MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Dose-escalation designs for combination & dose-schedule studies

Lecture 8: Model-free designs for combinations

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Motivation

The majority of proposals for combination studies are **model-based**.

While baring many advantages, there are potential drawbacks:

- The **search** of the MTC **is restricted** to particular surface;
- Might require **randomisation** (implicitly) for exploration of the surface;

Solution: Model-Free Designs

Model-Assisted Approaches

Bayesian Optimal Interval (BOIN) Design extension for dual-agent combinations:

- The probabilities of toxicities are modelled independently;
- Different combinations are not linked;
- Preserves features of rule-based designs;
- Share the same critisism as the single-agent version (see L4)

Curve-Free Approaches

A product of independent beta probabilities (PIPE) Design

- **Model-free** approach to avoid model choice;
- The probabilities of toxicities are modelled independently, and but then linked via monotonicity assumption;
- Use conjugate Bayesian methods $\rightarrow$ **no statistical software is needed** and Excel can do the calculations

Using the contour distribution

- Calculate the probability of being above the target toxicity level, TTL, (averaged over the contour distribution) for safety

0.2	**0.6**
0.05	**0.3**

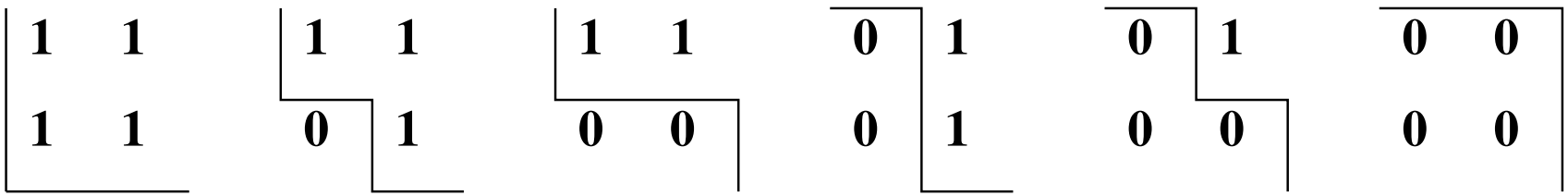
1	**1**
1	**1**

$$\text{Probability of this contour} =$$
$$P(Z > 0.33|p = 0.2) \times P(Z > 0.33|p = 0.6) \times$$
$$P(Z > 0.33|p = 0.05) \times P(Z > 0.33|p = 0.30)$$

Where Z has a beta distribution

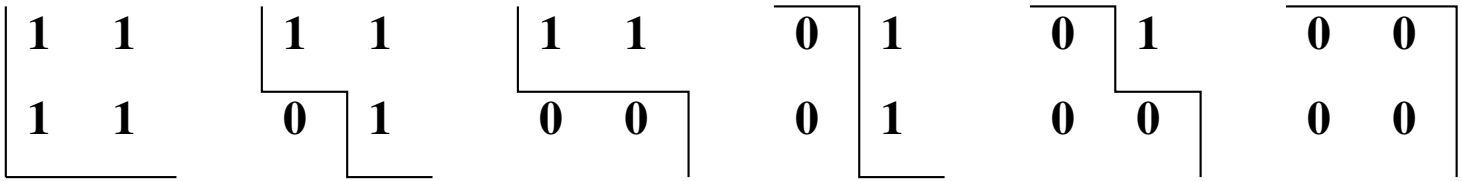
- Use the **most likely contour** for Decision making

Contour distribution



Contour distribution

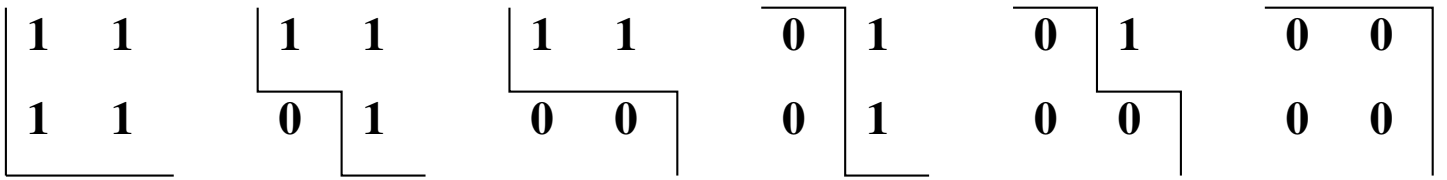
0.2	0.6
0.05	0.3



Contour Probs	0.13	0.18	0.17	0.2	0.19	0.13

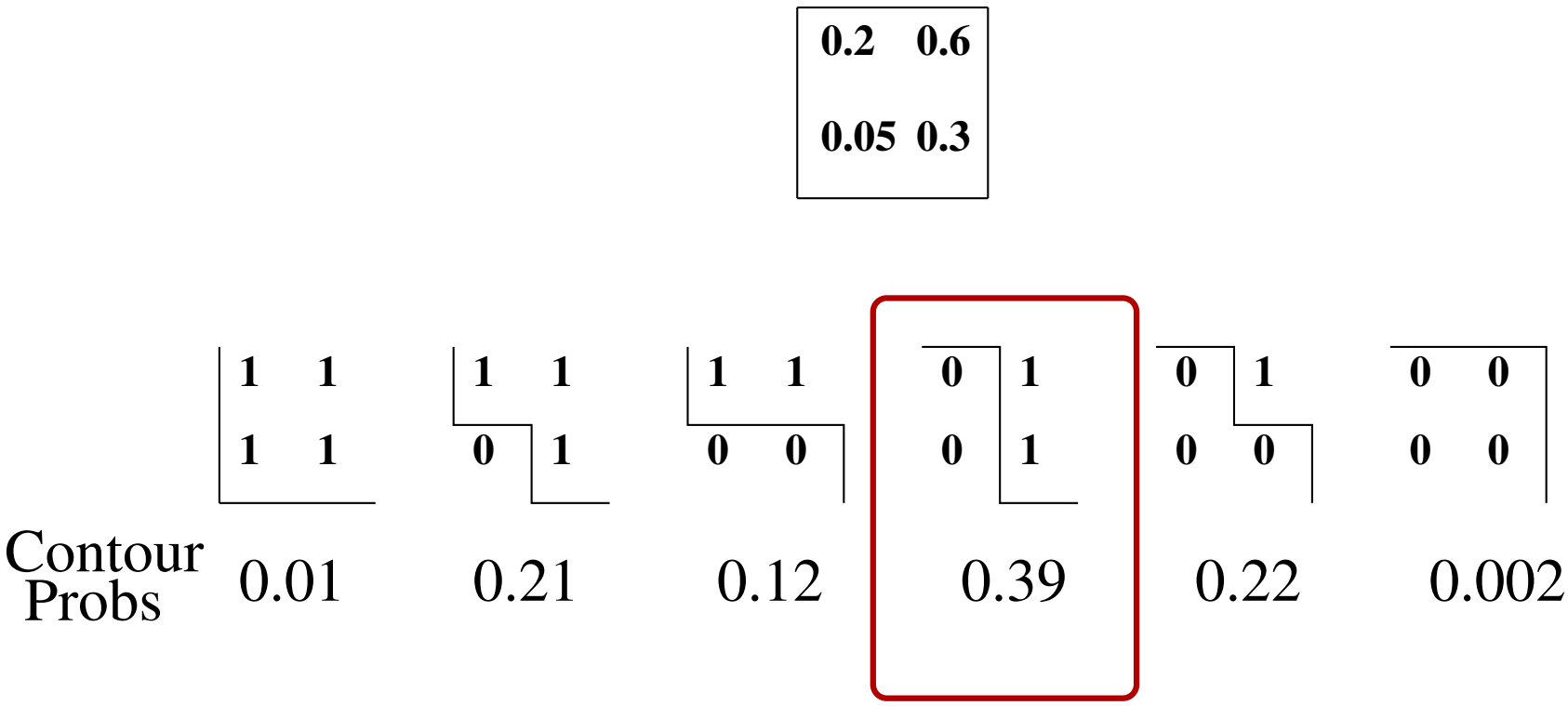
Contour distribution

0.2	0.6
0.05	0.3



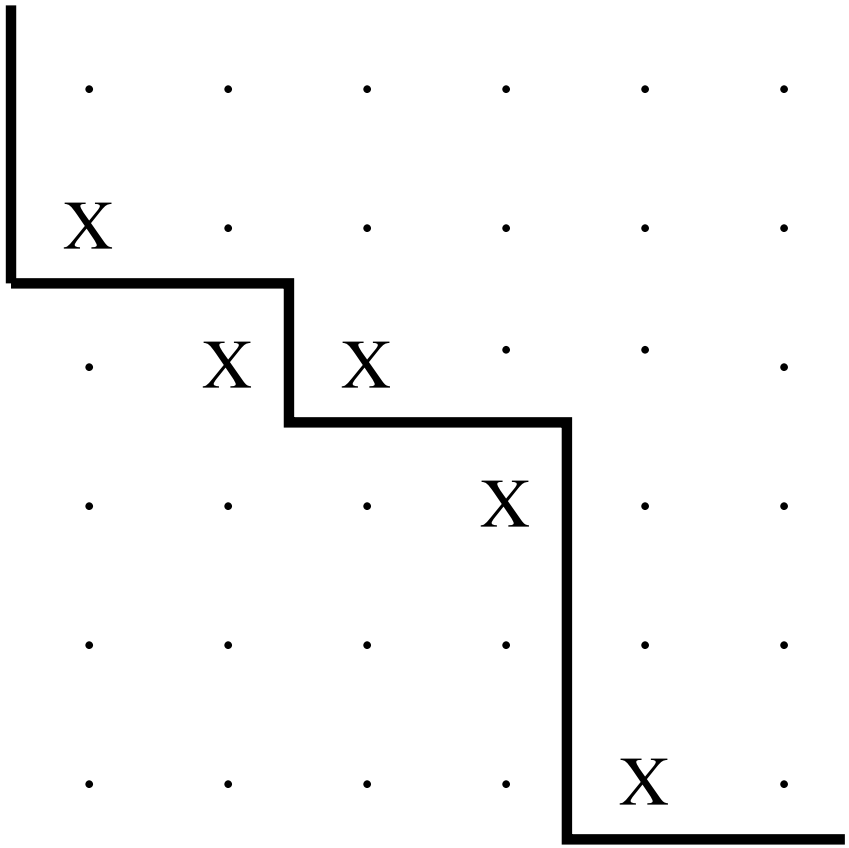
Contour Probs	0.01	0.21	0.12	0.39	0.22	0.002

Contour distribution



Contour distribution

Define a set of dose combinations that are allowed to be given.



Contour distribution

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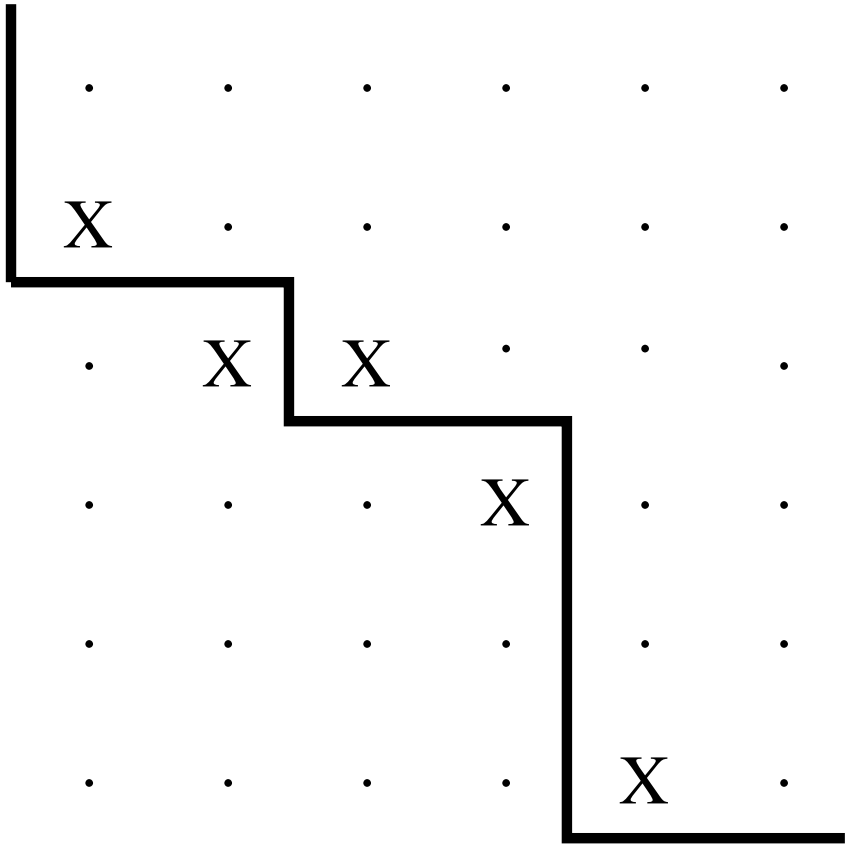
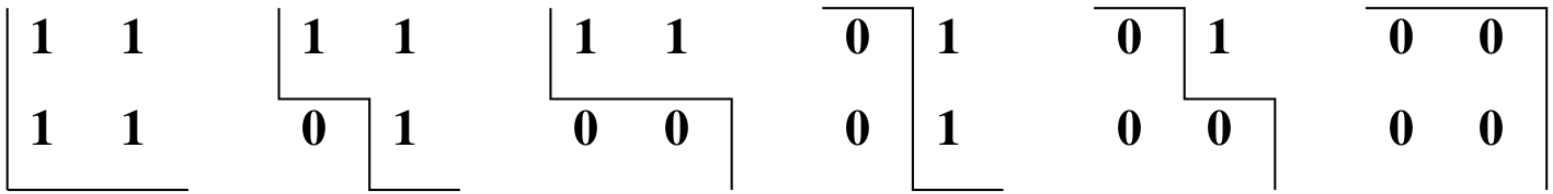


Note: there are several combination could be recommended if this was the final estimated contour

Calibration of prior distribution

In 2 $\times$ 2 setting with four combination, the following contours are possible



How the prior distribution of these contours should be specified? What would be a **weakly-informative prior**?

Consider a uniform one - each contour is equally likely.

- In 5 our of 6 contours, the first combo is non-toxic, and
- In 5 out of 6 contours, the last combo is toxic.

$\rightarrow$ difficult to get into or out of a “corner”

A careful calibration of prior is required before the trial.

Surface-Free Design

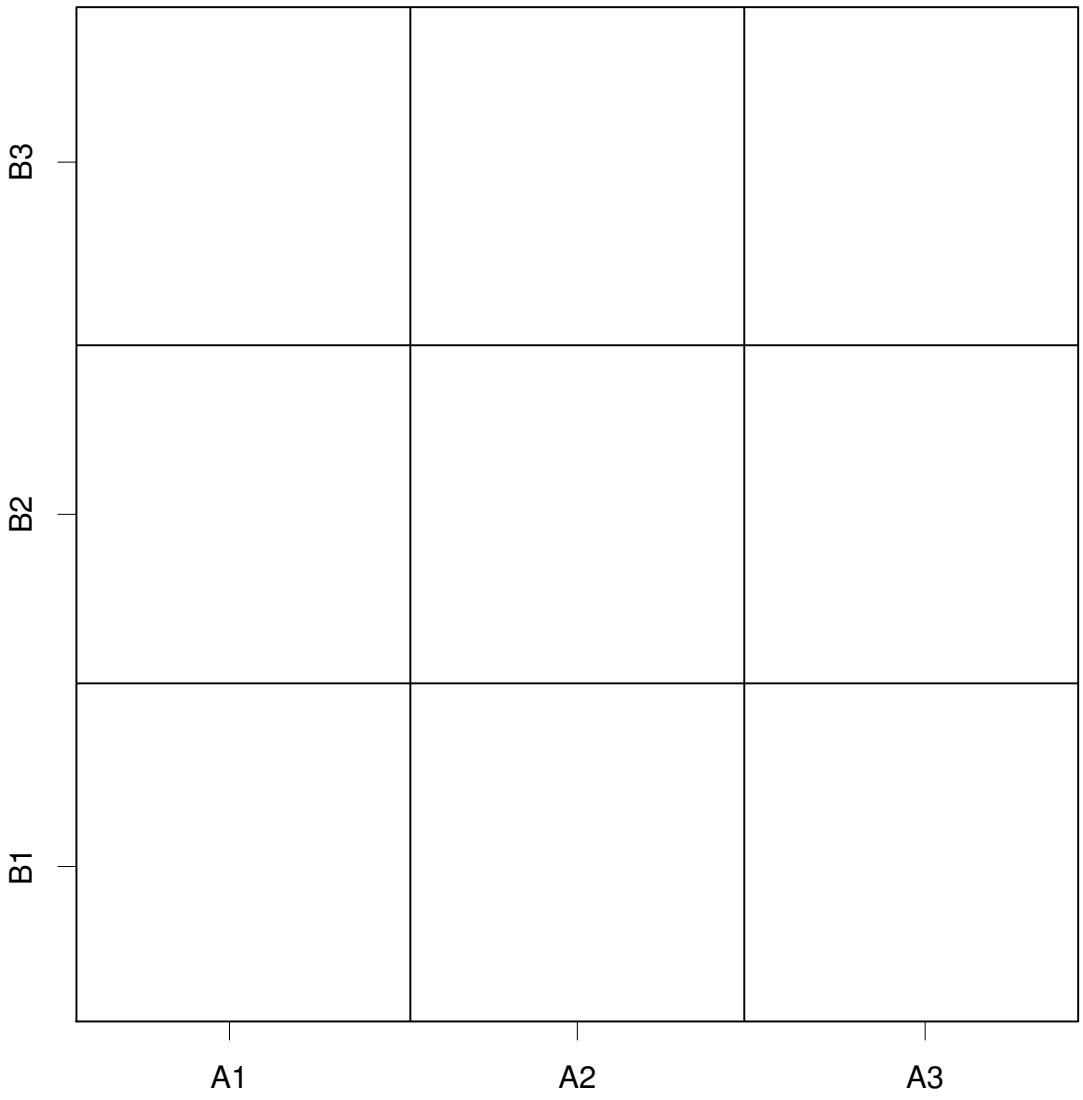
- PIPE was shown to perform better with randomisations;
- **Surface-Free Design (SFD)** is a model-free alternative that
  - Only relies on the monotonicity within each compound;
  - Does not require randomization ;
  - Does not require any pre-specified orderings;

  The proposed approaches **models the "connections"** between neighbouring combinations.

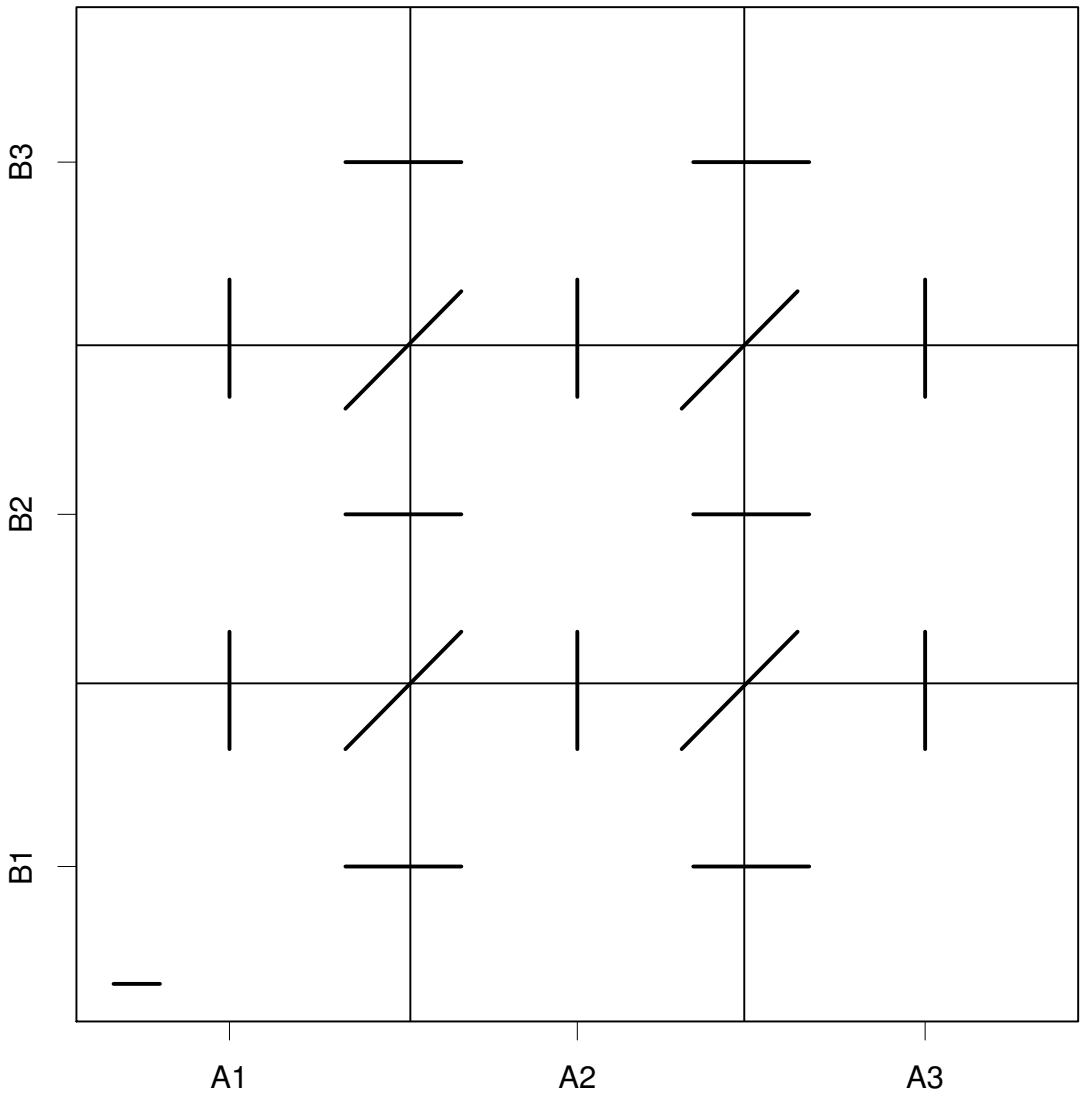
Illustration

- Consider a dual-agent combination study: A and B;
- 3 doses of each agent – 9 combinations;
- Start at the lowest combination;
- Cohorts of 3 patients;
- The maximum sample size $N = 36$.

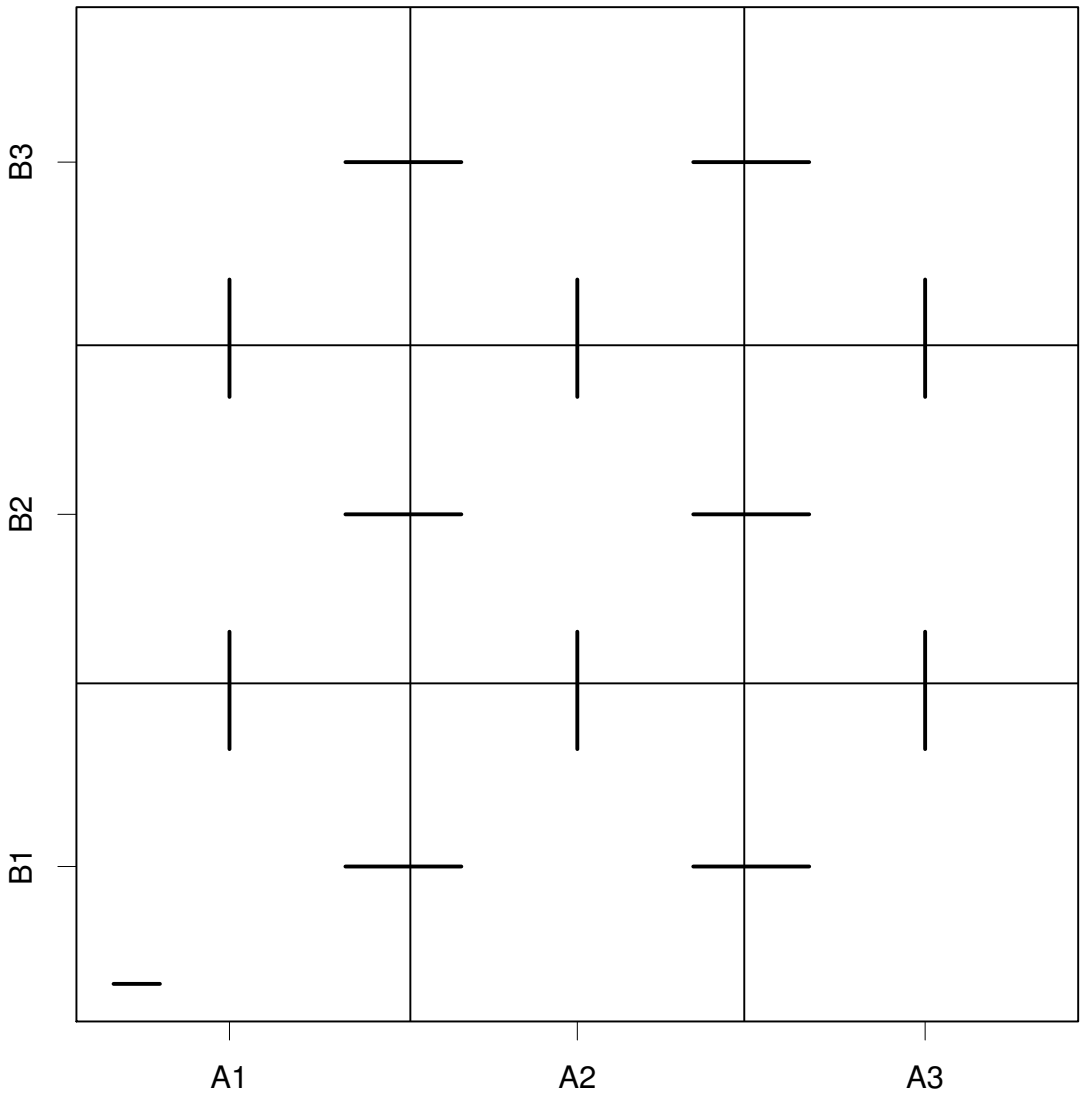
Model Construction



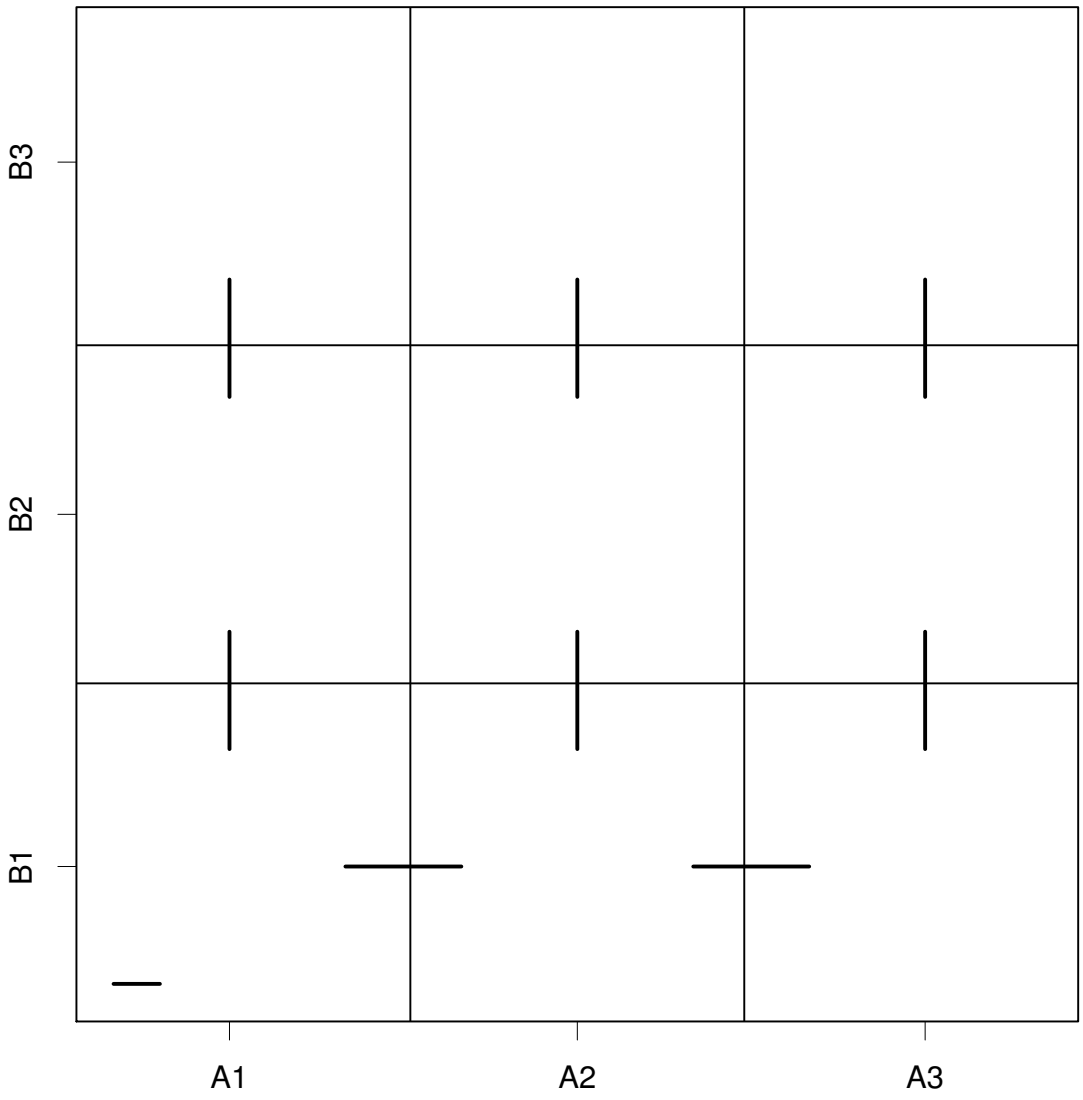
Model Construction



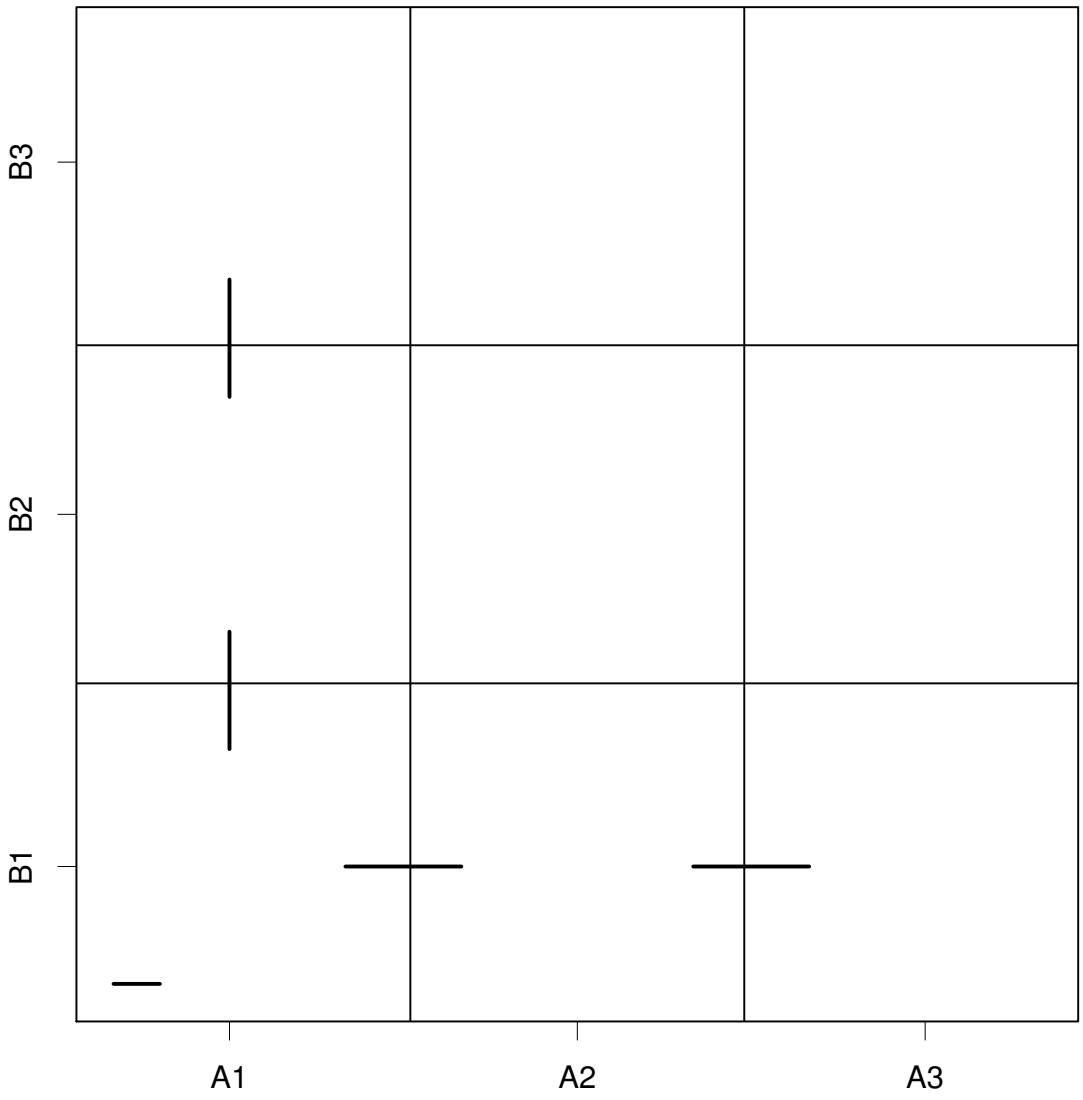
Model Construction



Model Construction



Model Construction



Model Parametrisation

θ – probability of *not observing* a toxicity given the lowest combo;

$\theta_i^{(j)}$ – ratio between probabilities of not observing toxicity between neighbouring combos ith and $(i-1)$th doses of A & jth dose of B:

$$\theta_i^{(j)} = \frac{1 - p_{i,j}}{1 - p_{i-1,j}}. \tag{1}$$

$\tau_j^{(i)}$ – ratio between probabilities of not observing a toxicity between neighbouring combos jth and $(j-1)$th doses of B & ith dose of A:

$$\tau_j^{(i)} = \frac{1 - p_{i,j}}{1 - p_{i,j-1}}. \tag{2}$$

No-interaction assumptions: $\tau_j^{(1)} = \tau_j^{(2)} = \tau_j^{(3)} = \tau_j$

Resulting Model:

$$p_{ij} = 1 - \theta\theta_2 \dots \theta_i \tau_2 \dots \tau_j \tag{3}$$

Inference

- $\theta_i \sim \mathcal{B}(a_i, b_i), \tau_j \sim \mathcal{B}(e_j, f_j)$ independent Beta RVs
- The distribution induced by the model is **a product-of-beta**.
- The posterior is obtained via Bayes theorem
- **The variance of the toxicity probability increases** as the dose of the agent increases.

Specification of Parameters - Prior Elicitation

Assume that clinicians provide toxicity estimates for each agent individually.

Let $\hat{p}_{i0}(0)$ be the prior point estimates of the toxicity risk for Agent A;
Let $\hat{p}_{0j}(0)$ be the prior point estimates of the toxicity risk Agent B.

The prior mean values of θ_i and τ_j could be found as

$$\hat{\theta}_i(0) = \frac{1 - \hat{p}_{i,0}(0)}{1 - \hat{p}_{i-1,0}(0)} \qquad \hat{\tau}_j(0) = \frac{1 - \hat{p}_{0,j}(0)}{1 - \hat{p}_{0,j-1}(0)}$$

The parameter corresponding to the lowest combination can be found as

$$\hat{\theta}(0) = 1 - \hat{p}_{0,1} - \hat{p}_{1,0} + \hat{p}_{0,1} \times \hat{p}_{1,0}.$$

Prior Elicitation Example

Prior mean estimates of the toxicity probabilities:

$$\hat{p}^{(A)}(0) = [0.05, 0.10, 0.20]^{\mathrm{T}} \qquad \hat{p}^{(B)}(0) = [0.10, 0.20, 0.30]^{\mathrm{T}}.$$

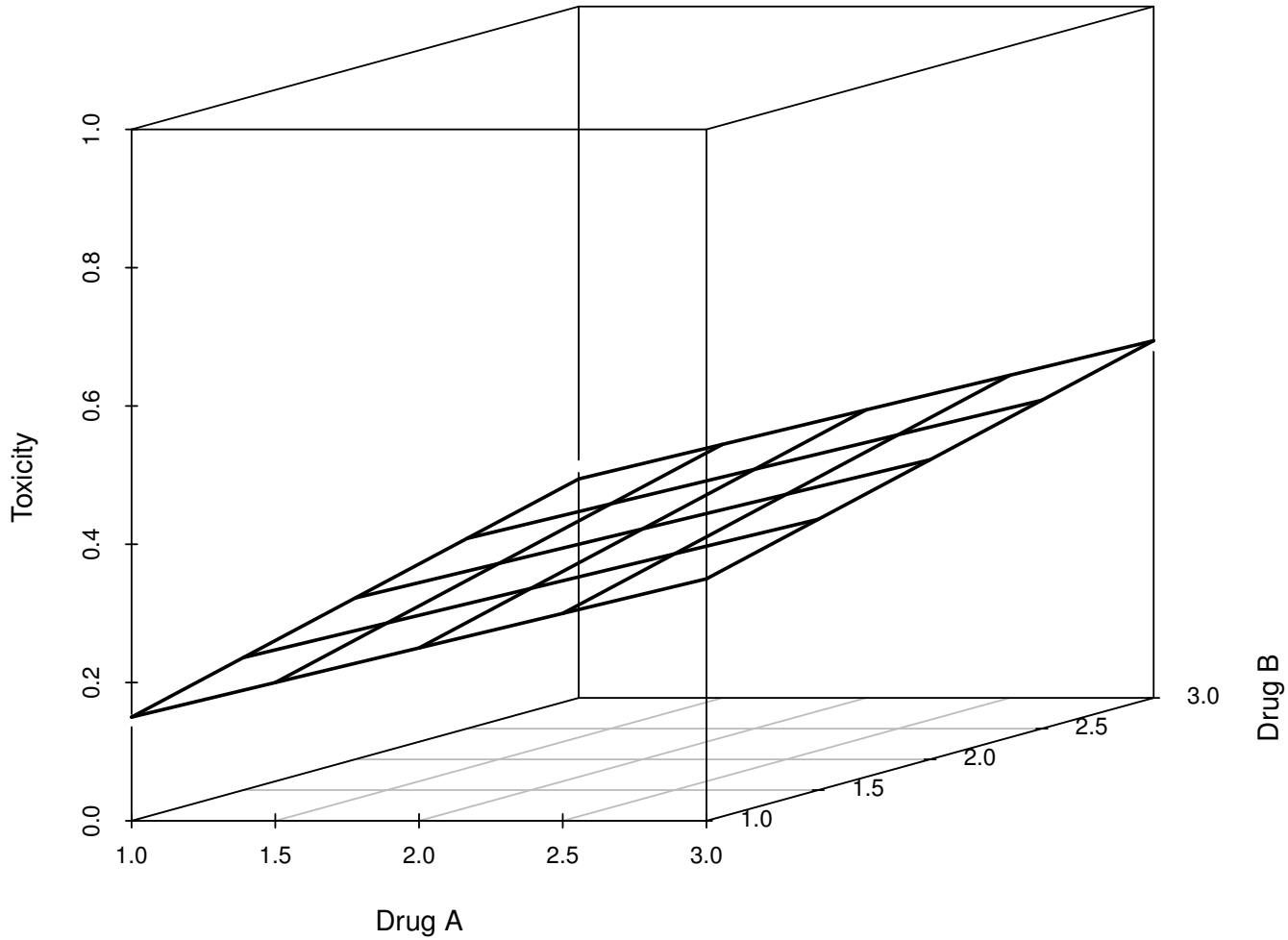
Then, $\hat{\theta}(0) = 1 - 0.10 - 0.05 + 0.10 \times 0.05 = 0.855$.

Using the prior information about agent A,

$$\hat{\theta}_2(0) = \frac{1 - \hat{p}_2^{(A)}}{1 - \hat{p}_1^{(A)}} = \frac{1 - 0.10}{1 - 0.05} \approx 0.947; \quad \hat{\theta}_3(0) = \frac{1 - 0.2}{1 - 0.1} \approx 0.888.$$

However, these only define the **location** of the mean. We also need to define the **uncertainty** around the prior distribution.

Prior Construction. Strength of Prior, $c = 1, 4, 10$



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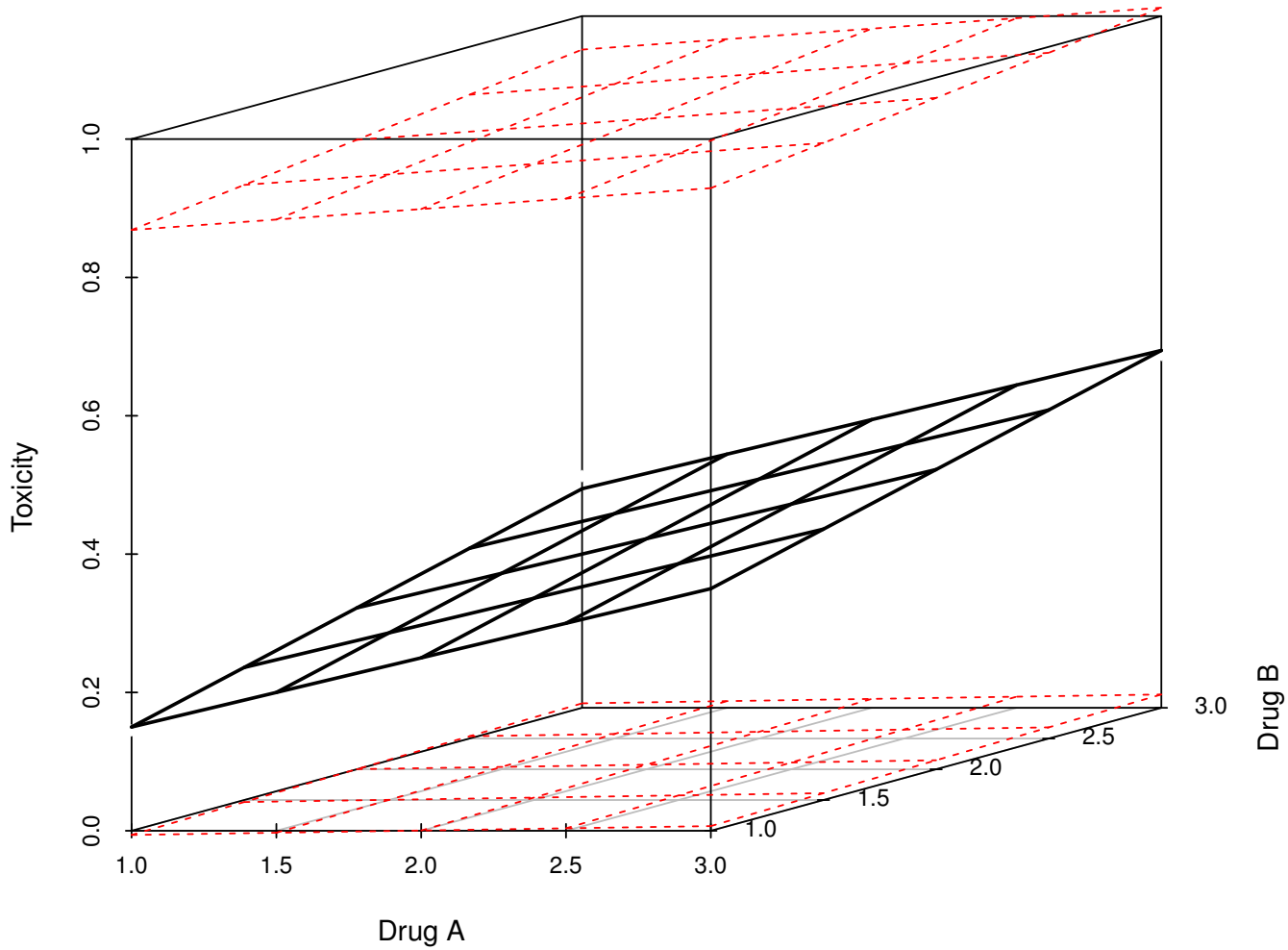

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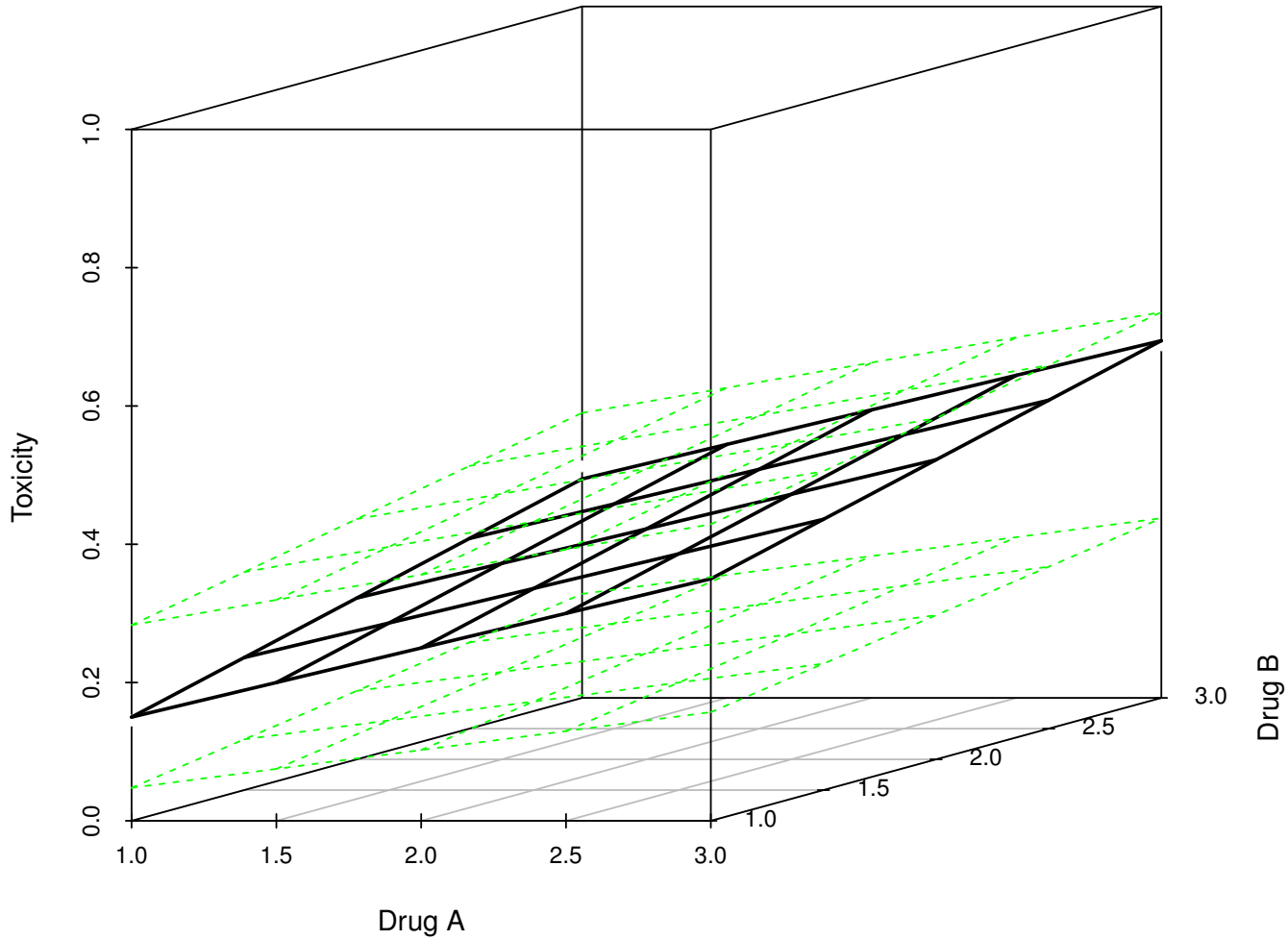

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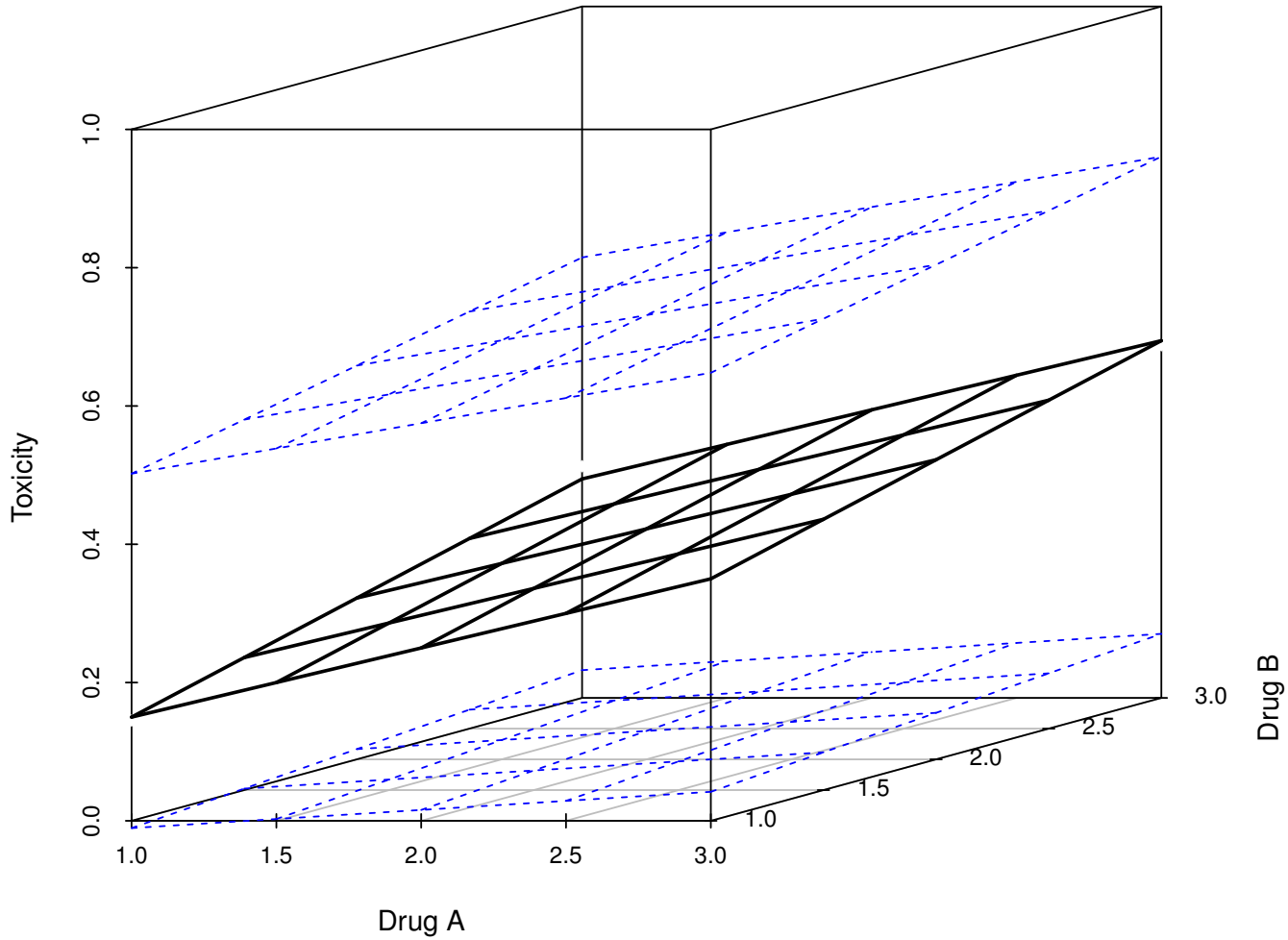


Prior Construction

- The strength of prior of each Beta prior distribution for the connection parameter of $c = 4$ (in blue) achieves the balances to drive the escalation;

- The first shape parameter, a_i, e_j, of the prior Beta distributions:

$$a_i = \hat{\theta}_i \times c; \qquad e_j = \hat{\tau}_j \times c$$

- The second shape parameter, b_i, f_j, of the prior Beta distributions:

$$b_i = (1 - \hat{\theta}_i) \times c; \qquad f_j = (1 - \hat{\tau}_j) \times c$$

Design

1. Define the prior distributions for the link parameters;
2. Assign the first cohort to the lowest combinations;
3. Once DLTs are observed, update the posterior of θ and τ;
4. Compute the toxicity risk estimates (after n patients):

$$\hat{p}_{ij}(n) = 1 - \hat{\theta}(n)\hat{\theta}_1(n)\ldots\hat{\theta}_i(n)\hat{\tau}_2(n)\ldots\hat{\tau}_j(n).$$

5. The combination $i^\star, j^\star$ minimising

$$T(\hat{p}_{ij}, \gamma) = |\hat{p}_{i,j} - TTL|$$

   is assigned to the next cohort of patients;
6. Continue until the maximum number of patients is reached; or stopped earlier for safety.

Early Stopping for Safety

The trial is terminated if

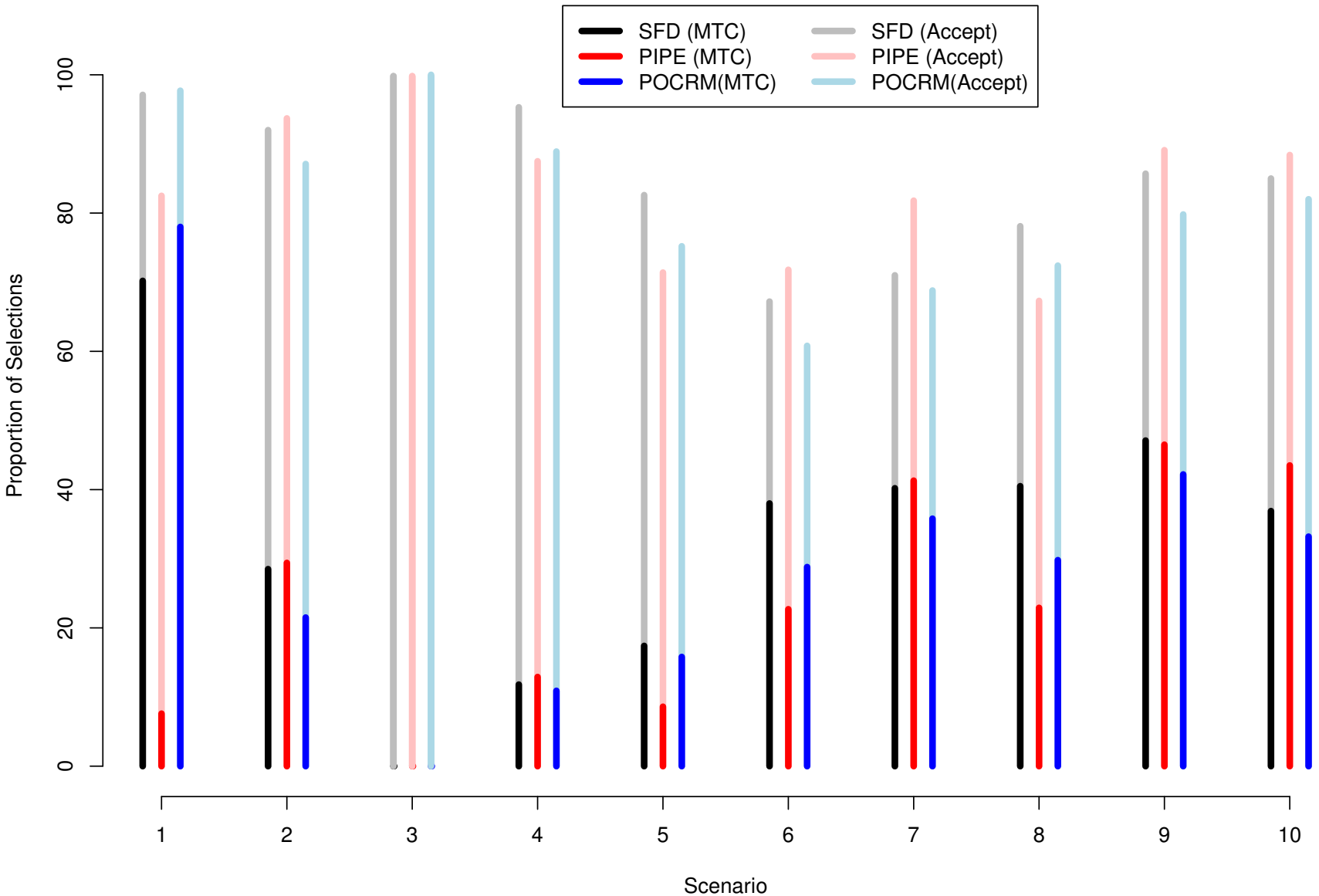
$$\mathbb{P}\left(p_{11} > TTL | \text{data}\right) > \zeta \tag{4}$$

where ζ is the threshold probability controlling the overdosing.

Simulation Study

- Compared to the **model-based** Partial Ordering Continual Reassessment Method (POCRM);
- Compared to the **model-free** PIPE Design;
- Selected the scenarios from the original publications;
- Matched the point estimates on combinations;

Numerical Results



Some comments

- Similar performance in terms of safety;
- Can be generalised to more than two agents;
- Combination-schedule problems?