nlmixr^2: an open-source package for pharmacometric modeling in R

PssN 2023 tutorial

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On behalf of the nlmixr2 development team:

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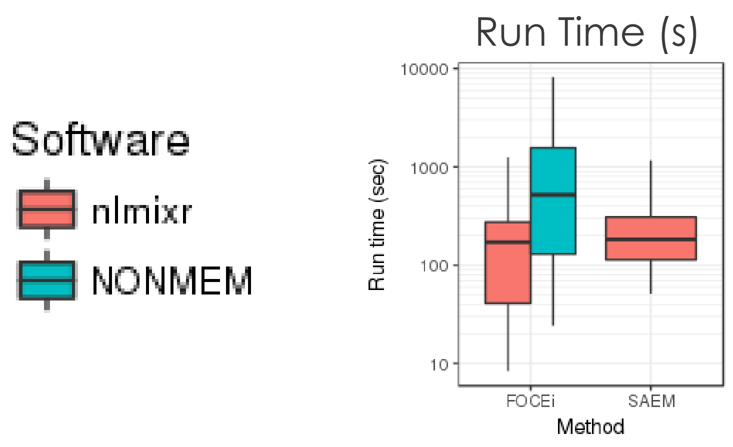
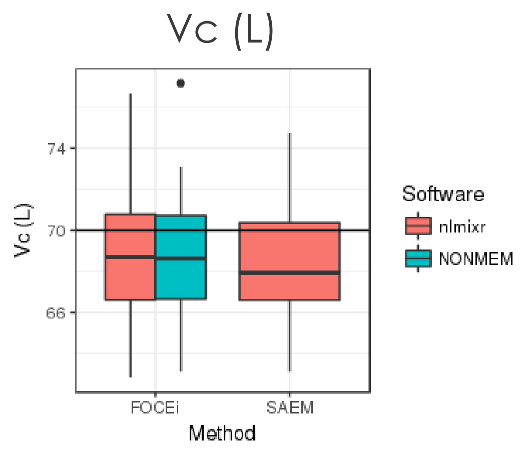
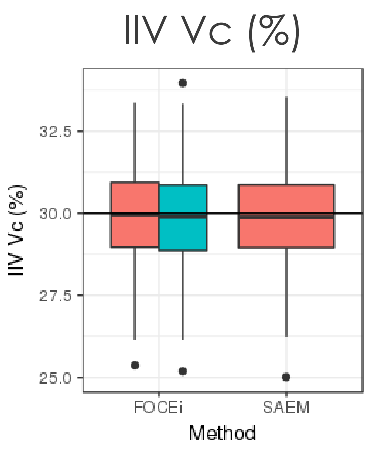
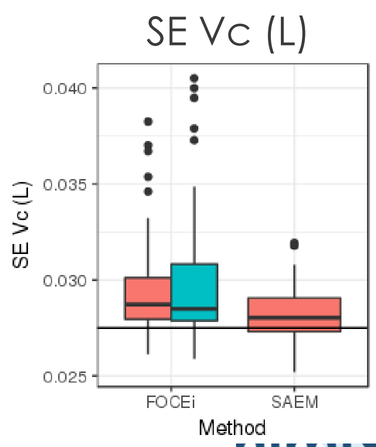
nlmixr^2 is a nonlinear mixed effects modeling R package with comparable performance to commercial software

- Run time for ODE model:
  - FOCEi: nlmixr runs faster than NONMEM
  - SAEM: nlmixr runs as fast as Monolix and both are faster than NONMEM
- Parameter Estimates were similar for all three NLME tools.
- One known submission/approval to FDA with nlmixr

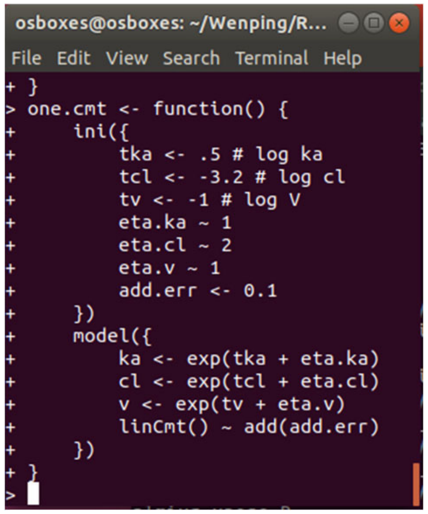








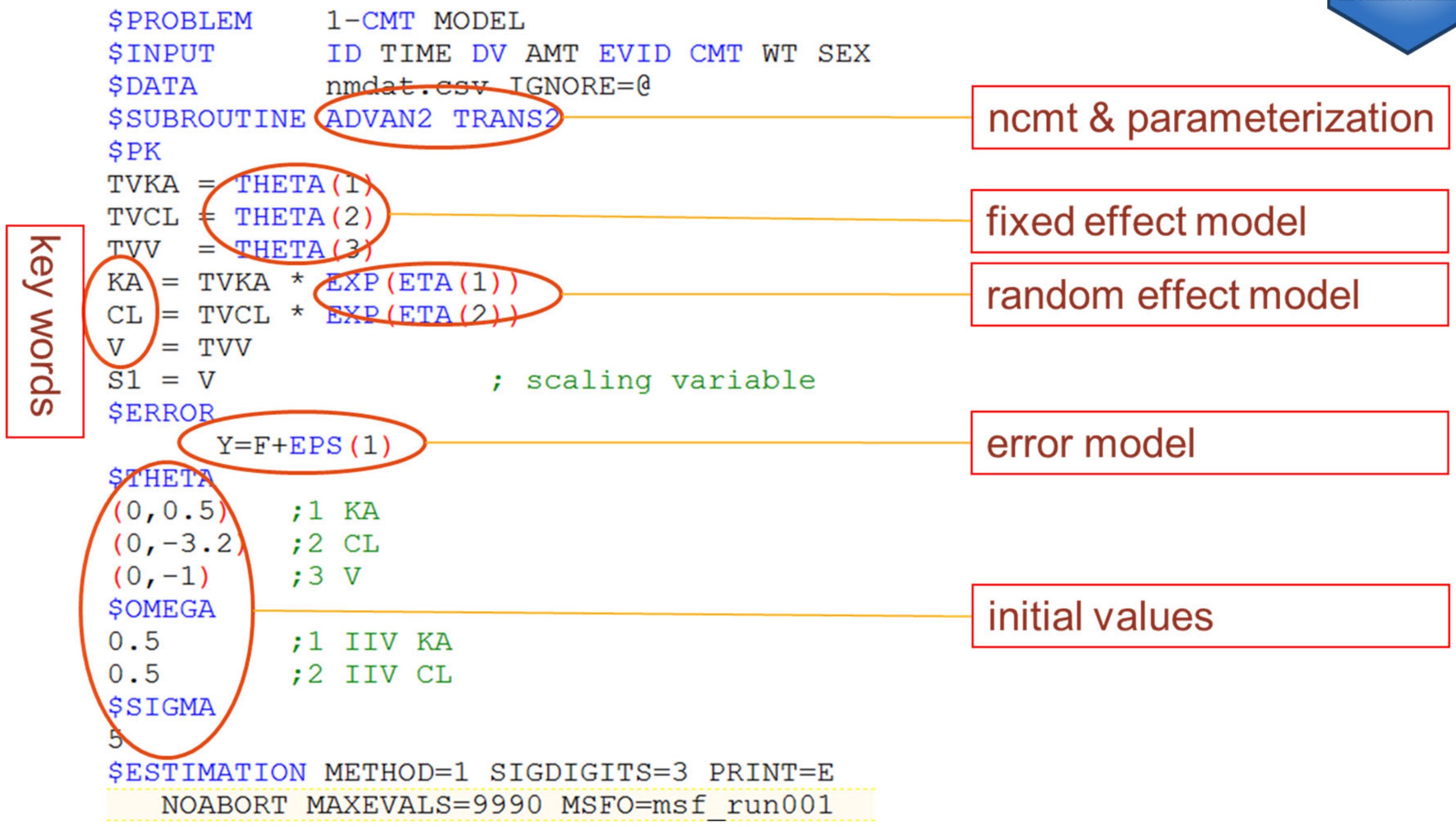
modeling syntax, running nlmixr^2 models and nlmixr^2 output


osboxes@osboxes: ~/Wenping/R...
File Edit View Search Terminal Help

```
+ }
> one.cmt <- function() {
+     ini({
+         tka <- .5 # log ka
+         tcl <- -3.2 # log cl
+         tv <- -1 # log V
+         eta.ka ~ 1
+         eta.cl ~ 2
+         eta.v ~ 1
+         add.err <- 0.1
+     })
+     model({
+         ka <- exp(tka + eta.ka)
+         cl <- exp(tcl + eta.cl)
+         v <- exp(tv + eta.v)
+         linCmt() ~ add(add.err)
+     })
+ }
>
```

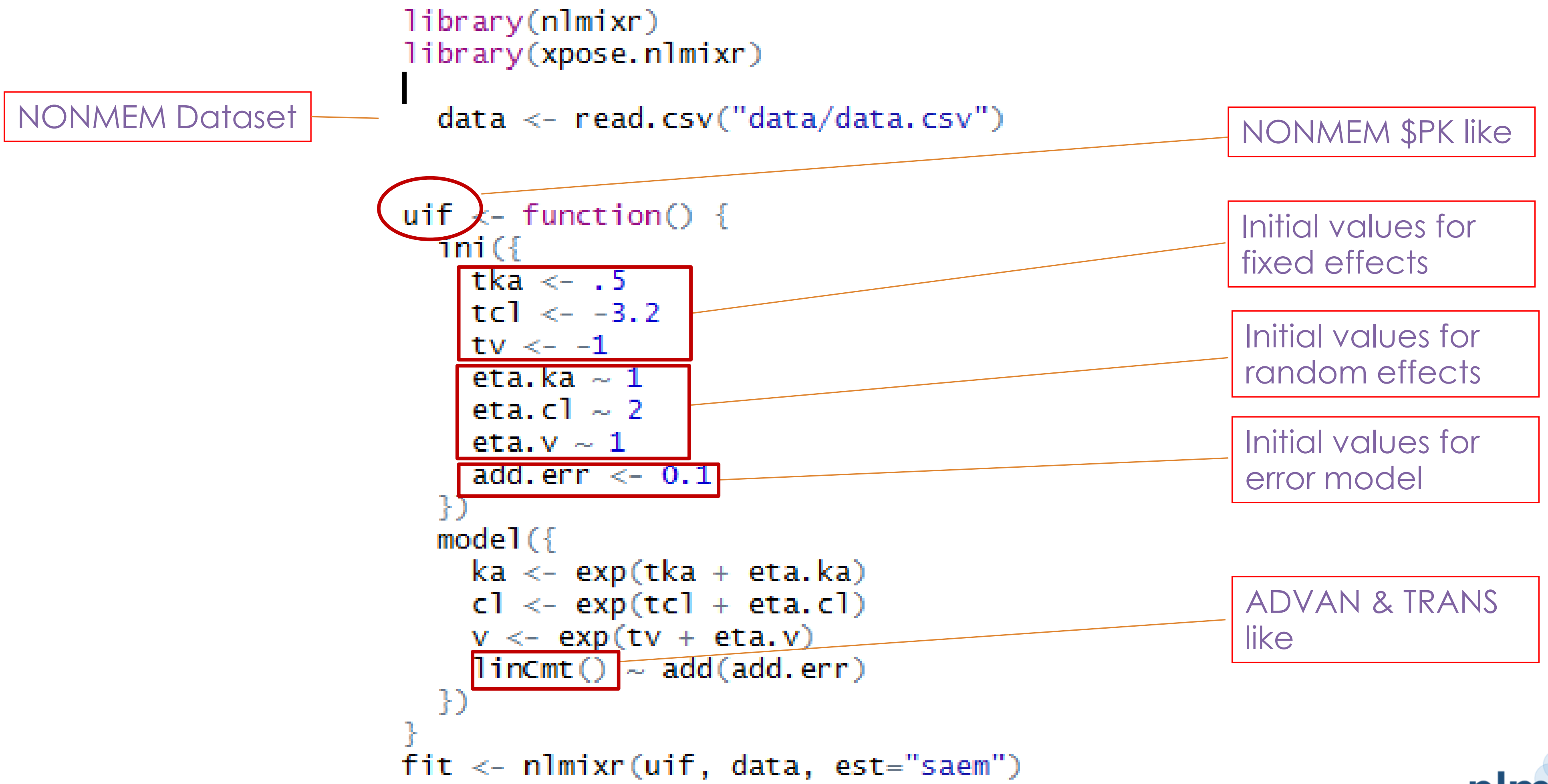
nlmixr2

Anatomy of a NONMEM control stream for a popPK model



```
$PROBLEM     1-CMT MODEL
$INPUT       ID TIME DV AMT EVID CMT WT SEX
$DATA        nmdat.csv IGNORE=@
$SUBROUTINE ADVAN2 TRANS2
$PK
TVKA  = THETA(1)
TVCL  = THETA(2)
TVV   = THETA(3)
KA  = TVKA * EXP(ETA(1))
CL  = TVCL * EXP(ETA(2))
V   = TVV
S1 = V                     ; scaling variable
$ERROR
      Y=F+EPS(1)
$THETA
(0,0.5)     ;1  KA
(0,-3.2)    ;2  CL
(0,-1)      ;3  V
$OMEGA
0.5         ;1  IIV KA
0.5         ;2  IIV CL
$SIGMA
5
$ESTIMATION METHOD=1 SIGDIGITS=3 PRINT=E
   NOABORT MAXEVALS=9990 MSFO=msf_run001
```

Anatomy of a nlmixr control stream for a popPK model compared to NONMEM



```
library(nlmixr)
library(xpose.nlmixr)

  data <- read.csv("data/data.csv")

uif <- function() {
  ini({
    tka <- .5
    tcl <- -3.2
    tv <- -1
    eta.ka ~ 1
    eta.cl ~ 2
    eta.v ~ 1
    add.err <- 0.1
  })
  model({
    ka <- exp(tka + eta.ka)
    cl <- exp(tcl + eta.cl)
    v <- exp(tv + eta.v)
    linCmt() ~ add(add.err)
  })
}
fit <- nlmixr(uif, data, est="saem")
```

NONMEM Dataset
NONMEM $PK like
Initial values for fixed effects
Initial values for random effects
Initial values for error model
ADVAN & TRANS like

A nlmixr model has two main parts: initialization and model

Initialization ini({ })

label() or # (interactive only)

```
ini({
    lCl   <- 1.6; label("log Cl (L/hr)")
    lVc    = log(90); label("log V (L)")
    lKa    = fix(1)  #log Ka (1/hr)
    add.sd = 0.2
    eta.Ka ~ 0.1 #IIV Ka
    eta.Cl + eta.Vc ~ c(0.1,
                        0.005, 0.1)

})
```

Lower triangular block matrix

- Population and Residual Estimates are defined using assign operators (**=**)
- Random Effects (ETAs) defined using a model formula (**~**; aka modelled by)

Model model({ })

Relationship of Fixed/Random Pars First

```
model({
    Cl = exp(lCl + eta.Cl)
    Vc = exp(lVc + eta.Vc)
    KA = exp(lKa + eta.Ka)

    linCmt() ~ add(add.sd)

})
```

- Parameters defined based on ini block
- Fixed/Random relationships defined first
- Model (Solved/RxODE) defined next
- Unexplained error defined by formula (**~**)

nlmixr uses defined parameters to select 1, 2 or 3 solved compartment model with linCmt() → closed-form solutions

Solved System Parameterization Support

1 Compartment	2 Compartment	3 Compartment
Cl, V	Cl, V, Q, Vp	Cl, Vc, Q1, Vp1, Q2 Vp2
Kel, V	Kel, k12, k21, V	Kel, k12, k21, k13, k31, V
A, alpha	A, alpha, B, beta	A, alpha, B, beta, C, gamma

nlmixr also uses parameter aliases; Examples:

- V =Vc = V1 and Q = Cld.
- Parameter case does not matter

Parameter aliases are context dependent.

- The first can be Volume = Vc, (Can start with V2)
- Second numbered Volume = Vp
- All NONMEM style parameters are supported.

CMT #1 = depot (w/Ka) / central (without Ka) compartment

Model model({ })

```
model({
     Cl  = exp(lCl + eta.Cl)
     Vc  = exp(lVc + eta.Vc)
     KA  = exp(lKa + eta.Ka)
     Vp  = exp(lVp)
     Cld = exp(lCld)
    linCmt() ~ prop(prop.sd)
})
```

- 1 compartment solved model is specified by linCmt()
- 2 and 3 compartment model is also specified by linCmt()
- Type of model depends on provided parameters

https://nlmixr2.github.io/rxode2/articles/rxode2-model-types.html#solved-compartment-models

A nlmixr model block in case of no closed-form solution or PD model and ODE model block is required → linCmt cannot be used

Initialisation ini({ })

label() or # (interactive only)

```
ini({
    lCl    = 1.6; label("log Cl  (L/hr)")
    lVc    = log(90); label("log V  (L)")
    lKa    = 1     #log Ka  (1/hr)
    prop.sd = 0.2
    eta.Ka ~ 0.1 #IIV Ka
    eta.Cl + eta.Vc ~ c(0.1,
                         0.005, 0.1)
})
```

Lower triangular block matrix

- Population and Residual Estimates are defined using assign operators (**=**)
- Random Effects (ETAs) defined using a model formula (**~**; aka modelled by)

Model model({ })

```
model({ 
    Cl   = exp(lCl + eta.Cl)
    Vc   = exp(lVc + eta.Vc)
    KA   = exp(lKa + eta.Ka)
    kel = Cl / Vc
    d/dt(depot) = -KA*depot
    d/dt(centr) =  KA*depot-kel*centr
    cp = centr / Vc
    cp ~ prop(prop.sd)
})
```

Relationship of Fixed/Random Pars First

➢ instead of linCMT

- Parameters defined based on ini block
- Fixed/Random relationships defined first
- Model (Solved/RxODE) defined next
- Unexplained error defined by formula (**~**)

Add Bioavailability (F) and lag time (alag) to the model

Initialisation ini({ })

label() or # (interactive only)

```
 ini({
    lCl    = 1.6; label("log Cl (L/hr)")
lVc    = log(90);  label("log V (L)")
    lKa    = 1      #log Ka (1/hr)
    lf     = log(1)
    lalag  = log(0.5)
    prop.sd = 0.2
    eta.Ka ~ 0.1 #IIV Ka
    eta.Cl + eta.Vc ~ c(0.1,
                         0.005, 0.1)
 })
```

Lower triangular block matrix

- Population and Residual Estimates are defined using assign operators (**=**)
- Random Effects (ETAs) defined using a model formula (**~**; aka modeled by)

Model model({ })

Relationship of Fixed/Random Pars First

```
model({
    Cl    = exp(lCl + eta.Cl)
    Vc    = exp(lVc + eta.Vc)
    KA    = exp(lKa + eta.Ka)
    fD    = exp(lf)
    lagD  = exp(lalag)
    kel = Cl / Vc
    d/dt(depot)  = -KA*depot
    alag(depot)  = lagD
    f(depot)     = fD
    d/dt(centr)  = KA*depot-kel*centr
    cp = centr / Vc
    cp ~ prop(prop.sd)
})
```

Can also add rate/dur for modeled duration and rate

Residual Error models and Multiple Endpoints

Error Model	Coding	Supported By
Additive/Normal	Y ~ add(add.sd)	nlme, fo, foi, foce, focei, saem
Proportional	Y ~ prop(prop.sd)	nlme, fo, foi, foce, focei, saem
Additive + Proportional	Y ~ add(add.sd) + prop(prop.sd)	nlme, fo, foi, foce, focei, saem
Lognormal/Exponential ***Note*: normal scale OBJF**	Y ~ lnorm(lnorm.sd)	fo, foi, foce, focei, saem
Power Model	Y ~ pow(pow.sd, pow)	fo, foi, foce, focei, saem
Additive + Power	Y ~ add(add.sd) + pow(pow.sd, d)	fo, foi, foce, focei, saem
Box-Cox transform both sides	Y ~ add(add.sd) +boxCox(lambda)	fo, foi, foce, focei, saem
Yeo-Johnson transform both sides	Y ~ add(add.sd) + yeoJohnson(lambda)	fo, foi, foce, focei, saem

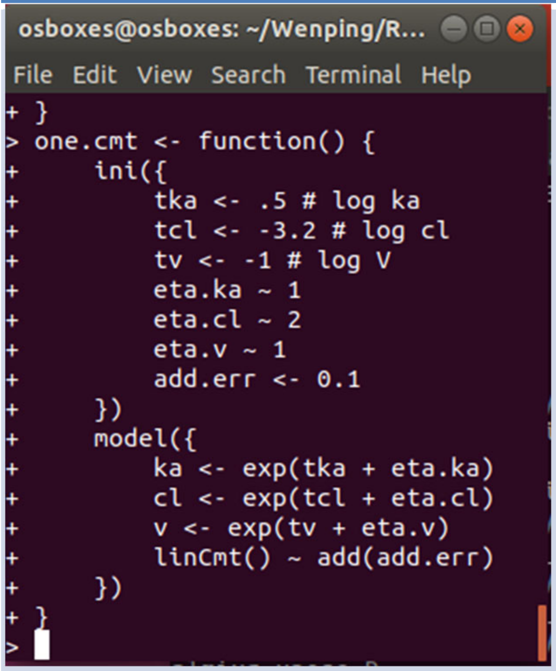
Multiple Endpoint:

```
PK ~ add(add.sd) + prop(prop.sd)  | depot
PD ~ add(pd.sd)                   | err
```

Now generalized llik for focei

Finalizing and checking a nlmixr model verifies nlmixr detects the correct solved model (or RxODE model), as well as showing the parsed initial estimates

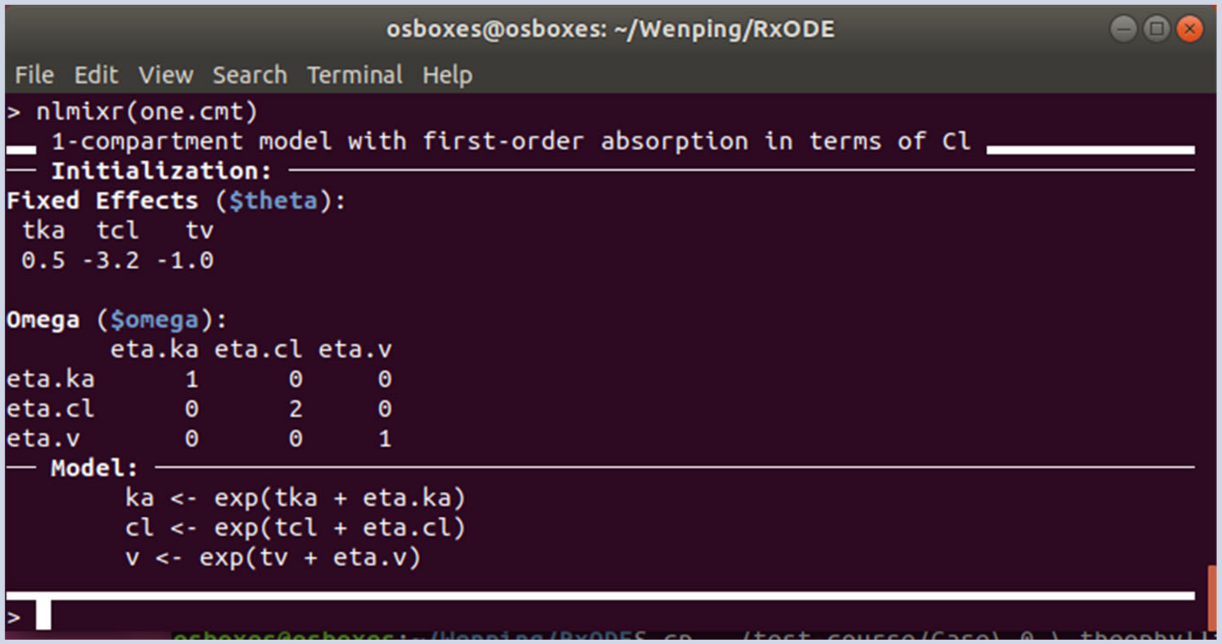
Finalising models



```
+ }
> one.cmt <- function() {
+     ini({
+         tka <- .5 # log ka
+         tcl <- -3.2 # log cl
+         tv <- -1 # log V
+         eta.ka ~ 1
+         eta.cl ~ 2
+         eta.v ~ 1
+         add.err <- 0.1
+     })
+     model({
+         ka <- exp(tka + eta.ka)
+         cl <- exp(tcl + eta.cl)
+         v <- exp(tv + eta.v)
+         linCmt() ~ add(add.err)
+     })
+ }
>
```

To finalize a model, put the **`ini`** and **`model`** in a named function

Checking how the model is parsed



```
> nlmixr(one.cmt)
── 1-compartment model with first-order absorption in terms of Cl ──────
── Initialization: ──────────────────────────────────────────────────────
Fixed Effects ($theta):
 tka   tcl    tv
 0.5 -3.2 -1.0

Omega ($omega):
              eta.ka eta.cl eta.v
eta.ka        1      0      0
eta.cl        0      2      0
eta.v         0      0      1
── Model: ───────────────────────────────────────────────────────────────
        ka <- exp(tka + eta.ka)
        cl <- exp(tcl + eta.cl)
        v <- exp(tv + eta.v)
─────────────────────────────────────────────────────────────────────────
>
```

By calling **`nlmixr`** on the named R function, it will tell you how **nlmixr** parsed the model; This is especially useful in checking what solved system **nlmixr** detected before running the entire model

Fitting nlmixr models takes the estimation method (with its options) and produces a nlmixr combined dataset/fit object

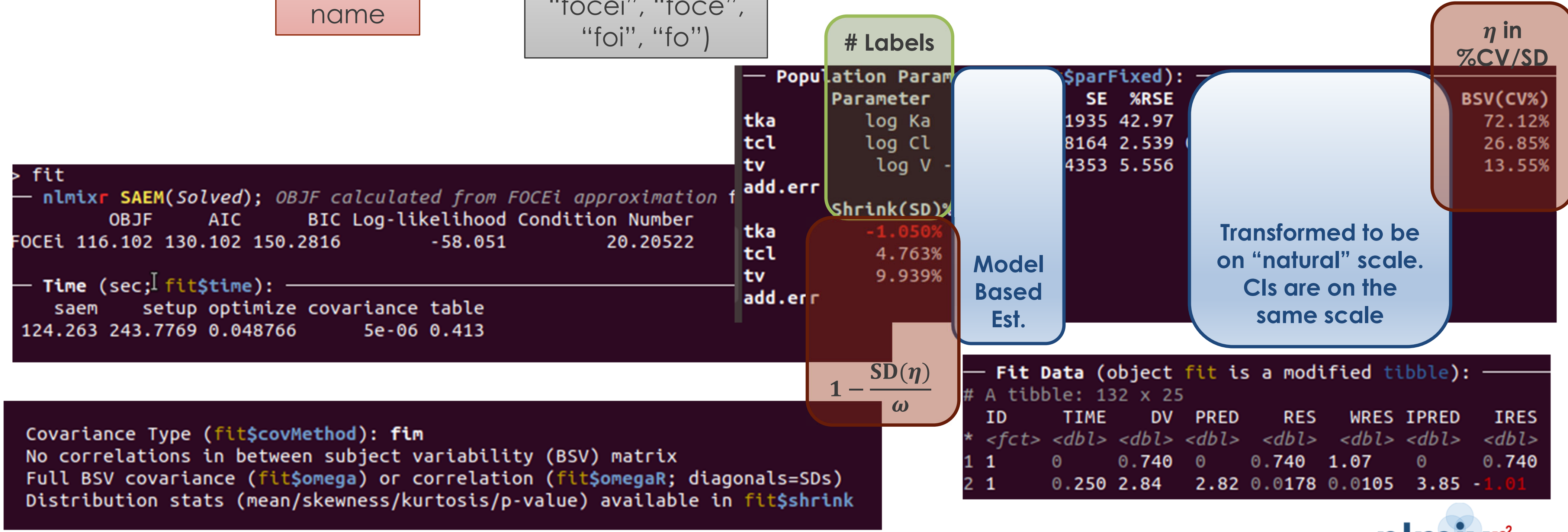
```
fit <- nlmixr(one.cmt, data, est = "saem", table=tableControl(cwres=TRUE, npde=TRUE))
```

Assigned R object

Function Name is run name

Estimation methods = (“nlme”, “saem”, “focei”, “foce”, “foi”, “fo”)

Optional if cwres and or npde calculations wanted



# Labels
η in %CV/SD
Model Based Est.
Transformed to be on “natural” scale. CIs are on the same scale
$1-\frac{\mathrm{SD}(\eta)}{\omega}$

```
> fit
── nlmixr SAEM(Solved); OBJF calculated from FOCEi approximation f
         OBJF     AIC      BIC Log-likelihood Condition Number
FOCEi 116.102 130.102 150.2816        -58.051         20.20522

── Time (sec; fit$time): ──────────────────────────────────────
     saem    setup optimize covariance table
 124.263 243.7769 0.048766      5e-06 0.413
```

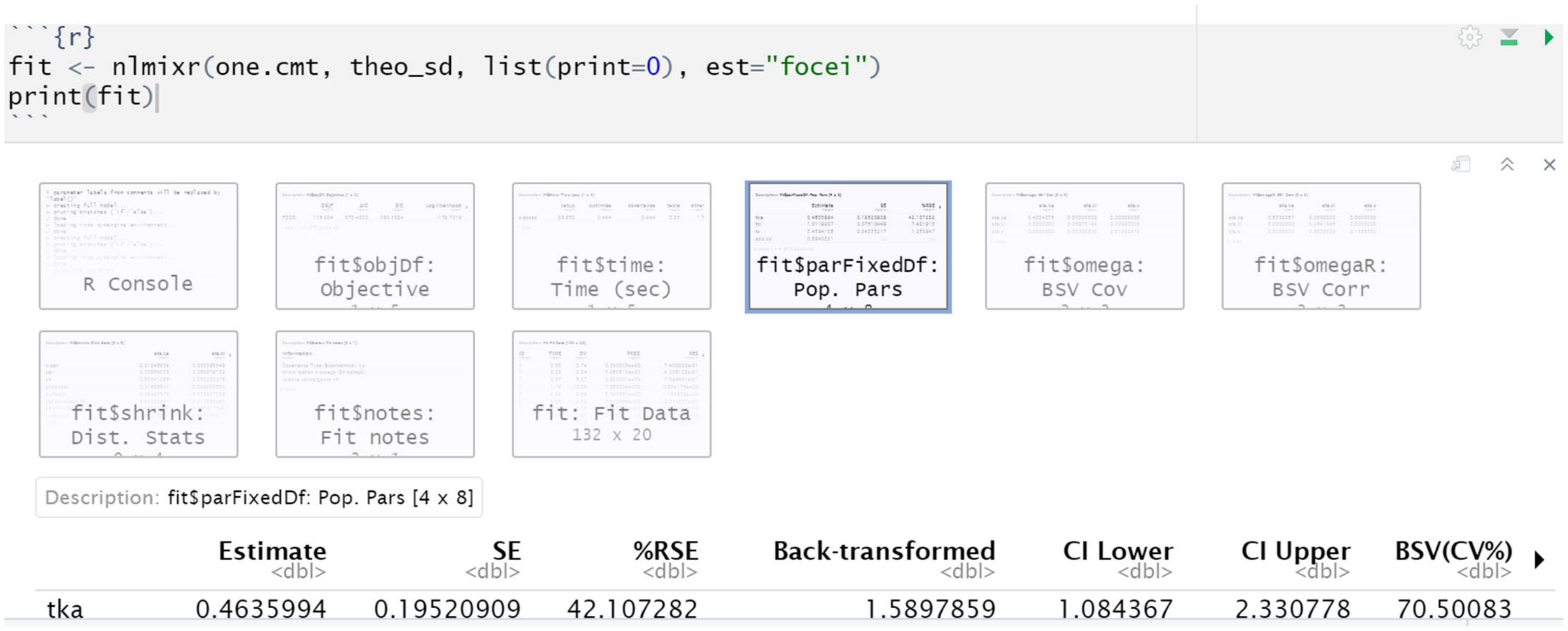
```
── Population Param                  $parFixed): ──
               Parameter               SE   %RSE                       BSV(CV%)
tka               log Ka             1935  42.97                         72.12%
tcl               log Cl             8164  2.539 (                       26.85%
tv                 log V -           4353  5.556                         13.55%
add.err

          Shrink(SD)%
tka          -1.050%
tcl           4.763%
tv            9.939%
add.err
```

```
 Covariance Type (fit$covMethod): fim
 No correlations in between subject variability (BSV) matrix
 Full BSV covariance (fit$omega) or correlation (fit$omegaR; diagonals=SDs)
 Distribution stats (mean/skewness/kurtosis/p-value) available in fit$shrink
```

```
── Fit Data (object fit is a modified tibble): ──
# A tibble: 132 x 25
  ID     TIME    DV  PRED    RES   WRES IPRED   IRES
* <fct> <dbl> <dbl> <dbl>  <dbl>  <dbl> <dbl>  <dbl>
1 1     0     0.740 0     0.740  1.07   0     0.740
2 1     0.250 2.84  2.82  0.0178 0.0105 3.85  -1.01
```

In Rstudio's Rmarkdown or notebook, the output is similar but in tabular form that is easier to click through



~~~
```{r}
fit <- nlmixr(one.cmt, theo_sd, list(print=0), est="focei")
print(fit)
```
~~~

Description: fit$parFixedDf: Pop. Pars [4 x 8]

	Estimate	SE	%RSE	Back-transformed	CI Lower	CI Upper	BSV(CV%)
	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>	<dbl>
tka	0.4635994	0.19520909	42.107282	1.5897859	1.084367	2.330778	70.50083

Inclusion of Covariates into a SAEM nlmixr model

Initialization ini({ })

```
 ini({
    lCl      = 1.6      #log Cl  (L/hr)
    lVc      = log(90)  #log V  (L)
    lKa      = fix(1)   #log Ka  (1/hr)
    beta.wt  = 0.75     #estimate of covariate effect
    prop.sd  = c(0,0.2,1)
    eta.Ka   ~ 0.1 #IIV Ka
    eta.Cl + eta.Vc ~ c(0.1,
                        0.005, 0.1)
})
```

SCM covariate building:

covarSearchAuto()

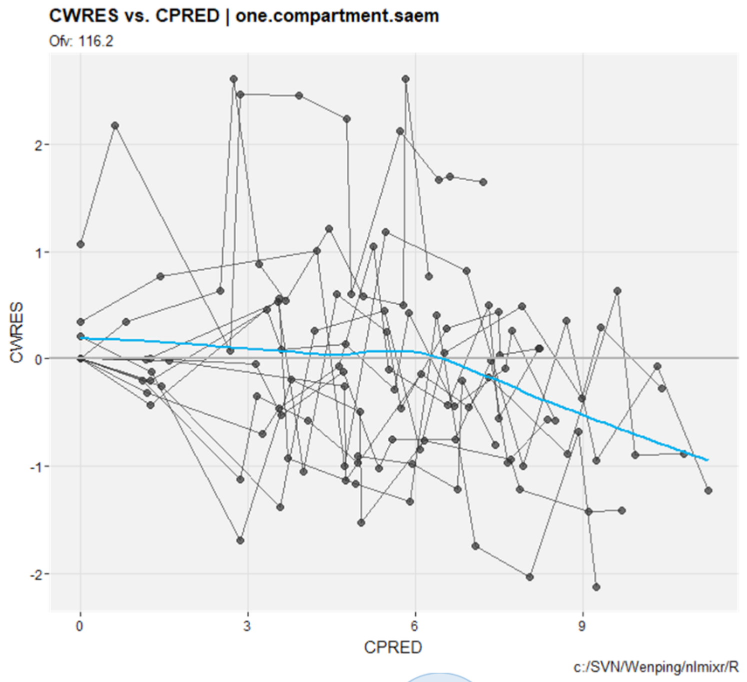
```
Cl = exp(   tCl   +     eta.Cl    +    beta.wt * lnWt70 )
```

tCl	eta.Cl	beta.wt * lnWt70
Fixed or Population Parameter	Random or Individual Parameter	Covariate Estimate times transformed covariate

$$\exp(t_{Cl} + e_{Cl})\left(\frac{\mathrm{WT}}{70}\right)^{\mathrm{WT}_{CL}}$$

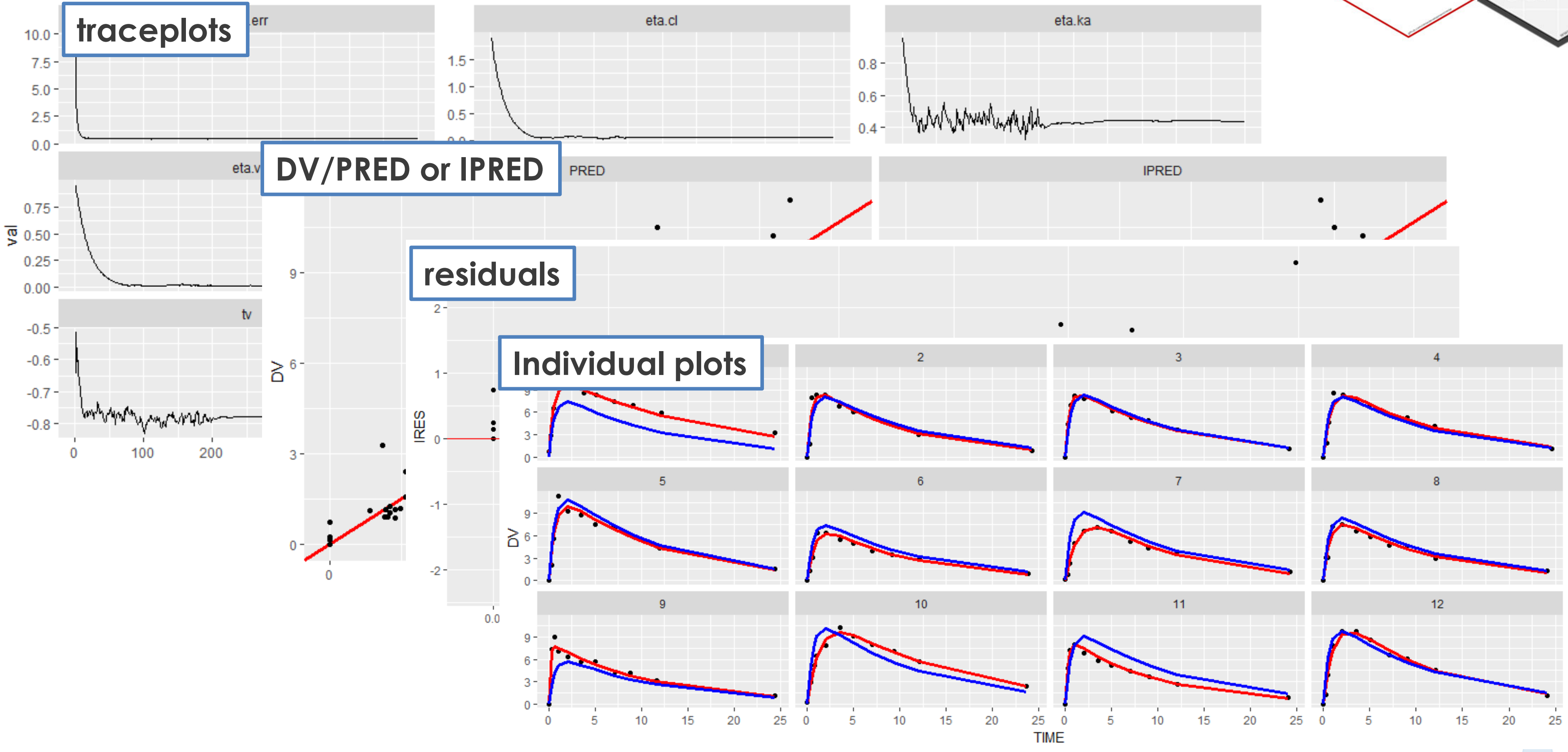
$$\exp(t_{Cl} + e_{Cl} + \mathrm{WT}_{CL} \cdot \mathrm{logWt70})$$

diagnostic plots from a nlmixr model



nlmixr2

Simple goodness of fit plots can be produced by a simple plot(fit)



Resources, documentation and further reading

- Home of nlmixr2, rxode2, xpose.nlmixr2, support packages (most recent versions)
  - https://github.com/nlmixr2 New version of nlmixr
- Documentation: continually evolving
  - https://nlmixr.org/
- Open course material:
- Twitter: @nlmixr
- LinkedIn: https://www.linkedin.com/groups/8621368/