Statistiques séquentielles et essais cliniques

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Statistiques biomédicales

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Plan

Citations

The classical theory of experimental design deals predominantly with experiments of predetermined size, presumably because the pioneers of the subject, particularly R. A. Fisher, worked in agricultural research, where the outcome of a field trial is not available until long after the experiment has been designed and started. It is interesting to speculate how differently statistical theory might have evolved if Fisher had been employed in medical or industrial research.
Armitage, P. (1993). Interim analyses in clinical trials. In Multiple Comparisons, Selection, and Applications in Biometry.

The process of examining and analyzing data accumulating in a clinical trial, either formally or informally, can introduce bias. Therefore all interim analyses, formal or informal, by any study participant, sponsor staff member, or data monitoring group should be described in full even if treatment groups were not identified. The need for statistical adjustment because of such analyses should be addressed. Minutes of meetings of the data monitoring group may be useful (and may be requested by the review division).
Food and Drug Administration (1988). Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications.

Tests : Rappel 1/3

Soit $X_1^n = (X_1, \ldots, X_n)$ un n-échantillon de X, une v.a.r de loi $\mathcal{L}$.
On considère les hypothèses antagonistes :

$$H_0 : \mathcal{L} \in \mathcal{L}_0 \text{ et } H_1 : \mathcal{L} \in \mathcal{L}_1, \text{ avec } \mathcal{L}_0 \cap \mathcal{L}_1 = \emptyset.$$

Un test de l'alternative H_0 contre H_1 est une statistique du n-échantillon, $T(X_1^n)$, qui ne prend que les valeurs 0 et 1 :

$$T(X_1^n) = \begin{cases} 1 & \text{et la décision est " } H_1 \text{ est vraie" (Rejet de } H_0 \text{),} \\ 0 & \text{et la décision est " } H_0 \text{ est vraie" (Non-rejet de } H_0 \text{).} \end{cases}$$

Le risque de première espèce du test T associée à la loi $\mathcal{L} \in \mathcal{L}_0$ est :

$$\alpha_{\mathcal{L}} = \mathbb{P}_{\mathcal{L}}(T(X_1^n) = 1) = \mathbb{P}(\text{ "Rejet de } H_0\text{" } \mid X \sim \mathcal{L}).$$

Le seuil de signification du test, noté α, est le plus petit nombre tel que, pour tout $\mathcal{L} \in \mathcal{L}_0$:

$$\alpha \geq \alpha_{\mathcal{L}}.$$

Cela correspond au plus grand risque de se tromper lorsque l'hypothèse H_0 est vraie.

Tests : Rappel 2/3

La p-valeur est la probabilité d'observer, en supposant que "H_0 est vraie", des réalisations de la statistique de test au moins aussi extrêmes que celles que nous avons observées.
Exemple : $X_i \sim \mathcal{N}(\mu, \sigma^2)$, $H_0 : \mu \leq 0$ $H_1 : \mu > 1$, test basé sur la statistique $Z = \sqrt{n}\,\overline{X}_n/\sqrt{\sigma^2}$ ($\sim \mathcal{N}(0,1)$ sous H_0). la p-valeur est $1 - \Psi(Z)$ où Ψ est la fonction de répartition de Z.

Le risque de seconde espèce du test T associée à la loi $\mathcal{L} \in \mathcal{L}_1$ est :

$$\begin{aligned} \beta_{\mathcal{L}} = & \quad 1 - \mathbb{P}_{\mathcal{L}}(T(X_1^n) = 1) = \mathbb{P}_{\mathcal{L}}(T(X_1^n) = 0) \\ = & \quad \mathbb{P}(\text{"Non-rejet de } H_0\text{"} \mid X \sim \mathcal{L}). \end{aligned}$$

Le risque β, est le plus petit nombre tel que, pour tout $\mathcal{L} \in \mathcal{L}_1$:

$$\beta \geq \beta_{\mathcal{L}}.$$

Note : Le risque β n'est pas toujours calculable. Cependant ce risque est intéressant car il apporte des informations sur la qualité du test. Il est souvent possible de le calculer dans des cas particuliers (on suppose que $\mathcal{L}_1 = \{\mathcal{L}\}$ où $\mathcal{L}$ est connue).

Un test, T, est uniformément plus puissant (UPP) au niveau α si pour tout test T' on a :

$$1-\beta_{\mathcal{L}} = \mathbb{P}_{\mathcal{L}}(T(X_1^n)=1) \leq 1-\beta'_{\mathcal{L}} = \mathbb{P}_{\mathcal{L}}(T'(X_1^n)=1),$$

pour tout $\mathcal{L} \in \mathcal{L}_1$

Théorème (Lemme de Neyman-Pearson)

Soit $X_1^n = (X_1, \ldots, X_n)$ un n-échantillon de vraisemblance $L(\theta; X_1^n)$. On considère les hypothèses $H_0 : \theta = \theta_0$ contre $H_1 : \theta = \theta_1$. Pour tout seuil α, il existe un test :

$$T(X_1) = \begin{cases} 1 & si \ \dfrac{L(\theta_1; X_1^n)}{L(\theta_0; X_1^n)} > c \\ \gamma & si \ \dfrac{L(\theta_1; X_1^n)}{L(\theta_0; X_1^n)} = c \\ 0 & si \ \dfrac{L(\theta_1; X_1^n)}{L(\theta_0; X_1^n)} < c \end{cases}.$$

avec c et γ telle que le test T ait pour seuil de signification α. Il s'agit de l'unique test UPP.

Test séquentiel : exemple 1

Dans une population, un vaccin produit une réponse immunitaire pour une proportion p de personnes. Soit S_n le nombre de personnes réagissant positivement au vaccin dans un échantillon de taille n. On teste $H_0 : p \leq p_0$ et $H_1 : p > p_1$.

Procédure 1 : On rejette H_0 si $S_n \geq r$, où r est une constante.

On pose $T = \min\{k \in \mathbb{N} : S_k = r\}$ et $T' = \min(T, n)$.

Procédure 2 : on s'arrête au temps aléatoire T'
et on décide de rejeter H_0 si et seulement si $T \leq n$.

Les régions de rejet de ces deux procédures sont les mêmes : $\{T \leq n\} = \{S_m \geq r\}$.
Ils ont donc la même fonction puissance.

L'une des deux procédures paraît beaucoup plus économes en données, non ?

Test séquentiel : exemple 2

Soit $X_1, X_2, \ldots$des variables aléatoires de lois $\mathcal{N}(\mu, 1)$. On teste $H_0 : \mu = 0$ et $H_1 : \mu \neq 0$. Le test standard pour une taille d'échantillon fixé n est un seuil de signification à 0.05 :

$$\text{Rejeter } H_0 \text{ si } |S_n| \geq 1.96\sqrt{n}, \text{ avec } S_n = \sum_{i=1}^{n} x_i.$$

Soit $b > 0$ et m une taille d'échantillon maximale pour la procédure de test séquentielle définie par :

Rejeter H_0 au premier $n \leq m$ (si il existe) tel que $|S_n| \geq b\sqrt{n}$, sinon "accepte" H_0.
Le seuil de signification de ce test est :

$$0.05 = \alpha(b, m) = \mathbb{P}_0(|S_n| \geq b\sqrt{n} \text{ for some } n \leq m),$$

avec $\mathbb{P}_0$ la probabilité sous H_0.

Question : le seuil de signification étant le même pour le test séquentiel et le test à échantillon fixé, que peut-on dire de b ?

Sequential Probability Ratio Test (SPRT)

Soit $X_1, X_2, \ldots$une suite de variables aléatoires de densité jointe $f_n(x_1, \ldots, x_n)$. On teste $H_0 : f_n = f_{0,n}$ contre $H_1 : f_n = f_{1,n}$. Le ratio de vraisemblance est :

$$r_n = \frac{f_{1,n}(x_1, \ldots, x_n)}{f_{0,n}(x_1, \ldots, x_n)}.$$

Le SPRT est défini par le choix de deux constantes $0 < A < B < \infty$ et les données $x_1, x_2, \ldots$ sont accumulées jusqu'au temps aléatoire :

$$N = \min\{n \in \mathbb{N} \cup \{\infty\} : \ r_n \notin]A, B[\},$$

et N est potentiellement infini. Le SPRT s'arrête au temps N et, lorsque $N < \infty$, prend la décision suivante :

Rejeter H_0 si $r_n \geq B$ et "accepter" H_0 si $r_n \leq A$.

Propriété du SPRT

Exercice : L'objectif est de déterminer des approximations des bornes A et B. On suppose que $N < \infty$ et on pose $\alpha = \mathbb{P}_0(r_N \geq B)$ et $\beta = \mathbb{P}_1(r_N \leq A)$.

1. Montrer que :

$$\alpha = \mathbb{E}_1(r_N^{-1} \times \mathbb{1}_{\{r_n \geq B\}}) \leq B^{-1}(1-\beta).$$

2. De même, montrer que : $\beta \leq A(1-\alpha)$.

Des inégalités ci-dessus on déduit que :

$$B \approx \frac{1-\beta}{\alpha} \text{ et } A \approx \frac{\beta}{1-\alpha}.$$

Test séquentiel par groupe

On compare deux traitements A et B. Soit $X_{A,1}, X_{A,2}, \ldots$ et $X_{B,1}, X_{B,2}, \ldots$ les échantillons de réponses des patients aux deux traitements (loi normales). Soit θ la différence de traitement. On teste $H_0 : \theta = 0$ contre $H_1 : \theta \neq 0$. On note α et β les erreurs de type I et II (quand $\theta = +-\delta$).

L'analyse est conduite entre chaque cohorte de patients.

- K cohortes de patients.
- n_k patients alloués à chaque traitement dans la cohorte k.
- $N_k = \sum_{i=1}^{k} n_k$, nombre de patients alloués à chaque groupe de traitement après la k-ième cohortes.
- Z_k, la statistique de test standardisé après la k-ième cohorte est :

$$Z_k = \frac{1}{\sqrt{2N_k\sigma^2}} \left(\sum_{i=1}^{N_k} X_{A,i} - \sum_{i=1}^{N_k} X_{B,i} \right)$$

- a_k et b_k les valeurs critiques à l'étape k : $Z_k \notin]a_k, b_k[$, on arrête et H_0 est rejetée ; sinon on continue jusqu'à K.

Les valeurs critiques sont choisies pour correspondre à α, l'erreur de type I.

La famille de test de Wang et Tsiatis

Règles :

- $\forall k \in \{1, \ldots, K\}$, $Z_k \notin]a_k, b_k[$: arrêt du test séquentiel, H_0 est rejetée.
- $\forall k \in \{1, \ldots, K-1\}$, $Z_k \in]a_k, b_k[$: les sujets du groupe suivant sont évalués, pas de décision.
- $Z_K \in]a_K, b_K[$: fin du test, H_0 n'est pas rejetée.

Dans la famille de tes de Wang et Tsiatis, les valeurs critiques après le groupe k, a_k et b_k sont fonctions de k, K et d'un paramètre Δ :

$$a_k = -c\left(\frac{k}{K}\right)^{\Delta-\frac{1}{2}} \quad \text{et} \quad b_k = c\left(\frac{k}{K}\right)^{\Delta-\frac{1}{2}}$$

Test de Pocock :

$\Delta = \frac{1}{2}$, les valeurs critiques sont constantes.

test de O'Brien et Fleming :

$\Delta = 0$, les valeurs critiques en valeur absolue diminuent.

Quelques idées pour déterminer les a_k et b_k

On suppose que les variables des échantillons $(X_{A,i})$ et $(X_{B,i})$ suivent les lois $\mathcal{N}(\mu_A, 1)$ et $\mathcal{N}(\mu_B, 1)$, resp. Sous l'hypothèse $H_0 : \theta = \mu_A - \mu_B = 0$. On a :

$$Z_k = \frac{1}{\sqrt{2N_k\sigma^2}} \left(\sum_{i=1}^{N_k} X_{A,i} - \sum_{i=1}^{N_k} X_{B,i} \right) \sim \mathcal{N}(\theta\sqrt{I_k}, 1)$$

avec $\sqrt{I_k} = \sqrt{N_k/2\sigma^2}$.

Exercice :

1. Quelle propriété bien connue a la séquence de v.a. Z_1, ..., Z_K.
2. Pour $k_1 \leq k_2$, montrer que :

$$Cov(Z_{k_1}, Z_{k_2}) = \sqrt{\frac{I_{k_2}}{I_{k_1}}}$$

et que :

$$Z_k\sqrt{I_k} - Z_{k-1}\sqrt{I_{k-1}} \sim \mathcal{N}(\theta\delta_k, \delta_k) \text{ avec } \delta_k = I_k - I_{k-1}.$$

3. Déterminer la densité de $Z_k \mid Z_1 = z_1, \ldots, Z_{k-1} = z_{k-1}$ en fonction de ϕ (la densité d'une loi normale centrée réduite), les I_k et les δ_k.

Idée : Les valeurs critique s'obtiennent par calculs numériques d'intégrales basées sur la loi jointe de $Z_1, \ldots, Z_K$.

Test de Pocock

Rejet de H_0 à l'étape k si : $|Z_k| > b_k(\alpha, K)$.

b_k	$\alpha = 0.01$	$\alpha = 0.05$	$\alpha = 0.1$
$K = 1$	2.576	1.960	1.645
$K = 2$	2.772	2.178	1.875
$K = 3$	2.873	2.289	1.992
$K = 4$	2.939	2.361	2.067
$K = 5$	2.986	2.413	2.122
$K = 6$	3.023	2.453	2.164
$K = 7$	3.053	2.485	2.197
$K = 8$	3.078	2.512	2.225
$K = 9$	3.099	2.555	2.249
$K = 10$	3.117	2.555	2.270
$K = 15$	3.182	2.626	2.344
$K = 20$	3.225	2.672	2.392

Question : Quelle est la probabilité qu'une variable aléatoire de loi normale centrée réduite soit supérieure à b_k en valeur absolue.

Note : La taille de l'échantillon pour atteindre un certain niveau de puissance peut être déterminée par des calculs similaires que ceux ayant donnés la table ci-dessus.

Test de O'Brien et Fleming

Rejet de H_0 à l'étape k si : $|Z_k| > c_k(\alpha, K) \times \sqrt{K/k}$.

c_k	$\alpha = 0.01$	$\alpha = 0.05$	$\alpha = 0.1$
$K = 1$	2.576	1.960	1.645
$K = 2$	2.580	1.977	1.678
$K = 3$	2.595	2.004	1.710
$K = 4$	2.609	2.024	1.733
$K = 5$	2.621	2.040	1.751
$K = 6$	2.631	2.053	1.765
$K = 7$	2.640	2.063	1.776
$K = 8$	2.648	2.072	1.786
$K = 9$	2.654	2.080	1.794
$K = 10$	2.660	2.087	1.801
$K = 15$	2.681	2.110	1.826
$K = 20$	2.695	2.126	1.842

Question : 1. La valeur critique finale associée à Z_k est plus petite pour les tests de O'Brien et Fleming que pour ceux de Pocock. Pourquoi ?
2. Quel test économise en moyenne le plus de sujet ? Celui de O'Brien et Fleming ou celui de Pocock ?

Plan

Contexte

L'efficacité comparée de deux ou plusieurs traitements est évaluée (variables binaires ou continue). L'éthique médicale impose que le maximum de patients possible soient soignés avec le traitement le plus efficace.

- Les patients arrive l'un après l'autre.
- On obtient la réponse du patient au traitement choisi avant de traiter le patient suivant.
- Un patient ne suit qu'un seul traitement.
- On ignore quel est le meilleur traitement et on ne possède pas d'autres informations que les réactions des patients déjà observés.
- La réaction des patients n'est pas toujours la même pour un même traitement (hétérogénéité de la réponse : aléatoire).
- On ne souhaite pas estimer l'efficacité précise de chaque traitement ; on veut allouer le plus de patients possible au traitement le plus efficace.

L'incertitude dû à l'aléatoire impose un dilemme entre exploitation et exploration, ou dit dans le contexte médicale entre traitement et expérimentation.

Problème : Chaque bras $k \in \{1, \dots, K\}$, est associé à une probabilité de gain $X_k \sim \nu_k$, avec $\mathbb{E}[X_k] = \mu_k$. On cherche à exploiter le meilleur bras $k^\star$ associé au gain moyen maximum :

$$\forall k \neq k^\star, \quad \mu^\star = \mu_{k^\star} \geq \mu_k.$$

Protocole séquentiel :

1. A chaque étape t, l'algorithme effectue une action en choisissant un bras $a_t \in \{1, \dots, K\}$ sur la base de toute l'information disponible.
2. On observe le gain X_{a_t} pour le bras choisi au temps t, mais on observe pas ce qui ce serait passé sur les autres bras.

But : On cherche à minimiser le pseudo-regret :

$$R_T = \mathbb{E}\left[\sum_{t=1}^{T} X_{k^\star} - X_{a_t}\right] = T\mu^\star - \mathbb{E}\left[\sum_{t=1}^{T} X_{a_t}\right].$$

Quelques algorithmes 1/3

Explore-Then-Commit algorithm :

- **Une première phase d'exploration** durant laquelle on essaye autant de fois chaque bras, sans regard pour les données accumulées.
- **Une seconde phase d'exploitation** durant laquelle on joue le bras associé au gain moyen possédant la moyenne empirique la plus haute durant la première phase.

Problème : l'algorithme explore and commit ne tient pas compte des données dans la première phase et ne revient pas sur sa décision dans la seconde phase. Pour choisir "idéalement" la longueur de la première, il faudrait connaître l'horizon T et les gaps entre le meilleur bras et les autres bras : $\Delta_k = \mu^\star - \mu_k$.

ϵ-greedy algorithm : Soit $\epsilon_t \in (0, 1)$. L'algorithme choisit :

- avec une probabilité $1 - \epsilon_t$, le meilleur bras en apparence au temps t (moyenne empirique)
- avec une probabilité ϵ_t, un bras au hasard uniforme parmi l'ensemble des bras.

$$\text{Si } \epsilon_t \approx \frac{K}{t\Delta^2}, \text{ alors } R_T \approx< \frac{K \log(T)}{\Delta^2}$$

Quelques algorithmes 2/3

UCB algorithm : On joue une fois chaque bras et pour $t \geq K+1$,

$$a_t = \underset{k \in \{1,\dots,K\}}{\arg\max}\ \hat{\mu}_{k,t} + \sqrt{\frac{2\log(t)}{N_t(k)}},$$

avec $\hat{mu}_{k,t}$, la moyenne empirique de gain au bras k et $N_t(k)$ le nombre de fois que le bras k a été joué.

Thompson sampling : Le gain associé à chaque bras k est associé à un a priori Π_k (au sens bayésien). Au temps t,

1. on effectue un tirage sous l'a posteriori de chaque bras : $X_{k,t} \sim \Pi_{k,t}$ (pseudo-données)
2. l'algorithme choisi le bras associé au plus haut tirage :

$$a_t = \underset{k \in \{1,\dots,K\}}{\arg\max}\ X_{k,t}.$$

Quelques algorithmes 3/3

Bayes UCB : Le gain associé à chaque bras k est associé à un a priori Π_k (au sens bayésien). Soit $q_{t,k}$ le quantile associé à chaque bras au temps t défini par :

$$\Pi_{t,k}(]-\infty; q_{t,k}) = 1 - \frac{1}{t\log(n)^c},$$

avec $\Pi_{t,k}$, l'a posteriori pour le bras k au temps t. On joue d'abord une fois chaque bras puis, au temps t, l'algorithme choisi le bras :

$$a_t = \underset{k\in\{1,\dots,K\}}{\arg\max}\ q_{t,k}.$$

Remarque : 1) Bayes-UCB est asymptotiquement optimale pour des gains suivant des loi de Bernoulli avec a priori de loi beta et $c \geq 5$. L'observation sur les bras sous-optimale est en $\log(T)$.
2) Il existe une version basée sur la divergence de Kullback-Leibler et l'inégalité de Chernoff (KL-UCB).

Plan

Early Phase clinical trial

Phase I : Screening for safety, first-in-person trials, small group of people (typically 20-80, expansion cohort).

Phase I for serious disease (as cancer, AIDS, rare disease) :
only patients are enrolled, a certain amount of toxicity is targeted,
dose finding study, maximum tolerated dose (MTD)

Phase II : Establishing the preliminary efficacy, phase IIa (dose finding study), phase IIb (testing efficacy, establishing therapeutic dose range).

- Drug combinations,
- Heterogeneity (biomarkers),
- Cycles of treament,
- Grades,
- Discrete or continuous range of doses,
- Expansion cohort,
- Toxicity/Efficacy (Phase I/II).
- Immuno-therapy and plateau

Mathematical context : Martingal, sequential design, parametric and semiparametric model, hierachical Bayesian model, reinforcement learning.

An historical design

In a "3+3 design," three patients are initially enrolled into a given dose cohort.

If there is no dose-limiting toxicity (DLT) seen ... , the trial proceeds to enroll additional participants into the next higher dose cohort.

Dose-limiting toxicities are generally defined as clinically relevant toxicities grade 3 or higher by the Common Terminology Criteria for Adverse Events.

If one patient manifests a DLT at a specific dose, an additional three individuals are accrued into that same dose cohort.

Development of DLTs in two or more out of six patients at a specific dose level indicates that the MTD has been exceeded ; further dose escalation is not pursued ... ;

The MTD is determined in the first cycle of therapy. The MTD is therefore defined as the highest dose level in which six patients were treated and, at most, one patient experienced a DLT during the first cycle of therapy.

If more than six patients are treated at any dose level, the MTD is exceeded if more than one-third of the patients experience a DLT.

1. KURZROCK R, et al. (2021) Moving Beyond 3+ 3 : The Future of Clinical Trial Design. *American Society of Clinical Oncology Educational Book*
2. Storer BE (1989). Design and analysis of phase I clinical trials. *Biometrics*.
3. Dixon WJ, Mood AM (1946). The statistical sign test. *J Am Stat Assoc*..

"3+3" : a rules-based design

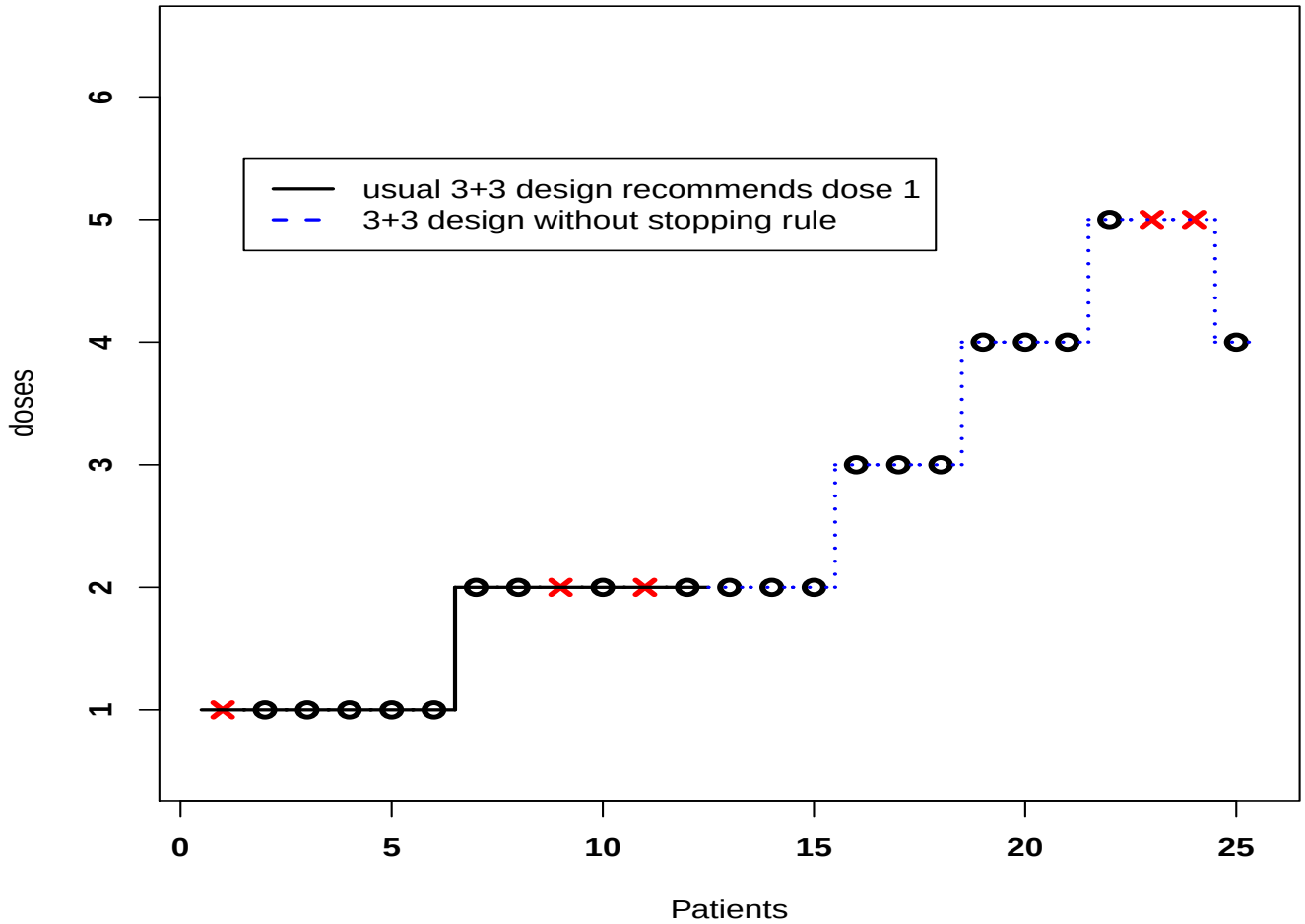


Figure – Black circle : patient does not experience a DLT ; Red cross : A DLT has been experienced.

Toxicity scenario

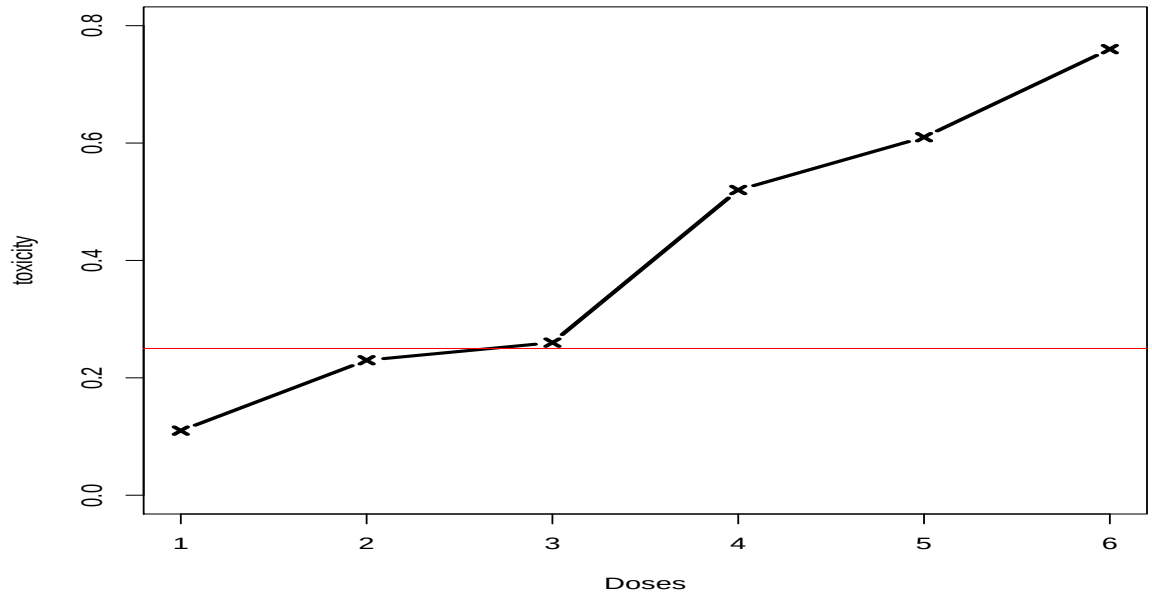
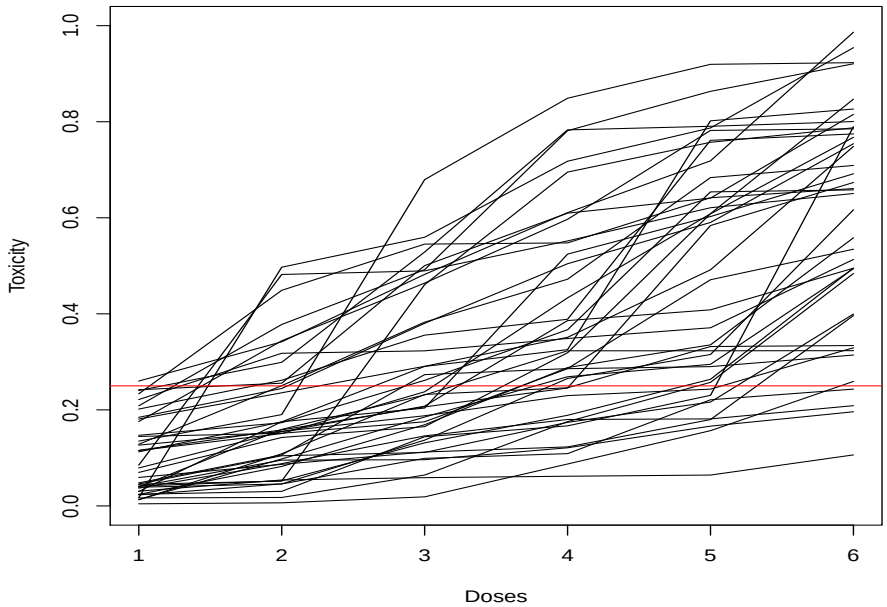


Figure – Toxicity probability at each dose. The black line are linear interpolation. The red line is the toxicity target : 25%. Unless explicitly stated, all the trial shown in this presentation are generated under this scenario : $\beta = (0.11, 0.23, 0.26, 0.52, 0.61, 0.76)$.

Storer BE (1989), *Biometrics* **:**

- The MTD is no longer define as a statistic of the data.
- There exists an underlying truth, a scenario of toxicity probability, and the MTD is the dose associated with the closest toxicity probability to the target.
- Comparison of differents designs on a bunch of scenarios (6 to 12 is considered reasonable by several authors).

Numerical experiment methodology



Sample of scenarios

Pseudo-Uniform class of scenarios, clertant et al. (2017), *JRSS (b)* :

1. A random scenario is generated by using uniform spacings conditionned to a uniform MTD,
2. Performance is assessed out of 100 000 random scenarios,
3. Results are more reliable if 100 000 scenarios are tested once than if 1000 scenarios are tested thousand times.

Treatment versus experimentation dilemma (D. Azriel et al (2011)) :

Precision measures	
PCS	Percentage of correct final selection of the MTD.
A	Accuracy index for the final selection.
PCA	Percentage of correct allocation at the MTD during the trial.
a	Accuracy index for allocation during the trial.
Safety measures	
P_{DLT}	Percentage of DLT during the trial.
PES	Percentage of trials that stop early.

Notation

Standard case : A single agent with binary response.

- $X \in D = \{1, \ldots, m\}$, the dose ; $Y \in \{0, 1\}$ the response.
- $Y|d$ is Bernoulli with parameter β_d, and : $\beta_1 < \ldots < \beta_m$.
- The target or threshold : α.

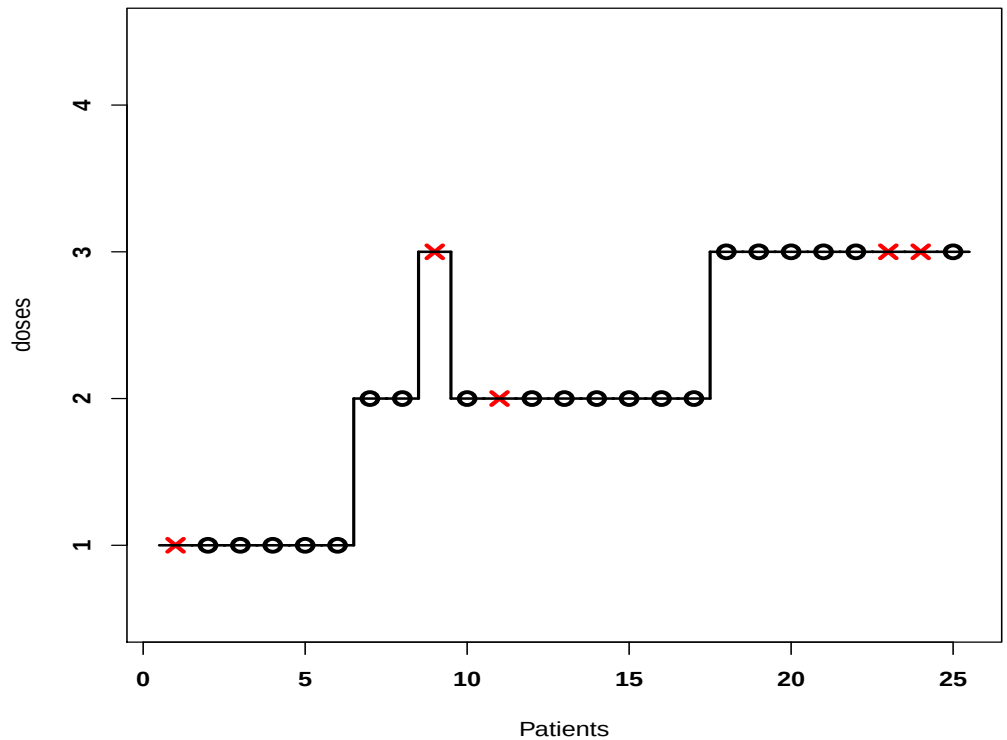
Maximum Tolerated Dose :

$$d^* = \arg\min_{d \in D} |\alpha - \beta_d|.$$

$\beta = (\beta_d)_{d \in D}$, the scenario.

Asymptotic theory :

$\sum_{i=1}^{n} \mathbb{1}_{\{X_i = d\}} (Y_i - \beta_d)$ is a martingal with respect to $\sigma(X_1^n, Y_1^n)$.
$\Rightarrow$ Law of large number, law of the iterated logarithm ...



A convergent trial.

Three classes of designs

CRM-type of designs (O'Quigley et al., 1990, *Biometrics*) :

CRM stands for continual reassessment methods.
It is based on a regression curve context, a model of the dose/toxicity relationship (scenario).
Sample sizes are small so that, in practice, approximating the true scenario across all doses is not a realistic objective. Instead, the model accomplish a more modest aim, that of approximating the true scenario at and close to the MTD.

CCD-type of designs (Ivanova et al., 2007, *Jour. of Statistical Planning and Inference*) :

CCD stands for Cumulative Cohort Design.
It means that the treatment allocation is "based on the information from all subjects that have been assigned to the dose, not just the information from the most recent group of subjects."
Based on all the observations at the current level, the decision would be to determine the most plausible of 3 hypotheses : the rate of DLT at the current level could either lie within some chosen interval, below that interval or above it.

SPM-type of designs (Clertant et al., 2017, *Journal of the Royal Statistical Society (b)*) :

The semiparametric dose finding method (SPM) is built as a compromise between the CRM and CCD-types of designs. It contains or approximates the two previous classes. This is a hierarchical Bayesian model where the first level is the MTD itself and the second level deals with the toxicity scenario conditioned to the possible MTD (nuisance parameter). It results in a probability distribution over the dose levels, i.e., the potential MTDs.

CRM, a sequential regression

The power model on a skeleton t :

$$\begin{array}{rccc} \Psi_t : & D \times A & \to & [0,1] \\ & (x,a) & \mapsto & \Psi_t(x|a) = t(x)^{\exp(a)} \end{array} .$$

Bayes : A prior G on the parameter space A.

Algorithm

Step 1 : According to the sample (X_1^n, Y_1^n), the posterior is G_n :

$$G_n(a) \propto \mathcal{L}_n(a) \times G(a).$$

Step 2 : The estimator of the MTD is built on the estimator of β_d :

$$\hat{\beta}_{n,d} = \mathbb{E}_{G_n}[\Psi_t(d|a)] \quad \text{or} \quad \hat{\beta}_{n,d} = \Psi_t(d|\hat{a}_n)\,,$$

with $\hat{a}_n = \mathbb{E}_{G_n}[a]$. The next dose is $X_{n+1} = \underset{d \in D}{\arg\min} |\hat{\beta}_{d,n} - \alpha|$.

CRM and coherence

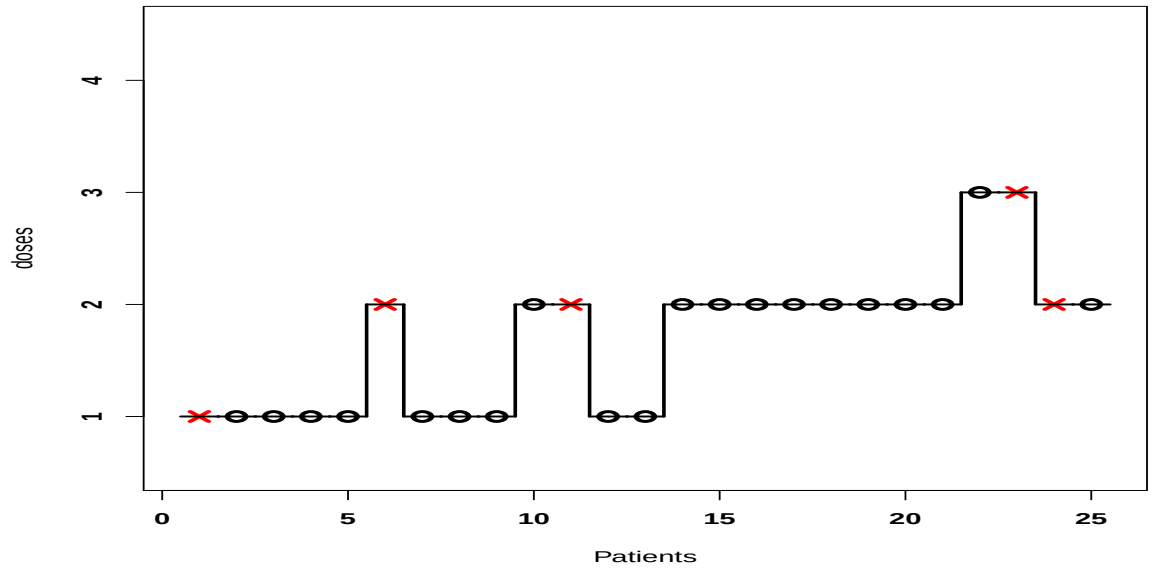


Figure – The trial is conducted by a two stage CRM using a power model and $\beta = (0.11, 0.23, 0.26, 0.52, 0.61, 0.76)$. Red cross : the patient experienced a DLT ; black circle : no DLT.

Whether the trial is ongoing, or completed, the principle is the same :
patient are treated at the best estimate of the MTD.

Coherence, Cheung K. (2005), *Biometrika* :
For one-by-one inclusions,

- a DLT cannot be followed by a recommendation to increase dose level.
- a non-DLT cannot be followed by a recommendation to decrease dose level.

The definition could be adapted to cohort inclusion : 2,3,4,... patients (toxicity rate is either below or above the target).

CRM and 2-parameter models

In the development of the CRM, the use of a Bayesian two parameter logistic model was studied and showed poor performance (BLRM, O'Quigley, 1990) :

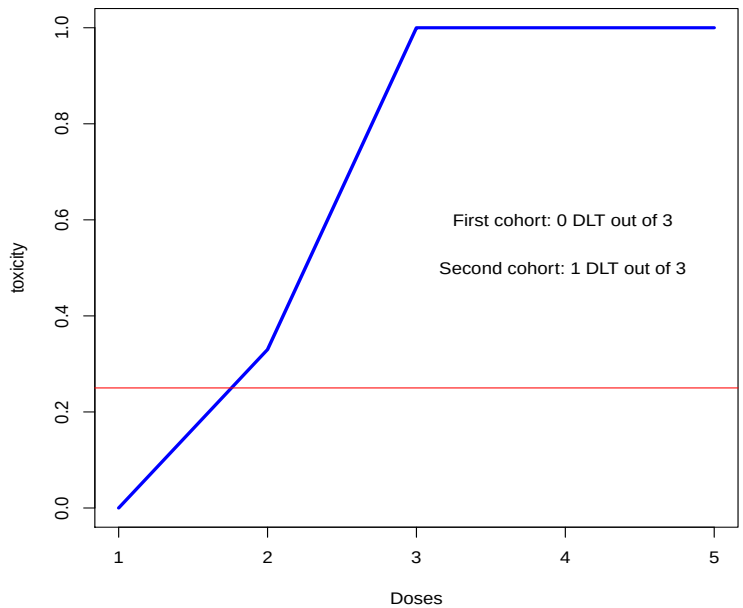
$$\Psi_t(x \mid a, b) = \frac{\exp\left(a + t(x) \times b\right)}{1 + \exp\left(a + t(x) \times b\right)}$$

An alternative design to standard BLRM is the EWOC (Babb J. et all, 1998, *Stat. in Med.*) : the estimator is the quartile of the posterior on the MTD. EWOC design is overly cautious thereby underdosing too many patients (Wheeler, 2018, Stat. Papers)

Behavior and properties :

- If we converge to the MTD, the model is not identifiable.
- The 2-parameter model is not consistent and not coherent (Iasonos A. et al, 2016 and Wheeler G. M., 2018).
- Not adaptable : the design get stuck at a level with no possibility to leaving it.
- High computational cost (MCMC algorithm).

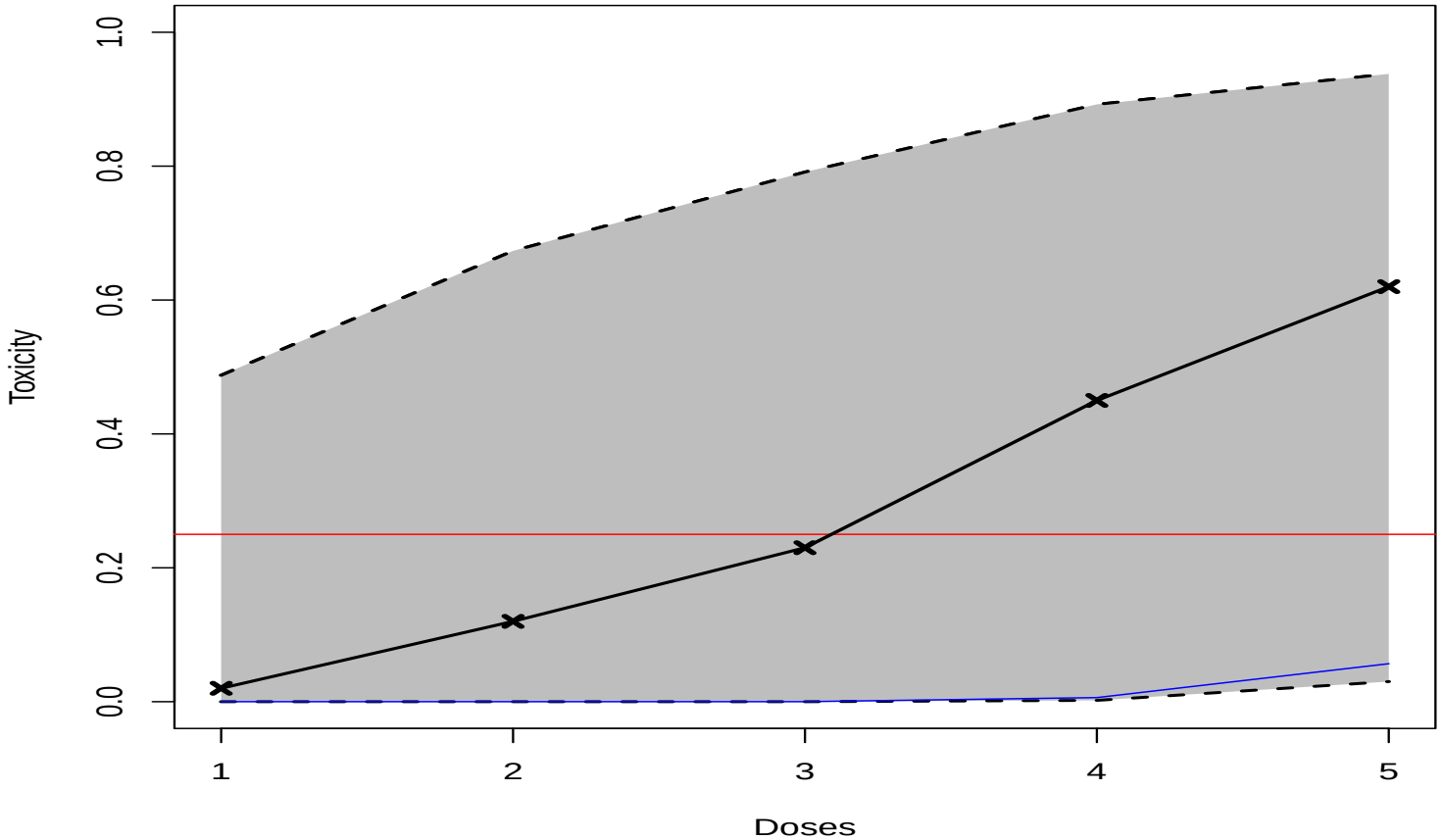
A carefull choice of prior could overcome some of this problem.



NeuSTART example.

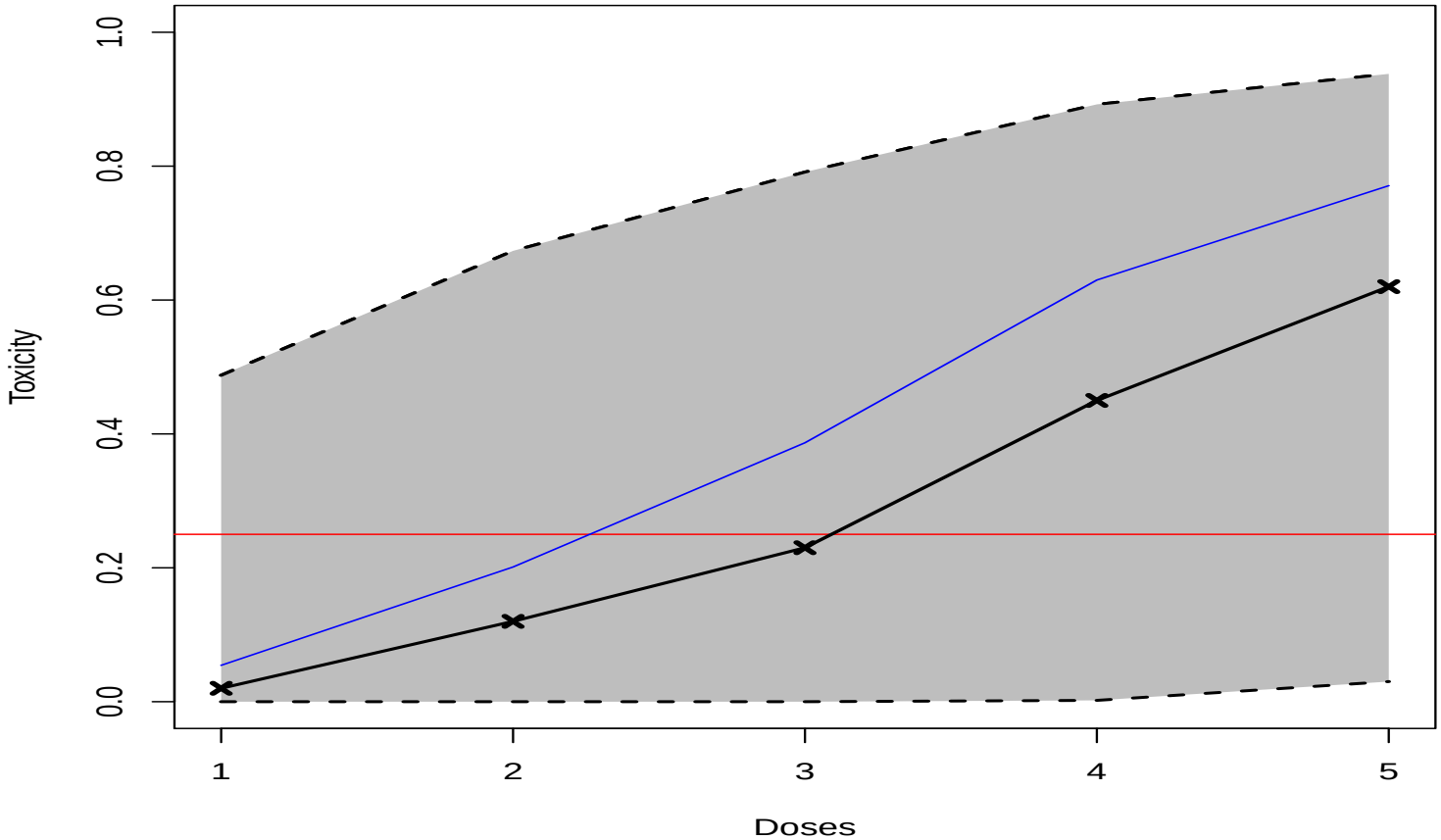
Adaptability : A string of DLTs (non-DLTs) will ultimately result in a recommendation to decrease (increase) the level whenever such a level is available.

CRM, sequential estimation



Target : $\alpha = 25\%$; Support of the CRM model in grey ;
A scenario in black ; $(\hat{\beta}_{n,d})_{d \in D}$ in blue.

CRM, sequential estimation



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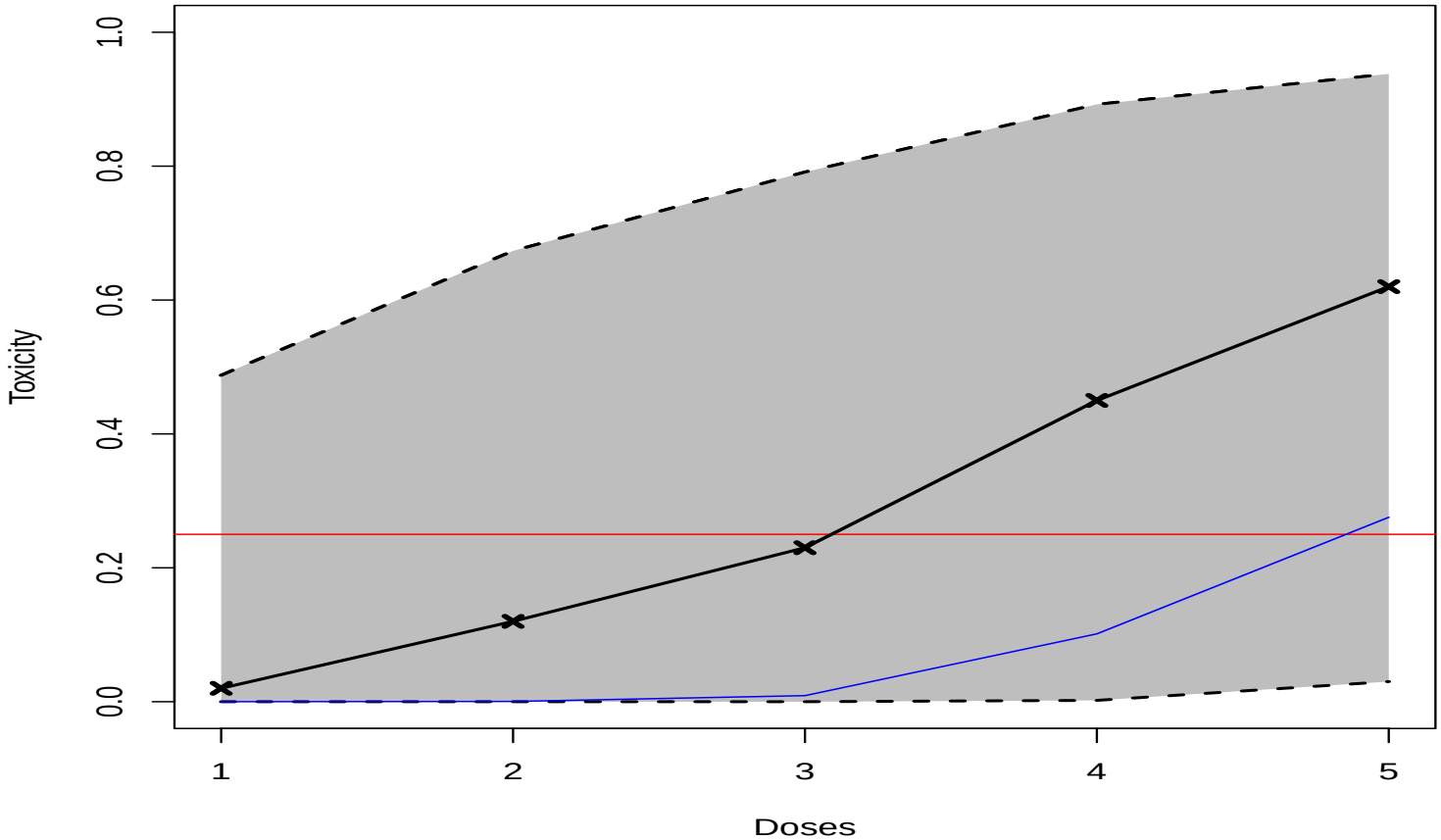

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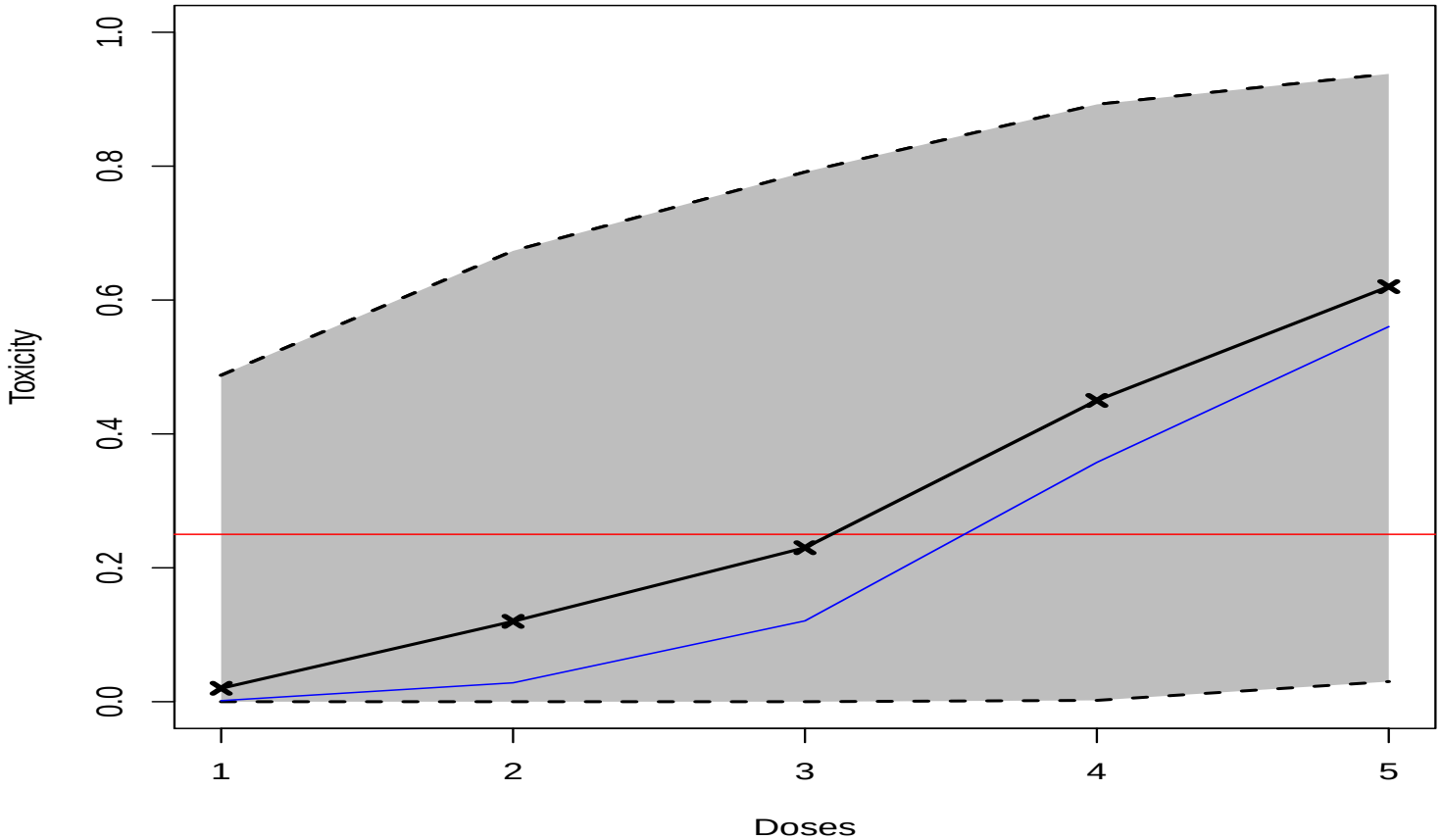

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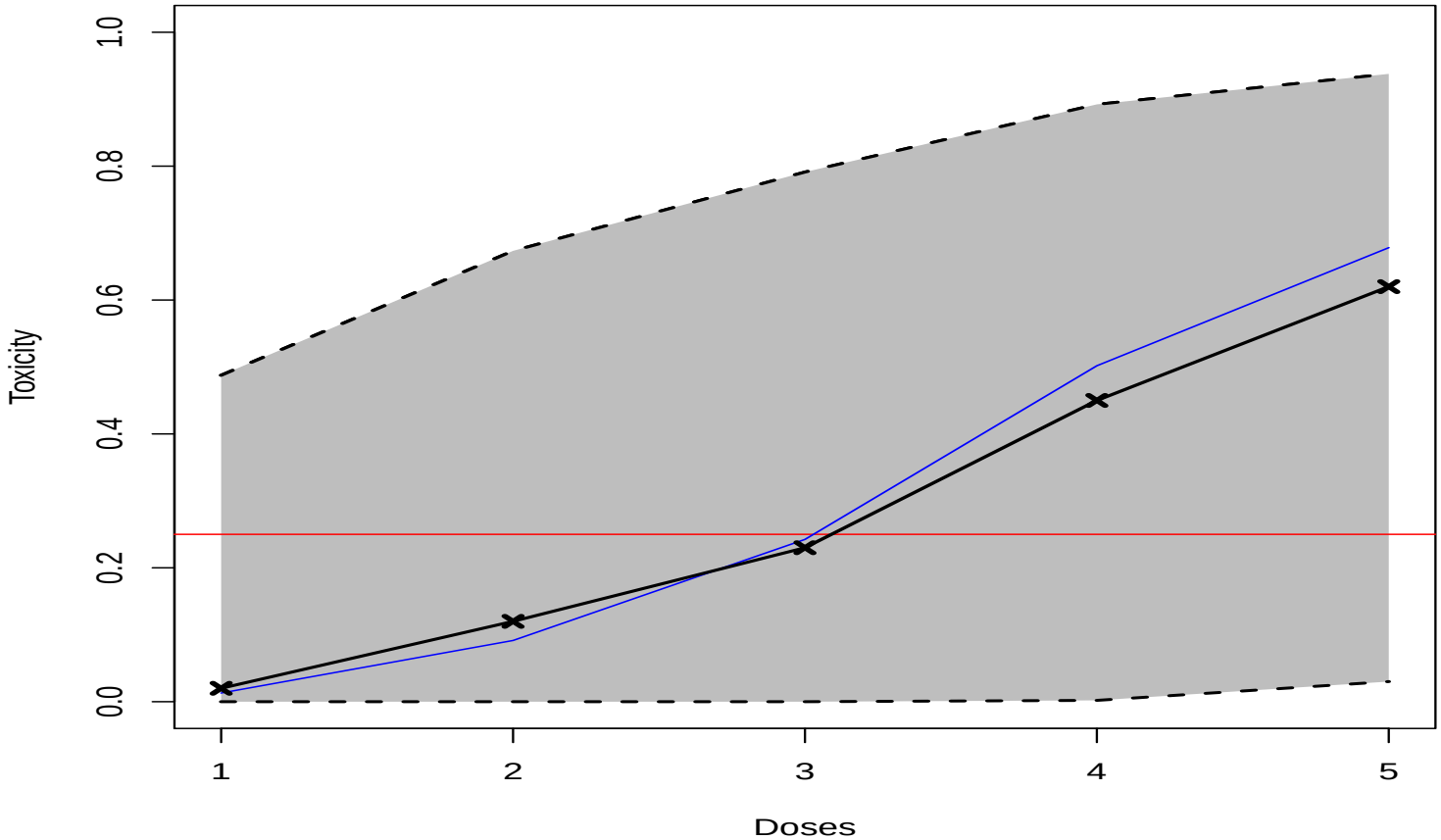
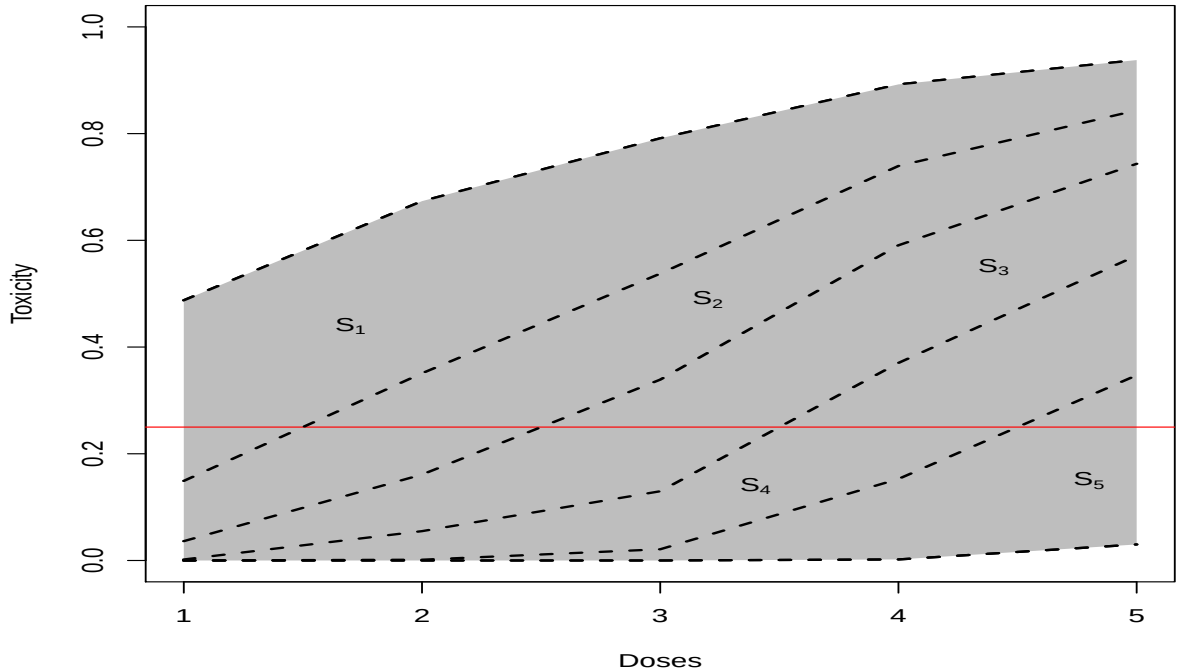
CRM, sequential estimation



Target : $\alpha = 25\%$; Support of the CRM model in grey ;
A scenario in black ; $(\hat{\beta}_{n,d})_{d \in D}$ in blue.

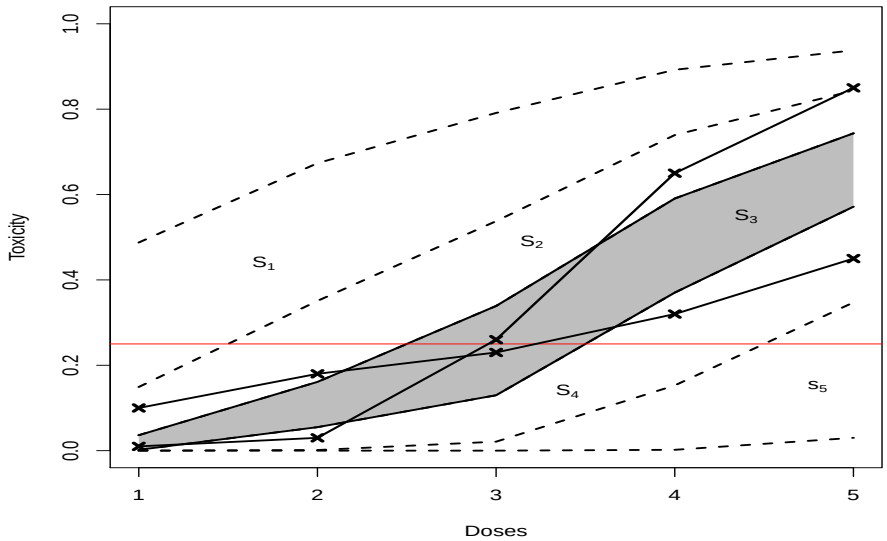
CRM, convergence, good and poor specification



The support S of prior G breaks down into m classes ($D = \{1, \ldots, m\}$).
In particular, S_3 gathers the parameter values for which the model associates dose 3 with the MTD :

$$\forall \theta \in D,\ S_\theta = \{a : \theta = \arg\min_{d \in D} |\Psi_t(d|a) - \alpha|\}$$

CRM, convergence, good and poor specification



Two scenarios in black with apparent poor specification.

- **Steep curve :** The CRM design converges almost surely to the MTD.
- **Flat curve :** Under certain data sequences, the CRM does not converge to dose 3.

Théorème

For all $d \in D$, let $a_d \in S$ such that : $\Psi(d, a_d) = \beta_d$ (perfect fit at dose d). The CRM is almost surely convergent to the MTD, if and only if :

1. $a_{d^\star} \in S_{d^\star}$, *with* $d^\star$ *the MTD.*
2. $\forall d \in D \setminus d^\star : \beta_d < \alpha$, *on a* $a_d \in \bigcap_{k=d+1}^{m} S_k$,
3. $\forall d \in D \setminus d^\star : \beta_d > \alpha$, *on a* $a_d \in \bigcap_{k=1}^{d-1} S_k$

In practice

Implementation of CRM designs in practice, extensive case studies of Iasonos A. et al (2014), *Journal of Clinical Oncology.*

The CRM design can be extended to sharing information arising from sources additional to the dose-levels themselves :

- The TITE-CRM deals with delayed toxicities, it encodes the data through a "survival" function (Cheung K., 2000, *Biometrics*),
- The PO-CRM focuses on trials for combination of agents (Wages N. A. et al, 2011, *Stat. in Medecine*) ; it explores the possible unknown order in a context of partial ordering.
- Models exploring a two dimensional curve of MTD (Tighiouart M. et al. , 2017, *Stat. in Medecine*),
- Model that account for efficacy and toxicity (O'Quigley et al., 2001, *Biometrics*),
- Model dealing with non-drug related toxicities (Iasonos et al., 2017, *JRSS (c)*),
- Model smoothing the transition to the dose expansion phase (Iasonos et al., 2016, *Comptemporary clinical trials*),
- Situations in which it is not always possible to give the full amount of the recommended dose (Devlin S.M., preprint, *JRSS (c)*).

General ideas of cumulative cohort type design

CCD-type designs are significant development away from 3+3 type designs :

Their allocation rule is based on the information from all patients that have been treated to the current dose, not just from the most recent cohort of subjects.

Their structure and operational mechanisms are identical.

They target an indifference interval of toxicity rate $I = [\alpha - c, \alpha + c] \subset [0, 1]$.

If observations at the current dose are in favor of

- a true rate of DLT below I, then escalate one level ($\mathcal{E}$),
- a true rate of DLT above I, then deescalate ($\mathcal{D}$),
- a true rate of DLT in I, then stay at the dose ($\mathcal{S}$).

Their main step of decision needs to be completed by ad hoc rules : a safety rule and a final decision rule.

Unlike model-based designs (CRM), cumulative cohort design ignores observations at the other dose levels that may contain crucial information on whether or not a decision to escalate or de-escalate is a good one.

Main step of decision

Most of the CCD-type designs might be rewritten
in the following setting (Clertant et al., 2019, *JRSS (c)*).

Consider three class of Bernoulli distributions corresponding to three priors on the toxicity probability in $[0,1]$: $\Lambda_{\mathcal{S}}$, $\Lambda_{\mathcal{E}}$ and $\Lambda_{\mathcal{D}}$ (Stay, Escalate, Deescalate). Π, a uniform distribution on decisions $\{\mathcal{S},\mathcal{E},\mathcal{D}\}$.

$$\Pi_n(i) \propto \left[\int \mathcal{L}_{(n_1,n_0)}(p)\Lambda_i(dp)\right] \Pi(i) \quad \text{and} \quad \hat{\theta}_n = \underset{i\in\{\mathcal{S},\mathcal{E},\mathcal{D}\}}{\arg\max}\, \Pi_n(i).$$

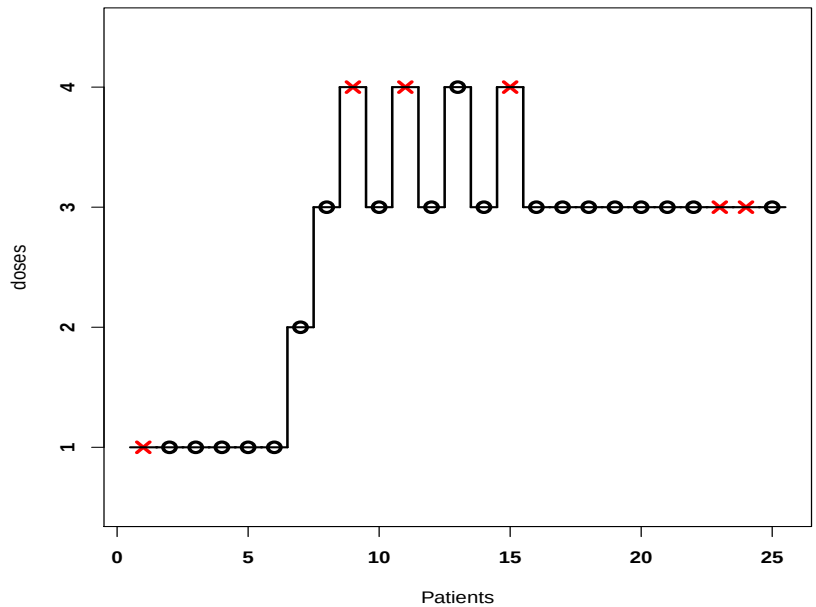
Designs	Priors
CCD, Ivanova et al., 2007, *J. of Stat. Plan. and Inf.* **local BOIN**, Liu et al., 2015, *JRSS (c)*	Three Dirac distributions : One at the target α and two on each side.
mTPI, Ji et al., 2010, *Clinical Trials*, **global BOIN**, Liu et al., 2015, *JRSS (c)* **Keyboard**, Yan, 2017, *Clin. Cancer Research* **mTPI2**, Guo et al., 2017, *Contemporary Clin. Trials*,	Three uniform distributions : one on the interval $I = [\alpha - c; \alpha + c]$, the two others weights intervals on each side of I

Table – Summary of CCD-type designs. mTPI and global BOIN are identical ; Keyboard and mTPI2 are identical ; local BOIN is "operationnaly identical" to Keyboard (or mTPI2).

Oscillations and ad hoc rules

CCD-type designs ignore information at adjacent doses. This has several harmfull consequences.

- no coherence (ex : escalation after a non DLT),
- no convergence to a dose in the indifference interval (the dose might be excluded by the necessary safety rule, see below).
- possible oscillations between an overly and an underly toxic doses (see figure).
- no interpolation and no extrapolation (a model is needed for the final recommendation).



Safety rules : A sequential Bayesian test based on observations at the current dose d : $H_0 : \beta_d \leq \alpha$ against $H_1 : \beta_d > \alpha$, with Jeffrey prior or uniform prior on $[0, 1]$. Usually, a 5% level test is applied between each step (whenever $n_d \geq 3$).

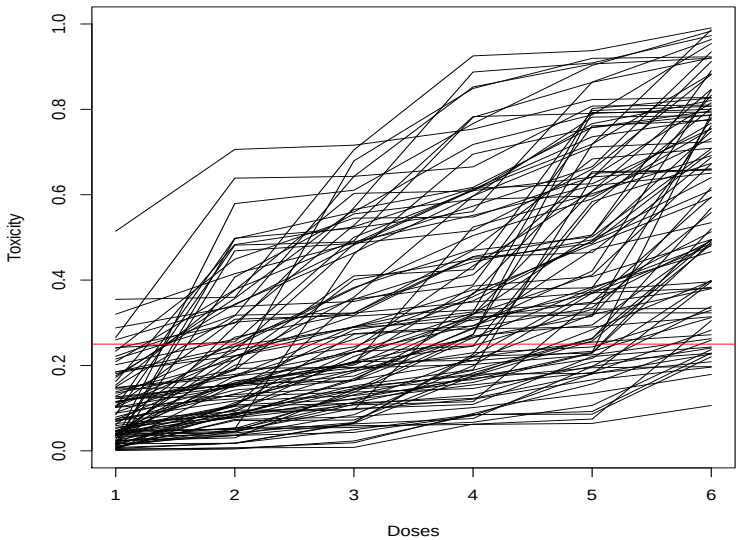
$$\text{Let } \beta_d \sim \mathcal{U}_{[0,1]} : \ \mathbb{P}(\beta_d \leq \alpha \mid \text{Obs. at Dose } d) < 5\% \Rightarrow \text{rejection of } \ H_0.$$

If H_0 is rejected, the range of doses only admits level below the current dose.
Problem : high rate of false positive due to the sequential nature of the test.
Remark : Applied at the first dose, the safety rule is an early stopping rule.

Final Decision rule : A model is fitted to choose the final recommended dose. Usually, an isotonic regression (PAVA algorithm).

Semiparametric Method (Clertant and O'Quigley, 2017, JRSS (b))

It uses a hierarchical Bayesian model where the first level deals with the toxicity scenario β and the second level is the parameter of interest, the MTD.



Scenarios sample

$\Lambda \otimes \Pi$ is the distribution on the scenarios

1. $\theta \in D$ is the **MTD** parameter : $\theta \sim \Pi$.
2. $\Lambda = (\Lambda_\theta)_{\theta \in D}$ is a distribution family conditioned to θ. Λ_θ weights vector β which satisfy the following constraints :

$$\forall d \in D\,,\ |\beta_\theta - \alpha| \leq |\beta_d - \alpha|.$$

The likelihood of β according to the sample (X_1^n, Y_1^n) is $\mathcal{L}_n(\beta)$.

Posterior on the parameter of interest :

$$\Lambda_\theta(d\beta|(X_1^n, Y_1^n)) \times \Pi(\theta|(X_1^n, Y_1^n)) \propto \mathcal{L}_n(\beta) \times \Lambda_\theta(d\beta)\,\Pi(\theta).$$

$$\Pi(\theta|(X_1^n, Y_1^n)) \propto \int \mathcal{L}_n(\beta)\,\Lambda_\theta(d\beta) \times \Pi(\theta).$$

Current estimator of next dose : $X_{n+1} = \widehat{\theta}_n = \arg\max \Pi_n(\theta)$.

Semiparametric Method (Clertant and O'Quigley, 2017, JRSS (b))

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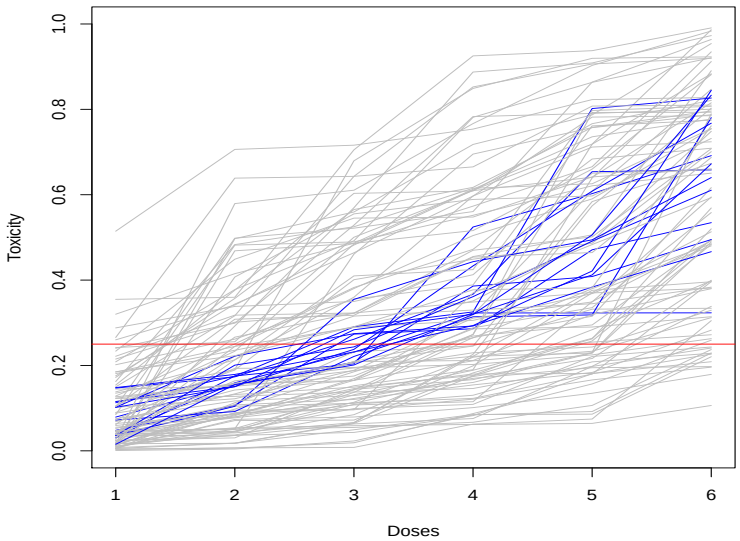


Scenarios sample and Λ_3

$\Lambda \otimes \Pi$ is the distribution on the scenarios

1. $\theta \in D$ is the **MTD** parameter : $\theta \sim \Pi$.
2. $\Lambda = (\Lambda_\theta)_{\theta \in D}$ is a distribution family conditioned to θ. Λ_θ weights vector β which satisfy the following constraints :

$$\forall d \in D\,,\ |\beta_\theta - \alpha| \leq |\beta_d - \alpha|.$$

The likelihood of β according to the sample (X_1^n, Y_1^n) is $\mathcal{L}_n(\beta)$.

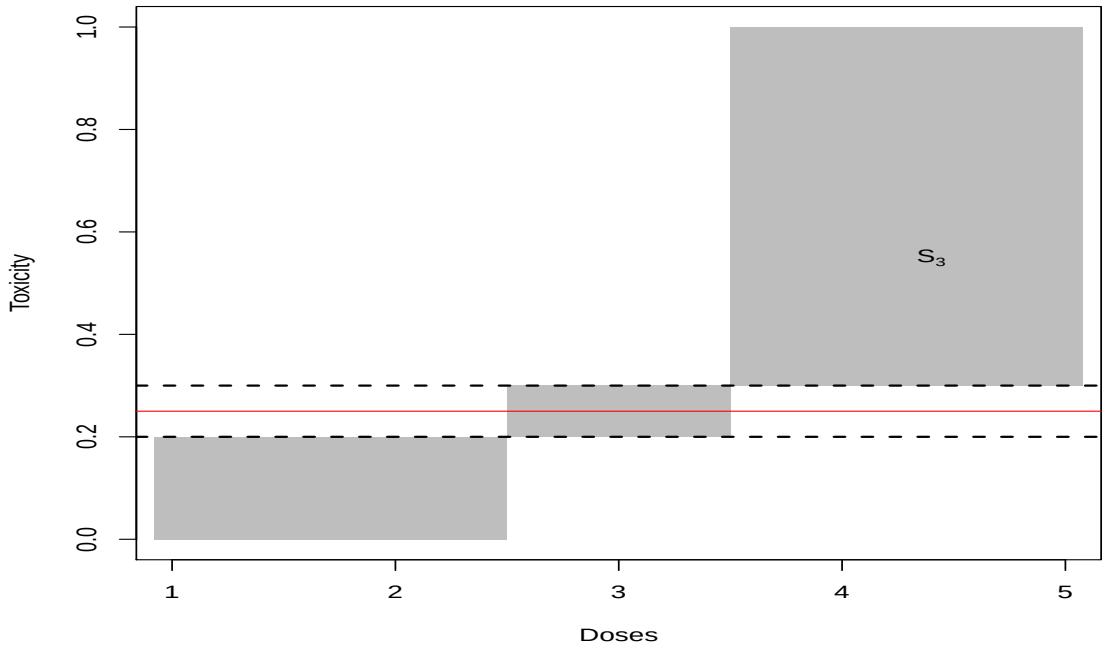
Posterior on the parameter of interest :

$$\Lambda_\theta(d\beta|(X_1^n, Y_1^n)) \times \Pi(\theta|(X_1^n, Y_1^n)) \propto \mathcal{L}_n(\beta) \times \Lambda_\theta(d\beta)\,\Pi(\theta).$$

$$\Pi(\theta|(X_1^n, Y_1^n)) \propto \int \mathcal{L}_n(\beta)\,\Lambda_\theta(d\beta) \times \Pi(\theta).$$

Current estimator of next dose : $X_{n+1} = \widehat{\theta}_n = \arg\max \Pi_n(\theta)$.

Conjugate prior model



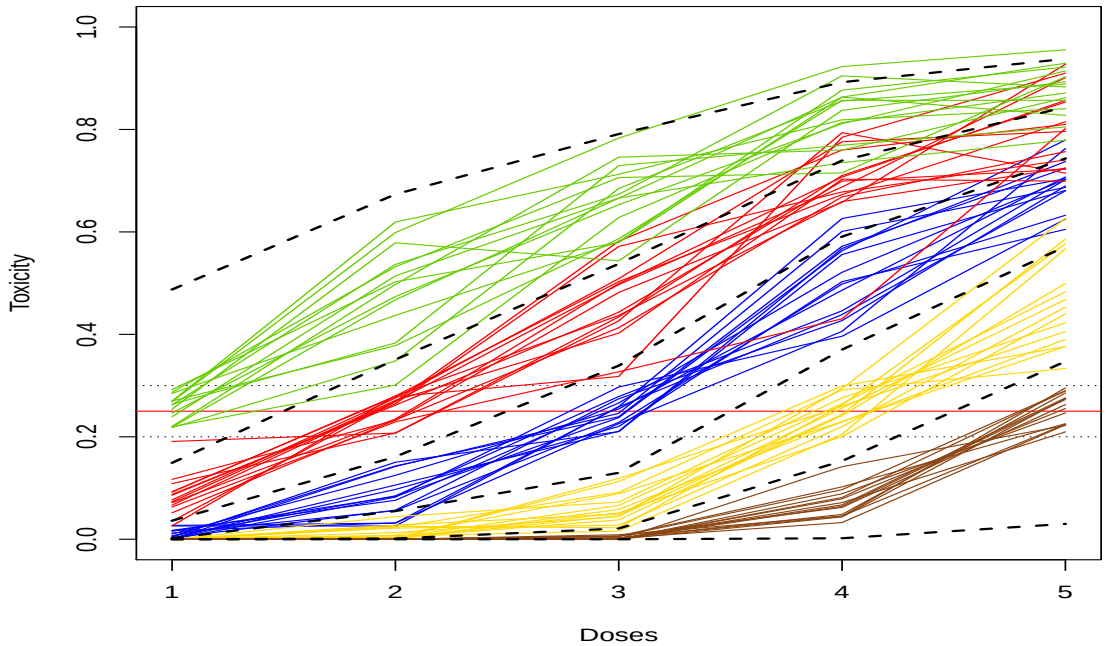
In Grey : Support of Λ_3.

Truncated beta distribution : Let $I = [\alpha - \epsilon, \alpha + \epsilon]$, $B = [0, \alpha - \epsilon]$ and $C = [\alpha + \epsilon, 1]$, with ϵ possibly equal to 0. We set :

$$\Lambda_\theta = \left[\prod_{j=1}^{\theta-1} \mathcal{B}_B(r_\theta^j,\, r_\theta^j)\right] \times \mathcal{B}_{I_\epsilon}(r_\theta^\theta, r_\theta^j) \times \left[\prod_{j=\theta+1}^{m} \mathcal{B}_A(r_\theta^j, r_\theta^j)\right] .$$

with $r_\theta^j = c\, v_\theta^j + 1$ and $r_\theta^j = c(1 - v_j^\theta) + 1$. Thus, c is the dispersion parameter and v_j^θ is the mode of Λ_θ at dose j.

Conjugate prior model



a CRM-like prior model.

Truncated beta distribution : Let $I = [\alpha - \epsilon, \alpha + \epsilon]$, $B = [0, \alpha - \epsilon]$ and $C = [\alpha + \epsilon, 1]$, with ϵ possibly equal to 0. We set :

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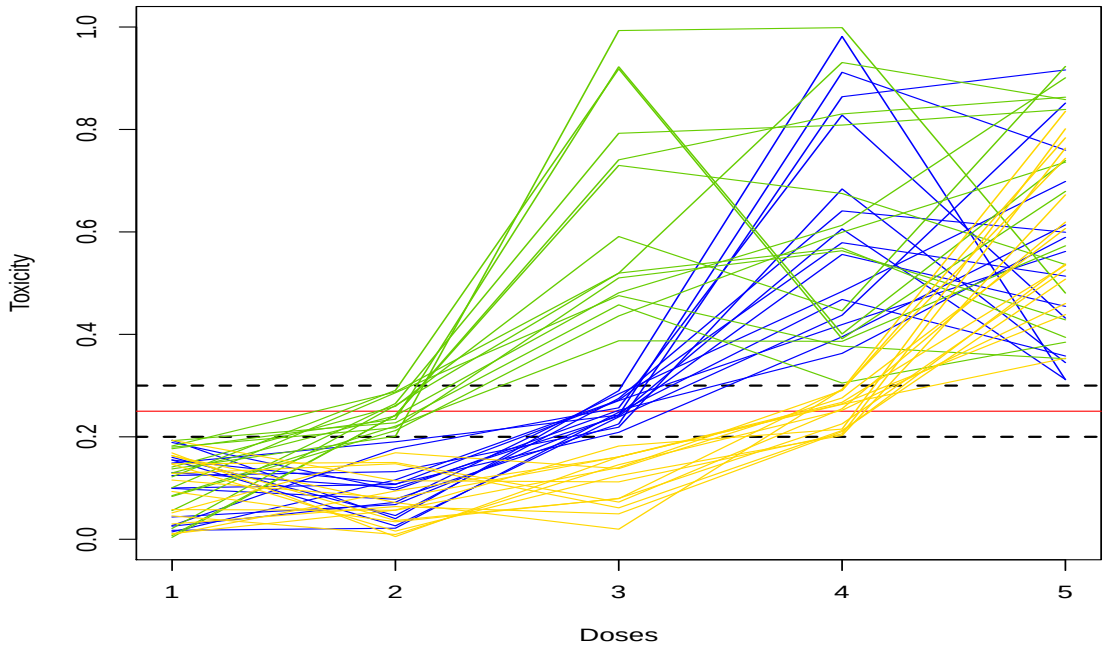
Conjugate prior model



Uniform distributions on each intervals for Λ_2, Λ_3 *and* Λ_4 *(SP-mTPI).*

Truncated beta distribution : Let $I = [\alpha - \epsilon, \alpha + \epsilon]$, $B = [0, \alpha - \epsilon]$ and $C = [\alpha + \epsilon, 1]$, with ϵ possibly equal to 0. We set :

$$\Lambda_\theta = \left[\prod_{j=1}^{\theta-1} \mathcal{B}_B(r_\theta^j,\, r_\theta^j)\right] \times \mathcal{B}_{I_\epsilon}(r_\theta^\theta, r_\theta^j) \times \left[\prod_{j=\theta+1}^{m} \mathcal{B}_A(r_\theta^j, r_\theta^j)\right] .$$

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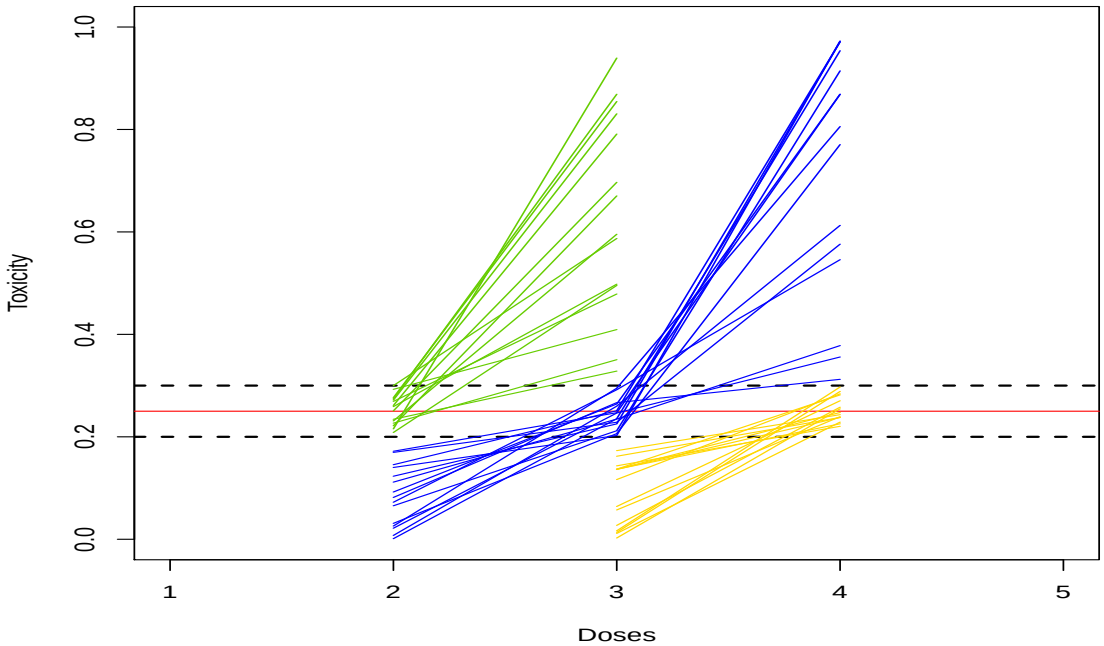
Conjugate prior model



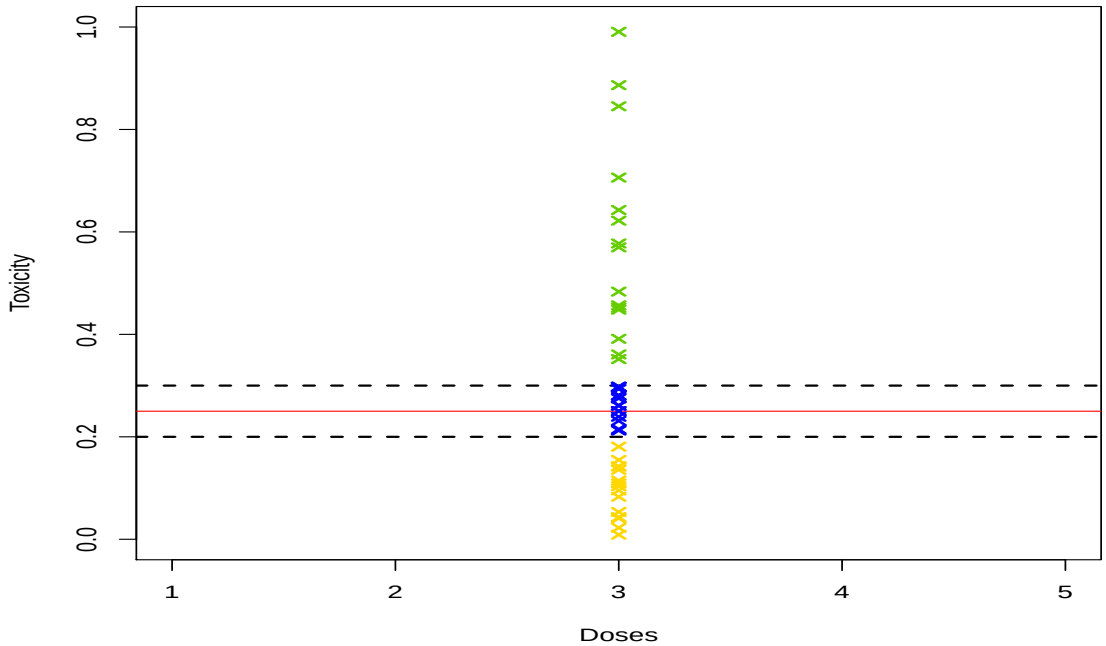
Uniform distributions on each intervals for Λ_2, Λ_3 and Λ_4 are equivalent to a sliding model on three doses (SP-mTPI).

Truncated beta distribution : Let $I = [\alpha - \epsilon, \alpha + \epsilon]$, $B = [0, \alpha - \epsilon]$ and $C = [\alpha + \epsilon, 1]$, with ϵ possibly equal to 0. We set :

$$\Lambda_\theta = \left[\prod_{j=1}^{\theta-1} \mathcal{B}_B(r_\theta^j,\, r_\theta^j)\right] \times \mathcal{B}_{I_\epsilon}(r_\theta^\theta, r_\theta^j) \times \left[\prod_{j=\theta+1}^{m} \mathcal{B}_A(r_\theta^j, r_\theta^j)\right] .$$

with $r_\theta^j = c\, v_\theta^j + 1$ and $r_\theta^j = c(1 - v_j^\theta) + 1$. Thus, c is the dispersion parameter and v_j^θ is the mode of Λ_θ at dose j.

Conjugate prior model



SP-mTPI with sample restricted at the current dose is mTPI.

Truncated beta distribution : Let $I = [\alpha - \epsilon, \alpha + \epsilon]$, $B = [0, \alpha - \epsilon]$ and $C = [\alpha + \epsilon, 1]$, with ϵ possibly equal to 0. We set :

$$\Lambda_\theta = \left[\prod_{j=1}^{\theta-1} \mathcal{B}_B(r_\theta^j,\, r_\theta^j)\right] \times \mathcal{B}_{I_\epsilon}(r_\theta^\theta, r_\theta^j) \times \left[\prod_{j=\theta+1}^{m} \mathcal{B}_A(r_\theta^j, r_\theta^j)\right] .$$

with $r_\theta^j = c\, v_\theta^j + 1$ and $r_\theta^j = c(1 - v_j^\theta) + 1$. Thus, c is the dispersion parameter and v_j^θ is the mode of Λ_θ at dose j.

Asymptotic behavior

The two consecutive doses associated with a probability of toxicity on each part of the threshold α are a (above) and b (below).

Définition

Consider the collection of doses associated with a toxicity belonging to $I = [\alpha \pm \epsilon]$: $\mathcal{E}(I, p) = \{j \in D : p_j \in I\}$.
(a) A method is ϵ-sensitive, if for all p such that $\mathcal{E}(I, p) \neq \emptyset$, we have :

$$\mathbb{P}\left[\exists N\,,\, \forall n > N : X_n \in \mathcal{E}(I, p)\right] = 1\,.$$

(b) A method is balanced, if for all p such that $\mathcal{E}(I, p) = \emptyset$, we have :

$$X_n \xrightarrow{S} \{a, b\}\,,\ a.s.,\ \text{i.e.,}\ \max_{x \in \{a,b\}} \left(\liminf_{n \to +\infty} d(X_n, x)\right) = 0\,,\ a.s.$$

Théorème

Under regularity assumptions on the prior model, the SPM is ϵ-sensitive and balanced (complementary behaviors).

Balanced behavior

When a method is balanced, there exist estimators on the basis of observations which are almost surely convergent to the MTD.

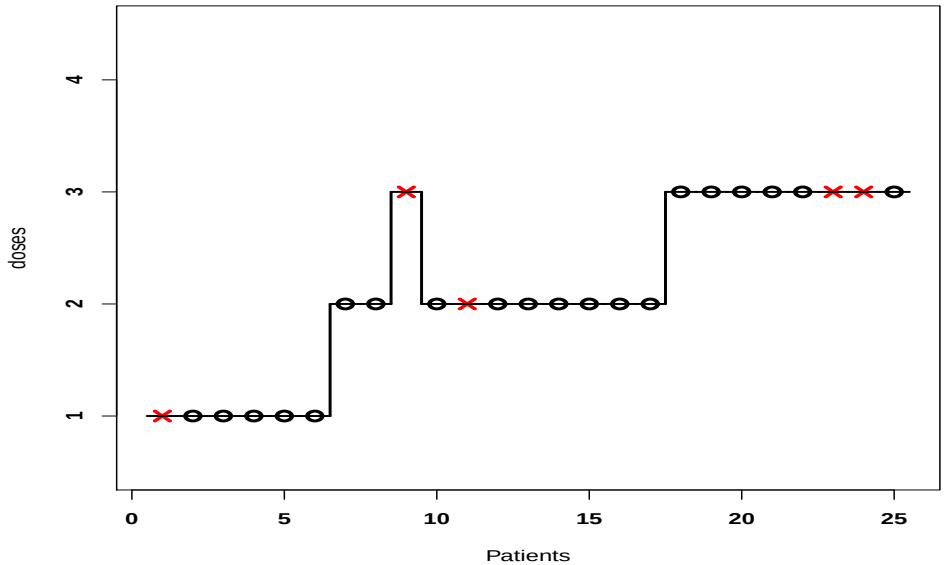
Théorème

*Assume that the central interval I is chosen equal to $\{\alpha\}$. Under assumptions **'Structure'**, **'Independence'** and some regularity properties on the prior model, the SPM is balanced in all circumstances and we have :*

$$\frac{n_b}{n_a} \underset{n\to+\infty}{\longrightarrow} \frac{D_{KL}(p_a||\alpha)}{D_{KL}(p_b||\alpha)} \quad , \quad \textit{with} \;\; n_d = \sum_{k=1}^{n} \mathbb{1}_{\{X_k=d\}}.$$

Suppose that $\alpha = 0.25$:
if $p_a = 0.35$ and $p_b = 0.23$, then $n_a \approx 4.3\%$ of n_b, asymptotically ;
if $p_a = 0.27$ and $p_b = 0.15$, then $n_b \approx 3.5\%$ of n_a, asymptotically.

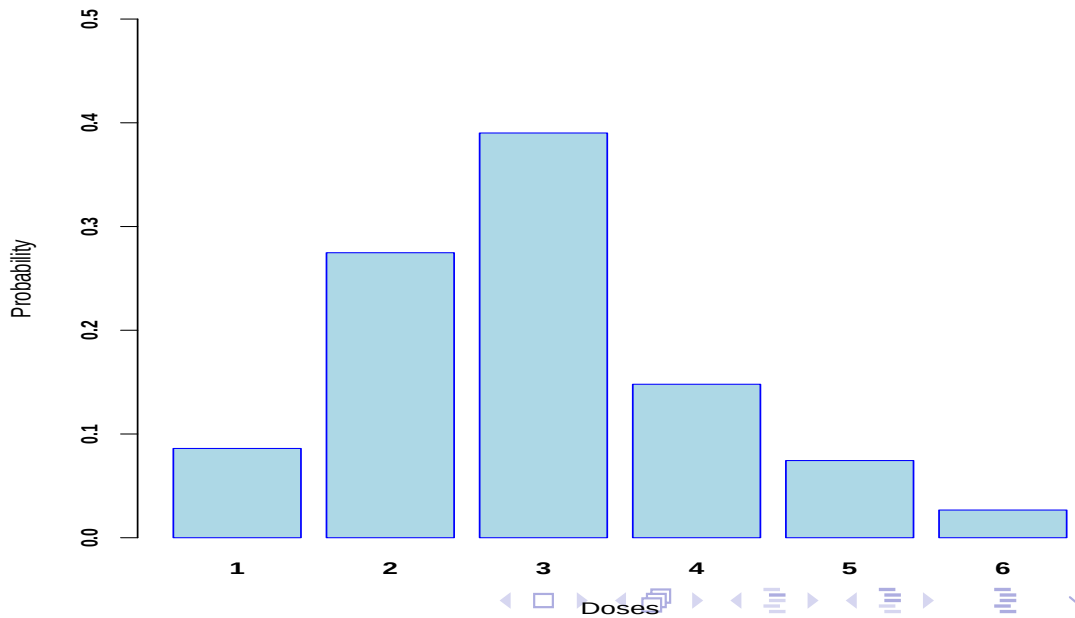
Estimate and credibility (confidence level)



A trial conducted with SPM (Clertant, 2022, JCO). The next recommended dose is the one maximizing the probability of being the MTD :

$$X_{n+1} = \underset{\theta \in D}{\arg\max} \Pi_n(\theta).$$

The final interpretation of the data collected during the trial : the probability for each dose of being the MTD (Π_{25}). Doses 2 and 3 gather 67% of the total probability mass.



Properties (1/2)

(1) Coherence	For one-by-one inclusions, a DLT (non-DLT) cannot be followed by a recommendation to increase (decrease) dose level.
(2) Adaptability	A string of DLTs (non-DLTs) will ultimately result in a recommendation to decrease (increase) the level whenever such a level is available.
(3) No unused observations	Escalation/de-escalation decisions should be based on ALL observations and not just some subset of it.
(4) Straightforward evaluation	Ability to update the model without heavy sampling (MCMC methods). While not essential in any single trial, it helps the investigators to test, calibrate and compare designs.
(5) Interval calibration	Ability for the clinical team to define indifference interval.
(6) Interval convergence	If the indifference interval contains the MTD, then the probability of recommending a final dose into this interval converges to one with increasing sample size.
(7) MTD estimation	Ability to provide a consistent estimate of the MTD with increasing sample size.
(8) Confidence in MTD estimate	Ability to quantify the accuracy of our estimates by providing a probability distribution on the range of doses.

Table – Summary of statistical properties that a good design ought possess

Properties (2/2)

Design class	**3+3**	**CRM**	BLRM	**CCD**	mTPI	mTPI2	BOIN	**SPM**
Coherence		✓						✓
Adaptability	✓	✓		✓	✓	✓	✓	✓
No unused observations		✓	✓					✓
Straightforward evaluation	✓	✓		✓	✓	✓	✓	✓
Interval calibration				✓	✓	✓	✓	✓
Interval convergence		✓						✓
MTD estimation								✓
Confidence in MTD estimate		✓	✓					✓

Table – Different designs and their properties. Umbrella designs are in bold.

Table – Some particular scenarios.

Doses		1	2	3	4	5	6
Scenario 1		**0.05**	**0.10**	**0.20**	**0.35**	**0.50**	**0.70**
PS	SP-CRM	2.3	22.7	54.0	19.7	01.2	0.0
	CRM	02.4	22.2	53.9	20.2	01.3	0.0
PA	SP-CRM	10.8	24.3	39.0	19.0	05.9	00.7
	CRM	12.3	22.1	37.7	20.4	06.4	00.8
Scenario 2		**0.20**	**0.26**	**0.28**	**0.3**	**0.35**	**0.50**
PS	SP-CRM	49.4	21.5	13.2	9.6	5.4	0.6
	CRM	48.1	19.5	14.3	11.2	6.0	0.6
PA	SP-CRM	47.4	20.6	13.5	9.1	7.0	2.1
	CRM	47.6	17.6	14.1	10.7	7.6	2.2
Scenario 3		**0.01**	**0.02**	**0.05**	**0.09**	**0.18**	**0.40**
PS	SP-CRM	0.0	0.2	2.8	20.3	59.2	17.3
	CRM	0.0	0.1	3.4	21.8	58.4	16.1
PA	SP-CRM	4.6	6.0	10.5	19.9	40.7	17.9
	CRM	4.9	5.3	9.7	20.7	40.1	19.0

PS : Percentage of final selection at each dose among 10 000 trials.
PA : Percentage of patients treated at each dose among 10 000 of 25 patients.

Table – Scenarios that differ from the CRM model.

Doses		1	2	3	4	5	6
Scenario 4		**0.0**	**0.0**	**0.0**	**0.23**	**0.3**	**0.35**
PS	SP-CRM	0.0	0.0	10.2	56.8	23.6	9.2
	CRM	0.0	0.0	10.5	52.3	26.9	10.2
PA	SP-CRM	4.0	4.0	19	38.8	22.8	11.1
	CRM	4.0	4.0	16.9	37.8	24.4	12.7
Scenario 5		**0.0**	**0.0**	**0.16**	**0.3**	**0.35**	**0.4**
PS	SP-CRM	0.0	2.3	51.7	31.5	11.1	3.2
	CRM	0.0	3.5	46.7	33.6	12.6	3.6
PA	SP-CRM	4.0	11.8	40.3	24.3	13.7	5.8
	CRM	4.7	11.0	36.3	26.7	14.5	6.5
Scenario 6		**0.01**	**0.02**	**0.05**	**0.11**	**0.14**	**0.21**
PS	SP-CRM	0.0	0.1	3.2	15.7	31.0	49.8
	CRM	0.0	0.1	3.4	15.5	31.2	49.6
PA	SP-CRM	4.6	5.8	10.8	16.7	26.7	35.1
	CRM	4.9	5.3	10.2	16.7	25.9	36.0

PS : Percentage of final selection at each dose among 10 000 trials.
PA : Percentage of patients treated at each dose among 10 000 of 25 patients.

Percentage of correct selection for scenario 6

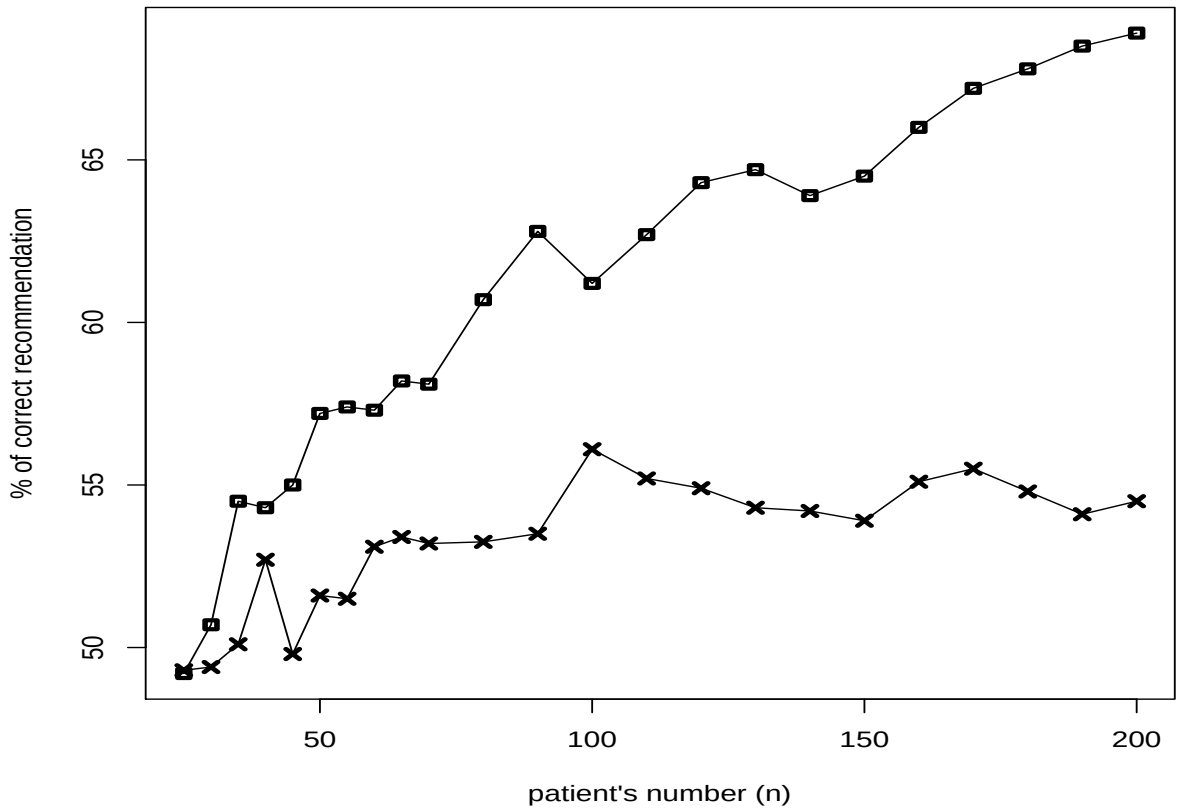
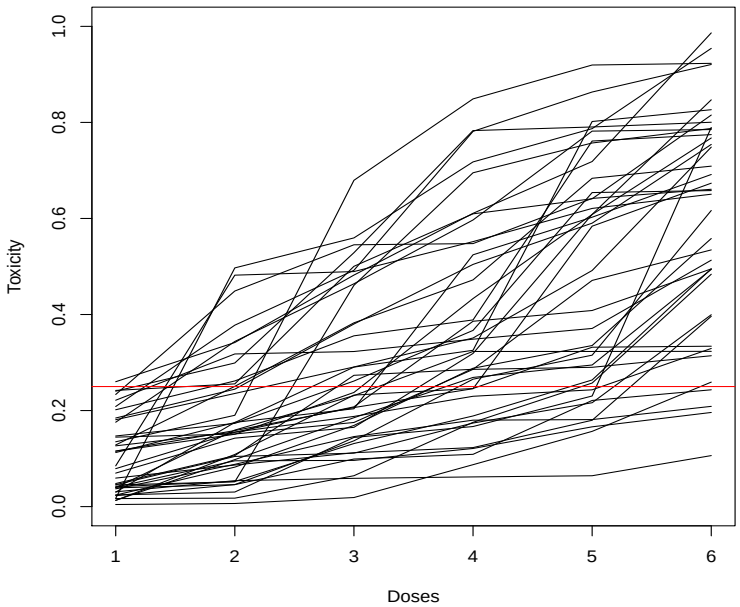


Figure – Clertant et al., 2019, JRSS (B) : For scenario 6, (PCS) as a function of the number of included patients in the study. ■ : SP-CRM ; × : CRM.

Numerical experiment methodology



Sample of scenarios

Pseudo-Uniform class of scenarios, clertant et al. (2017), *JRSS (b)* :

1. Select the MTD, k, uniformly in D
2. Select an upper bound $B_s = \alpha + (1-\alpha) \times M$; M has a Beta distribution depending on the MTD and the number of doses m : $M \sim B(\max\{m-k; 0.5\}, 1)$.
3. Generate a scenario which has the distibution of an ordered sample of m uniform random variables on $[0, B_s]$ conditioned by the event $\{MTD = k\}$.

Cheung K., 2011, *CRC Press* : One popular measure of accuracy based on the dispersion around α, $s = \sum_{d=1}^{m} (\beta_d - \alpha)^2$ is :

$$A_\beta = 1 - ms^{-1} \sum_{d=1}^{m} \rho_d (\beta_d - \alpha)^2$$

where β_d is the true toxicity probability at dose d and the vector $\rho = (\rho_d)_{d \in D}$ indicates the frequency of final recommendation at dose d; the accuracy is noted a_β, when the frequency of allocation is used .

Simulations on 100 000 scenarios

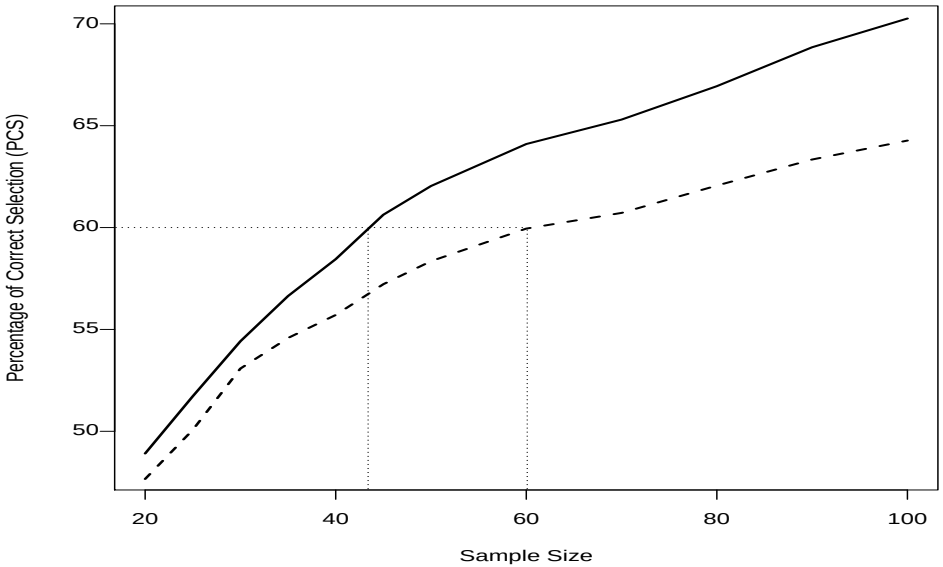
Table – All the methods tested on a sample of 100 000 trials generated by an algorithm using uniform spacings. The target is $\alpha = 25\%$ and 25 patients are enrolled.

Methods	PCS	A_β	PCA	a_β	P_{DLT}	PES
CCD	50.93	0.73	37.44	0.53	24.55	4.64
mTPI	50.27	0.72	37.55	0.52	25.21	4.55
BOIN	51.22	0.73	36.52	0.52	24.03	4.79
Keyboard	51.21	0.73	36.50	0.52	24.05	4.78
CRM	51.53	0.75	37.85	0.56	24.41	4.89
SPM	52.72	0.75	38.47	0.56	24.19	4.90

Treatment versus experimentation dilemma (D. Azriel et al (2011)) :

Precision measures	
PCS	Percentage of correct final selection of the MTD.
A_β	Accuracy index for the final selection.
PCA	Percentage of correct allocation at the MTD during the trial.
a_β	Accuracy index for allocation during the trial.
Safety measures	
P_{DLT}	Percentage of DLT during the trial.
PES	Percentage of trials that stop early.

Estimate and credibility (confidence level)



Clertant et al., 2018, J. of non-parametric stats : Percentage of correct selection (PCS) as afunction of the sample size ; SPMc : black curves ; CRM : dotted curves.

Clertant et al., 2019, JRSS (c) : Percentage of correct selection (PCS) as a function of the sample size ; BOIN : black curves ; SP-BOIN : dotted curves.