Package 'dfped'

October 13, 2022

Type Package

Title Extrapolation and Bridging of Adult Information in Early Phase Dose-Finding Paediatrics Studies

Version 1.1

Date 2018-03-25

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Description A unified method for designing and analysing dose-finding trials in paediatrics, while bridging information from adults, is proposed in the 'dfped' package. The dose range can be calculated under three extrapolation methods: linear, allometry and maturation adjustment, using pharmacokinetic (PK) data. To do this, it is assumed that target exposures are the same in both populations. The working model and prior distribution parameters of the dose-toxicity and dose-efficacy relationships can be obtained using early phase adult toxicity and efficacy data at several dose levels through 'dfped' package. Priors are used into the dose finding process through a Bayesian model selection or adaptive priors, to facilitate adjusting the amount of prior information to differences between adults and children. This calibrates the model to adjust for misspecification if the adult and paediatric data are very different. User can use his/her own Bayesian model written in Stan code through the 'dfped' package. A template of this model is proposed in the examples of the corresponding R functions in the package. Finally, in this package you can find a simulation function for one trial or for more than one trial. These methods are proposed by Petit et al, (2016) <doi:10.1177/0962280216671348>.

License GPL (>= 3)

Depends R (>= 3.0.2), rstan(>= 2.8.1), stats4

Imports ggplot2 (>= 2.0.0), methods, stats, graphics, grDevices

SystemRequirements C++11

LazyData true

NeedsCompilation yes

URL http://github.com/artemis-toumazi/dfped

BugReports http://github.com/artemis-toumazi/dfped/issues

RoxygenNote 6.0.1

Repository CRAN

Date/Publication 2018-03-27 21:19:01 UTC

R topics documented:

dfped-package *Extrapolation and Bridging of Adult Information in Early Phase Dose-Finding Paediatrics Studies*

Description

A unified method for designing and analysing dose-finding trials in paediatrics, while bridging information from adults, is proposed in the 'dfped' package. The dose range can be calculated under three extrapolation methods: linear, allometry and maturation adjustment, using pharmacokinetic (PK) data. To do this, it is assumed that target exposures are the same in both populations. The working model and prior distribution parameters of the dose-toxicity and dose-efficacy relationships can be obtained using early phase adult toxicity and efficacy data at several dose levels through 'dfped' package. Priors are used into the dose finding process through a Bayesian model selection or adaptive priors, to facilitate adjusting the amount of prior information to differences between adults and children. This calibrates the model to adjust for misspecification if the adult and paediatric data are very different. User can use his/her own Bayesian model written in Stan code through the 'dfped' package. A template of this model is proposed in the examples of the corresponding R functions in the package. Finally, in this package you can find a simulation function for one trial or for more than one trial. These methods are proposed by Petit et al, (2016) <doi:10.1177/0962280216671348>.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

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References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

albAge *Concentration of albumin according to age.*

Description

Compute the value of albumin (alb) concentration (g/L) according to age (year) for children - Truncated at 10000 days, i.e. 27 y.o.

Usage

```
albAge(age)
```

Arguments

age	The age of child.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

concCh, alpha1AGage

Examples

```
age <- 8
albAge(age)
```

---

alpha1AGage *Concentration of alpha1-acid glycoprotein according to age.*

Description

Compute the value of alpha1-acid glycoprotein (alpha1AG) concentration (g/L) according to age (year) for children.

Usage

```
alpha1AGage(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

concCh, albAge

Examples

```
age <- 2
alpha1AGage(age)
```

Cladu *Clearance of the unbound fraction of a specific molecule for the adult population.*

Description

Compute the clearance of the unbound fraction of a specific molecule for the adult population.

Usage

```
Cladu(Clad, fuAd, Fad)
```

Arguments

Clad	The apparent clearance for adults.
fuAd	Unbound bioavailability for adults for the molecule.
Fad	Bioavailability for adults.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

See Also

Clchu

Examples

```
Cl_ad <- 3.95
F_ad <- 0.6
fu_ad <- 1
Cladu(Cl_ad, fu_ad, F_ad)
```

`Clch.Allo` *Paediatric clearance according to the allometry adjustment (AA) for a specific age.*

Description

Compute the paediatric clearance according to the allometry adjustment (AA) for a specific age.

Usage

```
Clch.Allo(age, w, Clad, Wad)
```

Arguments

`age`	The age of child.
`w`	The weight of child.
`Clad`	Apparent clearance of adult.
`Wad`	Weight of adult (or average weight in the adult population).

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

`Clch.Linear`, `Clch.Mat`

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    W <- children$Weight
    W_ad <- 70
```

```
    Cl_ad <- 3.95

    Clch_allo <- Clch.Allo(AGE, W, Cl_ad, W_ad)

## End(Not run)
```

`Clch.Linear` *Paediatric clearance according to the linear adjustment (LA) for a specific age.*

Description

Compute the paediatric clearance according to the linear adjustment (LA) for a specific age.

Usage

```
Clch.Linear(age, w, Clad, Wad)
```

Arguments

`age`	The age of child.
`w`	The weight of child.
`Clad`	The apparent clearance of adult.
`Wad`	Weight of adult (or average weight in the adult population).

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

`Clch.Allo`, `Clch.Mat`

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    W <- children$Weight
    W_ad <- 70
    Cl_ad <- 3.95

    Clch.Linear(AGE, W, Cl_ad, W_ad)

## End(Not run)
```

Clch.Mat *Paediatric clearance according to the maturation adjustment (MA) for a specific age.*

Description

Compute the paediatric clearance according to the maturation adjustment (MA) for a specific age.

Usage

```
Clch.Mat(age, w, Clad, Wad, dataMolecule)
```

Arguments

age	The age of child.
w	The weight of child.
Clad	The apparent clearance of adult.
Wad	Weight of adult (or average weight in the adult population).
dataMolecule	The database of molecule.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

Clch.Allo, Clch.Linear

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    W <- children$Weight
    W_ad <- 70
    Cl_ad <- 3.95

    F_ad <- 0.6
    Eg <- 0
    Eh <- 0.058
    f_abs <- F_ad/((1 - Eh)*(1-Eg))
    fu_ad <- 1
    perc_CYPh <- data.frame("CYP3A4_5" = 0.7, "CYP1A2" = 0.3)
    perc_CYPg <- data.frame("CYP3A4_5" = 1)
    perc_alb <- 1
    perc_alpha1AG <- 0

    data_molecule <- list(F_ad, f_abs, Eg, Eh, fu_ad, perc_CYPg, perc_CYPh, perc_alb,
                          perc_alpha1AG)

    Clch.Mat(AGE, W, Cl_ad, W_ad, data_molecule)

## End(Not run)
```

Clchu *Clearance of the unbound fraction of a specific molecule for the paediatric population.*

Description

Compute the clearance of the unbound fraction of a specific molecule for the paediatric population.

Usage

```
Clchu(age, w, Clad, Wad, fabs, fuAd, Fad, Eg, Eh, percCYPh)
```

Arguments

age	The age of children.
w	The weight of child.
Clad	The apparent clearance in the adult population.
Wad	The weight of adult (or average weight in the adult population).
fabs	Coefficient of absorption for the molecule.
fuAd	Unbound bioavailability for adults for the molecule.
Fad	Bioavailability for adults.
Eg	Coefficient of intestinal extraction.
Eh	Coefficient of hepatic extraction.
percCYPh	Vector giving the percentage of the molecule metabolised for each cytochrome in the liver in adults. Dataframe with two column - column 1: CYP name, column 2: percentage of the molecule metabolised.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

Cladu

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    W <- children$Weight
    W_ad <- 70
    Cl_ad <- 3.95
    F_ad <- 0.6
    Eg <- 0
    Eh <- 0.058
    f_abs <- F_ad/((1 - Eh)*(1-Eg))
```

```
    fu_ad <- 1
    perc_CYPh <- data.frame("CYP3A4_5" = 0.7, "CYP1A2" = 0.3)

    Clchu(AGE, W, Cl_ad, W_ad, f_abs, fu_ad, F_ad, Eg, Eh, perc_CYPh)

## End(Not run)
```

---

concAd *Concentration of a specific molecule in plasma for the adult population.*

Description

Compute the concentration of a specific molecule in plasma for the adult population according to the percentage binding with albumin and alpha1-acid glycoprotein.

Usage

```
concAd(percAlb, percAlpha1AG)
```

Arguments

percAlb	Percentage of the molecule binding with albumin.
percAlpha1AG	Percentage of the molecule binding with alpha1-acid glycoprotein.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

concCh

Examples

```
perc_alb <- 1
perc_alpha1AG <- 0
concAd(perc_alb, perc_alpha1AG)
```

concCh *Concentration of a specific molecule in plasma for the paediatric population.*

Description

Compute the concentration of a specific molecule in plasma for the paediatric population according to age, the percentage binding with albumin and alpha1-acid glycoprotein.

Usage

```
concCh(age, percAlb, percAlpha1AG)
```

Arguments

age	The age of children.
percAlb	Percentage of the molecule binding with albumin.
percAlpha1AG	Percentage of the molecule binding with alpha1-acid glycoprotein.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

concAd

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    perc_alb <- 1
    perc_alpha1AG <- 0
    concCh(AGE, perc_alb, perc_alpha1AG)
```

```
## End(Not run)
```

---

doseChoice *Choice of the next given dose level.*

Description

Algorithm giving the next dose which is the safe most successful dose (sMSD).

Usage

```
doseChoice(probaTox, probaEff, p, targetTox, givenDose)
```

Arguments

probaTox	The probability of toxicity estimated with STAN model.
probaEff	The probability of efficacy estimated with STAN model.
p	The probability of success.
targetTox	The target of toxicity.
givenDose	The vector of doses given to patients so far.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Examples

```
r <- 0.10
q <- 0.17
p <- 0.9
targetTox <- 0.6
givenDose <- 2
newDose <- doseChoice(r, q, p, targetTox, givenDose)
newDose
```

doseRange *Dose-range for the paediatric population according to adult clearance, adult doses and paediatric clearance.*

Description

This function gives the dose-range for paediatrics, given the adult apparent clearance, the paediatric apparent clearance (known or estimated) and the adult doses. The paediatric apparent clearance can be estimated using the maturation adjustment (through the function `Clch.Mat`), allometric adjustment (through the function `Clch.Allo`) or linear adjustment (through the function `Clch.Linear`).

Usage

```
doseRange(Clch, Clad, doseAd)
```

Arguments

`Clch`	The paediatric apparent clearance which can be calculated using the maturation (`Clch.Mat`) or allocation (`Clch.Allo`) or linear adjustment (`Clch.Linear`) functions for a specific age.
`Clad`	The clearance of adult.
`doseAd`	The dose which is given to adult.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

See Also

`skeleton`

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########


    # Doses of adults
    doseAd <- data.frame("d1" = 100, "d2" = 150,"d3" = 200,"d4"= 250,"d5" =300)
```

```
Cl_ad <- 3.95
children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
AGE <- children$Age
W <- children$Weight
W_ad <- 70
Cl_ad <- 3.95
F_ad <- 0.6
Eg <- 0
Eh <- 0.058
f_abs <- F_ad/((1 - Eh)*(1-Eg))
fu_ad <- 1
perc_CYPh <- data.frame("CYP3A4_5" = 0.7, "CYP1A2" = 0.3)
perc_CYPg <- data.frame("CYP3A4_5" = 1)
perc_alb <- 1
perc_alpha1AG <- 0

data_molecule <- list(F_ad, f_abs, Eg, Eh, fu_ad, perc_CYPg, perc_CYPh, perc_alb,
                      perc_alpha1AG)

# Compute the clearance of children using maturation adjustment via
# the function Clch.Mat().
Clch_mat <- Clch.Mat(AGE, W, Cl_ad, W_ad, data_molecule)

doseRange(Clch_mat, Cl_ad, doseAd)

## End(Not run)
```

`Fch` *Paediatric bioavailability according to age.*

Description

Bioavailability of a child according to his/her age.

Usage

```
Fch(age, fabs, Eg, Eh, percCYPg, percCYPh)
```

Arguments

`age`	The age of children.
`fabs`	Coefficient of the absorption.
`Eg`	Coefficient of intestinal extraction.
`Eh`	Coefficient of hepatic extraction.
`percCYPg`	Vector giving the percentage of the molecule metabolised for each cytochrome in the guts in adults. Dataframe with two column - column 1: CYP name, column 2: percentage of the molecule metabolised.

percCYPh — Vector giving the percentage of the molecule metabolised for each cytochrome in the liver in adults. Dataframe with two column - column 1: CYP name, column 2: percentage of the molecule metabolised.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

Clch.Mat

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    F_ad <- 0.6
    Eg <- 0
    Eh <- 0.058
    f_abs <- F_ad/((1 - Eh)*(1-Eg))
    perc_CYPg <- data.frame("CYP3A4_5" = 1)
    perc_CYPh <- data.frame("CYP3A4_5" = 0.7, "CYP1A2" = 0.3)
    Fch(AGE, f_abs, Eg, Eh, perc_CYPg, perc_CYPh)

## End(Not run)
```

---

fuCh — *Unbound fraction of the molecule in the plasma for children.*

Description

Unbound fraction of the molecule in the plasma for children.

Usage

```
fuCh(age, fuAd, percAlb, percAlpha1AG)
```

Arguments

age	The age of children.
fuAd	Unbound fraction of the molecule in adults.
percAlb	Percentage of the molecule binding with albumin.
percAlpha1AG	Percentage of the molecule binding with alpha1-acid glycoprotein.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

Clch.Mat

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
    fu_ad <- 1
    perc_alb <- 1
    perc_alpha1AG <- 0

    fuCh(AGE, fu_ad, perc_alb, perc_alpha1AG)

## End(Not run)
```

KCYP1A2 *Fraction of adult CYP1A2 abundance according to age.*

Description

Compute the value of the fraction of adult CYP1A2 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP1A2(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP2B6, KCYP2C8, KCYP2C9, KCYP2C18_19, KCYP2D6, KCYP2E1, KCYP3A4_5, KCYP3A

Examples

```
age <- 1
KCYP1A2(age)
```

KCYP2B6 *Fraction of adult CYP2B6 abundance according to age.*

Description

Compute the value of the fraction of adult CYP2B6 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP2B6(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2C8, KCYP2C9, KCYP2C18_19, KCYP2D6, KCYP2E1, KCYP3A4_5, KCYP3A

Examples

```
age <- 4
KCYP2B6(age)
```

KCYP2C18_19 *Fraction of adult CYP2C18/CYP2C19 abundance according to age.*

Description

Compute the value of the fraction of adult CYP2C18/CYP2C19 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP2C18_19(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C8, KCYP2C9, KCYP2D6, KCYP2E1, KCYP3A4_5, KCYP3A

Examples

```
age <- 18
KCYP2C18_19(age)
```

KCYP2C8 *Fraction of adult CYP2C8 abundance according to age.*

Description

Compute the value of the fraction of adult CYP2C8 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP2C8(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C9, KCYP2C18_19, KCYP2D6, KCYP2E1, KCYP3A4_5, KCYP3A

Examples

```
age <- 2
KCYP2C8(age)
```

KCYP2C9 *Fraction of adult CYP2C9 abundance according to age.*

Description

Compute the value of the fraction of adult CYP2C9 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP2C9(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C8, KCYP2C18_19, KCYP2D6, KCYP2E1, KCYP3A4_5, KCYP3A

Examples

```
age <- 3
KCYP2C9(age)
```

KCYP2D6 *Fraction of adult CYP2D6 abundance according to age.*

Description

Compute the value of the fraction of adult CYP2D6 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP2D6(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C8, KCYP2C9, KCYP2C18_19, KCYP2E1, KCYP3A4_5, KCYP3A

Examples

```
age <- 2
KCYP2D6(age)
```

KCYP2E1 *Fraction of adult CYP2E1 abundance according to age.*

Description

Compute value of the fraction of adult CYP2E1 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP2E1(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C8, KCYP2C9, KCYP2C18_19, KCYP2D6, KCYP3A4_5, KCYP3A

Examples

```
age <- 2
KCYP2E1(age)
```

KCYP3A *Fraction of adult CYP3A abundance according to age.*

Description

Compute the value of the fraction of adult CYP3A abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP3A(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C8, KCYP2C9, KCYP2C18_19, KCYP2D6, KCYP3A4_5, KCYP2E1

Examples

```
age <- 2
KCYP3A(age)
```

KCYP3A4_5 *Fraction of adult CYP3A4/CYP3A5 abundance according to age.*

Description

Compute the value of the fraction of adult CYP3A4/CYP3A5 abundance according to the children age. It is described by a hyperbolic function.

Usage

```
KCYP3A4_5(age)
```

Arguments

age	The age of children.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Johnson T., Rostami-Hodjegan A. and Tucker G. (2006) Prediction of clearance of eleven drugs and associated variability in neonates, infants and children, Clin. Pharmacokinet., 45:931-956.

See Also

KCYP1A2, KCYP2B6, KCYP2C8, KCYP2C9, KCYP2C18_19, KCYP2D6, KCYP3A, KCYP2E1

Examples

```
age <- 1
KCYP3A4_5(age)
```

`kickoffControl` *Control for presence of at least toxicities and efficacies for the good run of bCRM model.*

Description

An algorithm that control if we have at least one 0 and one 1 for both efficacy and toxicity.

Usage

```
kickoffControl(tox, currentDose, cohortSize, nbDoses)
```

Arguments

`tox`	The vector of toxicity outcomes.
`currentDose`	The current dose of a patient.
`cohortSize`	The size of the cohort; must be integer.
`nbDoses`	The maximum number of the doses.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Examples

```
## Not run:
tox <- c(0.1301477, 0.2774171, 0.4184642, 0.6486846, 0.8257219)
currentDose <- 3
cohortSize <- 1
nbDoses <- 5
kickoffControl(tox, currentDose, cohortSize, nbDoses)

## End(Not run)
```

`metaPhase` *Meta-analysis function of dose-finding studies proposed by Zohar et al, (2011).*

Description

A function of meta-analysis for dose-finding studies in clinical trials proposed by Zohar et al, (2011).

Usage

```
metaPhase(dataTox, doses, nbSimu)
```

Arguments

`dataTox`	A database of the toxicity outcomes for each patient; must be a dataframe.
`doses`	The drug's dose levels.
`nbSimu`	The number of simulations.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Zohar, S., et al, (2011) An approach to meta-analysis of dose-finding studies, Statistics in Medicine.

See Also

`skeleton`

Examples

```
## Not run:
    pardos_2006 <- rbind(c(100,0/3, 3), c(150, 1/3,3), c(200, 0/3, 3), c(250, 3/6, 6))
    thepot_2014 <- rbind(c(100, 0/5, 5), c(150,3/25, 25))
    calvo_2007 <- rbind(c(150, 1/25, 25))
    raizer_2010 <- rbind(c(150,11/99, 99))
    vanDenBent_2009 <- rbind( c(200, 6/54, 54))
    sheikh_2012 <- rbind(c(150, 0.544, 307))
    rocheNTC00531934 <- rbind(c(150, 0.186, 59))
    dataTox <- rbind(pardos_2006, thepot_2014, calvo_2007, raizer_2010, vanDenBent_2009,
                  rocheNTC00531934, sheikh_2012)
    dataTox <- data.frame(dataTox)
    colnames(dataTox) <- c("doses", "proba", "nbPatients")
```

```
    nbTox <- dataTox$proba*dataTox$nbPatients
    dataTox <- data.frame(dataTox, nbTox)
    doses <- c(100,150,200, 250)
    nbSimu <- 10

    metaPhase(dataTox, doses, nbSimu)

## End(Not run)
```

`priorChoice` *Decision function for the choice of variance (sigmaHI or sigmaLI) in the adaptive prior variance calibration.*

Description

Algorithm of the decision function for the choice of variance (sigmaHI or sigmaLI) in the adaptive prior variance calibration.

Usage

```
priorChoice(tox, givenDose, skeletonTox, lesb)
```

Arguments

`tox`	The vector of toxicity.
`givenDose`	The vector of doses given to patients so far.
`skeletonTox`	Skeleton of toxicity for the BMA bivariate CRM or the bivariate CRM model.
`lesb`	A vector containing the parameters b; (resp. 0 <- b1 < ... < bk < 1).

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Zhang J., Braun T., and J. Taylor. (2013) Adaptive prior variance calibration in the bayesian continual reassessment method. Stat. Med.

See Also

`doseChoice`

Examples

```
tox <-  c(0.10, 0.21, 0.33, 0.55, 0.76)
givenDose <- 2

skeleton_tox1 <- c(0.10, 0.21, 0.33, 0.55, 0.76)
skeleton_tox2 <- c(0.21, 0.33, 0.55, 0.76, 0.88)
skeleton_tox3 <- c(0.05, 0.10, 0.21, 0.33, 0.55)
skeleton_tox4 <- c(0.025, 0.05,0.1, 0.21, 0.33)
skeleton_tox5 <- c(0.0125, 0.025, 0.05,0.1, 0.21)

skeletonTox <-  data.frame(skeleton_tox1, skeleton_tox2, skeleton_tox3,
                           skeleton_tox4, skeleton_tox5)

lesb <- c(0.10, 0.16, 0.23, 0.25, 0.30)
priorChoice(tox, givenDose, skeletonTox, lesb)
```

---

sigmaEss *The variance of the effective sample size (ESS).*

Description

Let $\pi_{ESS}(\alpha)$ be the prior normal distribution $\mathcal{N}(\mu_\alpha, \sigma^2_{\alpha,ESS})$. The variance $\sigma^2_{\alpha,ESS}$ was fixed such that the information introduced by the prior would be equivalent to the information introduced by a fixed number of patients, which was calibrated to control the amount of information. This approach is based on the effective sample size (ESS): the higher the ESS, the more informative the prior. For an ESS m^*, parameters $(\mu_\alpha, \sigma^2_{\alpha,ESS})$ were chosen such that

$$min_m \delta(m, \mu_\alpha, \sigma^2_{\alpha,ESS})) = m^*$$

Usage

```
sigmaEss(mStar, sigma, Mmin, Mmax, meana, c, wm, Tmc)
```

Arguments

mStar	The number of patients anticipated for the trial.
sigma	The vector of sigma.
Mmin	The minimum number of patients for which the effective sample size (ESS) is computed.
Mmax	The maximum number of patients for which the effective sample size (ESS) is computed.
meana	Mean value of the prior distribution (known or chosen).
c	The maximum number of iteration for the algorithm to compute the ESS. See references for more details.
wm	The working model.
Tmc	The number of draw in the normal distribution in the ESS algorithm. See references for more details.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Morita S., Thall P.F., and Muller P. (2008) Determining the effective sample size of a parametric prior. Biometrics.

Morita S. (2011) Application of the continual reassessment method to a phase I dose-finding trial in japanese patients: East meets west. Stat. Med.

Examples

```
## Not run:
    wm_mat <- c(0.10, 0.21, 0.33, 0.55, 0.76 )
    wm_allo <- c(0.13, 0.27, 0.48, 0.70, 0.88)
    wm_linear <- c(0.07, 0.13, 0.21, 0.33, 0.55)
    c <- 10000
    meana <- 0.88
    Tmc <- 100000
    Mmax <- 30
    Mmin <- 1
    sigma_vect <- seq(0.1, 2, by = 0.01)
    mStar <- 30
    sigmaEss(mStar, sigma_vect, Mmin, Mmax, meana, c, wm_mat, Tmc)

## End(Not run)
```

---

sigmaHI *Compute the informative prior variance for the adaptive prior.*

Description

Compute the informative prior variance for the adaptive prior based on the assumption that every dose has the same probability to be the maximum tolerated dose (MTD), i.e. uniform distribution.

Usage

```
sigmaHI(wm, meanbeta, a = NULL, model, tau, threshold)
```

Arguments

wm	The selected working model; for example the skeleton of toxicity; must be a vector.
meanbeta	The mean value of variable beta.

a	The variable a; the default value is NULL.
model	A valid model; for example "power_log" model.
tau	The target of toxicity.
threshold	A threshold of the model.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Zhang J., Braun T., and J. Taylor. Adaptive prior variance calibration in the bayesian continual reassessment method. Stat. Med., 32:2221-34, 2013.

See Also

sigmaLI

Examples

```
targetTox <- 0.25            # target of toxicity

####### Skeleton ###########

skeleton_tox1 <- c(0.10, 0.21, 0.33, 0.55, 0.76)
skeleton_tox2 <- c(0.21, 0.33, 0.55, 0.76, 0.88)
skeleton_tox3 <- c(0.05, 0.10, 0.21, 0.33, 0.55)
skeleton_tox4 <- c(0.025, 0.05, 0.1, 0.21, 0.33)
skeleton_tox5 <- c(0.0125, 0.025, 0.05, 0.1, 0.21)
skeletonTox <-  data.frame(skeleton_tox1, skeleton_tox2, skeleton_tox3,
                    skeleton_tox4, skeleton_tox5)
mu <- -0.34
sigmaHI <- sigmaHI(skeletonTox[ ,1], mu, a = NULL, "power_log", targetTox, 0.80)
```

---

sigmaLI *Compute the least informative prior variance for the adaptive prior.*

Description

Compute the least informative prior variance for the adaptive prior based on the assumption that every dose has the same probability to be the maximum tolerated dose (MTD), i.e. uniform distribution.

Usage

```
sigmaLI(wm, meanbeta, a = NULL, model, tau)
```

Arguments

wm	The selected working model; for example the skeleton of toxicity; must be a vector.
meanbeta	The mean value of variable beta.
a	The variable a; defaults to NULL.
model	A valid model; for example the "power_log" model.
tau	The target of toxicity.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com> Caroline Petit <caroline.petit@crc.jussieu.fr> Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Zhang J., Braun T., and J. Taylor. Adaptive prior variance calibration in the bayesian continual reassessment method. Stat. Med., 32:2221-34, 2013.

See Also

sigmaHI

Examples

```
targetTox <- 0.25            # target of toxicity

####### Skeleton ############

skeleton_tox1 <- c(0.10, 0.21, 0.33, 0.55, 0.76)
skeleton_tox2 <- c(0.21, 0.33, 0.55, 0.76, 0.88)
skeleton_tox3 <- c(0.05, 0.10, 0.21, 0.33, 0.55)
skeleton_tox4 <- c(0.025, 0.05, 0.1, 0.21, 0.33)
skeleton_tox5 <- c(0.0125, 0.025, 0.05, 0.1, 0.21)
skeletonTox <-  data.frame(skeleton_tox1, skeleton_tox2, skeleton_tox3,
                   skeleton_tox4, skeleton_tox5)
mu <- -0.34
sigmaLI <- sigmaLI(skeletonTox[ ,1], mu, a = NULL, "power_log", targetTox)
```

simu *A simulation of a single dose-finding trials in paediatrics.*

Description

Simulate a single dose-finding clinical trial with the given scenarios of toxicity and efficacy.

Usage

```
simu(targetTox, targetEff, skeletonTox, skeletonEff, startingDose,
    nbSubjects, crmModel, cohortSize, scenarioTox, scenarioEff,
    nbDesign, mu, sd = NULL, lesb, sigmaLI, sigmaHI, adaptivePrior)
```

Arguments

targetTox	Target/threshold of toxicity; must be a integer/double.
targetEff	Target/threshold of efficacy; must be a integer/double.
skeletonTox	Skeleton of toxicity for the BMA bivariate CRM, or the bivariate CRM. Must be a dataframe with the number of row corresponding to the number of doses and the number of columns corresponding to the number of working models for toxicity.
skeletonEff	Skeleton of efficacy for the BMA bivariate CRM, or the bivariate CRM. Must be a dataframe with the number of row corresponding to the number of doses and the number of columns corresponding to the number of working models for efficacy.
startingDose	First dose to be assigned; must be an integer.
nbSubjects	Maximum number of allocated patients; must be an integer.
crmModel	A model for STAN in C++.
cohortSize	The size of the cohorts for the 3+3 based algorithm before kickoff of the CRM; must be an integer.
scenarioTox	Toxicity scenario for the simulations with the probability of toxicity for each dose; must be a vector of length the number of doses.
scenarioEff	Efficacy scenario for the simulations; must be a vector of length the number of doses.
nbDesign	The number of different designs for the model selection using the Watanabe-Akaike information criteria (WAIC); must be an integer.
mu	The mean value which the model is using.
sd	The standard deviation.
lesb	A vector consisting of the variables b.
sigmaLI	The standard deviation when the model using non-informative prior.
sigmaHI	The standard deviation when the model using informative prior.
adaptivePrior	TRUE if you want to use as a prior an adaptive prior; FALSE otherwise.

Author(s)

Artemis Toumazi <artemis.toumazi@gmail.com>, Caroline Petit <caroline.petit@crc.jussieu.fr>, Sarah Zohar <sarah.zohar@inserm.fr>

References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

See Also

simulation

Examples

```
## Not run:
    library(rstan)
    adaptivePrior <- TRUE

    ####### Targets  ###########

    targetTox <- 0.25   # target of toxicity
    targetEff <- 0.20   # target of efficacy

    ####### Skeleton ###########

    skeleton_tox1 <- c(0.10, 0.21, 0.33, 0.55, 0.76)
    skeleton_tox2 <- c(0.21, 0.33, 0.55, 0.76, 0.88)
    skeleton_tox3 <- c(0.05, 0.10, 0.21, 0.33, 0.55)
    skeleton_tox4 <- c(0.025, 0.05,0.1, 0.21, 0.33)
    skeleton_tox5 <- c(0.0125, 0.025, 0.05,0.1, 0.21)

    skeleton_eff <- c(0.04937516, 0.20496890, 0.43388003, 0.64409781, 0.79313693)
    skeleton_tox <-  data.frame(skeleton_tox1, skeleton_tox2, skeleton_tox3,
                        skeleton_tox4, skeleton_tox5)
    skeleton_eff <-  data.frame(skeleton_eff, skeleton_eff, skeleton_eff,
                        skeleton_eff, skeleton_eff)

    ############# Priors ############
    priorModel  <- list(rep(1/5,5), 0.001)
    sd <- 0.65
    mu <- -0.34

    ####### Trial settings  #############

    startingDose <- 1
    nbSubjects <- 15
    cohortSize <- 3

    nbDesign <- length(skeleton_tox[1,])
    nbDoses <- length(scenario_tox)
```

```
lesb <- calcul.bi(skeleton_tox[,1], mu, a = NULL, "power_log", targetTox)
sigmaLI <- sigmaLI(skeleton_tox[,1],  mu, a = NULL, "power_log", targetTox)
sigmaHI <- sigmaHI(skeleton_tox[,1],  mu, a = NULL, "power_log", targetTox, 0.80)

################## Scenarios ##############

scenario_tox <- c(0.1301477, 0.2774171, 0.4184642, 0.6486846, 0.8257219)
scenario_eff <- c(0.07945205, 0.20000000, 0.33686856, 0.59537737, 0.80996173)

stancode <- 'data {
    int <lower = 0> J; //nb of patients
    int <lower = 0> K; // nb of doses and dose reference
    real r[K]; // skeleton for tox - K doses
    real q[K]; // skeleton for efficacy - K doses
    int y[J]; // toxicity of patient j
    int v[J]; // efficacy of patient j
    int d[J]; // dose received by patient j
    real moy; // mean for the normal prior of toxicity
    real standardError; //standard error of the normal prior of toxicity
}
parameters {
    real <lower = 0> alpha;
    real  <lower = 0> beta;
}
transformed parameters{
  real <lower = 0, upper = 1> varphi[K]; // marginal probability of toxicity for dose k
   real <lower = 0, upper = 1> psi[K]; // marginal probability of efficacy for dose k
    // defining the marginal probabilities for each value of a and b for each dose
    real p01[K]; // tox = 0, eff = 1
    real p10[K]; // tox = 1, eff = 0
    real p11[K]; // tox = 1, eff = 1
    real p00[K]; // tox = 0, eff = 0

    vector[J] logLike;

    for (k in 1:K){
        varphi[k] = exp(alpha*log(r[k]));
        psi[k] = exp(beta*log(q[k]));
    }


    // computing the marginal probabilities for each dose
        for (k in 1:K){
            p01[k] = (1-varphi[k])*psi[k];
            p10[k] = varphi[k]*(1-psi[k]);
            p00[k] = (1-varphi[k])*(1-psi[k]);
            p11[k] = varphi[k]*psi[k];
        }
    // Computing the log-likelihood
        for (j in 1:J){
            logLike[j] = y[j]*v[j]*log(p11[d[j]]) + y[j]*(1-v[j])*log(p10[d[j]])
            + (1-y[j])*v[j]*log(p01[d[j]]) + (1-y[j])*(1-v[j])*log(p00[d[j]]);
```

```
        }

    }
    model {
        // priors
        alpha ~lognormal(moy, standardError);
        beta ~ lognormal(0,sqrt(1.34));
        increment_log_prob(sum(logLike));
    }'

    crm_model <- stan_model(model_code = stancode)

    ################## Simulation ##############

    simu(targetTox, targetEff, skeleton_tox, skeleton_eff,
        startingDose, nbSubjects, crm_model, cohortSize, scenario_tox,
        scenario_eff, nbDesign, mu, sd = sd, lesb,
        sigmaLI, sigmaHI, adaptivePrior)

## End(Not run)
```

`simulation` *Simulate one or "n" dose-finding trials in paediatrics.*

Description

It starts the process of simulations for a required number of simulated trials and return NULL. A dataframe is saved in the url named as "save_name" with the number of rows equals to the number of simulations lines and 26 columns containing the different estimates, the selected dose of each trial, etc.

Usage

```
simulation(stanModel, scenarioTox, scenarioEff, nbSubjects,
           nbSimu, skeletonTox, skeletonEff, targetTox, targetEff,
           cohortSize, startingDose, sd = NULL, mu,
           adaptivePrior, saveName)
```

Arguments

`stanModel`	A compiled STAN model.
`scenarioTox`	Toxicity scenario for simulations, with the probability of toxicity for each dose; must be a vector of length the number of doses.
`scenarioEff`	Efficacy scenario for simulations; must be a vector of length the number of doses.
`nbSubjects`	The maximum number of allocated patients; must be an integer.
`nbSimu`	The number of simulated trials; must be an integer.

skeletonTox	The skeleton of toxicity for the BMA bivariate CRM or the bivariate CRM; must be a dataframe with the number of rows corresponding to the number of doses and the number of columns corresponding to the number of working models for toxicity.
skeletonEff	The skeleton of efficacy for the BMA bivariate CRM or the bivariate CRM; must be a dataframe with the number of rows corresponding to the number of doses and the number of columns corresponding to the number of working models for efficacy.
targetTox	Target/threshold of toxicity; must be a double.
targetEff	Target/threshold of efficacy; must be a double.
cohortSize	The size of the cohorts for the 3+3 based algorithm before kickoff of the CRM; must be an integer.
startingDose	First dose to be assigned; must be an integer.
sd	The standard deviation; defaults to NULL.
mu	The mean value which using the model.
adaptivePrior	TRUE if you want to use as a prior an adaptive prior; FALSE otherwise.
saveName	The name of the RData that simulation will be stored; must be a string.

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References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Zohar, S., et al, (2011) An approach to meta-analysis of dose-finding studies, Statistics in Medicine.

See Also

simu

Examples

```
## Not run:
    library("rstan")
    adaptivePrior <- TRUE

    targetTox <- 0.25            # target of toxicity
    targetEff <- 0.20            # target of efficacy

    ####### Skeleton ###########

    skeleton_tox1 <- c(0.10, 0.21, 0.33, 0.55, 0.76)
    skeleton_tox2 <- c(0.21, 0.33, 0.55, 0.76, 0.88)
```

```
skeleton_tox3 <- c(0.05, 0.10, 0.21, 0.33, 0.55)
skeleton_tox4 <- c(0.025, 0.05, 0.1, 0.21, 0.33)
skeleton_tox5 <- c(0.0125, 0.025, 0.05, 0.1, 0.21)

skeleton_eff <- c(0.04937516, 0.20496890, 0.43388003, 0.64409781, 0.79313693)

skeleton_tox <-  data.frame(skeleton_tox1, skeleton_tox2, skeleton_tox3,
                    skeleton_tox4, skeleton_tox5)
skeleton_eff <-  data.frame(skeleton_eff, skeleton_eff, skeleton_eff,
                    skeleton_eff, skeleton_eff)

########## Priors ############

priorModel  <- list(rep(1/5,5), 0.001)
sd <- 0.65
mu <- -0.34

####### Trial settings  #############

startingDose <- 1
nbSubjects <- 15
cohortSize <- 3

####### Number of simulation desired  ############

nbSimu <- 10

################# CRM model ################
############# Prior Normal #################

stancode <- 'data {
    int <lower = 0> J; //nb of patients
    int <lower = 0> K; // nb of doses and dose reference
    real r[K]; // skeleton for tox - K doses
    real q[K]; // skeleton for efficacy - K doses
    int y[J]; // toxicity of patient j
    int v[J]; // efficacy of patient j
    int d[J]; // dose received by patient j
    real moy; // mean for the normal prior of toxicity
    real standardError; //standard error of the normal prior of toxicity
    }
    parameters {
        real <lower = 0> alpha;
        real  <lower = 0> beta;
    }
    transformed parameters{
        real <lower = 0, upper = 1> varphi[K];
        // marginal probability of toxicity for dose k
        real <lower = 0, upper = 1> psi[K];
        // marginal probability of efficacy for dose k

       // defining the marginal probabilities for each value of a and b for each dose
        real p01[K]; // tox = 0, eff = 1
```

```
            real p10[K]; // tox = 1, eff = 0
            real p11[K]; // tox = 1, eff = 1
            real p00[K]; // tox = 0, eff = 0

            vector[J] logLike;

            for (k in 1:K){
                varphi[k] = exp(alpha*log(r[k]));
                psi[k] = exp(beta*log(q[k]));
            }


            // computing the marginal probabilities for each dose
                for (k in 1:K){
                    p01[k] = (1-varphi[k])*psi[k];
                    p10[k] = varphi[k]*(1-psi[k]);
                    p00[k] = (1-varphi[k])*(1-psi[k]);
                    p11[k] = varphi[k]*psi[k];
                }
            // Computing the log-likelihood
                for (j in 1:J){
                    logLike[j] = y[j]*v[j]*log(p11[d[j]]) + y[j]*(1-v[j])*log(p10[d[j]])
                    + (1-y[j])*v[j]*log(p01[d[j]]) + (1-y[j])*(1-v[j])*log(p00[d[j]]);
                }

        }
        model {
            // priors
            alpha ~lognormal(moy, standardError);
            beta ~ lognormal(0,sqrt(1.34));
            increment_log_prob(sum(logLike));
    }'

    stan_model <- stan_model(model_code = stancode)

    ################## Scenarios ##############

    scenario_tox <- c(0.1301477, 0.2774171, 0.4184642, 0.6486846, 0.8257219)
    scenario_eff <- c(0.07945205, 0.20000000, 0.33686856, 0.59537737, 0.80996173)

    ################ Simulation BMA - Normal prior  ################

    simulation(stan_model, scenario_tox, scenario_eff, nbSubjects,
               nbSimu, skeleton_tox, skeleton_eff, targetTox, targetEff,
               cohortSize, startingDose, sd, mu, TRUE, tempfile())

## End(Not run)
```

---

skeleton *Build a working model.*

Description

The construction of the working model's skeleton.

Usage

```
skeleton(doseChildren, doseAdult, dataTox, dataAuc = NULL, Clad,
         Clch, nbSimu, graph = TRUE)
```

Arguments

doseChildren	The paediatric dose level.
doseAdult	The adult dose level.
dataTox	The database of the toxicities.
dataAuc	The database of the AUC; defaults to NULL.
Clad	The clearance of the adults.
Clch	Paediatric clearance (known or estimated). An estimate can be computed using maturation adjustment (MA), allometric adjustment (AA) or linear adjustment (LA) for a specific group of age.
nbSimu	The number of simulation using in meta analysis function metaPhase.
graph	A choice to plot the estimates using the function plotEstimates in the end of the working model. Indicates graph = TRUE to plot or otherwise graph = FALSE; defaults to TRUE.

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References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

See Also

plotEstimates, metaPhase

Examples

```
## Not run:
    ########
   # Note: For this example we are using a paediatric database that we have including data of
    # children from 0 to 19 years old.
    ########

    children <- read.csv("/Users/artemistoumazi/paediatric_data_p3m/children_0_19.csv")
    AGE <- children$Age
```

```
W <- children$Weight

W_ad <- 70
Cl_ad <- 3.95

F_ad <- 0.6
Eg <- 0
Eh <- 0.058
f_abs <- F_ad/((1 - Eh)*(1-Eg))
fu_ad <- 1
perc_CYPh <- data.frame("CYP3A4_5" = 0.7, "CYP1A2" = 0.3)
perc_CYPg <- data.frame("CYP3A4_5" = 1)
perc_alb <- 1
perc_alpha1AG <- 0

data_molecule <- list(F_ad, f_abs, Eg, Eh, fu_ad, perc_CYPg, perc_CYPh,
                      perc_alb, perc_alpha1AG)
Clch_mat <- Clch.Mat(AGE, W, Cl_ad, W_ad, data_molecule)

####################################
########## WORKING MODEL ###########
####################################

children <- data.frame(children, Clch_mat)

########## Children from 2 to 5 years old
children2_5 <- children[children$Age >= 2 & children$Age <= 5  ,]
Cl_ch <-  mean(children2_5$Clch_mat)

# Doses for paediatric using maturation adjustment
dCh_mat_2_5 <- c(30, 45, 55, 70, 85)

Cl_ad <- 3.95
AUCThomas <- c(20,40, 60)
probaToxThomas <- c(0.1,0.25, 0.55)


################# Non-parametric PAVA estimate ###################

# data from the publications of toxicity in the erlotinib
pardos_2006 <- rbind(c(100,0/3, 3), c(150, 1/3,3), c(200, 0/3, 3), c(250, 3/6, 6))
thepot_2014 <- rbind(c(100, 0/5, 5), c(150,3/25, 25))
calvo_2007 <- rbind(c(150, 1/25, 25))
raizer_2010 <- rbind(c(150,11/99, 99))
vanDenBent_2009 <- rbind( c(200, 6/54, 54))
sheikh_2012 <- rbind(c(150, 0.544, 307))
rocheNTC00531934 <- rbind(c(150, 0.186, 59))


dataTox <- rbind(pardos_2006, thepot_2014, calvo_2007, raizer_2010, vanDenBent_2009,
                 rocheNTC00531934, sheikh_2012)
dataTox <- data.frame(dataTox)
colnames(dataTox) <- c("doses", "proba", "nbPatients")
```

```
    nbTox <- dataTox$proba*dataTox$nbPatients
    dataTox <- data.frame(dataTox, nbTox)

    data_auc <- data.frame(AUCThomas, probaToxThomas )
    dose_children <- dCh_mat_2_5[1:4]
    dose_adult <- c(100,150,200, 250)
    graph <- TRUE

    skeleton(dose_children, dose_adult, dataTox, data_auc, Cl_ad, Cl_ch, nbSimu = 10,
             graph = TRUE)

## End(Not run)
```

`waic` *Function for the Watanabe-Akaike information criteria (WAIC)*

Description

Model selection can be performed for each working model (WM) using the Watanabe-Akaike information criteria (WAIC) developed by Watanabe.

Usage

```
waic(stanfit, s)
```

Arguments

`stanfit`	Estimates obtained with the STAN fit. You can use the `fitDataj` function which is giving the next fit of the model from STAN.
`s`	Integer specifying the number of models used to compute the WAIC selection.

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References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

Watanabe S. Asymptotic Equivalence of Bayes cross vallidation and widely applicable information criterion in singular learning theory, volume 11. 2010.

Examples

```
## Not run:
for(s in 1:nbDesign){
fitj <- fitDataj(stan_model, nbPatientsj, nbDoses, tox, eff, given_dose,
 skeleton_tox, skeleton_eff, mu, sigma, s)
waicj <- waic(stanfit=fitj, s)
}

## End(Not run)
```

`weightCYPsum` *Proportion of the molecule metabolised by the CYPs for a child according to age.*

Description

Proportion of the molecule metabolised by the CYPs. A weighted sum is computed. For each CYP, the proportion metabolised in adults is multiplied with the fraction of CYP (KCYP) available for a child according to age.

Usage

```
weightCYPsum(age, percCYP)
```

Arguments

`age`	The age of child.
`percCYP`	Dataframe giving the percentage of the molecule metabolised for each cytochrome in adults. Dataframe with two column - column 1: CYP name, column 2: percentage of the molecule metabolised.

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References

Petit, C., et al, (2016) Unified approach for extrapolation and bridging of adult information in early phase dose-finding paediatric studies, Statistical Methods in Medical Research, <doi:10.1177/0962280216671348>.

See Also

`Clchu`, `Fch`

Examples

```
age <- 2
perc_CYP <- data.frame("CYP3A4_5" = 0.7, "CYP1A2" = 0.3)
weightCYPsum(age, perc_CYP)
```

Index