dfpk: an R package for a practical implementation of PK measurements in dose-finding studies

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Introduction

Dose-finding, aiming at finding the maximum tolerated dose (MTD), and pharmacokinetics (PK) studies are the first in human studies in the development process of a new treatment. In the literature, to date only few attempts have been made to combine PK and dose-finding and no software implementation is available. We implemented the five PK-based dose-finding methods developed in [1] in an R package, called `dfpk` [2].

Dose-finding methods

In Bayesian methods, probability of toxicity $p_T(d)$ at dose d, $d \in \{d_1,\dots,d_K\}$, is estimated after each cohort and the dose assigned to the next cohort is computed using posterior distributions. We model this probability also as a function of exposure z. In the following, we use $z = \log(AUC)$. z is used in the dose-finding designs in different ways, that is as covariate or dependent variable or both ways.

Concentration (AUC, C_{max})

Dose → Toxicity

CRM:

$$\text{logit}(p_T(d_k,\beta)) = \tilde{d}_k^{e^{\beta}}$$

with skeleton $\{\tilde{d}_1,\dots,\tilde{d}_K\}$.

DTOX:

$p_T(d,\boldsymbol{\beta}) = \Phi(-\beta_0 + \beta_1 \log(d))$ with Φ the CDF of the standard normal distribution

Concentration (AUC, C_{max})

Dose → Toxicity

PKCOV:

$\text{logit}(p_T(d,\Delta z_d,\boldsymbol{\beta})) = -\beta_0 + \beta_1 \log(d_k) + \beta_2 \log(\Delta z_d)$ with Δz the difference between log(AUC) of patient and log(AUC of population)

Concentration (AUC, C_{max})

Dose → Toxicity

PKCRM:

Minimum MTD suggested by the CRM and the PKLIM model.

PKLIM:

$z \sim N(\beta_0 + \beta_1 \log(d), \nu^2)$ and toxicity is defined as z above a threshold L.

Concentration (AUC, C_{max})

Dose → Toxicity

PKLOG:

PKLIM model + $\text{logit}(p_T(z,\boldsymbol{\beta})) = -\beta_2 + \beta_3 z$ And the probability of toxicity versus dose is computed through ab expectation.

PKPOP:

PKLIM model + $\text{logit}(p_T(z,\boldsymbol{\beta})) = -\beta_2 + \beta_3 z_{pop}$

PKTOX:

PKLIM model + $p_T(z,\boldsymbol{\beta}) = \Phi(-\beta_2 + \beta_3 z)$.

All methods share the same dose-escalation rule idea, that is the dose chosen for the next cohort enrolled, is the one whose probability of toxicity is the nearest to the target selected by the trial investigators. A no-skipping rule is given, defined by if not all doses have been tested previously, the dose is chosen from a subset which contains all the doses already evaluated and the immediate next higher dose level. Moreover, the final recommended MTD is given by the dose that would have been administered for the $(n+1)$st subject enrolled in the trial. We added also a stopping rule for each method.

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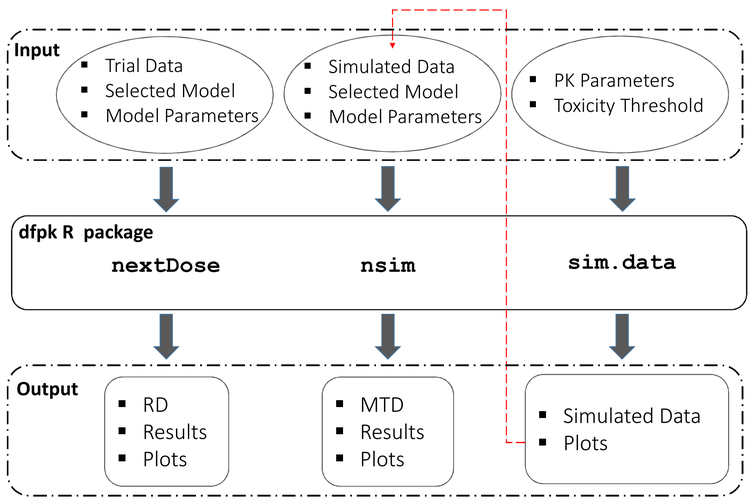
dfpk package



During the trial, the already accrued patient data ("Trial data" in Figure 1) can be used in the `nextDose` function in order to determine the next recommended dose, or the MTD at the end of trial. Plots are also available after the estimation process. When planning a new trial, datasets containing PK and toxicity measurements, can be simulated directly by the user ("Simulated data") or through the `sim.data` function, and used in the `nsim`, which will perform n simulated clinical trials. Also in this case, plots with graphical representations support the numeric results. Bayesian parameter estimation is carried out using the `rstan` package while `ggplot2` package is used to create plots.

nextDose

It requires the method name, the binary toxicity outcomes and the PK measurements for each patient, the panel of doses, the toxicity threshold and the parameter for the prior distributions. If any argument is not specified then, the function will use the corresponding default choice that is proposed by [1].

```
nextDose(model, y, AUCs, doses, x, theta, options, prob = 0.9, betapriors = NULL,
                    thetaL = NULL, p0 = NULL, L = NULL, deltaAUC = NULL)
```

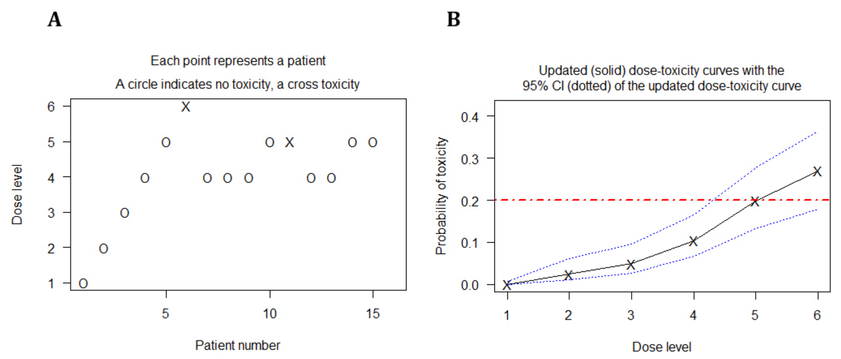
Input:

model	The dose-finding model chosen
y	A binary vector of patient's toxicity outcomes
AUCs	A vector with the computed AUC values of each patient
doses	A vector with the doses panel
x	A vector with the dose level assigned to patients
theta	The toxicity target
options	List with the Stan model's options

```
> doses <- c(12.59972,34.65492,44.69007,60.80685,
83.68946,100.37111)
> theta <- 0.2 > options <- list(nchains = 4, niter =
4000, nadapt = 0.9)
> AUCs <- c(1.20, 5.50, 6.88, 3.31, 3.64, 10.27, 3.89,
3.09, 2.54, 5.53, 8.52, 4.64, 11.05, 10.25, 5.23)
> x <- c(1, 2, 3, 4, 5, 6, 4, 4, 4, 5, 5, 4, 4, 5, 5)
> y <- c(0, 0, 0, 0, 0, 1, 0, 0, 0, 0, 1, 0, 0, 0, 0)
> nextD <- nextDose(model = "pktox", y=y, AUCs=AUCs,
  doses=doses, x=x, theta=theta, options=options)
```

Output example:

```
The Next Recommended Dose:
[1] 5
Estimated probability of toxicity:
[1] 0.0004 0.0225 0.0473 0.1026 0.1984 0.2714
```



sim.data

This function generates and stores PK and toxicity data in order to be used for simulation. It generates at each dose the toxicity value related to AUC with an underlying one PK compartimental model with linear absorption in function of k_a, CL, and V. Subject's CL and V are sampled from log-normal distributions. Toxicity for the ith patient if $\alpha_i AUC_i \geq \tau_T L^{-1} h$, where α_i was assumed to come from a lognormal distribution with zero mean and standard deviation ω_α and τ_T is a given threshold

```
sim.data(PKparameters, omegaIIV, omegaAlpha, sigma, doses, limitTox, timeSampling, N)
```

The result is stored in the R "scen" object, which regroups the subject's PK parameters, the concentration measurements for all patients and the simulated toxicities values at each dose level. It is included as an example. Similar dataframes can be generated directly by the user and passed to `nsim`.

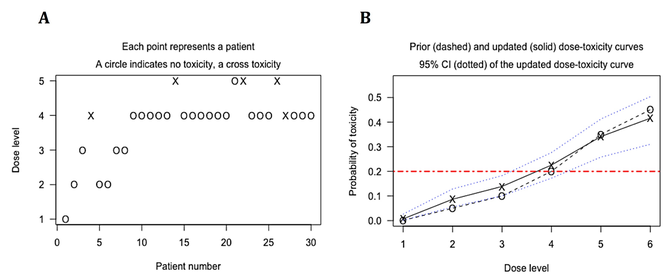
nsim

In the simulated trial, the dose is escalated stepwise cohort by cohort until the first toxicity response is observed and then the chosen dose-finding method design is applied (two-stage design).

```
nsim(doses, N, cohort, icon, theta, model, simulatedData, TR, prob = 0.9, AUCmethod = 2,
        options = list(nchains = 4, niter = 4000, nadapt = 0.8), betapriors = NULL,
        thetaL = NULL, p0 = 0, L = 0)
```

Example:

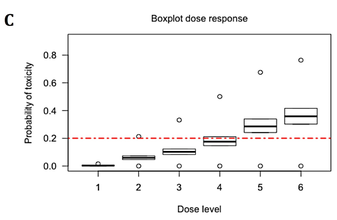
```
> icon <- c(2, 3, 4, 5, 6, 9, 19, 28, 38, 48)
                    #sampling time points to be used
> simResult <- nsim(doses, N=30, cohort=1, icon, theta=0.2,
        model="pktox",simulatedData=gen.scen, TR=10,
        options=options, AUCmethod=1)
```



Output:

```
Dose-Finding Results:
Dose                        1     2     3     4     5     6
Truth Probabilities     0.001 0.05 0.10 0.20 0.35 0.45
Selected % MTD          0.030 0.10 0.10 0.59 0.17 0.00

Recommendation is based on a target toxicity probability
of: 0.2
```



Discussion

The developed user-friendly R package `dfpk` supports the design of innovative dose-finding studies using PK information. As presented in [1], including PK measurement in methods as PKLOGIT and PKTOK, allows a better estimation of the dose-response curve. On the other hand, in the PKCRM, the PK acts as a second safety constraint on AUC and it helps to reduce overdosing.

References:

[1] Ursino M, Zohar S, Lentz F, Friede T, Stallard N, Comets E. Dose-finding methods using pharmacokinetics in small populations. Biometrical Journal, 2017; in press

[2] https://CRAN.R-project.org/package=dfpk