MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Dose-escalation designs for combination & dose-schedule studies

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Practical 4: Dose-escalation with a model-free design

You are asked to design a Phase I combination dose-escalation clinical trial in patients with melanoma. The study will look into combinations of two drugs, decitabine (drug A) and pegylated interferon (drug B), which was rationally selected for the clinical study based on preclinical data showing the synergistic antitumor activity of the combination of the two agents. Both agents were studied independently in single-agent clinical trials for a relatively long time, which provided extensive information on the prior estimates. Decitabine was given intravenously over 1h daily for 5 days, on days 1–5 during a 28-day treatment cycle, and pegylated interferon was given by subcutaneous injection once weekly during the same cycle. Three dose levels of decitabine were studied in the combination trial (mg/m$_2$/day): 5, 10, 15 (denoted by A_1, A_2 and A_3); and three dose levels of Pegylated interferon α-2b μg/kg: 1.5, 3 and 4.5 (denoted by B_1, B_2, B_3). The combination grid is displayed as:

(A_1, B_1) [1]	(A_2, B_1) [2]	(A_3, B_1) [3]
(A_1, B_2) [4]	(A_2, B_2) [5]	(A_3, B_2) [6]
(A_1, B_3) [7]	(A_2, B_3) [8]	(A_3, B_3) [9]

The objective is to identify the maximum tolerated combination corresponding to the 30% risk of toxicity. The dose-skipping, as well as diagonal escalation, is not allowed. Up to 36 patients in the cohort of 3 patients will be recruited. Following the discussions with clinicians, the following prior mean estimates of the toxicity probabilities for three dose levels of each drug are assumed

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

You are asked to design this combination study. Given in the shape of the combination-toxicity curve, you are asked to explore the use of the model-free design, Surface-Free Design. The design with a safety constraint and following the literature, the overdosing constant is fixed at 0.7.

Run the file `SFD-Functions.R` to upload the required functions for the Surface-Free Design. You can then use `template4.R` as a starting point.

(a) The Surface-Free Designs requires specification of the prior distribution of each interaction parameter. Using the prior information provided by the clinicians, find the parameters of the Beta prior distribution for the "connection" parameters of the model. *Note: Surface-Free Design parametrises the probability of no DLT.*

The probability of no toxic response at the lowest combination can then be found as $\hat{\theta}(0) = 1 - 0.10 - 0.05 + 0.10 \times 0.05 = 0.855$. Further, using the prior information about agent A given as a monotherapy, one can obtain that $\hat{\theta}_2(0) = \frac{1-\hat{p}_2^{(A)}}{1-\hat{p}_1^{(A)}} = \frac{1-0.10}{1-0.05} \approx 0.947$, $\hat{\theta}_3(0) = \frac{1-0.2}{1-0.1} \approx 0.888$, and for the agent B, $\hat{\tau}_2(0) = \frac{1-\hat{p}_2^{(B)}}{1-\hat{p}_1^{(B)}} = \frac{1-0.20}{1-0.10} \approx 0.899$, $\hat{\tau}_3(0) = \frac{1-0.30}{1-0.20} = 0.875$.
Following the lecture, it is advised to use a slightly informative prior on each connection, i.e. around $c = 4$ can be chosen. This results in

```
> a.prior
[1] 3.420000 3.555556 3.500000 3.789474 3.555556
> b.prior
[1] 0.5800000 0.4444444 0.5000000 0.2105263 0.4444444
```

The first value corresponds to the prior for the starting combination, followed by two values corresponding to τ, followed by 2 values corresponding to θ

(b) Function `sfd.design.next()` fits the surface-free model and provides the recommendation for the next combination (using notations 1–9). Run the function using the prior information only (no data). Examine output. Does the specified prior correspond to optimistic or pessimistic beliefs about the overall toxicity?

No data input:

```
doses.exp<-mat.or.vec(1,9)
doses.tox<-mat.or.vec(1,9)
datan<-c(doses.exp)
datas<-c(doses.tox)
```

Running the design:

```
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
+                         current.combo=1,
+                         no.skipping=T,safety=T,
+                         c.overdose=0.70)
> design
$Combination.Notation
     [,1] [,2] [,3]
[1,]    1    2    3
[2,]    4    5    6
[3,]    7    8    9
```

```
$Next.Combo
[1] 2

$Tox.Est
      [,1]  [,2]  [,3]
[1,] 0.145 0.243 0.334
[2,] 0.190 0.283 0.369
[3,] 0.282 0.364 0.441

$Tox.Est.Constrained
      [,1]  [,2] [,3]
[1,] 0.145 0.243    1
[2,] 0.190 1.000    1
[3,] 1.000 1.000    1

$Overdose
      [,1]  [,2]  [,3]
[1,] 0.158 0.334 0.514
[2,] 0.225 0.412 0.591
[3,] 0.409 0.579 0.737

$Stop
[1] 0
```

The mid-combination correspond to the TTL, hence, these are prior MTCs. The starting combination has the toxicity risk of 15% and the highest one is unsafe. Hence, the prior beliefs are neither overly pessimitic nor overly optimistic and present a relevant situation of choosing the combination grid. We believe that the target is in the middle but allow lower and higher combination around them if we are wrong.

(c) Learning from your previous experience, you decide to investigate the individual trial behaviour before going into the simulation study. Follow the escalation path recommended by the SFD, assume that first 3 cohorts have no DLTs, and the 4th cohort had 2/3 DLTs. What is the recommendation now? Is it intuitive?

After first 0/3 at Combo 1, the recommendation is to escalate to Combo 2

```
doses.exp<-c(3,0,0,0,0,0,0,0,0)
doses.tox<-c(0,0,0,0,0,0,0,0,0)

datan<-c(doses.exp)
```

```
datas<-c(doses.tox)

design<-sfd.design.next(datas=datas,datan=datan,
                        target=0.30,
                        a.prior=a.prior,b.prior=b.prior,
                        current.combo=1,
                        no.skipping=T,safety=T,
                        iterations=10^4,
                        c.overdose=0.70)
design$Next.Combo
[1] 2
```

After first 0/3 at Combo 2, the recommendation is to escalate to Combo 3

```
> doses.exp<-c(3,3,0,0,0,0,0,0,0)
> doses.tox<-c(0,0,0,0,0,0,0,0,0)
>
> datan<-c(doses.exp)
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
+                         current.combo=2,
+                         no.skipping=T,safety=T,
+                         iterations=10^4,
+                         c.overdose=0.70)
> design$Next.Combo
[1] 3
```

After first 0/3 at Combo 3, the recommendation is to escalate to Combo 6

```
> doses.exp<-c(3,3,3,0,0,0,0,0,0)
> doses.tox<-c(0,0,0,0,0,0,0,0,0)
>
> datan<-c(doses.exp)
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
+                         current.combo=3,
```

```
+                          no.skipping=T,safety=T,
+                          iterations=10^4,
+                          c.overdose=0.70)
> design$Next.Combo
[1] 6
```

After 2/3 at Combo 6, the recommendation is to go to Combo 8

```
> doses.exp<-c(3,3,3,0,0,3,0,0,0)
> doses.tox<-c(0,0,0,0,0,2,0,0,0)
>
> datan<-c(doses.exp)
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                          target=0.30,
+                          a.prior=a.prior,b.prior=b.prior,
+                          current.combo=6,
+                          no.skipping=T,safety=T,
+                          iterations=10^4,
+                          c.overdose=0.70)
> design$Next.Combo
[1] 8
```

The last recommendation is intuitive given no DLTs before that but 2/3, the model estimates that these toxicities are linked to the last increase in the dose $A_2 \rightarrow A_3$) (i.e. the last connection in the model. Hence, the decision is to try the highest safe combination with lower dose of A.

(d) The escalation path above assumes the particular number of DLTs. Now, you would like to have a deeper look into the escalation decisions and check what the model's recommendation will be given 0, 1, 2, 3 DLTs on the next recommended dose. Use the data observed so far and following the last model recommendation from previous point (c). Are the suggested recommendation intuitive? If yes, why? If no, what changes to the design parameters can you proposed to tackle this?

After 0/3 at Combo 8 $\rightarrow$ Combo 9 is safe to try but Combo 6 has closer to TTL estimate.

```
> doses.exp<-c(3,3,3,0,0,3,0,3,0)
> doses.tox<-c(0,0,0,0,0,2,0,0,0)
>
> datan<-c(doses.exp)
```

```
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
+                         current.combo=8,
+                         no.skipping=T,safety=T,
+                         iterations=10^4,
+                         c.overdose=0.70)
> design$Next.Combo
[1] 6
> design$Tox.Est
      [,1]  [,2]  [,3]
[1,] 0.052 0.103 0.231
[2,] 0.114 0.162 0.282
[3,] 0.170 0.215 0.327
```

After 1/3 at Combo 8 → Stay at Combo 8 as escalation is unsafe.

```
> doses.exp<-c(3,3,3,0,0,3,0,3,0)
> doses.tox<-c(0,0,0,0,0,2,0,1,0)
>
> datan<-c(doses.exp)
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
+                         current.combo=8,
+                         no.skipping=T,safety=T,
+                         iterations=10^4,
+                         c.overdose=0.70)
> design$Next.Combo
[1] 8
> design$Tox.Est
      [,1]  [,2]  [,3]
[1,] 0.065 0.137 0.239
[2,] 0.168 0.231 0.323
[3,] 0.259 0.316 0.397
> design$Overdose
      [,1]  [,2]  [,3]
[1,] 0.011 0.075 0.306
```

```
[2,] 0.172 0.290 0.554
[3,] 0.371 0.521 0.752
```

After 2/3 at Combo 8 → de-escalate to Combo 5.

```
> doses.exp<-c(3,3,3,0,0,3,0,3,0)
> doses.tox<-c(0,0,0,0,0,2,0,2,0)
>
> datan<-c(doses.exp)
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
+                         current.combo=8,
+                         no.skipping=T,safety=T,
+                         iterations=10^4,
+                         c.overdose=0.70)
> design$Next.Combo
[1] 5
> design$Tox.Est
      [,1]  [,2]  [,3]
[1,] 0.073 0.146 0.236
[2,] 0.243 0.303 0.377
[3,] 0.365 0.415 0.477
> design$Overdose
      [,1]  [,2]  [,3]
[1,] 0.020 0.102 0.308
[2,] 0.349 0.489 0.701
[3,] 0.639 0.779 0.898
```

After 3/3 at Combo 8 → de-escalate to Combo 4.

```
> doses.exp<-c(3,3,3,0,0,3,0,3,0)
> doses.tox<-c(0,0,0,0,0,2,0,3,0)
>
> datan<-c(doses.exp)
> datas<-c(doses.tox)
>
> design<-sfd.design.next(datas=datas,datan=datan,
+                         target=0.30,
+                         a.prior=a.prior,b.prior=b.prior,
```

```
+                          current.combo=8,
+                          no.skipping=T,safety=T,
+                          iterations=10^4,
+                          c.overdose=0.70)
> design$Next.Combo
[1] 4
> design$Tox.Est
      [,1]  [,2]  [,3]
[1,] 0.075 0.158 0.235
[2,] 0.309 0.371 0.428
[3,] 0.474 0.521 0.565
> design$Overdose
      [,1]  [,2]  [,3]
[1,] 0.028 0.140 0.309
[2,] 0.493 0.641 0.789
[3,] 0.829 0.929 0.968
```

One can argue that these represent intuitive escalation decisions.

(e) Once you are satisfied with the individual trajectories for the first cohorts, you need to investigate the behaviour under various possible trajectories via a simulation study. Assume that the true toxicity scenario is

0.02	0.05	0.12
0.10	0.20	0.30
0.15	0.30	0.50

Start with a code that will sequentially allocate the cohorts with the decision-making after each cohort driven by the SFD (using `sfd.design.next()`). Then, run this sequential trial 100 times. What is the proportion of each combination being recommended? What other metrics did you have a look at? Can you recommend such a design? Do you need any further investigations before making any final recommendation?

Overall, the design has good OC: the proportion of optimal selection is around 60%, and the proportion of overly toxic selections is small. More scenarios is needed to make a definitive conclusion.