Backfill cohorts

Introduction

Backfilling cohorts are increasingly used in dose escalation studies, see Barnett et al. (2023). The idea is that once a dose level has been tested and found to be safe, then while the dose escalation continues at higher dose levels, additional patients can be enrolled at the lower dose levels to gather more data on safety and/or efficacy. This is particularly useful in trials where patient recruitment is slow or when there is a need to gather more information on lower dose levels for regulatory or clinical reasons.

Sometimes health authorities are asking to include the backfilling cohorts in the simulations to check the operating characteristics (especially PMDA). In addition, it is useful to get more precise operating characteristics for the overall trial by actually simulating the backfilling cohorts, when they are part of the actual clinical trial design.

Hence, with `crmPack` it is now possible to include backfilling cohorts in the simulations. This vignette illustrates how to do this.

Framework

Conceptually the backfilling details are part of the design of a trial. Therefore the details are included via a dedicated slot `backfill` in the `Design` class. It contains an object of class `Backfill`, which captures these details via the following slots:

- `cohort_size`: How large are the backfilling cohorts? Here an object of class `CohortSize` is used.
- `total_size`: What is the overall maximum number of patients across all backfill cohorts?
- `opening`: When can a backfill cohort be opened or recruited into? Here an object of a new `Opening` rules class is used. These rules can be based on e.g. dose level, current highest/maximum safe dose, efficacy responses, etc.
- `recruitment`: How fast can patients be recruited into backfill cohorts? Here an object of a new `Recruitment` class is used. You can choose between immediate recruitment vs. a ratio compared to active dose escalation cohort (e.g. when active cohort has 3 patients recruited then here only 1/3 so 1 patient per cycle to backfill cohorts).
- `priority`: When there are multiple open backfill cohorts, which one should be recruited into first? Here a simple string is used to specify the priority rule (first "lowest" dose, first "highest" dose, or "random").

Additional parts of the backfill cohort framework comprise:

- The `Data` objects have a slot `backfilled` identifying whether each patient was backfilled or not, and the slot `response` identifies whether each patient had a response (1) or not (0). When these are not actively set by the user, then they default to no patients backfilled (all `FALSE`) and no response data available (all `NA`).
- Some `Stopping` rules can optionally exclude backfill patients for assessing whether a trial can be stopped or not. This is currently the case for the `StoppingPatientsNearDose` rule.

Examples

Standard components

We start with the standard components of a CRM design, which are not changed by the backfilling framework - except that for the `StoppingPatientsNearDose` rule we can now choose whether to include backfill patients or not.

```r
library(crmPack)
#> Loading required package: ggplot2
#> Registered S3 method overwritten by 'crmPack':
#>   method        from
#>   print.gtable gtable
#> Type crmPackHelp() to open help browser
#> Type crmPackExample() to open example

# Define the dose-grid.
emptydata <- Data(
    doseGrid = c(0.1, 0.2, 0.5, 1, 3, 5, 10, 15, 20, 25, 40, 50, 60, 70, 80, 100)
)

# Define the dose-toxicity model.
model <- LogisticLogNormal(
    mean = c(-0.85, 1),
    cov = matrix(c(5, -0.5, -0.5, 5), nrow = 2),
    ref_dose = 56
)

# Choose the rule for selecting the next dose.
myNextBest <- NextBestNCRM(
    target = c(0.2, 0.35),
    overdose = c(0.35, 1),
    max_overdose_prob = 0.25
)

# Choose the rule for stopping.
myStopping1 <- StoppingMinCohorts(nCohorts = 3)
myStopping2 <- StoppingTargetProb(
    target = c(0.2, 0.35),
    prob = 0.5
)
myStopping3 <- StoppingMinPatients(nPatients = 40)
myStopping4 <- StoppingPatientsNearDose(nPatients = 10L, percentage = 30, include_backfill = FALSE)
myStopping <- (myStopping1 & myStopping2 & myStopping4) |
    myStopping3 |
    StoppingMissingDose()

# Choose the rule for dose increments.
myIncrements <- IncrementsRelative(
    intervals = c(0, 20, 50),
    increments = c(1, 0.67, 0.33)
)
```

No backfill cohorts

First we can define a design without backfill cohorts, which is the default behaviour when no backfill details are specified:

```r
design_no_backfill <- Design(
    model = model,
    nextBest = myNextBest,
    stopping = myStopping,
    increments = myIncrements,
    cohort_size = CohortSizeConst(3),
    data = emptydata,
    startingDose = 3
)
design_no_backfill@backfill
```

No backfill cohorts at all will be opened.

Note that this concise statement is produced by dedicated `knit_print` methods for the `Backfill` class, which help with the consistent reporting of `crmPack` design details in vignettes and reports.

Simple backfill cohorts

Let's continue with the simplest case of backfill cohorts. Here we define backfill cohorts of size 3 patients each, with a maximum of 12 backfill patients in total. Backfill cohorts can be opened at any time (i.e. immediately), and recruitment into backfill cohorts is immediate (i.e. as fast as dose escalation cohorts). When multiple backfill cohorts are open, then the lowest dose level is recruited into first.

```
backfill_simple <- Backfill(
    cohort_size = CohortSizeConst(3),
    total_size = 12,
    opening = OpeningMinCohorts(min_cohorts = 1),
    recruitment = RecruitmentUnlimited(),
    priority = "lowest"
)
backfill_simple
```

Cohort size: A constant size of 3 participants.

Opening rule: If 1 or more cohorts have been treated in total.

Recruitment: Unlimited recruitment of backfill patients is allowed.

Total number of backfill patients: 12 backfill patients.

Priority of higher vs. lower dose backfill cohorts: lowest dose.

We can now add this backfill specification to the design:

```
design_simple_backfill <- design_no_backfill
design_simple_backfill@backfill <- backfill_simple
```

More complex backfill cohorts

Now let's make things a bit more complex. We define a random number of patients for each backfill cohort, with a minimum of 1 patient and a maximum of 6 patients. Backfill cohorts can only be opened once at least 3 dose escalation cohorts have been completed. Note that this will lead to a delayed opening of potentially multiple backfill cohorts. In addition, at least one response must have been observed at the cohort's dose level or below before it could be opened for backfill. We will be able to specify the assumed dose-response probability function in the `simulate` method call later. Recruitment into backfill cohorts is slower than dose escalation cohorts, with a ratio of 1 backfill patient for every 2 dose escalation patients. When multiple backfill cohorts are open, then the highest dose level is recruited into first. The total maximum number of backfill patients is set to 20.

```
backfill_complex <- Backfill(
    cohort_size = CohortSizeRandom(min_size = 1, max_size = 6),
    opening = OpeningMinCohorts(min_cohorts = 3) &
```

```
      OpeningMinResponses(
        min_responses = 1,
        include_lower_doses = TRUE
    ),
    recruitment = RecruitmentRatio(ratio = 1/2),
    priority = "highest",
    total_size = 20
)
backfill_complex
```

Cohort size: A random cohort size drawn uniformly between 1 and 6 participants.

Opening rule: If both of the following rules are satisfied:

- If 3 or more cohorts have been treated in total.
- If 1 or more responses have been observed at this dose or lower.

Recruitment: Backfill patients are recruited at a ratio of 0.5 per patient in the main trial cohort.

Total number of backfill patients: 20 backfill patients.

Priority of higher vs. lower dose backfill cohorts: highest dose.

Note how we can combine multiple opening rules using the `&` operator. This is analogous to how stopping rules can be combined. Indeed, it is also possible to use the `|` operator to combine opening rules with an "or" logic.

Again we add this backfill specification to the design:

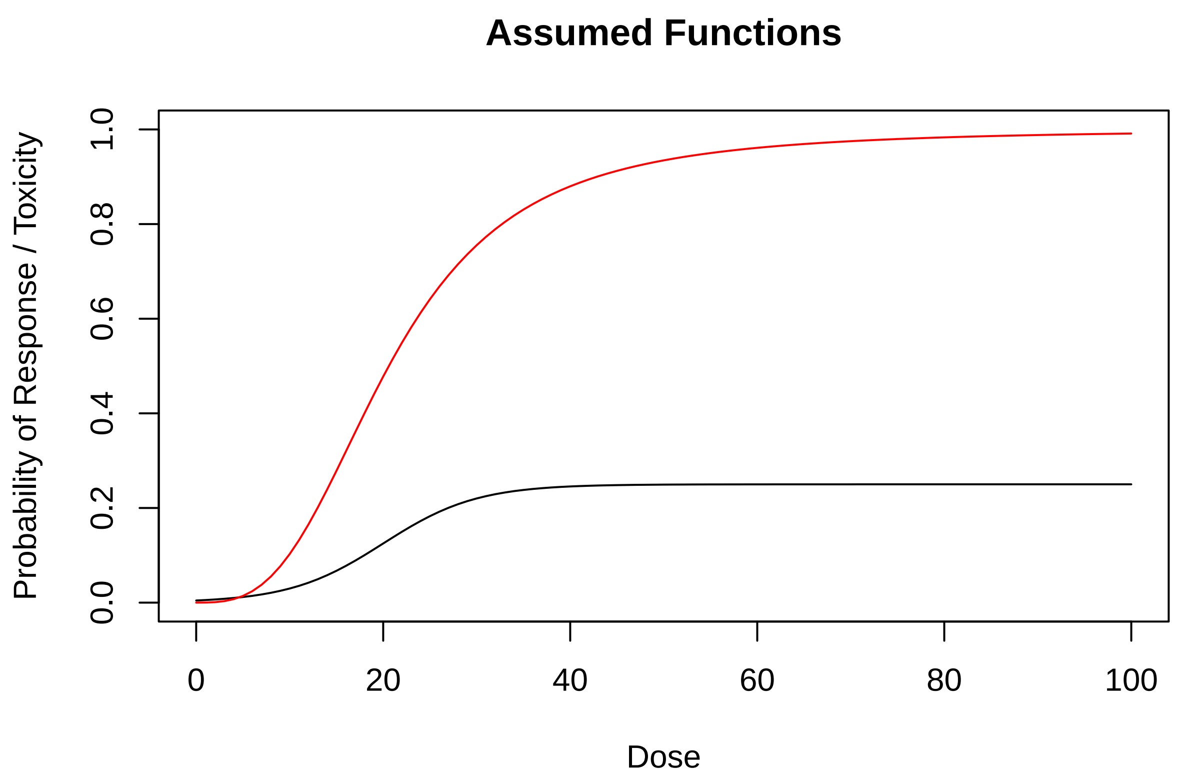
```
design_complex_backfill <- design_no_backfill
design_complex_backfill@backfill <- backfill_complex
```

Simulations with backfill cohorts

Now we can run trial simulations including backfill cohorts. Here we illustrate this with both the simple and the complex backfill cohort designs defined above. For the complex backfill design we also need to specify the assumed dose-response probability function. Similarly as for the dose-toxicity function, it might be worth to consider a few different scenarios in practice.

```
# Assumed dose-response probability function.
mytruthResponse <- function(dose) {
    plogis(- 4 + 0.2 * dose) / 4
}
curve(mytruthResponse(x), from = 0, to = max(emptydata@doseGrid),
      xlab = "Dose", ylab = "Probability of Response / Toxicity",
      main = "Assumed Functions", ylim = c(0, 1))

myTruth <- probFunction(design_simple_backfill@model, alpha0 = 3, alpha1 = 3)
curve(myTruth(x), from = 0, to = max(emptydata@doseGrid),
      add = TRUE, col = "red")
```



Now we can run the simulations for this particular scenario:

```r
# For real applications, use e.g. McmcOptions() with defaults.
mcmcOptions <- McmcOptions(burnin = 10, step = 1, samples = 100)

# Simple backfill design simulation:
sims_simple <- simulate(
    design_simple_backfill,
    truth = myTruth,
    nsim = 10, # For real applications, increase to 1000 e.g.
    seed = 819,
    mcmcOptions = mcmcOptions,
    parallel = FALSE,
    firstSeparate = FALSE
)

# Complex backfill design simulation:
sims_complex <- simulate(
    design_complex_backfill,
    truth = myTruth,
    truthResponse = mytruthResponse,
    nsim = 10, # For real applications, increase to 1000 e.g
    seed = 819,
    mcmcOptions = mcmcOptions,
    parallel = FALSE,
    firstSeparate = FALSE
)
```

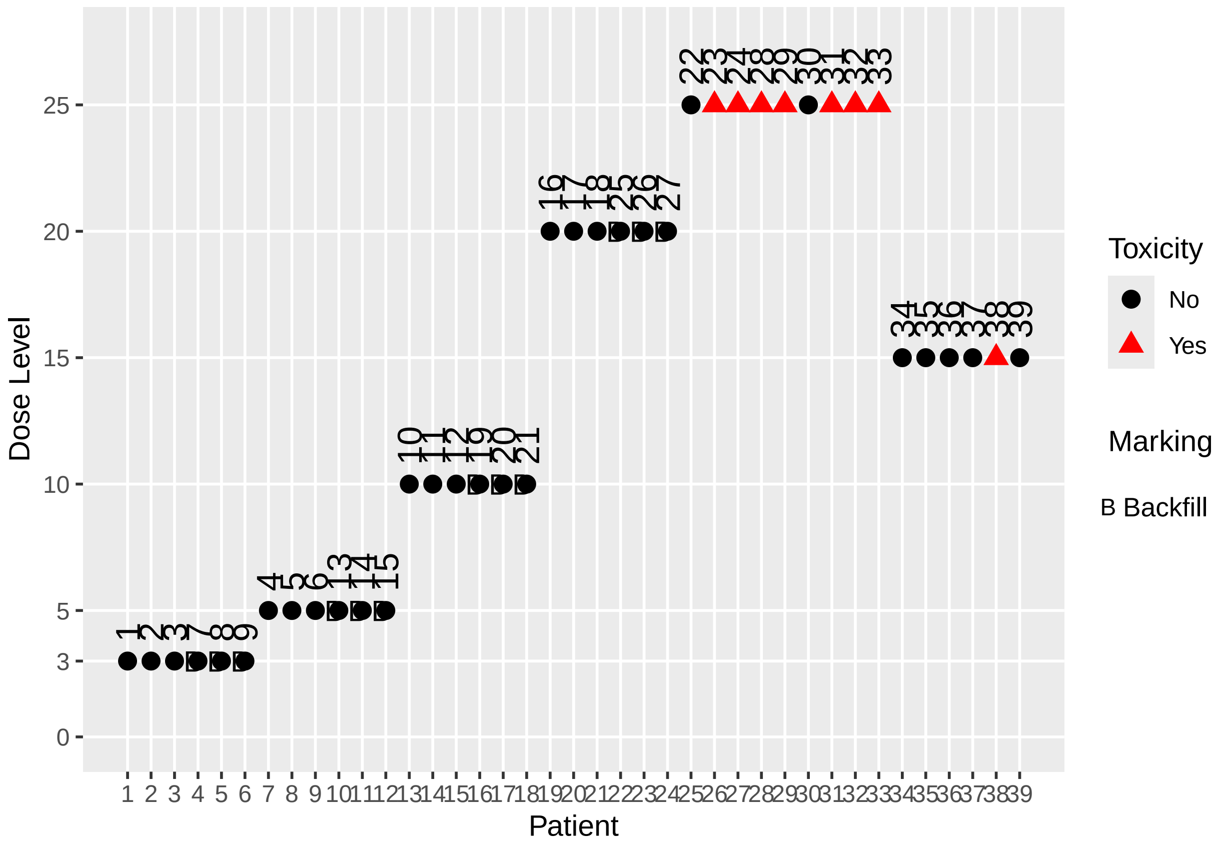
We can see that it is still very simple and straightforward to run simulations including backfill cohorts.

Investigating single trial data

The data for each simulated trial is available in the list in the `data` slot of the returned `Simulations` object, and we can also plot it.

For example, the 3rd simulated trial with the simple backfill design looks like this:

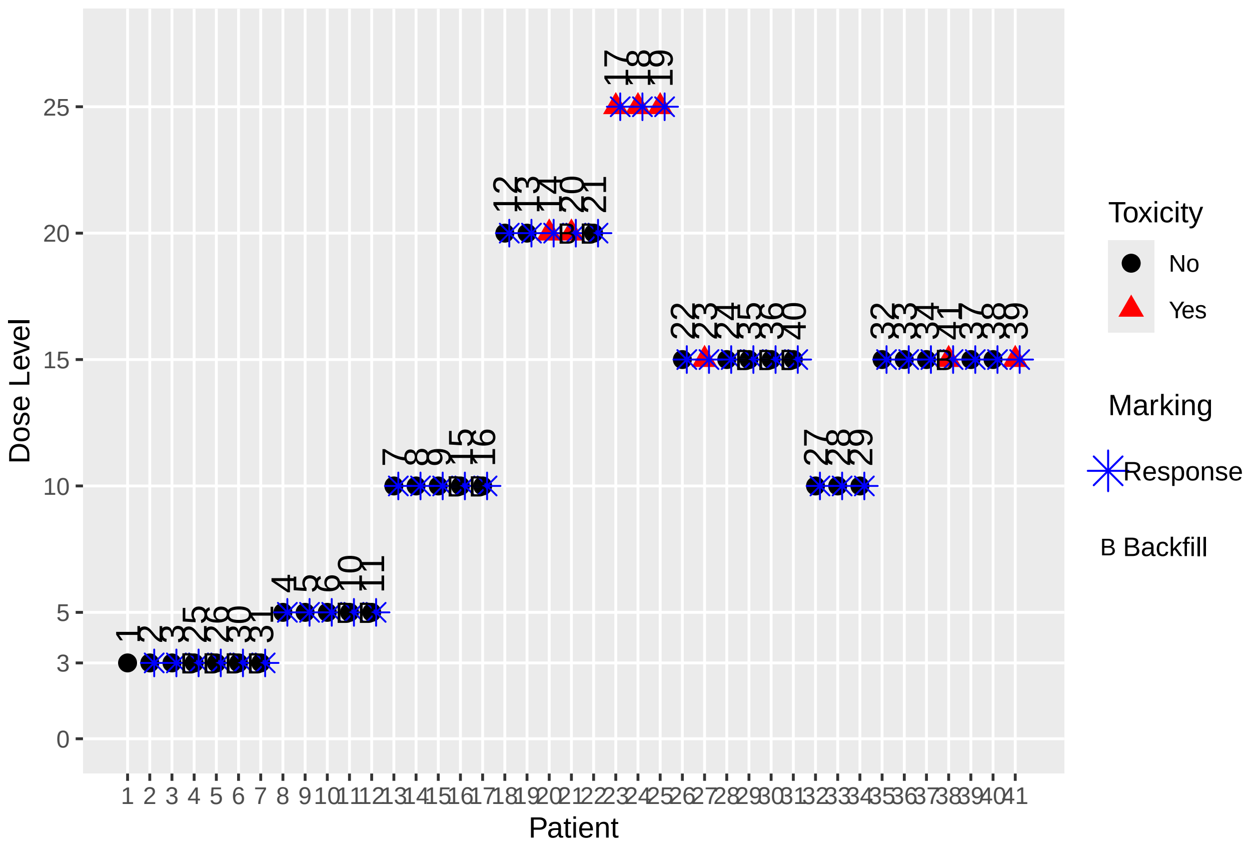
```r
plot(sims_simple@data[[3]], mark_backfill = TRUE)
```



We can see from the patient IDs, which are assigned sequentially in time, when the backfill patients were recruited (those with a "B" mark on the left of the points). For example, we see that the highest dose which was backfilled is 20, after which the maximum of 12 backfill patients was reached.

Similarly we can also plot the data from a simulated trial with the complex backfill design. Here we show the 5th simulated trial, and because the backfill cohort rule is also based on responses, we also mark the response data:

```r
plot(sims_complex@data[[5]], mark_backfill = TRUE, mark_response = TRUE)
```



Here we can see that the starting dose cohort at dose 3 as well as the next one at dose 5 did not produce any responses, hence no backfill cohorts could be opened at these dose levels. Only after dose escalation reached dose 10 in cohort 3 and a response was observed there, a backfill cohort could be started there.

Investigating simulation results

For now we can do some manual investigations of the simulation results to see how many backfill patients were recruited in each simulation:

```r
get_backfill_counts <- function(sims) {
    sapply(sims@data, \(d) sum(d@backfilled))
}
backfill_counts_simple <- get_backfill_counts(sims_simple)
backfill_counts_complex <- get_backfill_counts(sims_complex)
table(backfill_counts_simple)
#> backfill_counts_simple
#> 12
#> 10
table(backfill_counts_complex)
#> backfill_counts_complex
#> 10 12 13 14
#>  1  1  1  7
```

So we see that for all 10 simulations in the simple design, the maximum number of 12 backfill patients were recruited. For the 10 simulations of the complex design the situation is more varied: In half of the 10 simulations no backfill patients were recruited at all e.g., but in some including the trial no. 5 we looked at above we saw 8 backfill patients.

Let's also look at the dose distribution of the backfill patients. We can extract the backfill doses from each simulated trial like this:

```
get_backfill_doses <- function(sims) {
    lapply(sims@data, \(d) d@x[d@backfilled])
}
backfill_doses_simple <- get_backfill_doses(sims_simple)
backfill_doses_complex <- get_backfill_doses(sims_complex)
```

For example, the first 3 trials simulated with the simple backfill design had the following backfill doses:

```
head(backfill_doses_simple, 3)
#> [[1]]
#>  [1]  3  3  3  5  5  5 10 10 10 15 15 15
#>
#> [[2]]
#>  [1]  3  3  3  3  3  3  5  5  5 10 10 10
#>
#> [[3]]
#>  [1]  3  3  3  5  5  5 10 10 10 20 20 20
```

We can e.g. create a table showing the distribution of the backfill doses across all simulations:

```
all_backfill_doses_simple <- unlist(backfill_doses_simple)
table(all_backfill_doses_simple)
#> all_backfill_doses_simple
#>  3  5 10 15 20
#> 36 33 33  6 12

all_backfill_doses_complex <- unlist(backfill_doses_complex)
table(all_backfill_doses_complex)
#> all_backfill_doses_complex
#>  3  5 10 15 20 25
#> 13 22 41 35 17  5
```

So we see e.g. that all backfill patients in the complex design were recruited at doses 3, 5, 10, 15, 20, 25.

Limitations

Note that the `examine` method does not include backfill cohorts, because he examination paths would get too complex to understand easily. In addition, it seems not needed to include backfill cohorts for the quick check for which the `examine` method is intended.

Currently the backfill cohort simulation is supported only for standard `Design` objects. It is not supported for `DADesign` or `DualDesign` objects, although these inherit from the `Design` class. This is because these more complex designs have additional complexities that need to be addressed before backfilling can be supported. We plan to implement backfill cohort simulation for these, and potentially other design classes, in future releases of `crmPack`, depending on the demand from users.

Backwards Compatibility

We have looked into the S4 class framework details and it is a known issue that when we add new slots to existing classes, and then load old saved objects of this class without this slot, then these objects will not be usable. In Bioconductor they even created a special package `updateObject` to deal with this issue (see here for details).

We think that this is not warranted in our case, because typically the code for running simulations and analyses is retained by users of `crmPack`. Therefore it is best to rerun this code with the new package version including the additional slots.

References

Barnett, H., O. Boix, D. Kontos, and T. Jaki. 2023. “Backfilling Cohorts in Phase I Dose-Escalation Studies.” *Clinical Trials* 20 (3): 261–68. https://doi.org/10.1177/17407745231160092.