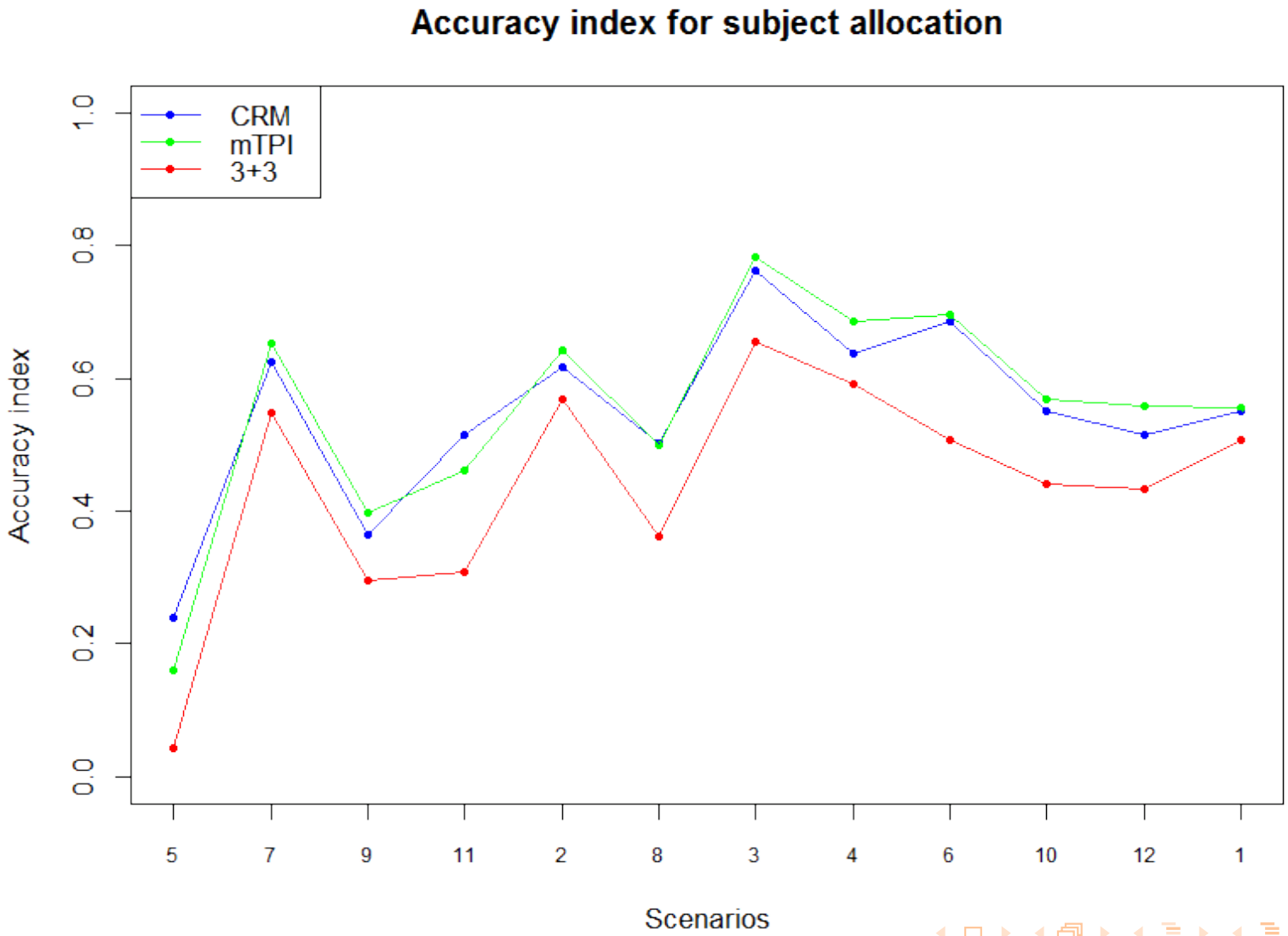

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