NMdata: A fast R package for efficient data preparation, consistency-checking and post-processing in PK/PD modeling

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Introduction

What is NMdata?

NMdata is

An R package that can help

- Creating event-based data sets for PK/PD modeling
- Keeping Nonmem code updated to match contents of datasets
- Read all output data and combine with input data from Nonmem runs
- supply output list file (.lst), and the reader is very flexible and automated

Designed to fit in to the user's setup and coding preferences

- NMdata comes with a configuration tool that can be used to tailor default behaviour to the user's system configuration and preferences.

NMdata is not

- A plotting package
- A tool to retrieve details about model runs
- A calculation or simulation toolbox
- A "silo" that requires you to do things in a certain way
- No tools in NMdata requires other NMdata tools to be used

- The data creation tools should be relevant independently of estimation/simulation tool.
- Latest stable release is 0.0.7.2. Plan is to release 0.1.0 on CRAN.

Motivation

- As large a potential pharmacometrics has for illuminating the unknown in drug development, it is dangerously technical.
- The risk is to have too little time for modeling, reflection, and understanding key questions. `NMdata` can be a help in freeing time to more high-level tasks.
- During the first 2-3 years I spent in pharmacometrics, I must have spent half the time coding, desparately trying to get Nonmem to behave and to understand the properties of the estimates I obtained.
- Most of us develop our own ways to avoid some of the many difficulties in this process. This takes a lot of time and is most often only because we don't have adequate tools at hand.
- I generalized some of my solutions and collected them in `NMdata`.
- Almost every single line of code in the package is motivated by bad experiences. Errors, fear of errors, time wasted on debugging and double checking.
- I have no intention of missioning these approaches to others. But if you find something interesting, feel free to take advantage.

Getting started

Use recent development version Notice: This should not be used for final scripts

```
library(remotes)
install_github("philipdelff/NMdata",
               upgrade="never")
```

Using a specific release. See list of releases at https://github.com/philipdelff/NMdata/releases

```
library(remotes)
install_github("philipdelff/NMdata@v0.0.7.2",
               upgrade="never")
```

```
library(NMdata)
```

```
## Welcome to NMdata. Best place to browse NMdata documentation is
## https://philipdelff.github.io/NMdata/
```

Three vignettes are available so far (see "Vignettes" tab when visiting URL above):

- Data creation tools
- Automated and general reader of Nonmem data
- FAQ

For a quick overview (after installation), do:

```
help(package="NMdata")
```

All functions and their arguments are documented in their help files.

Data set creation

Compare compatibility of data sets for rbind and merge: compareCols

- In order to rbind or merge data sets, they must be compatible in
- presence of columns, depending of desired outcome
- equally importantly, the classes of the common columns.
- compareCols provides an overview of these properties for any number of data sets.
- By default, only discrepancies are returned.
- Using diff.only=FALSE will give the complete list of columns in the two datasets.

A slightly modified version of the pk dataset has been created.

- Rows have been omitted
- CYCLE has been removed, and
- AMT has been recoded to character

```
compareCols(pk,pk.reduced)
```

```
## Dimensions:
##          data nrows ncols
## 1:         pk  1502    22
## 2: pk.reduced   751    21
##
## Columns that differ:
##    column      pk pk.reduced
## 1:  CYCLE integer       <NA>
## 2:    AMT integer  character
##
## Columns where no differences were found: BLQ, CM
## DV, EVENTU, EVID, FLAG, ID, NAME, NOMTIME, PART,
## PROFTIME, STUDY, TIME, TIMEUNIT, TRTACT, WEIGHTE
## flag.
```

Before merging or stacking, we may want to

- recode AMT in one of the datasets to get the class we need

Rename columns based on contents

renameByContents

- Nonmem almost entirely relies on numeric data values.
- The source data will often contain character variables, i.e. columns with non-numeric data values. We want to use these and other non-numerics in post-processing.
- If the column names reflect whether the values are numeric, mistakes and double-checking can be avoided.
- `renameByContents` renames columns if a function of their contents returns `TRUE`.

NMisNumeric

- `NMisNumeric` is a function that tests if the contents are numeric to `Nonmem`.
- Subject ID `"1039"` (character class) will be a numeric in Nonmem, `"1-039"` will not.
- We invert that, and those that Nonmem cannot interpret as numeric become lowercase.

All column names are capital case. We rename to lowercase those that Nonmem will not be able to interpret as numeric.

```
pk <- renameByContents(data=pk,
                       fun.test=NMisNumeric,
                       fun.rename = tolower,
                       invert.test = TRUE)
```

compareCols shows that four columns were renamed:

```
compareCols(pk.old,pk)
```

```
## Dimensions:
##      data nrows ncols
## 1: pk.old  1502    22
## 2:     pk  1502    22
##
## Columns that differ:
##      column    pk.old        pk
## 1:   EVENTU character      <NA>
## 2:     NAME character      <NA>
## 3: TIMEUNIT character      <NA>
## 4:   TRTACT character      <NA>
## 5:   eventu      <NA> character
## 6:     name      <NA> character
## 7: timeunit      <NA> character
## 8:   trtact      <NA> character
##
## Columns where no differences were found: AMT, BLQ, CMT,
## CYCLE, DOSE, DV, EVID, FLAG, ID, NOMTIME, PART, PROFDAY,
## PROFTIME, STUDY, TIME, WEIGHTB, eff0, flag.
```

Automated checking of merges

- Merges are a very common source of data creation bugs.
- Merges likely leave you with an unexpected number of rows, some repeated or some omitted.
- `mergeCheck` is a wrapper of `merge` which only accepts the results if

The rows that come out of the merge are the exact same as in one of the existing datasets, only columns added from the second dataset

- This limitation of the scope of the merge allows for a high degree of automated checks of consistency of the results.
- This is not to say that merges beyond the scope of `mergeCheck` are relevant or necessary. But if `mergeCheck` covers your needs, it's a real time saver in terms of automated checks.

mergeCheck is not a new implementation of merge. It's an implementation of checks.

- `mergeCheck` uses `merge.data.table`. The contribution is the checks that no rows are lost, duplicated or added.
- The order of rows in the resulting data is always the same as the first dataset supplied.

Is `mergeCheck` slower?

- If you don't use data.table already, `mergeCheck` is likely to be way faster than what you use already.
- The checking overlay should be neglegible.
- If checks fail, an additional merge is done to help user identify problems. This may cost significant additional time but is likely to save you coding and (at least) the same calculation time anyway.

mergeCheck

Example: Would your standard checks of merges capture this?

Say we want to add a covariate from a `dt.cov`. We expect the number of rows to be unchanged from `pk`. `mergeCheck` more strictly requires that we get all and only the *same* rows:

Without `mergeCheck`

```
## The resulting dimensions are correct
pkmerge <- merge(pk,dt.cov,by="ID")
dims(pk,dt.cov,pkmerge)
```

```
##       data nrows ncols
## 1:      pk  1502    22
## 2:  dt.cov   150     2
## 3: pkmerge  1502    23
```

```
## But we now have twice as many rows for this subject
dims(pk[ID==31],pkmerge[ID==31])
```

```
##                  data nrows ncols
## 1:      pk[ID == 31]    10    22
## 2: pkmerge[ID == 31]    20    23
```

`mergeCheck` throws an error

. . . and suggests what is wrong

```
try(mergeCheck(pk,dt.cov,by="ID"))
```

```
## Rows disappeared during merge.
## Rows duplicated during merge.
## Overview of dimensions of input and output data:
##      data nrows ncols
## 1:     pk  1502    23
## 2: dt.cov   150     2
## 3: result  1502    24
## Overview of values of by where number of rows in x changes:
##     ID N.x N.result
## 1:  31  10       20
## 2: 180  10        0
## Error in mergeCheck(pk, dt.cov, by = "ID") :
##   Merge added and/or removed rows.
```

Conclusion

If you only want to add columns by a merge, `mergeCheck` does all the necessary checks for you.

Exclusion flags

Keep track of data exclusions - don't discard!

- It is good practice not to discard unwanted records from a dataset but to flag them and omit them in model estimation.
- When reporting the analysis, we need to account for how many data records were discarded due to which criteria.
- The implementation in `NMdata` is based on sequentially checking exclusion conditions.
- The information is represented in one numerical column for Nonmem, and one (value-to-value corresponding) character column for the rest of us.

FlagsAssign

- `flagsAssign` applies the conditions sequentially, by increasing or decreasing value of `FLAG`.
- You can use any expression that can be evaluated *row-wise* within the data.frame. In this case, `BLQ` has to exist in `pk`.
- If you need to evaluate a condition based on multiple rows (say inadequate dosing history for a subject), do that first, and include a column representing this condition.
- `FLAG=0` means that none of the conditions were met and row is kept in analysis. This cannot be customized.
- In `Nonmem`, you can include `IGNORE=(FLAG.NE.0)` in `$DATA` or `$INFILE`.

```
dt.flags <- fread(text="FLAG,flag,condition
10,Below LLOQ,BLQ==1
100,Negative time,TIME<0")

pk <- flagsAssign(pk,tab.flags=dt.flags,subset.data="EVID==0")
```

```
## Coding FLAG = 100, flag = Negative time
## Coding FLAG = 10, flag = Below LLOQ
```

```
pk[EVID==1,FLAG:=0]
pk[EVID==1,flag:="Dosing"]
```

flagsCount

- An overview of the number of observations disregarded due to the different conditions is then obtained using `flagsCount`:
- `flagsCount` includes a `file` argument to save the the table right away.

```
flagsCount(data=pk[EVID==0],tab.flags=dt.flags)
```

```
##                  flag N.left Nobs.left N.discard N.disc.cum Nobs.discard Nobs.disc.cum
## 1: All available data    150      1352        NA          0           NA             0
## 2:      Negative time    150      1350         0          0            2             2
## 3:         Below LLOQ    131       755        19         19          595           597
## 4:       Analysis set    131       755        NA         19           NA           597
```

- Now pick the columns you want and format your table for the report.

Finalize data for Nonmem

Advice: always include a unique row identifier

Why

A unique identifier is needed in order to

- Track rows in analysis data back to source data
- Reliably combine (by merge) output with input data

The identifier should be

- Numeric
- For Nonmem to be able to read it
- Integer
- To avoid risk of rounding
- It is *not* a problem if represented as a `double` in `R`
- Increasing
- Not strictly necessary
- Avoid confusion
- May be useful for post-processing to have a single column to order by

Sort rows and add a row counter

- with `data.table`

```
## order
setorder(pk,ID,TIME,EVID)
## add counter
pk[,ROW:=.I]
```

- Or, with `dplyr` (I'm not very familiar with `dplyr`)

```
pk <- pk %>%
    arrange(ID,TIME,EVID) %>%
    mutate(ROW=1:n())
```

NMorderColumns

- The order of columns in Nonmem is important for two reasons.
- Non-numeric Characters in a variable read into Nonmem will make the run fail
- The number of variables you can read into Nonmem is restricted (may not apply to recent Nonmem versions)
- `NMorderColumns` uses a mix of recognition of column names and analysis of the column contents to sort the columns.
- First: Standard columns (`ID`, `TIME`, `EVID` etc.) and usable columns first
- Columns that cannot be converted to numeric are put in the back
- Additional columns to place earlier (argument `first`) or late (`last`) can be specified.
- See `?NMorderColumns` for more options.
- `NMorderColumns` does not sort rows, nor does it modify any contents of columns.

```
pk.old <- copy(pk)
pk <- NMorderColumns(pk,first="WEIGHTB")
```

We may want to add `MDV` and rerun `NMorderColumns`.

```
data.table(old=colnames(pk.old),new=colnames(pk))
```

```
##           old       new
##  1:        ID       ROW
##  2:  NOMTIME        ID
##  3:      TIME   NOMTIME
##  4:      EVID      TIME
##  5:       CMT      EVID
##  6:       AMT       CMT
##  7:        DV       AMT
##  8:     STUDY        DV
##  9:       BLQ   WEIGHTB
## 10:     CYCLE      FLAG
## 11:      DOSE     STUDY
## 12:      PART       BLQ
## 13:   PROFDAY     CYCLE
## 14: PROFTIME      DOSE
## 15:  WEIGHTB       PART
## 16:      eff0   PROFDAY
## 17:    eventu PROFTIME
## 18:      name      eff0
## 19: timeunit    eventu
## 20:    trtact      flag
## 21:      FLAG      name
## 22:      flag timeunit
## 23:       ROW    trtact
##           old       new
```

NMwriteData

For the final step of writing the dataset, `NMwriteData` is provided.

- `NMwriteData` *never* modifies the data.
- Checks character variables for Nonmem compatibility (commas not allowed)
- writes a `csv` file with appropriate options for Nonmem compatibility
- Default is to also write an `rds` file for R
- Contents identical to R object including all information (such as factor levels) which cannot be saved in csv.
- If you use `NMscanData` to read Nonmem results, this information can be used automatically.
- Provides a proposal for text to include in the `$INPUT` and `$DATA` sections of the Nonmem control streams.

The csv writer is very simple

These are the only steps involved between the supplied data set and the written csv.

- `scipen` is small to maximize precision.

```
file.csv <- fnExtension(file,".csv")
fwrite(data,na=".",quote=FALSE,row.names=FALSE,scipen=0,file=file.csv)
```

All arguments to `fwrite` can be modified using the `args.fwrite` argument.

```
NMwriteData(pk,file="derived/pk.csv")
```

```
## Data written to file(s):
## derived/pk.csv
## derived/pk.rds
## For NONMEM:
## $INPUT ROW ID NOMTIME TIME EVID CMT AMT DV WEIGHTB
## FLAG STUDY BLQ CYCLE DOSE PART PROFDAY PROFTIME eff0
## $DATA derived/pk.csv
## IGN=@
## IGNORE=(FLAG.NE.0)
```

- `eff0` is the last column in `pk` that `Nonmem` can make use of (remember `NMisNumeric` from earlier?)
- `NMwriteData` detected the exclusion flag and suggests to include it in `$DATA`.

Update Nonmem control streams

- `NMwriteSection` is a function that replaces sections (like $DATA or $TABLE) of nonmem control streams.
- `NMwriteData` returns a list that can be directly processed by `NMwriteSection`
- In `NMwriteData`, several arguments modify the proposed text the proposed text for the Nonmem run, see `?NMwriteData`.

Tips

- `NMwriteData` is very useful for many other sections, like `$TABLE`, or even `$PK`. But not `$THETA` and `$OMEAGE` (because they are specific to each model).
- `NMwriteData` by defaults saves a backup of the overwritten control streams.
- `NMwriteData` has a section *reader* counterpart in `NMreadSection`
- `NMextractDataFile` takes a control stream/list file and extracts the input data file name/path. You can use this to identify the model runs in which to update `$DATA`.

```
nmCode <- NMwriteData(pk,file="derived/pk.csv",
                      write.csv=FALSE,
### arguments that tailors text for Nonmem
                      nmdir.data="../derived",
                      nm.drop="PROFDAY",
                      nm.copy=c(CONC="DV"),
                      nm.rename=c(BBW="WEIGHTB"),
                      ## PSN compatibility
                      nm.capitalize=TRUE)
```

```
## Data _not_ witten to any files.
## For NONMEM:
## $INPUT ROW ID NOMTIME TIME EVID CMT AMT CONC=DV BBW
## FLAG STUDY BLQ CYCLE DOSE PART PROFDAY=DROP PROFTIME
## EFFO
## $DATA ../derived/pk.csv
## IGN=@
## IGNORE=(FLAG.NE.0)
```

```
## example: pick run1*.mod
models <- list.files("../models",pattern="run1.+\\.mod$",
                     full.names=T)
## update $INPUT and $DATA
lapply(models,NMwriteSection,list.sections=nmCode)
## update $INPUT
lapply(models,
       NMwriteSection,section="INPUT",newlines=nmCode$INPUT)
```

Automated documentation of data

Ensure that the data can be traced back to the data generation script

- If the argument `script` is supplied to `NMwriteData`, a little meta information is saved together with the output file(s).
- For csv files, the meta data is written to a txt file next to the csv file.
- For rds files, the meta data is attached to the object saved in the `rds` file.
- `NMstamp` is used under the hood. You can use `NMstamp` on any R object to attach similar meta information.
- Additional arguments (essentially anything) can be passed from `NMwriteData` to `NMstamp` using the argument `args.stamp`.
- `NMstamp` and `NMinfo` write and read an "attribute" called `NMdata`.

```
NMwriteData(pk,file="derived/pk.csv",
            script = "NMdata_Rpackage.Rmd",quiet=T)
list.files("derived")
```

```
## [1] "pk_meta.txt" "pk.csv"      "pk.rds"
```

```
## NMreadCsv reads the metadata .txt file if found
pknm <- NMreadCsv("derived/pk.csv")
NMinfo(pknm)
```

```
## $dataCreate
## $dataCreate$DataCreateScript
## [1] "NMdata_Rpackage.Rmd"
##
## $dataCreate$CreationTime
## [1] "2022-06-06 22:22:58 EDT"
##
## $dataCreate$writtenTo
## [1] "derived/pk.csv"
```

```
## The .rds file contains the metadata already
pknm2 <- readRDS("derived/pk.rds")
NMinfo(pknm2)
```

```
## $dataCreate
## $dataCreate$DataCreateScript
## [1] "NMdata_Rpackage.Rmd"
##
## $dataCreate$CreationTime
## [1] "2022-06-06 22:22:58 EDT"
##
## $dataCreate$writtenTo
## [1] "derived/pk.rds"
```

Retrieving data from Nonmem runs

NMscanData

`NMscanData` is an automated and general reader of Nonmem.

- It returns one data set combining all information from input data and all output tables.

Based on the list file (`.lst`) it will:

- Read and combine output tables
- If wanted, read input data and restore variables that were not output from the `Nonmem` model
- If wanted, also restore rows from input data that were disregarded in `Nonmem` (e.g. observations or subjects that are not part of the analysis)
- Perform multiple consistency checks

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```
file1.lst <- system.file("examples/nonmem/xgxr003.lst",
                         package="NMdata")
res0 <- NMscanData(file1.lst,merge.by.row=FALSE)
```

```
## No missing values identified
## Model:  xgxr003
##
## Used tables, contents shown as used/total:
##                  file     rows columns     IDs
##       xgxr003_res.txt  905/905     7/7 150/150
##  xgxr003_res_vols.txt  905/905     3/7 150/150
##    xgxr003_res_fo.txt  150/150     1/2 150/150
##     xgxr1.csv (input) 905/1502   21/24 150/150
##              (result)      905    32+2     150
## Input and output data combined by translation of
## Nonmem data filters (not recommended).
##
## Distribution of rows on event types in returned data:
##  EVID CMT output result
##     0   2    755    755
```

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Based on the list file (.lst) it will:

- Read and combine output tables
- If wanted, read input data and restore variables that were not output from the Nonmem model
- If wanted, also restore rows from input data that were disregarded in Nonmem (e.g. observations or subjects that are not part of the analysis)
- Perform multiple consistency checks

```
file1.lst <- system.file("examples/nonmem/xgxr003.lst",
                         package="NMdata")
res0 <- NMscanData(file1.lst,merge.by.row=FALSE)
```

```
## No missing values identified
## Model:  xgxr003
##
## Used tables, contents shown as used/total:
##                  file     rows columns     IDs
##       xgxr003_res.txt  905/905     7/7 150/150
##  xgxr003_res_vols.txt  905/905     3/7 150/150
##     xgxr003_res_fo.txt  150/150     1/2 150/150
##      xgxr1.csv (input) 905/1502   21/24 150/150
##              (result)      905    32+2     150
## Input and output data combined by translation of
## Nonmem data filters (not recommended).
##
## Distribution of rows on event types in returned data:
##  EVID CMT output result
##     0   2    755    755
```

```
class(res0)
```

```
## [1] "NMdata"     "data.table" "data.frame"
```

```
dims(res0)
```

```
##    data nrows ncols
## 1: res0   905    34
```

```
head(res0,n=2)
```

```
##    ROW ID NOMTIME TIME EVID CMT AMT DV FLAG STUDY     KA
## 1:   1 31       0    0    1   1   3  0    0     1 0.1812
## 2:  11 32       0    0    1   1   3  0    0     1 0.1812
##          Q PRED RES WRES    V2     V3 BLQ CYCLE DOSE PART
## 1: 2307400    0   0    0 0.042 0.1785   0     1    3    1
## 2: 2307400    0   0    0 0.042 0.1785   0     1    3    1
##    PROFDAY PROFTIME WEIGHTB   eff0        CL EVENTU   NAME
## 1:       1        0  87.031 56.461 0.7245691     mg Dosing
## 2:       1        0 100.620 45.096 0.7245691     mg Dosing
##    TIMEUNIT TRTACT   flag trtact   model nmout
## 1:    Hours   3 mg Dosing   3 mg xgxr003  TRUE
## 2:    Hours   3 mg Dosing   3 mg xgxr003  TRUE
```

Remember the unique row identifier

Using a unique row identifier for merging data is highly recommended:

```
res1 <- NMscanData(file.nm("xgxr001.lst"),merge.by.row=TRUE)
```

```
## Model:  xgxr001
##
## Used tables, contents shown as used/total:
##               file     rows columns     IDs
##    xgxr001_res.txt  905/905   16/16 150/150
##  xgxr1.csv (input) 905/1502   22/24 150/150
##           (result)      905    38+2     150
##
## Input and output data merged by: ROW
##
## Distribution of rows on event types in returned data:
##  EVID CMT output result
##     0   2    755    755
##     1   1    150    150
##   All All    905    905
```

```
class(res0)
```

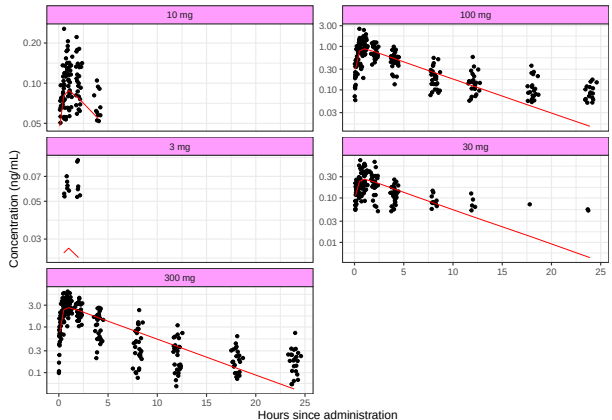
```
## [1] "NMdata"     "data.table" "data.frame"
```

- Starting from `NMdata 0.0.8`, the default behavior will be to merge by `col.row` if found.
- Default value of `col.row` is `ROW`. We shall see later how to modify this.

NMscanData

Example: quickly get from a list file to looking at the model

```
## Using data.table for easy summarize
res1 <- NMscanData(file1.lst,merge.by.row=TRUE,
                   as.fun="data.table",quiet=TRUE)
## Derive geometric mean pop predictions by
## treatment and nominal sample time. Only
## use sample records.
res1[EVID==0,
     gmPRED:=exp(mean(log(PRED))),
     by=.(trtact,NOMTIME)]
```



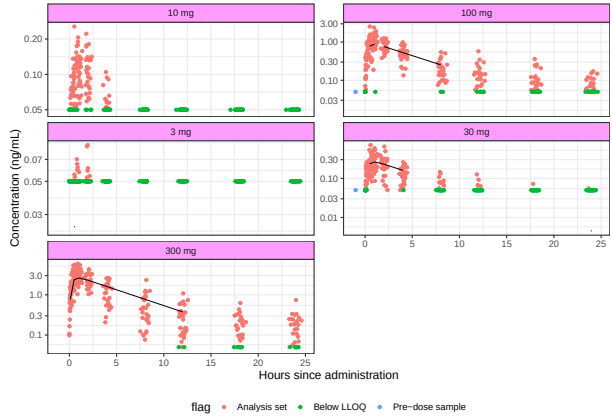
Recover discarded rows

```
res2 <- NMscanData(file1.lst,
                   merge.by.row=TRUE,recover.rows=TRUE)
```

```
## Model:  xgxr003
##
## Used tables, contents shown as used/total:
##                  file      rows columns      IDs
##       xgxr003_res.txt   905/905     7/7 150/150
##  xgxr003_res_vols.txt   905/905     3/7 150/150
##     xgxr003_res_fo.txt   150/150     1/2 150/150
##      xgxr1.csv (input) 1502/1502   21/24 150/150
##              (result)      1502    32+2      150
##
## Input and output data merged by: ROW
##
## Distribution of rows on event types in returned data:
##  EVID CMT input-only output result
##     0   1          2      0      2
##     0   2        595    755   1350
##     1   1          0    150    150
##   All All        597    905   1502
```

- No information is carried from output tables to recovered input data rows. For instance, it could make sense to merge back unique values within subjects (like subject level parameter estimates). Such "back-filling" must be done manually.

```
## Warning: Removed 7 row(s) containing missing values
## (geom_path).
```



Compare models

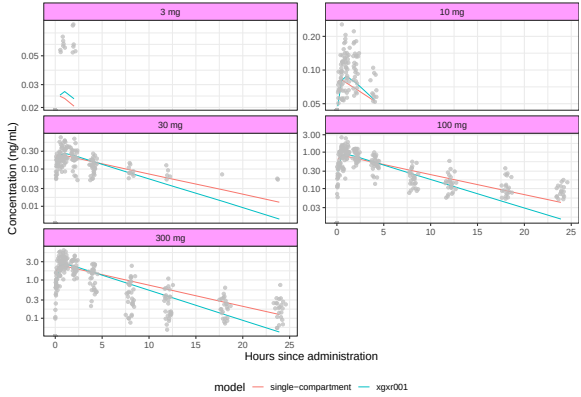
Example: Renaming and combining models by 'rbind'

```
NMdataConf(as.fun="data.table")
NMdataConf(col.row="ROW")
NMdataConf(merge.by.row=TRUE)
```

```
## notice fill is an option to rbind with data.table
lst.1 <- system.file("examples/nonmem/xgxr001.lst",
                     package="NMdata")
lst.2 <- system.file("examples/nonmem/xgxr014.lst",
                     package="NMdata")
res1.m <- NMscanData(lst.1,quiet=TRUE)
res2.m <- NMscanData(lst.2,quiet=TRUE,
                     modelname="single-compartment")

res.mult <- rbind(res1.m,res2.m,fill=T)
res.mult[EVID==0&nmout==TRUE,
         gmPRED:=exp(mean(log(PRED))),
         by=.(model,trtact,NOMTIME)]
## NMdata class gone because of rbind
class(res.mult)
```

```
## [1] "data.table" "data.frame"
```



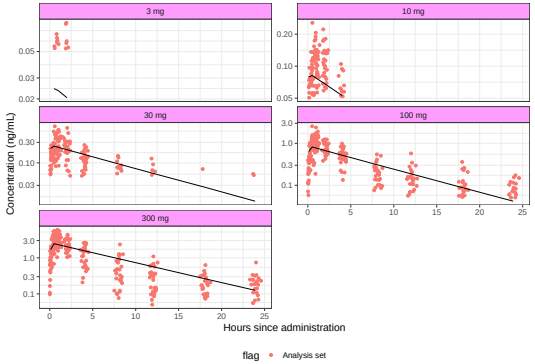
Preserve all input data properties

By default, NMscanData will look for an rds file next to the csv file (same file name, only extension .rds different).

- If this is found, it will be read, providing an enriched (e.g. conserving factor levels and any other information).
- There are no checks of consistency of rds file against delimited file read by Nonmem.
- I am interested in ideas on how to do this. If we can avoid reading the csv file, it would be highly prefered.
- You get the rds automatically if using NMwriteData.
- Disable looking for the rds by argument use.rds=FALSE.
- Default value of use.rds can be modified with NMdataConf.

The plots are correctly ordered by doses - because they are ordered by factor levels as in rds input data.

```
lst <- system.file("examples/nonmem/xgxr014.lst",
                   package="NMdata")
res14 <- NMscanData(lst,quiet=TRUE)
```



The NMdata class

Most important message: an NMdata object can be used as if it weren't.

Methods defined for NMdata:

- summary: The information that is written to the console if quiet=FALSE.

Simple other methods like rbind and similar are defined by dropping the NMdata class and then perform the operation.

- NMinfo lists metadata from NMdata objects and only works on NMdata objects. Components in metadata are (as available):
- NMinfo(res1,"details"): How was the data read and combined?
- NMinfo(res1,"dataCreate"): Meta data found attached to the input data file.
- NMinfo(res1,"input.colnames"): The translation table of input column names from input to output
- NMinfo(res1,"input.filters"): The "filters" (IGNORE/ACCEPT) from Nonmem and how they are applied in R.
- NMinfo(res1,"tables"): What tables were read and how?
- NMinfo(res1,"columns"): What columns were read from what tables?

```
class(res1)
```

```
## [1] "NMdata"     "data.table" "data.frame"
```

```
NMinfo(res1,"details")
```

```
## $model
## [1] "xgxr003"
##
## $call
## [1] "NMscanData(file1.lst, merge.by.row = TRUE, as.fun = \"data.table\", "
## [2] "    quiet = TRUE)"
##
## $time.NMscanData
## [1] "2022-06-06 22:22:58 EDT"
##
## $file.lst
## [1] "/home/philip/wdirs/NMdata/inst/examples/nonmem/xgxr003.lst"
##
## $file.mod
## [1] "/home/philip/wdirs/NMdata/inst/examples/nonmem/xgxr003.mod"
##
## $time.ok
## [1] "Not checked"
##
## $dir.data
## NULL
##
## $input.used
## [1] TRUE
##
## $rows.recovered
## [1] FALSE
##
## $merge.by.row
## [1] TRUE
##
## $col.row
## [1] "ROW"
##
```

The NMdata class

What data was read?

Table-specific information

```
NMinfo(res1,"tables")
```

```
##    source                 name nrow ncol nid level
## 1: output      xgxr003_res.txt  905    7  NA   row
## 2: output xgxr003_res_vols.txt  905    7 150   row
## 3: output   xgxr003_res_fo.txt  150    2 150    id
## 4:  input           xgxr1.csv 1502   24 150  <NA>
##        scope has.col.row has.col.id full.length filetype
## 1:       all        TRUE      FALSE        TRUE   output
## 2:       all       FALSE       TRUE        TRUE   output
## 3: firstonly       FALSE       TRUE       FALSE   output
## 4:      <NA>        TRUE       TRUE          NA     text
##      format          file.mtime
## 1:          2022-01-10 23:10:36
## 2:  tF13.4 2022-01-10 23:10:36
## 3: ,1PE15.8 2022-01-10 23:10:36
## 4:     <NA> 2022-05-14 21:44:15
##                                                                    file
## 1:      /home/philip/wdirs/NMdata/inst/examples/nonmem/xgxr003_res.txt
## 2: /home/philip/wdirs/NMdata/inst/examples/nonmem/xgxr003_res_vols.txt
## 3:   /home/philip/wdirs/NMdata/inst/examples/nonmem/xgxr003_res_fo.txt
## 4:    /home/philip/wdirs/NMdata/inst/examples/nonmem/../data/xgxr1.csv
##    noheader file.logtime
## 1:    FALSE           NA
## 2:    FALSE           NA
## 3:    FALSE           NA
## 4:       NA           NA
```

Column-specific information

(The `nrows` and `topn` arguments are arguments to `print.data.table` to get a top and bottom snip of the table.)

```
print(NMinfo(res1,"columns"),nrows=20,topn=10)
```

```
##     variable                 file     source level COLNUM
##  1:      ROW      xgxr003_res.txt     output   row      1
##  2:       ID xgxr003_res_vols.txt     output   row      2
##  3: NOMTIME            xgxr1.csv      input   row      3
##  4:     TIME            xgxr1.csv      input   row      4
##  5:     EVID            xgxr1.csv      input   row      5
##  6:      CMT            xgxr1.csv      input   row      6
##  7:      AMT            xgxr1.csv      input   row      7
##  8:       DV      xgxr003_res.txt     output   row      8
##  9:     FLAG            xgxr1.csv      input   row      9
## 10:    STUDY            xgxr1.csv      input   row     10
## ---
## 33:    model                 <NA> NMscanData model     33
## 34:    nmout                 <NA> NMscanData   row     34
## 35:       DV xgxr003_res_vols.txt     output   row     NA
## 36:     PRED xgxr003_res_vols.txt     output   row     NA
## 37:      RES xgxr003_res_vols.txt     output   row     NA
## 38:     WRES xgxr003_res_vols.txt     output   row     NA
## 39:      ROW            xgxr1.csv      input   row     NA
## 40:       ID            xgxr1.csv      input   row     NA
## 41:       DV            xgxr1.csv      input   row     NA
## 42:       ID   xgxr003_res_fo.txt     output    id     NA
```

What to do when Nonmem results seem meaningless?

Check of usual suspect: DATA

- `NMcheckColnames` lists column names
- As in input data set
- As in Nonmem `$DATA`
- As inferred by `NMscanInput` (and `NMscanData`)
- This will help you easily check if `$DATA` matches the input data file.
- This is a new function that will be available in the next `NMdata` release
- A more advanced idea is some automated guessing if mistakes were made. This is currently not on the todo list

In this case, input column names are aligned with `$DATA`

```
NMcheckColnames(lst)
```

```
## Read rds input data file:
## /home/philip/wdirs/NMdata/inst/examples/nonmem/../data/xgxr2.rds.
##     datafile    INPUT   nonmem   result compare
##  1:      ROW      ROW      ROW      ROW      OK
##  2:       ID       ID       ID       ID      OK
##  3:  NOMTIME  NOMTIME  NOMTIME  NOMTIME      OK
##  4:     TIME     TIME     TIME     TIME      OK
##  5:     EVID     EVID     EVID     EVID      OK
##  6:      CMT      CMT      CMT      CMT      OK
##  7:      AMT      AMT      AMT      AMT      OK
##  8:       DV       DV       DV       DV      OK
##  9:     FLAG     FLAG     FLAG     FLAG      OK
## 10:    STUDY    STUDY    STUDY    STUDY      OK
## 11:      BLQ      BLQ      BLQ      BLQ      OK
## 12:    CYCLE    CYCLE    CYCLE    CYCLE      OK
## 13:     DOSE     DOSE     DOSE     DOSE      OK
## 14:     PART     PART     PART     PART      OK
## 15:  PROFDAY  PROFDAY  PROFDAY  PROFDAY      OK
## 16: PROFTIME PROFTIME PROFTIME PROFTIME      OK
## 17:  WEIGHTB  WEIGHTB  WEIGHTB  WEIGHTB      OK
## 18:     eff0     eff0     eff0     eff0      OK
## 19:   EVENTU     <NA>     <NA>   EVENTU    <NA>
## 20:     NAME     <NA>     <NA>     NAME    <NA>
## 21: TIMEUNIT     <NA>     <NA> TIMEUNIT    <NA>
## 22:   TRTACT     <NA>     <NA>   TRTACT    <NA>
## 23:     flag     <NA>     <NA>     flag    <NA>
## 24:   trtact     <NA>     <NA>   trtact    <NA>
##     datafile    INPUT   nonmem   result compare
```

What should I do for my models to be compatible with `NMscanData`?

- The answer to this should be as close to "nothing" as possible - that's more or less the aim of the function.
- (As always) you just have to make sure that the information that you need is present in input data and output data.
- No need to output information that is unchanged from input, but make sure to output what you need (like `IPRED`, `CWRES`, `CL`, `ETA1` etc which cannot be found in input). Always output the row identifier!
- Some of these values can be found from other files generated by `Nonmem` but notice: `NMscanData` only uses input and output data.
- Including a unique row identifier in both input and output data is the most robust way to combine the tables.
- Everything will most likely work even if you don't
- I would not take "most likely" when robustness is available.
- In `firstonly` tables, include the subject ID or the row identifier.

NMscanData limitations

The most important limitation to have in mind is not related to NMscanData iteself

- If merging with input data, the input data must be available as was when the model was run.
- Option 1: "Freeze" model runs together with data. NMfreezeModels does that and will be included in NMdata after a little more testing.
- Option 2 (platform-dependent): Nonmem can be run in a wrapper script that either copies the input data, or runs NMscanData and saves the output in a compressed file format (like rds).

Even if limitations of NMscanData may be several, they are all rare. There is a very good chance you will never run into any of them.

- Not all data filter statements implemented. Nested ACCEPT and IGNORE statements are not supported at this point. The resulting number of rows after applying filters is checked against row-level output table dimensions (if any available).
- Disjoint rows with common ID values are currently not supported together with firstonly or lastonly tables. This is on the todo list.
- The RECORDS and NULL options in $DATA are not implemented. If using RECORDS, please use the col.row option to merge by a unique row identifier.
- Character time variables not interpreted. If you need this, we can implement it relatively easily.
- Only output tables returning either all rows or one row per subject can be merged with input. Tables written with options like FIRSTLASTONLY (two rows per subject) and OBSONLY are disregarded with a warning (you can read them with NMscanTables). LASTONLY is treated like FIRSTONLY, i.e. as ID-level information if not available elsewhere.

Data read building blocks

`NMscanData` uses a few simpler functions to read all the data it can find. These functions may be useful when you don't want the full automatic package provided by `NMscanData`.

- `NMreadTab`
  - Fast read and format output tables from Nonmem
  - Handles the "`TABLE NO.`" counter
  - If you simulate a large number of subjects in Nonmem and get a large (gigabytes) output data file, this will be extremely fast compared to almost anything else.
- `NMscanTables` (uses `NMreadTab`)
  - Given a control stream or list file, read all output tables
- `NMreadCsv`
  - Fast read delimited (input data) files
- `NMscanInput` (uses `NMreadCSV`)
  - Given a control stream or list file, read input data.
  - Optionally reads and applies Nonmem ignore/accept statements
  - Optionally translates column names according to names used in Nonmem

Configuration of NMdata defaults

NMdataConf

Tailor 'NMdata' default behavior to your setup and preferences

- `NMdataConf` supports changing many default argument values, simplifying coding.
- Notice, values are reset when `library(NMdata)` or `NMdataConf(reset=TRUE)` are called.
- See all currently used values by `NMdataConf()`.

My initialization of scripts often contain this:

```
library(NMdata)
NMdataConf(as.fun="data.table"
### this is the default value
           ,col.row="ROW"
### Recommended but _right now_ not default
           ,merge.by.row=TRUE
### You can switch this when script is final
           ,quiet=FALSE)
```

Other commonly used settings in `NMdataConf` are

- `as.fun`: a function to apply to all objects before returning them from `NMdata` functions. If you use `dplyr/tidyverse`, do (notice, no quotes!):

```
library(tibble)
NMdataConf(as.fun=tibble::as_tibble)
```

- `use.input`: Should `NMscanData` combine (output data) with input data? (default `TRUE`)
- `recover.rows`: Should `NMscanData` Include rows not processed by Nonmem? (default `FALSE`).
- `file.mod`: A function that translates the list file path to the input control stream file path. Default is to replace extension with `.mod`.
- `check.time`: Default is `TRUE`, meaning that output (list file and tables) are expected to newer than input (control stream and input data). If say you copy files between systems, this check may not make sense.

Why does NMdata not use options()?

R has a system for handling settings. NMdata does not use that.

- Main reason: NMdataConf can check both setting/argument names and values for consistency.

```
try(NMdataConf(asfun=tibble::as_tibble))
```

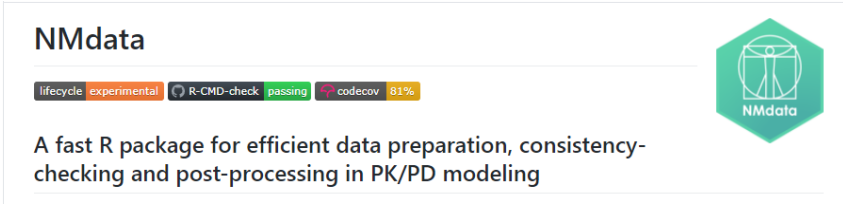
```
## Error : Option not found
```

```
try(NMdataConf(use.input="FALSE"))
```

```
## Error : use.input must be logical
```

- A few extra features are available with NMdataConf:
- Reset all settings: NMdataConf(reset=TRUE)
- Reset individual settings: NMdataConf(use.input=NULL, as.fun=NULL)
- Retrieve all current settings: NMdataConf()

How is NMdata qualified?



- NMdata contains very little calculations (only exception may be flagsAssign/flagsCount)
- Historic bugs have mostly resulted in uninformative errors due to e.g. failure in processing text. Never a wrong data set.
- NMdata includes 190 "unit tests" where results of function calls with different datasets and arguments are compared to expected results
- Tests are consistently run before any release of the package
- The tests are crucial in making sure that fixing one bug or introducing a new feature does not introduce new bugs
- The testing approach is as recommended in "R packages" by Hadley Wickham and Jennifer Bryan https://r-pkgs.org/tests.html.
- If you have a specific example you want to make sure is tested in the package, we will include the test in the package

Next steps for `NMdata`

Next steps for `NMdata`

- The next milestone is submitting the package to CRAN
- Aiming for end of June
- Most important task before is revision of vignettes
- Abstract submitted to ACoP
- The following would be great help in making `NMdata` more accessible and useful
- Testing - please use the package and provide feedback
- Review of documentation, vignettes, and descriptions/explanations on website
- Graphical representations and illustrations.
- A tidyverse workflow for a new vignette
- If you have ideas you want to contribute, let's discuss!
- Before or after first version on CRAN
- `NMcheckData`: Check data syntax/format compatibility with Nonmem
- `NMfreezeModels`: Save Nonmem models with input data and all results to ensure reproducibility of output
- After first version on CRAN
- Functions to generate dosing regimens for simulations and nominal-time datasets
- Functions for easy documentation of column contents (description, units, 1:1 relationships between character and numeric columns)

Summary

Summary

Data creation
- `renameByContents` -
- `compareCols`
- `mergeCheck`
- `flagsAssign`/`flagsCount`
- `NMorderColumns`
- (`NMcheckData`)
- `NMwriteData`
- `NMstamp`/`NMinfo`

Read/write Nonmem control streams
- `NMreadSection`/`NMwriteSection`

Retrieve data from Nonmem runs
- `NMscanData`
- `summary`, `NMinfo`
- `NMscanInput`, `NMreadCsv`
- `NMscanTables`, `NMreadTab`
- `NMcheckColnames`

Adjust behavior to your preferences
- `NMdataConf`

Other
- (`NMfreezeModels`)

The plan is submission to CRAN this month!

`NMdata` functions under development

NMcheckData: Check data syntax for Nonmem compatibility

Aim: check data for all potential Nonmem compatibility issues and other obvious errors.

- Currently checks for:
- Presence, no NA, and compatibility of TIME, EVID, ID, CMT
- DV must be NA at dosing events
- If available MDV and col.flagn must be numeric and non-missing
- EVID one of 0,1,2,3,4
- ID's are disjoint
- TIME is positive and increasing within constant ID
- CMT is a positive integer
- MDV represents is.na(DV)
- Todo
- Many checks will be added and most of them are simple to implement
- Has to accept many more alternative ways to code the data
- It is experimental but safe
- 'NMcheckData is a "look but don't touch" function, so worst case is output is confusing.
- You could get a strange error due to "holes" in the function that haven't yet been implemented.

```
res.check <- NMcheckData(pk)
```

```
##  column              check  N Nid
##    EVID Subject has no obs 19  19
##     MDV   Column not found  1   0
```

```
res.check
```

```
##    row ID column              check  level ROW
## 1   NA 31   EVID Subject has no obs     ID  NA
## 2   NA 32   EVID Subject has no obs     ID  NA
## 3   NA 33   EVID Subject has no obs     ID  NA
## 4   NA 34   EVID Subject has no obs     ID  NA
## 5   NA 36   EVID Subject has no obs     ID  NA
## 6   NA 37   EVID Subject has no obs     ID  NA
## 7   NA 38   EVID Subject has no obs     ID  NA
## 8   NA 39   EVID Subject has no obs     ID  NA
## 9   NA 42   EVID Subject has no obs     ID  NA
## 10  NA 44   EVID Subject has no obs     ID  NA
## 11  NA 45   EVID Subject has no obs     ID  NA
## 12  NA 46   EVID Subject has no obs     ID  NA
## 13  NA 49   EVID Subject has no obs     ID  NA
## 14  NA 52   EVID Subject has no obs     ID  NA
## 15  NA 53   EVID Subject has no obs     ID  NA
## 16  NA 56   EVID Subject has no obs     ID  NA
## 17  NA 57   EVID Subject has no obs     ID  NA
## 18  NA 58   EVID Subject has no obs     ID  NA
## 19  NA 60   EVID Subject has no obs     ID  NA
## 20  NA NA    MDV   Column not found column  NA
```

```
pkmod <- copy(pk)
pkmod[,MDV:=as.numeric(is.na(DV))]
pkmod[ID==33&EVID==1,CMT:=NA]
res.check <- NMcheckData(pkmod)
```

```
##  column              check  N Nid
```

NMfreezeModels

In order to ensure reproducibility, any output has to be produced based on arvhived/frozen Nonmem models.

The components that need to be "frozen" are

- Nonmem control streams
- input data
- estimation results (output tables, .lst, .ext etc.)
- simulation code (say mrgsolve scripts)
- ?

`NMfreezeModels` does freeze

- input control streams
- input data
- all output tables
- all nonmem results files

Limitations

- NMfreezeModels does not provide a solution for the simulation code at this point. I am very interested in how we can do this.
- Only supports collections of models with one common input dataset
- The permissions of the frozen folder should be read-only. However, that means that once the freeze it's done, you can no longer add code or descriptions. It all has to be handled in the freeze procedure.

Safe model reader

- A function to read frozen Nonmem results and mrgsolve code to ensure that the right simulation model and parameter values are used
- Obviously, this is closely related to the way mrgsolve code is frozen together with nonmem code.

Other tools

tracee

- `ggwrite`: Saves images in sizes made for powerpoint, including stamps (time, source, output filename). It can save multiple plots at once as one file (pdf) or multiple files.

ggwrite: Flexible saving of tracable output

ggwrite is a wrapper of png and pdf (and dev.off) with convenience features such as

- Support for multiple plots at once
- saved as either multiple files, named by list element names if wanted (or just numbered)
- or a single pdf with one plot per page
- Stamping with creation time, script name, and output name
- "canvas" sizes made for powerpoint or full-screen display (see ?canvasSize)
- Custom canvases are very simple to create
- Independent save and show arguments for very simple conditional behavior
- save defaults to TRUE if a filename is given
- show defaults to the inverse of save

Save pls1, as one file and as multiple files, named by the dose levels.

```
writeOutput <- TRUE
script <- "path/to/script.R"
ggwrite(pls1,file="results/individual_profiles.png",
        stamp=script,canvas="wide-screen",useNames=TRUE,
        save=writeOutput)
ggwrite(pls1,file="results/individual_profiles.pdf",
        stamp=script,canvas="wide-screen",useNames=TRUE,
        save=writeOutput,onefile=TRUE)
list.files("results")
```

- Showing a bottom-right snip of results/individual_profiles_trtact300mg.png: