Examples of initialised Uargs/Dargs

Emmanuelle Comets

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Context

Objective

- provide examples of previous initialisations, including matrices, indices, etc...
- later: print out side-by-side comparison of previous initialisation and new structures to check consistency

Initialisation step

- Dargs: mostly elements related to model and data
- Uargs: indices and design matrices
- varList: elements to do with variability (omega and transformation, hwich parameters have IIV)
- also opt: list of options needed during the run

Setting up data and options

Options

- **TODO**
  - add computation of nbiter.tot within the call to saemixControl
  - add checks at the beginning of the algorithm to compute derived options (nbiter.tot, nbiter.sa,...) in case they have been modified after the call to *saemixControl()*

Dataset

Creating an SaemixData object with PK/PD data by hand. New structure for data but most elements remain the same as previously

```
## Initialisation of data object:
```

```
## Object of class SaemixData
##     longitudinal data for use with the SAEM algorithm
## Dataset pkpd
##     Structured data: dv ~ time + amt | id
## Outcomes: conc, effect
##     X variable for graphs: time (hr)
## Dataset characteristics:
##     number of subjects:     32
##     number of observations: 479
##     average/min/max nb obs: 14.97  /  13  /  21
```

```
## First 10 lines of data:
##     id time amt   dv ytype cens mdv   wt sex age
## 1  100  0.5 100  0.0     1    0   0 66.7   1  50
## 2  100  1.0 100  1.9     1    0   0 66.7   1  50
## 3  100  2.0 100  3.3     1    0   0 66.7   1  50
## 4  100  3.0 100  6.6     1    0   0 66.7   1  50
## 5  100  6.0 100  9.1     1    0   0 66.7   1  50
## 6  100  9.0 100 10.8     1    0   0 66.7   1  50
## 7  100 12.0 100  8.6     1    0   0 66.7   1  50
## 8  100 24.0 100  5.6     1    0   0 66.7   1  50
## 9  100 24.0 100 44.0     2    0   0 66.7   1  50
## 10 100 36.0 100  4.0     1    0   0 66.7   1  50
```

Defining a function to output the results of initialisation

Initialisation for various models

Example 1 - PK model without covariates

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
- covariates: none
- variability: one level
  - diagonal matrix

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  1  0  0
## cl  0  1  0
## vd  0  0  1
```

```
## Initialisation of model, model 1:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   estim     1     0.3
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
```

```
##              name                                                  value
## 1            nobs                                                      0
## 2    fixedpsi.ini                          c(ka = 1, vd = 5, cl = 0.1)
## 3           betas                                   0.00,  1.61, -2.30
## 4         allpar0                      1, 5, 0.1, 0.3, 0.5, 0.7, 1, 0.2
## 5         nchains                                                     2
## 6   nb.parameters                                                     3
## 7        nb.betas                                                     3
## 8         nb.etas                                                     3
```

```
## 9       nb.parest                                                          8
## 10     indx.betaC                                                 integer(0)
## 11     indx.betaI                                                        1:3
## 12        ind.res                                                        1:2
## 13   indest.omega                                                 c(1, 5, 9)
## 14      i0.omega2                                                 integer(0)
## 15      i1.omega2                                                        1:3
## 16    j.covariate                                                 c(1, 5, 9)
## 17   j0.covariate                                                 integer(0)
## 18      ind.fix10                                                 integer(0)
## 19      ind.fix11                                                        1:3
## 20       ind.fix1                                                        1:3
## 21       ind.fix0                                                 integer(0)
## 22           pres                                                  c(1, 0.2)
## 23        ind.eta                                                        1:3
## 24       ind0.eta                                                       NULL
## 25    diag(omega)                          c(ka = 0.3, cl = 0.5, vd = 0.7)
## 26 domega2 (col1) 0.273861278752583, 0.353553390593274, 0.418330013267038
## 27          MCOV0                                                      empty
## 28           COV0                                                      empty
## 29           COV1                                                  see below
## 30           COV2                                                  see below
## 31      flag.fmin                                                      FALSE
## Omega
##     ka  cl  vd
## ka 0.3 0.0 0.0
## cl 0.0 0.5 0.0
## vd 0.0 0.0 0.7
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    0    1    0
## [3,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]     [,2]      [,3]
## [1,]    0 0.000000  0.000000
## [2,]    0 1.609438  0.000000
## [3,]    0 0.000000 -2.302585
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]): empty
## COV0 (COV[,ind.fix10]): empty
## COV1 (initialised as COV[,ind.fix1]):
##      [,1] [,2] [,3]
## [1,]    1    1    1
## [2,]    1    1    1
## [3,]    1    1    1
## [4,]    1    1    1
## [5,]    1    1    1
## [6,]    1    1    1
## COV2 (t(COV)%*%COV):
##      [,1] [,2] [,3]
## [1,]   32   32   32
## [2,]   32   32   32
## [3,]   32   32   32
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
```

```
##      [,1] [,2] [,3]
## [1,]    0    0    0
## [2,]    0    0    0
## [3,]    0    0    0
## [4,]    0    0    0
## [5,]    0    0    0
## [6,]    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id
## 1   1
## 19  1
## 32  1
## 51  1
## 68  1
## 86  1
## Starting population parameters (mean.phi)
##      [,1]     [,2]      [,3]
## [1,]    0 1.609438 -2.302585
## [2,]    0 1.609438 -2.302585
## [3,]    0 1.609438 -2.302585
## [4,]    0 1.609438 -2.302585
## [5,]    0 1.609438 -2.302585
## [6,]    0 1.609438 -2.302585
## Starting individual parameters (phiM)
##             [,1]     [,2]      [,3]
## [1,] -0.28146260 1.593051 -1.392747
## [2,]  0.11534305 1.656258 -2.724791
## [3,] -0.03815966 1.263408 -2.127993
## [4,]  0.77677363 1.525022 -2.177037
## [5,] -0.48605462 1.741272 -2.395231
## [6,] -0.37179363 1.611391 -2.541293
```

Example 2 - PK model without covariates

- continuous outcome with proportional error model
- fixed effect parameters
  - 3 parameters
- covariates: none
- variability: one level
  - no IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  0  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 2:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
```

```
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   estim     1     0
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
```

```
##              name                        value
## 1            nobs                            0
## 2    fixedpsi.ini c(ka = 1, vd = 5, cl = 0.1)
## 3           betas          0.00,  1.61, -2.30
## 4         allpar0        1, 5, 0.1, 1, 1, 0.5
## 5         nchains                            2
## 6   nb.parameters                            3
## 7        nb.betas                            3
## 8         nb.etas                            3
## 9       nb.parest                            7
## 10     indx.betaC                 integer(0)
## 11     indx.betaI                        1:3
## 12        ind.res                          1
## 13   indest.omega              c(5, 6, 8, 9)
## 14      i0.omega2                  c(ka = 1)
## 15      i1.omega2                        2:3
## 16    j.covariate                 c(1, 5, 9)
## 17   j0.covariate                          1
## 18      ind.fix10                          1
## 19      ind.fix11                        2:3
## 20       ind.fix1                        1:3
## 21       ind.fix0                 integer(0)
## 22           pres                        0.5
## 23        ind.eta                        1:3
## 24       ind0.eta                 integer(0)
## 25    diag(omega)   c(ka = 1, cl = 1, vd = 1)
## 26 domega2 (col1)              0.5, 0.5, 0.5
## 27          MCOV0                  see below
## 28           COV0                  see below
## 29           COV1                  see below
## 30           COV2                  see below
## 31      flag.fmin                       TRUE
## Omega
##    ka cl vd
## ka  1  0  0
## cl  0  1  0
## vd  0  0  1
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    0    1    0
## [3,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]     [,2]      [,3]
## [1,]    0 0.000000  0.000000
## [2,]    0 1.609438  0.000000
## [3,]    0 0.000000 -2.302585
```

```
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]):
##      [,1]
## [1,]    0
## COV0 (COV[,ind.fix10]):
##      [,1]
## [1,]    1
## [2,]    1
## [3,]    1
## [4,]    1
## [5,]    1
## [6,]    1
## COV1 (initialised as COV[,ind.fix1]):
##      [,1] [,2] [,3]
## [1,]    1    1    1
## [2,]    1    1    1
## [3,]    1    1    1
## [4,]    1    1    1
## [5,]    1    1    1
## [6,]    1    1    1
## COV2 (t(COV)%*%COV):
##      [,1] [,2] [,3]
## [1,]   32   32   32
## [2,]   32   32   32
## [3,]   32   32   32
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##      [,1] [,2] [,3]
## [1,]    0    0    0
## [2,]    0    0    0
## [3,]    0    0    0
## [4,]    0    0    0
## [5,]    0    0    0
## [6,]    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id
## 1   1
## 19  1
## 32  1
## 51  1
## 68  1
## 86  1
## Starting population parameters (mean.phi)
##      [,1]     [,2]      [,3]
## [1,]    0 1.609438 -2.302585
## [2,]    0 1.609438 -2.302585
## [3,]    0 1.609438 -2.302585
## [4,]    0 1.609438 -2.302585
## [5,]    0 1.609438 -2.302585
## [6,]    0 1.609438 -2.302585
## Starting individual parameters (phiM)
##             [,1]      [,2]      [,3]
## [1,]  0.27291240 1.8992009 -1.441942
## [2,] -0.80337088 1.5425707 -2.645883
## [3,]  0.23235755 2.1004527 -2.209420
## [4,] -0.57735731 1.9372978 -2.213561
```

```
## [5,] -0.15598699 0.5836735 -1.561694
## [6,]  0.02568607 1.4416583 -3.615166
```

Example 3 - PK model without covariates

- continuous outcome with proportional error model
- fixed effect parameters
  - 3 parameters
  - ka fixed to its initial value
- covariates: none
- variability: one level
  - no IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  0  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 3:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   fixed     1     0
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
```

```
##              name                                value
## 1            nobs                                    0
## 2    fixedpsi.ini          c(ka = 1, vd = 5, cl = 0.1)
## 3           betas                   0.00,  1.61, -2.30
## 4         allpar0             1, 5, 0.1, 0.5, 0.7, 0.5
## 5         nchains                                    2
## 6   nb.parameters                                    3
## 7        nb.betas                                    3
## 8         nb.etas                                    2
## 9       nb.parest                                    6
## 10     indx.betaC                       integer(0)
## 11     indx.betaI                              1:3
## 12        ind.res                                   1
## 13   indest.omega                    c(5, 6, 8, 9)
## 14      i0.omega2                        c(ka = 1)
## 15      i1.omega2                              2:3
## 16    j.covariate                       c(1, 5, 9)
## 17   j0.covariate                       integer(0)
## 18      ind.fix10                       integer(0)
## 19      ind.fix11                              2:3
## 20       ind.fix1                              2:3
```

```
## 21       ind.fix0                                      1
## 22           pres                                    0.5
## 23        ind.eta                                    2:3
## 24       ind0.eta                              c(ka = 1)
## 25    diag(omega)        c(ka = 0, cl = 0.5, vd = 0.7)
## 26 domega2 (col1) 0.353553390593274, 0.418330013267038
## 27          MCOV0                                   empty
## 28           COV0                                   empty
## 29           COV1                              see below
## 30           COV2                              see below
## 31      flag.fmin                                  FALSE
## Omega
##    ka       cl       vd
## ka  0 0.000000 0.000000
## cl  0 0.500000 0.295804
## vd  0 0.295804 0.700000
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    0    1    0
## [3,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]     [,2]      [,3]
## [1,]    0 0.000000  0.000000
## [2,]    0 1.609438  0.000000
## [3,]    0 0.000000 -2.302585
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]): empty
## COV0 (COV[,ind.fix10]): empty
## COV1 (initialised as COV[,ind.fix1]):
##      [,1] [,2]
## [1,]    1    1
## [2,]    1    1
## [3,]    1    1
## [4,]    1    1
## [5,]    1    1
## [6,]    1    1
## COV2 (t(COV)%*%COV):
##      [,1] [,2] [,3]
## [1,]   32   32   32
## [2,]   32   32   32
## [3,]   32   32   32
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##      [,1] [,2] [,3]
## [1,]    0    0    0
## [2,]    0    0    0
## [3,]    0    0    0
## [4,]    0    0    0
## [5,]    0    0    0
## [6,]    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id
## 1   1
## 19  1
## 32  1
```

```
## 51  1
## 68  1
## 86  1
## Starting population parameters (mean.phi)
##      [,1]     [,2]      [,3]
## [1,]    0 1.609438 -2.302585
## [2,]    0 1.609438 -2.302585
## [3,]    0 1.609438 -2.302585
## [4,]    0 1.609438 -2.302585
## [5,]    0 1.609438 -2.302585
## [6,]    0 1.609438 -2.302585
## Starting individual parameters (phiM)
##      [,1]      [,2]      [,3]
## [1,]    0 0.9495182 -2.821037
## [2,]    0 1.9740416 -1.591133
## [3,]    0 1.4464737 -2.058744
## [4,]    0 2.2224343 -1.747242
## [5,]    0 1.4131761 -2.025995
## [6,]    0 1.7612154 -2.021120
```

Example 4 - PK model with covariates including fixed covariate effects

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
- covariates: untransformed for the old version where the names must be the same
  - sex on ka
  - weight and age on cl (effect of weight fixed to 0.75)
  - weight and sex on vd (effect of weight fixed to 1)
- variability: one level
  - IIV on all parameters
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  1  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 4:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   estim     1     1
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
## Covariate model:
##     ka cl vd
## sex  1  0  1
```

```
## wt   0  1  1
## age  0  1  0
## Fixed parameters in covariate model:
##     ka cl vd
## sex  0  0  0
## wt   0  1  1
## age  0  0  0
```

	name	value
1	nobs	0
2	fixedpsi.ini	c(ka = 1, vd = 5, cl = 0.1)
3	betas	0.00, 0.20, 1.61, 0.75, -0.50, -2.30, 1.00, 0.40
4	allpar0	1, 0.2, 5, 0.75, -0.5, 0.1, 1, 0.4, 1, 0.5, 0.7, 1, 0.2
5	nchains	2
6	nb.parameters	3
7	nb.betas	8
8	nb.etas	3
9	nb.parest	14
10	indx.betaC	c(2, 4, 5, 7, 8)
11	indx.betaI	c(1, 3, 6)
12	ind.res	1:2
13	indest.omega	c(1, 5, 6, 8, 9)
14	i0.omega2	integer(0)
15	i1.omega2	1:3
16	j.covariate	c(1, 2, 11, 12, 13, 22, 23, 24)
17	j0.covariate	integer(0)
18	ind.fix10	integer(0)
19	ind.fix11	1:8
20	ind.fix1	1:8
21	ind.fix0	integer(0)
22	pres	c(1, 0.2)
23	ind.eta	1:3
24	ind0.eta	NULL
25	diag(omega)	c(ka = 1, cl = 0.5, vd = 0.7)
26	domega2 (col1)	0.5, 0.353553390593274, 0.418330013267038
27	MCOV0	empty
28	COV0	empty
29	COV1	see below
30	COV2	see below
31	flag.fmin	FALSE

```
## Omega
##    ka       cl       vd
## ka  1 0.000000 0.000000
## cl  0 0.500000 0.295804
## vd  0 0.295804 0.700000
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    1    0    0
## [3,]    0    1    0
## [4,]    0    1    0
## [5,]    0    1    0
## [6,]    0    0    1
## [7,]    0    0    1
```

```
## [8,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]      [,2]      [,3]
## [1,]  0.0  0.000000  0.000000
## [2,]  0.2  0.000000  0.000000
## [3,]  0.0  1.609438  0.000000
## [4,]  0.0  0.750000  0.000000
## [5,]  0.0 -0.500000  0.000000
## [6,]  0.0  0.000000 -2.302585
## [7,]  0.0  0.000000  1.000000
## [8,]  0.0  0.000000  0.400000
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]): empty
## COV0 (COV[,ind.fix10]): empty
## COV1 (initialised as COV[,ind.fix1]):
##    id   wt id sex age id   wt sex
## 1   1 66.7  1   1  50  1 66.7   1
## 19  1 66.7  1   1  50  1 66.7   1
## 32  1 66.7  1   1  31  1 66.7   1
## 51  1 80.0  1   1  40  1 80.0   1
## 68  1 40.0  1   0  46  1 40.0   0
## 86  1 75.3  1   1  43  1 75.3   1
## COV2 (t(COV)%*%COV):
##         id       wt     id    sex     age     id       wt    sex
## id    32.0   2240.1   32.0   27.0   992.0   32.0   2240.1   27.0
## wt  2240.1 161793.4 2240.1 1983.4 69157.5 2240.1 161793.4 1983.4
## id    32.0   2240.1   32.0   27.0   992.0   32.0   2240.1   27.0
## sex   27.0   1983.4   27.0   27.0   820.0   27.0   1983.4   27.0
## age  992.0  69157.5  992.0  820.0 34170.0  992.0  69157.5  820.0
## id    32.0   2240.1   32.0   27.0   992.0   32.0   2240.1   27.0
## wt  2240.1 161793.4 2240.1 1983.4 69157.5 2240.1 161793.4 1983.4
## sex   27.0   1983.4   27.0   27.0   820.0   27.0   1983.4   27.0
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##    [,1] [,2] [,3]
## 1     0    0    0
## 19    0    0    0
## 32    0    0    0
## 51    0    0    0
## 68    0    0    0
## 86    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id   wt sex age
## 1   1 66.7   1  50
## 19  1 66.7   1  50
## 32  1 66.7   1  31
## 51  1 80.0   1  40
## 68  1 40.0   0  46
## 86  1 75.3   1  43
## Starting population parameters (mean.phi)
##       [,1]      [,2]     [,3]
## [1,] 13.34 -22.64056 64.79741
## [2,] 13.34 -22.64056 64.79741
## [3,] 13.34 -13.14056 64.79741
## [4,] 16.00 -17.64056 78.09741
## [5,]  8.00 -21.39056 37.69741
```

```
## [6,] 15.06 -19.14056 73.39741
## Starting individual parameters (phiM)
##           [,1]      [,2]     [,3]
## [1,] 14.563672 -22.42472 64.91500
## [2,] 13.273419 -22.94483 64.73555
## [3,] 14.163671 -13.64840 64.19588
## [4,] 16.501408 -17.84868 78.34875
## [5,]  7.707923 -20.90988 37.87450
## [6,] 14.859708 -18.92206 73.60128
```

Example 5 - PK model with covariates including fixed covariate effects and fixed parameters

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
  - ka fixed to its initial value
- covariates: untransformed for the old version where the names must be the same
  - no covariate on ka
  - sex, weight and age on cl (effect of weight fixed to 0.75)
  - weight and age on vd (effect of weight fixed to 1)
- variability: one level
  - IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  1  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 5:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   fixed     1     1
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
## Covariate model:
##     ka cl vd
## sex  0  1  0
## wt   0  1  1
## age  0  1  1
## Fixed parameters in covariate model:
##     ka cl vd
## sex  0  0  0
## wt   0  1  1
## age  0  0  0
```

```
##              name                                                    value
```

```
## 1            nobs                                                                  0
## 2    fixedpsi.ini                                  c(ka = 1, vd = 5, cl = 0.1)
## 3           betas     0.00,  1.61,  0.20,  0.75, -0.50, -2.30,  1.00, -0.15
## 4         allpar0 1, 5, 0.2, 0.75, -0.5, 0.1, 1, -0.15, 1, 0.5, 0.7, 1, 0.2
## 5         nchains                                                               2
## 6   nb.parameters                                                               3
## 7        nb.betas                                                               8
## 8         nb.etas                                                               3
## 9       nb.parest                                                              13
## 10     indx.betaC                                          c(3, 4, 5, 7, 8)
## 11     indx.betaI                                                c(1, 2, 6)
## 12        ind.res                                                         1:2
## 13   indest.omega                                          c(1, 5, 6, 8, 9)
## 14      i0.omega2                                                integer(0)
## 15      i1.omega2                                                       1:3
## 16    j.covariate                          c(1, 10, 11, 12, 13, 22, 23, 24)
## 17   j0.covariate                                                integer(0)
## 18      ind.fix10                                                integer(0)
## 19      ind.fix11                                                       2:8
## 20       ind.fix1                                                       2:8
## 21       ind.fix0                                                         1
## 22           pres                                                c(1, 0.2)
## 23        ind.eta                                                       1:3
## 24       ind0.eta                                                      NULL
## 25    diag(omega)                               c(ka = 1, cl = 0.5, vd = 0.7)
## 26 domega2 (col1)                  0.5, 0.353553390593274, 0.418330013267038
## 27          MCOV0                                                      empty
## 28           COV0                                                      empty
## 29           COV1                                                   see below
## 30           COV2                                                   see below
## 31      flag.fmin                                                      FALSE
## Omega
##    ka       cl       vd
## ka  1 0.000000 0.000000
## cl  0 0.500000 0.295804
## vd  0 0.295804 0.700000
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    0    1    0
## [3,]    0    1    0
## [4,]    0    1    0
## [5,]    0    1    0
## [6,]    0    0    1
## [7,]    0    0    1
## [8,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]      [,2]      [,3]
## [1,]    0  0.000000  0.000000
## [2,]    0  1.609438  0.000000
## [3,]    0  0.200000  0.000000
## [4,]    0  0.750000  0.000000
## [5,]    0 -0.500000  0.000000
## [6,]    0  0.000000 -2.302585
```

```
## [7,]    0  0.000000  1.000000
## [8,]    0  0.000000 -0.150000
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]): empty
## COV0 (COV[,ind.fix10]): empty
## COV1 (initialised as COV[,ind.fix1]):
##    id   wt sex age id sex age
## 1   1 66.7   1  50  1   1  50
## 19  1 66.7   1  50  1   1  50
## 32  1 66.7   1  31  1   1  31
## 51  1 80.0   1  40  1   1  40
## 68  1 40.0   0  46  1   0  46
## 86  1 75.3   1  43  1   1  43
## COV2 (t(COV)%*%COV):
##                id       wt    sex     age     id    sex     age
##       32.0   32.0   2240.1   27.0   992.0   32.0   27.0   992.0
## id    32.0   32.0   2240.1   27.0   992.0   32.0   27.0   992.0
## wt  2240.1 2240.1 161793.4 1983.4 69157.5 2240.1 1983.4 69157.5
## sex   27.0   27.0   1983.4   27.0   820.0   27.0   27.0   820.0
## age  992.0  992.0  69157.5  820.0 34170.0  992.0  820.0 34170.0
## id    32.0   32.0   2240.1   27.0   992.0   32.0   27.0   992.0
## sex   27.0   27.0   1983.4   27.0   820.0   27.0   27.0   820.0
## age  992.0  992.0  69157.5  820.0 34170.0  992.0  820.0 34170.0
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##    [,1] [,2] [,3]
## 1     0    0    0
## 19    0    0    0
## 32    0    0    0
## 51    0    0    0
## 68    0    0    0
## 86    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id   wt sex age
## 1   1 66.7   1  50
## 19  1 66.7   1  50
## 32  1 66.7   1  31
## 51  1 80.0   1  40
## 68  1 40.0   0  46
## 86  1 75.3   1  43
## Starting population parameters (mean.phi)
##      [,1]        [,2]      [,3]
## [1,]    0  -9.3005621 -8.802585
## [2,]    0  -9.3005621 -8.802585
## [3,]    0   0.1994379 -5.952585
## [4,]    0  -1.6405621 -7.302585
## [5,]    0 -13.3905621 -9.202585
## [6,]    0  -4.0805621 -7.752585
## Starting individual parameters (phiM)
##             [,1]        [,2]      [,3]
## [1,]  0.72050332  -9.3143528 -8.925735
## [2,]  0.29493535  -9.0793630 -8.456997
## [3,] -0.37976055  -0.6697858 -5.942574
## [4,] -0.09784431  -1.4533827 -7.221808
## [5,]  0.35461619 -13.5932027 -9.588122
## [6,] -0.40052077  -3.5929761 -8.056560
```

Example 6 - PK model with covariates including fixed covariate effects and fixed parameters, and no IIV on one parameter

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
  - ka fixed to its initial value
- covariates: untransformed for the old version where the names must be the same
  - sex on ka
  - wt and age on cl (effect of weight fixed to 0.75)
  - weight and sex on vd (effect of weight fixed to 1)
- variability: one level
  - no IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  0  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 6:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   fixed     1     0
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
## Covariate model:
##     ka cl vd
## sex  1  0  1
## wt   0  1  1
## age  0  1  0
## Fixed parameters in covariate model:
##     ka cl vd
## sex  0  0  0
## wt   0  1  1
## age  0  0  0
```

```
##              name                                                    value
## 1            nobs                                                        0
## 2    fixedpsi.ini                              c(ka = 1, vd = 5, cl = 0.1)
## 3           betas  0.00,  0.20,  1.61,  0.75, -0.50, -2.30,  1.00,  0.15
## 4         allpar0      1, 0.2, 5, 0.75, -0.5, 0.1, 1, 0.15, 1, 1, 1, 0.2
## 5         nchains                                                       2
## 6   nb.parameters                                                       3
## 7        nb.betas                                                       8
## 8         nb.etas                                                       3
## 9       nb.parest                                                      12
## 10     indx.betaC                                        c(2, 4, 5, 7, 8)
```

```
## 11     indx.betaI                                                c(1, 3, 6)
## 12        ind.res                                                      1:2
## 13   indest.omega                                             c(5, 6, 8, 9)
## 14      i0.omega2                                                 c(ka = 1)
## 15      i1.omega2                                                      2:3
## 16    j.covariate                          c(1, 2, 11, 12, 13, 22, 23, 24)
## 17   j0.covariate                                                        1
## 18      ind.fix10                                                        2
## 19      ind.fix11                                                      3:8
## 20       ind.fix1                                                      2:8
## 21       ind.fix0                                                        1
## 22           pres                                                c(1, 0.2)
## 23        ind.eta                                                      1:3
## 24       ind0.eta                                               integer(0)
## 25    diag(omega)                                c(ka = 1, cl = 1, vd = 1)
## 26 domega2 (col1)                                           0.5, 0.5, 0.5
## 27          MCOV0                                               see below
## 28           COV0                                               see below
## 29           COV1                                               see below
## 30           COV2                                               see below
## 31      flag.fmin                                                   FALSE
## Omega
##    ka cl vd
## ka  1  0  0
## cl  0  1  0
## vd  0  0  1
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    1    0    0
## [3,]    0    1    0
## [4,]    0    1    0
## [5,]    0    1    0
## [6,]    0    0    1
## [7,]    0    0    1
## [8,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]      [,2]      [,3]
## [1,]  0.0  0.000000  0.000000
## [2,]  0.2  0.000000  0.000000
## [3,]  0.0  1.609438  0.000000
## [4,]  0.0  0.750000  0.000000
## [5,]  0.0 -0.500000  0.000000
## [6,]  0.0  0.000000 -2.302585
## [7,]  0.0  0.000000  1.000000
## [8,]  0.0  0.000000  0.150000
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]):
##      [,1]
## [1,]  0.2
## COV0 (COV[,ind.fix10]):
##      wt
## 1  66.7
## 19 66.7
## 32 66.7
```

```
## 51 80.0
## 68 40.0
## 86 75.3
## COV1 (initialised as COV[,ind.fix1]):
##      wt id sex age id   wt sex
## 1  66.7  1   1  50  1 66.7   1
## 19 66.7  1   1  50  1 66.7   1
## 32 66.7  1   1  31  1 66.7   1
## 51 80.0  1   1  40  1 80.0   1
## 68 40.0  1   0  46  1 40.0   0
## 86 75.3  1   1  43  1 75.3   1
## COV2 (t(COV)%*%COV):
##         id       wt     id    sex     age     id       wt    sex
## id    32.0   2240.1   32.0   27.0   992.0   32.0   2240.1   27.0
## wt  2240.1 161793.4 2240.1 1983.4 69157.5 2240.1 161793.4 1983.4
## id    32.0   2240.1   32.0   27.0   992.0   32.0   2240.1   27.0
## sex   27.0   1983.4   27.0   27.0   820.0   27.0   1983.4   27.0
## age  992.0  69157.5  992.0  820.0 34170.0  992.0  69157.5  820.0
## id    32.0   2240.1   32.0   27.0   992.0   32.0   2240.1   27.0
## wt  2240.1 161793.4 2240.1 1983.4 69157.5 2240.1 161793.4 1983.4
## sex   27.0   1983.4   27.0   27.0   820.0   27.0   1983.4   27.0
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##    [,1] [,2] [,3]
## 1     0    0    0
## 19    0    0    0
## 32    0    0    0
## 51    0    0    0
## 68    0    0    0
## 86    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id   wt sex age
## 1   1 66.7   1  50
## 19  1 66.7   1  50
## 32  1 66.7   1  31
## 51  1 80.0   1  40
## 68  1 40.0   0  46
## 86  1 75.3   1  43
## Starting population parameters (mean.phi)
##       [,1]      [,2]     [,3]
## [1,] 13.34 -22.64056 64.54741
## [2,] 13.34 -22.64056 64.54741
## [3,] 13.34 -13.14056 64.54741
## [4,] 16.00 -17.64056 77.84741
## [5,]  8.00 -21.39056 37.69741
## [6,] 15.06 -19.14056 73.14741
## Starting individual parameters (phiM)
##           [,1]      [,2]     [,3]
## [1,] 14.043923 -23.43925 63.90354
## [2,] 14.175552 -22.77425 64.68975
## [3,] 13.603913 -14.12970 63.58279
## [4,] 15.820797 -17.86123 77.71813
## [5,]  8.053016 -20.94561 37.99855
## [6,] 15.709872 -19.62895 73.70937
```

Example 7 - PK model with covariates including fixed parameters and no IIV on one parameter

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
  - ka fixed to its initial value
- covariates: untransformed for the old version where the names must be the same
  - wt and age on cl
  - weight and sex on vd
- variability: one level
  - no IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  0  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 7:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   fixed     1     0
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
## Covariate model:
##     ka cl vd
## wt   0  1  1
## age  0  1  0
## sex  0  0  1
## Fixed parameters in covariate model:
##     ka cl vd
## wt   0  0  0
## age  0  0  0
## sex  0  0  0
```

```
##              name                                                value
## 1            nobs                                                    0
## 2    fixedpsi.ini                       c(ka = 1, vd = 5, cl = 0.1)
## 3           betas   0.00,  1.61,  0.75, -0.50, -2.30,  1.00,  0.15
## 4         allpar0 1, 5, 0.75, -0.5, 0.1, 1, 0.15, 0.5, 0.7, 1, 0.2
## 5         nchains                                                   2
## 6   nb.parameters                                                   3
## 7        nb.betas                                                   7
## 8         nb.etas                                                   2
## 9       nb.parest                                                  11
## 10     indx.betaC                                  c(3, 4, 6, 7)
## 11     indx.betaI                                     c(1, 2, 5)
## 12        ind.res                                            1:2
```

```
## 13   indest.omega                                    c(5, 6, 8, 9)
## 14      i0.omega2                                        c(ka = 1)
## 15      i1.omega2                                              2:3
## 16    j.covariate                     c(1, 9, 10, 11, 19, 20, 21)
## 17   j0.covariate                                     integer(0)
## 18      ind.fix10                                     integer(0)
## 19      ind.fix11                                            2:7
## 20       ind.fix1                                            2:7
## 21       ind.fix0                                              1
## 22           pres                                      c(1, 0.2)
## 23        ind.eta                                             2:3
## 24       ind0.eta                                      c(ka = 1)
## 25    diag(omega)                   c(ka = 0, cl = 0.5, vd = 0.7)
## 26 domega2 (col1)            0.353553390593274, 0.418330013267038
## 27          MCOV0                                           empty
## 28           COV0                                           empty
## 29           COV1                                       see below
## 30           COV2                                       see below
## 31      flag.fmin                                           FALSE
## Omega
##    ka       cl       vd
## ka  0 0.000000 0.000000
## cl  0 0.500000 0.295804
## vd  0 0.295804 0.700000
## LCOV (design matrix nb.muteta x nb.modpar):
##      [,1] [,2] [,3]
## [1,]    1    0    0
## [2,]    0    1    0
## [3,]    0    1    0
## [4,]    0    1    0
## [5,]    0    0    1
## [6,]    0    0    1
## [7,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##      [,1]      [,2]      [,3]
## [1,]    0  0.000000  0.000000
## [2,]    0  1.609438  0.000000
## [3,]    0  0.750000  0.000000
## [4,]    0 -0.500000  0.000000
## [5,]    0  0.000000 -2.302585
## [6,]    0  0.000000  1.000000
## [7,]    0  0.000000  0.150000
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]): empty
## COV0 (COV[,ind.fix10]): empty
## COV1 (initialised as COV[,ind.fix1]):
##    id   wt sex id   wt age
## 1   1 66.7   1  1 66.7  50
## 19  1 66.7   1  1 66.7  50
## 32  1 66.7   1  1 66.7  31
## 51  1 80.0   1  1 80.0  40
## 68  1 40.0   0  1 40.0  46
## 86  1 75.3   1  1 75.3  43
## COV2 (t(COV)%*%COV):
##                id       wt    sex     id       wt     age
```

```
##       32.0   32.0   2240.1   27.0   32.0   2240.1   992.0
## id    32.0   32.0   2240.1   27.0   32.0   2240.1   992.0
## wt  2240.1 2240.1 161793.4 1983.4 2240.1 161793.4 69157.5
## sex   27.0   27.0   1983.4   27.0   27.0   1983.4   820.0
## id    32.0   32.0   2240.1   27.0   32.0   2240.1   992.0
## wt  2240.1 2240.1 161793.4 1983.4 2240.1 161793.4 69157.5
## age  992.0  992.0  69157.5  820.0  992.0  69157.5 34170.0
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##    [,1] [,2] [,3]
## 1     0    0    0
## 19    0    0    0
## 32    0    0    0
## 51    0    0    0
## 68    0    0    0
## 86    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id   wt sex age
## 1   1 66.7   1  50
## 19  1 66.7   1  50
## 32  1 66.7   1  31
## 51  1 80.0   1  40
## 68  1 40.0   0  46
## 86  1 75.3   1  43
## Starting population parameters (mean.phi)
##      [,1]     [,2]     [,3]
## [1,]    0 51.13444 71.89741
## [2,]    0 51.13444 71.89741
## [3,]    0 51.13444 69.04741
## [4,]    0 61.10944 83.69741
## [5,]    0 31.60944 44.59741
## [6,]    0 57.58444 79.44741
## Starting individual parameters (phiM)
##      [,1]     [,2]     [,3]
## [1,]    0 50.81734 71.73329
## [2,]    0 50.56122 71.94311
## [3,]    0 51.12418 69.97130
## [4,]    0 61.73158 84.32051
## [5,]    0 31.61331 44.49436
## [6,]    0 58.30645 80.19543
```

Example 8 - PK model with covariates including fixed and estimated covariate parameters, and no IIV on one parameter

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
- covariates: untransformed for the old version where the names must be the same
  - sex and wt on ka (wt fixed)
  - wt and age on cl
  - weight and sex on vd
- variability: one level
  - no IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
## ka  0  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 8:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   estim     1.5   0
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
## Covariate model:
##     ka cl vd
## sex  1  1  1
## wt   1  1  1
## age  0  1  0
## Fixed parameters in covariate model:
##     ka cl vd
## sex  0  0  0
## wt   1  0  0
## age  0  0  0
```

```
##              name
## 1            nobs
## 2    fixedpsi.ini
## 3           betas
## 4         allpar0
## 5         nchains
## 6   nb.parameters
## 7        nb.betas
## 8         nb.etas
## 9       nb.parest
## 10     indx.betaC
## 11     indx.betaI
## 12        ind.res
## 13   indest.omega
## 14      i0.omega2
## 15      i1.omega2
## 16    j.covariate
## 17   j0.covariate
## 18      ind.fix10
## 19      ind.fix11
## 20       ind.fix1
## 21       ind.fix0
## 22           pres
## 23        ind.eta
## 24       ind0.eta
```

```
## 25    diag(omega)
## 26 domega2 (col1)
## 27          MCOV0
## 28           COV0
## 29           COV1
## 30           COV2
## 31      flag.fmin
##                                                                                value
## 1                                                                                  0
## 2                                                      c(ka = 1.5, vd = 5, cl = 0.1)
## 3   0.405,  0.200,  0.500,  1.609,  0.200,  0.750, -0.500, -2.303,  1.000,  0.150
## 4                  1.5, 0.2, 0.5, 5, 0.2, 0.75, -0.5, 0.1, 1, 0.15, 1, 1, 1, 0.2
## 5                                                                                  2
## 6                                                                                  3
## 7                                                                                 10
## 8                                                                                  3
## 9                                                                                 15
## 10                                                    c(2, 3, 5, 6, 7, 9, 10)
## 11                                                              c(1, 4, 8)
## 12                                                                    1:2
## 13                                                           c(5, 6, 8, 9)
## 14                                                               c(ka = 1)
## 15                                                                    2:3
## 16                                    c(1, 2, 3, 14, 15, 16, 17, 28, 29, 30)
## 17                                                                    1:3
## 18                                                                    1:3
## 19                                                                   4:10
## 20                                                                   1:10
## 21                                                                integer(0)
## 22                                                                 c(1, 0.2)
## 23                                                                    1:3
## 24                                                                integer(0)
## 25                                                c(ka = 1, cl = 1, vd = 1)
## 26                                                            0.5, 0.5, 0.5
## 27                                                                see below
## 28                                                                see below
## 29                                                                see below
## 30                                                                see below
## 31                                                                     TRUE
## Omega
##    ka cl vd
## ka  1  0  0
## cl  0  1  0
## vd  0  0  1
## LCOV (design matrix nb.muteta x nb.modpar):
##       [,1] [,2] [,3]
##  [1,]    1    0    0
##  [2,]    1    0    0
##  [3,]    1    0    0
##  [4,]    0    1    0
##  [5,]    0    1    0
##  [6,]    0    1    0
##  [7,]    0    1    0
##  [8,]    0    0    1
```

```
##  [9,]    0    0    1
## [10,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##            [,1]      [,2]      [,3]
##  [1,] 0.4054651  0.000000  0.000000
##  [2,] 0.2000000  0.000000  0.000000
##  [3,] 0.5000000  0.000000  0.000000
##  [4,] 0.0000000  1.609438  0.000000
##  [5,] 0.0000000  0.200000  0.000000
##  [6,] 0.0000000  0.750000  0.000000
##  [7,] 0.0000000 -0.500000  0.000000
##  [8,] 0.0000000  0.000000 -2.302585
##  [9,] 0.0000000  0.000000  1.000000
## [10,] 0.0000000  0.000000  0.150000
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]):
##           [,1]
## [1,] 0.4054651
## [2,] 0.2000000
## [3,] 0.5000000
## COV0 (COV[,ind.fix10]):
##    id   wt sex
## 1   1 66.7   1
## 19  1 66.7   1
## 32  1 66.7   1
## 51  1 80.0   1
## 68  1 40.0   0
## 86  1 75.3   1
## COV1 (initialised as COV[,ind.fix1]):
##    id   wt sex id   wt sex age id   wt sex
## 1   1 66.7   1  1 66.7   1  50  1 66.7   1
## 19  1 66.7   1  1 66.7   1  50  1 66.7   1
## 32  1 66.7   1  1 66.7   1  31  1 66.7   1
## 51  1 80.0   1  1 80.0   1  40  1 80.0   1
## 68  1 40.0   0  1 40.0   0  46  1 40.0   0
## 86  1 75.3   1  1 75.3   1  43  1 75.3   1
## COV2 (t(COV)%*%COV):
##         id       wt    sex     id       wt    sex     age     id       wt
## id    32.0   2240.1   27.0   32.0   2240.1   27.0   992.0   32.0   2240.1
## wt  2240.1 161793.4 1983.4 2240.1 161793.4 1983.4 69157.5 2240.1 161793.4
## sex   27.0   1983.4   27.0   27.0   1983.4   27.0   820.0   27.0   1983.4
## id    32.0   2240.1   27.0   32.0   2240.1   27.0   992.0   32.0   2240.1
## wt  2240.1 161793.4 1983.4 2240.1 161793.4 1983.4 69157.5 2240.1 161793.4
## sex   27.0   1983.4   27.0   27.0   1983.4   27.0   820.0   27.0   1983.4
## age  992.0  69157.5  820.0  992.0  69157.5  820.0 34170.0  992.0  69157.5
## id    32.0   2240.1   27.0   32.0   2240.1   27.0   992.0   32.0   2240.1
## wt  2240.1 161793.4 1983.4 2240.1 161793.4 1983.4 69157.5 2240.1 161793.4
## sex   27.0   1983.4   27.0   27.0   1983.4   27.0   820.0   27.0   1983.4
##        sex
## id    27.0
## wt  1983.4
## sex   27.0
## id    27.0
## wt  1983.4
## sex   27.0
```

```
## age  820.0
## id    27.0
## wt  1983.4
## sex   27.0
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##    [,1] [,2] [,3]
## 1     0    0    0
## 19    0    0    0
## 32    0    0    0
## 51    0    0    0
## 68    0    0    0
## 86    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id   wt sex age
## 1   1 66.7   1  50
## 19  1 66.7   1  50
## 32  1 66.7   1  31
## 51  1 80.0   1  40
## 68  1 40.0   0  46
## 86  1 75.3   1  43
## Starting population parameters (mean.phi)
##           [,1]        [,2]     [,3]
## [1,] 14.245465  -9.3005621 64.54741
## [2,] 14.245465  -9.3005621 64.54741
## [3,] 14.245465   0.1994379 64.54741
## [4,] 16.905465  -1.6405621 77.84741
## [5,]  8.405465 -13.3905621 37.69741
## [6,] 15.965465  -4.0805621 73.14741
## Starting individual parameters (phiM)
##          [,1]        [,2]     [,3]
## [1,] 14.12039  -9.0739345 64.47321
## [2,] 13.90284  -9.2450306 65.29360
## [3,] 14.70016   0.4821332 65.18593
## [4,] 16.92615  -1.2900916 78.68453
## [5,]  7.89513 -13.8941079 37.90238
## [6,] 16.30589  -5.3189986 73.21070
```

Example 9 - PK model with covariates including covariate effects, no IIV on one parameter, no fixed parameter

- continuous outcome with combined error model
- fixed effect parameters
  - 3 parameters
- covariates: untransformed for the old version where the names must be the same
  - sex and age on ka
  - wt and age on cl
  - weight and sex on vd
- variability: one level
  - no IIV on ka
  - correlation between CL and V

```
## Variability level: iiv (associated with id )
##     variance-covariance model
##    ka cl vd
```

```
## ka  0  0  0
## cl  0  1  1
## vd  0  1  1
```

```
## Initialisation of model, model 9:
```

```
## Nonlinear mixed-effects model
##   Model function
##   with 1 outcome:  conc
##   Nb of parameters: 3
##       parameter names:  ka cl vd
##       distribution:
##    Parameter Distribution Estimated mu.CI omega.CI
## ka ka        log-normal   estim     1     0
## vd cl        log-normal   estim     5     0.5
## cl vd        log-normal   estim     0.1   0.7
## Covariate model:
##     ka cl vd
## sex  1  0  1
## age  1  1  0
## wt   0  1  1
## Fixed parameters in covariate model:
##     ka cl vd
## sex  0  0  0
## age  0  0  0
## wt   0  0  0
```

```
##              name                                                                value
## 1            nobs                                                                    0
## 2    fixedpsi.ini                                    c(ka = 1, vd = 5, cl = 0.1)
## 3           betas  0.00,  0.20, -0.50,  1.61,  0.75, -0.50, -2.30,  1.00,  0.15
## 4         allpar0       1, 0.2, -0.5, 5, 0.75, -0.5, 0.1, 1, 0.15, 1, 1, 1, 0.2
## 5         nchains                                                                 2
## 6   nb.parameters                                                                 3
## 7        nb.betas                                                                 9
## 8         nb.etas                                                                 3
## 9       nb.parest                                                                14
## 10     indx.betaC                                            c(2, 3, 5, 6, 8, 9)
## 11     indx.betaI                                                     c(1, 4, 7)
## 12        ind.res                                                           1:2
## 13   indest.omega                                                 c(5, 6, 8, 9)
## 14      i0.omega2                                                     c(ka = 1)
## 15      i1.omega2                                                           2:3
## 16    j.covariate                          c(1, 2, 3, 13, 14, 15, 25, 26, 27)
## 17   j0.covariate                                                          1:3
## 18      ind.fix10                                                          1:3
## 19      ind.fix11                                                          4:9
## 20       ind.fix1                                                          1:9
## 21       ind.fix0                                                    integer(0)
## 22           pres                                                     c(1, 0.2)
## 23        ind.eta                                                           1:3
## 24       ind0.eta                                                    integer(0)
## 25    diag(omega)                                  c(ka = 1, cl = 1, vd = 1)
## 26 domega2 (col1)                                              0.5, 0.5, 0.5
## 27          MCOV0                                                  see below
```

```
## 28           COV0                                                    see below
## 29           COV1                                                    see below
## 30           COV2                                                    see below
## 31      flag.fmin                                                         TRUE
## Omega
##    ka cl vd
## ka  1  0  0
## cl  0  1  0
## vd  0  0  1
## LCOV (design matrix nb.muteta x nb.modpar):
##       [,1] [,2] [,3]
##  [1,]    1    0    0
##  [2,]    1    0    0
##  [3,]    1    0    0
##  [4,]    0    1    0
##  [5,]    0    1    0
##  [6,]    0    1    0
##  [7,]    0    0    1
##  [8,]    0    0    1
##  [9,]    0    0    1
## MCOV (LCOV filled with parameter value on phi scale):
##       [,1]      [,2]      [,3]
##  [1,]  0.0  0.000000  0.000000
##  [2,]  0.2  0.000000  0.000000
##  [3,] -0.5  0.000000  0.000000
##  [4,]  0.0  1.609438  0.000000
##  [5,]  0.0  0.750000  0.000000
##  [6,]  0.0 -0.500000  0.000000
##  [7,]  0.0  0.000000 -2.302585
##  [8,]  0.0  0.000000  1.000000
##  [9,]  0.0  0.000000  0.150000
## MCOV0 (MCOV[ind.fix10,i0.omega2,drop=FALSE]):
##      [,1]
## [1,]  0.0
## [2,]  0.2
## [3,] -0.5
## COV0 (COV[,ind.fix10]):
##    id   wt sex
## 1   1 66.7   1
## 19  1 66.7   1
## 32  1 66.7   1
## 51  1 80.0   1
## 68  1 40.0   0
## 86  1 75.3   1
## COV1 (initialised as COV[,ind.fix1]):
##    id   wt sex id sex age id   wt age
## 1   1 66.7   1  1   1  50  1 66.7  50
## 19  1 66.7   1  1   1  50  1 66.7  50
## 32  1 66.7   1  1   1  31  1 66.7  31
## 51  1 80.0   1  1   1  40  1 80.0  40
## 68  1 40.0   0  1   0  46  1 40.0  46
## 86  1 75.3   1  1   1  43  1 75.3  43
## COV2 (t(COV)%*%COV):
##         id       wt    sex     id    sex     age     id       wt     age
```

```
## id    32.0   2240.1   27.0   32.0   27.0   992.0   32.0   2240.1   992.0
## wt  2240.1 161793.4 1983.4 2240.1 1983.4 69157.5 2240.1 161793.4 69157.5
## sex   27.0   1983.4   27.0   27.0   27.0   820.0   27.0   1983.4   820.0
## id    32.0   2240.1   27.0   32.0   27.0   992.0   32.0   2240.1   992.0
## sex   27.0   1983.4   27.0   27.0   27.0   820.0   27.0   1983.4   820.0
## age  992.0  69157.5  820.0  992.0  820.0 34170.0  992.0  69157.5 34170.0
## id    32.0   2240.1   27.0   32.0   27.0   992.0   32.0   2240.1   992.0
## wt  2240.1 161793.4 1983.4 2240.1 1983.4 69157.5 2240.1 161793.4 69157.5
## age  992.0  69157.5  820.0  992.0  820.0 34170.0  992.0  69157.5 34170.0
## dstatCov (COV[,ind.fix0,drop=FALSE]%*%MCOV[ind.fix0,]):
##    [,1] [,2] [,3]
## 1     0    0    0
## 19    0    0    0
## 32    0    0    0
## 51    0    0    0
## 68    0    0    0
## 86    0    0    0
## Mcovariates (column of 1's if IIV + covariates):
##    id   wt sex age
## 1   1 66.7   1  50
## 19  1 66.7   1  50
## 32  1 66.7   1  31
## 51  1 80.0   1  40
## 68  1 40.0   0  46
## 86  1 75.3   1  43
## Starting population parameters (mean.phi)
##       [,1]      [,2]     [,3]
## [1,] 12.84 -22.64056 71.89741
## [2,] 12.84 -22.64056 71.89741
## [3,] 12.84 -13.14056 69.04741
## [4,] 15.50 -17.64056 83.69741
## [5,]  8.00 -21.39056 44.59741
## [6,] 14.56 -19.14056 79.44741
## Starting individual parameters (phiM)
##           [,1]      [,2]     [,3]
## [1,] 12.612552 -21.67566 72.53378
## [2,] 12.937978 -22.52066 70.97977
## [3,] 13.219146 -13.33444 69.08399
## [4,] 15.351156 -18.22007 83.68759
## [5,]  8.036423 -20.87616 43.87951
## [6,] 14.747689 -18.78832 79.33837
```