Title

menl — Nonlinear mixed-effects regression

Description

menl fits nonlinear mixed-effects models in which some or all fixed and random effects enter nonlinearly. These models are also known as multilevel nonlinear models or hierarchical nonlinear models. The overall error distribution of the nonlinear mixed-effects model is assumed to be Gaussian. Different covariance structures are provided to model random effects and to model heteroskedasticity and correlations within lowest-level groups.

Quick start

Nonlinear mixed-effects regression of y on x1 and x2 with random intercepts B0 by id

```
menl y = {a}*(1-exp(-({b0}+{b1}*x1+{b2}*x2+{B0[id]})))
```

Same as above, but using the more efficient specification of the linear combination

```
menl y = {a}*(1-exp(-{xb: x1 x2 B0[id]}))
```

Same as above, but using define() to specify the linear combination

```
menl y = {a}*(1-exp(-{xb:})), define(xb: x1 x2 B0[id])
```

Same as above, but perform restricted maximum-likelihood estimation instead of the default maximum-likelihood estimation

```
menl y = {a}*(1-exp(-{xb:})), define(xb: x1 x2 B0[id]) reml
```

Specify your own initial values for fixed effects, but use the default expectation-maximization (EM) method to obtain initial values for random-effects parameters

```
menl y = {a}*(1-exp(-{xb:})), define(xb: x1 x2 B0[id])           ///
    initial({a} 1 {xb:x1} 1 {xb:x2} 0.5 {xb:_cons} 2, fixed)
```

Include random intercepts A0 by id to allow parameter a to vary between levels of id, and specify the xb suboption to indicate that a: contains a linear combination rather than a scalar parameter

```
menl y = {a:}*(1-exp(-{xb:})), define(xb: x1 x2 B0[id])          ///
    define(a: A0[id], xb)
```

Include a random slope on continuous variable x2 in the linear combination, and allow correlation between random slopes B1 and intercepts B0

```
menl y = {a}*(1-exp(-{xb:})), define(xb: x1 x2 B0[id] c.x2#B1[id]) ///
    covariance(B0 B1, unstructured)
```

Specify a heteroskedastic within-subject error variance that varies as a power of x2

```
menl y = {a}*(1-exp(-{xb:})), define(xb: x1 x2 B0[id] c.x2#B1[id]) ///
    covariance(B0 B1, unstructured) resvariance(power x2)
```

Display random-effects and within-group error parameters as standard deviations and correlations

```
    menl, stddeviations
```

Fit a nonlinear marginal regression of y on variables x1, x2, and x3 with an exchangeable covariance structure for the within-id errors

```
    menl y = {phi1}*(1-exp(-0.5*(x1-{phi2: x2 i.x3}))),          ///
        rescovariance(exchangeable, group(id))
```

Three-level nonlinear regression of y on variable time and factor variable f with random intercepts S0 by lev3 and W0 by lev2 nested within lev3, using an AR(1) correlation structure for the residuals

```
    menl y = {phi1:}+{phi2:}*exp(-{phi3}*time),                  ///
        define(phi1: i.f S0[lev3]) define(phi2: i.f W0[lev3>lev2]) ///
        rescorrelation(ar 1, t(time))
```

Three-level nonlinear regression of y on x1 with random intercepts W0 and slopes W1 on continuous x1 by lev3 and with random intercepts S0 and slopes S1 on x1 by lev2 nested within lev3, using unstructured covariance for W0 and W1 and exchangeable covariance for S0 and S1

```
    menl y = {phi1:}+{b1}*cos({b2}*x1),                          ///
        define(phi1:x1 W0[lev3] S0[lev3>lev2]                    ///
                      c.x1#(W1[lev3] S1[lev3>lev2]))             ///
        covariance(W0 W1, unstructured)                          ///
        covariance(S0 S1, exchangeable)
```

Same as above, but assume that residuals are independent but have different variances for males and females

```
    menl y = {phi1:}+{b1}*cos({b2}*x1),                          ///
        define(phi1:x1 W0[lev3] S0[lev3>lev2]                    ///
                      c.x1#(W1[lev3] S1[lev3>lev2]))             ///
        covariance(W0 W1, unstructured)                          ///
        covariance(S0 S1, exchangeable)                          ///
        rescovariance(identity, by(female))
```

Menu

Statistics > Multilevel mixed-effects models > Nonlinear regression

Syntax

`menl` *depvar* = <*menlexpr*> [*if*] [*in*] [, *options*]

<*menlexpr*> defines a nonlinear regression function as a substitutable expression that contains model parameters and random effects specified in braces `{}`, as in `exp({b}+{U[id]})`; see *Random-effects substitutable expressions* for details.

options	Description
Model	
`mle`	fit model via maximum likelihood; the default
`reml`	fit model via restricted maximum likelihood
`define(`*name*`:`<*resubexpr*>`)`	define a function of model parameters; this option may be repeated
`covariance(`*covspec*`)`	variance–covariance structure of the random effects; this option may be repeated
`initial(`*initial_values*`)`	initial values for parameters
Residuals	
`rescovariance(`*rescovspec*`)`	covariance structure for within-group errors
`resvariance(`*resvarspec*`)`	heteroskedastic variance structure for within-group errors
`rescorrelation(`*rescorrspec*`)`	correlation structure for within-group errors
Time series	
`tsorder(`*varname*`)`	specify time variable to determine the ordering for time-series operators
`tsinit({`*name*`:}=`<*resubexpr*>`)`	specify initial conditions for lag operators used with named expressions; this option may be repeated
`tsmissing`	keep observations with missing values in *depvar* in computation
Reporting	
`level(#)`	set confidence level; default is `level(95)`
`variance`	show random-effects and within-group error parameter estimates as variances and covariances; the default
`stddeviations`	show random-effects and within-group error parameter estimates as standard deviations and correlations
`noretable`	suppress random-effects table
`nofetable`	suppress fixed-effects table
`estmetric`	show parameter estimates as stored in `e(b)`
`nolegend`	suppress table expression legend
`noheader`	suppress output header
`nogroup`	suppress table summarizing groups
`nostderr`	do not estimate standard errors of random-effects parameters
`lrtest`	perform a likelihood-ratio test to compare the nonlinear mixed-effects model with ordinary nonlinear regression
`notsshow`	do not show ts setting information
display_options	control columns and column formats, row spacing, line width, display of omitted variables and base and empty cells, and factor-variable labeling

EM options	
emiterate(#)	number of EM iterations; default is emiterate(25)
emtolerance(#)	EM convergence tolerance; default is emtolerance(1e-10)
emlog	show EM iteration log
Maximization	
menlmaxopts	control the maximization process
coeflegend	display legend instead of statistics

collect is allowed; see **[U] 11.1.10 Prefix commands**.

coeflegend does not appear in the dialog box.

See **[U] 20 Estimation and postestimation commands** for more capabilities of estimation commands.

The syntax of *covspec* is

rename1 rename2 [...] , *vartype*

vartype	Description
independent	one unique variance parameter per random effect; all covariances are 0; the default
exchangeable	equal variances for random effects and one common pairwise covariance
identity	equal variances for random effects; all covariances are 0
unstructured	all variances and covariances to be distinctly estimated

The syntax of *rescovspec* is

rescov [, *rescovopts*]

rescov	Description
identity	uncorrelated within-group errors with one common variance; the default
independent	uncorrelated within-group errors with distinct variances
exchangeable	within-group errors with equal variances and one common covariance
ar [#]	within-group errors with autoregressive (AR) structure of order #, AR(#); ar 1 is implied by ar
ma [#]	within-group errors with moving-average (MA) structure of order #, MA(#); ma 1 is implied by ma
ctar1	within-group errors with continuous-time AR(1) structure
toeplitz [#]	within-group errors have Toeplitz structure of order #; toeplitz implies that all matrix off-diagonals be estimated
banded [#]	within-group errors with distinct variances and covariances within first # off-diagonals; banded implies all matrix bands (unstructured)
unstructured	within-group errors with distinct variances and covariances

The syntax of *resvarspec* is

resvarfunc [, *resvaropts*]

resvarfunc	Description
identity	equal within-group error variances; the default
linear *varname*	within-group error variance varies linearly with *varname*
power *varname* | _yhat	variance function is a power of *varname* or of predicted mean
exponential *varname* | _yhat	variance function is exponential of *varname* or of predicted mean
distinct	distinct within-group error variances

The syntax of *rescorrspec* is

rescorr [, *rescorropts*]

rescorr	Description
identity	uncorrelated within-group errors; the default
exchangeable	within-group errors with one common correlation
ar [#]	within-group errors with AR(#) structure; ar 1 is implied by ar
ma [#]	within-group errors with MA(#) structure; ma 1 is implied by ma
ctar1	within-group errors with continuous-time AR(1) structure
toeplitz [#]	within-group errors have Toeplitz correlation structure of order #; toeplitz implies that all matrix off-diagonals be estimated
banded [#]	within-group errors with distinct correlations within first # off-diagonals; banded implies all matrix bands (unstructured)
unstructured	within-group errors with distinct correlations

Options

Model

mle and reml specify the statistical method for fitting the model.

mle, the default, specifies that the model be fit using maximum likelihood (ML).

reml specifies that the model be fit using restricted maximum likelihood (REML), also known as residual maximum likelihood.

define(*name*:<*resubexpr*>) defines a function of model parameters, <*resubexpr*>, and labels it as *name*. This option can be repeated to define multiple functions. The define() option is useful for expressions that appear multiple times in the main nonlinear specification *menlexpr*: you define the expression once and then simply refer to it by using {*name*:} in the nonlinear specification. This option can also be used for notational convenience. See Random-effects substitutable expressions for how to specify <*resubexpr*>. <*resubexpr*> within define() may not contain the lagged predicted mean function.

covariance(*rename1* *rename2* [...], *vartype*) specifies the structure of the covariance matrix for the random effects. *rename1*, *rename2*, and so on, are the names of the random effects to be correlated (see Random effects), and *vartype* is one of the following: independent, exchangeable, identity, or unstructured. Instead of *renames*, you can specify *restub** to refer to random effects that share the same *restub* in their names.

`independent` allows for a distinct variance for each random effect and assumes that all covariances are 0; the default.

`exchangeable` specifies one common variance for all random effects and one common pairwise covariance.

`identity` is short for "multiple of the identity"; that is, all variances are equal, and all covariances are 0.

`unstructured` allows for all variances and covariances to be distinct. If p random effects are specified, the unstructured covariance matrix will have $p(p+1)/2$ unique parameters.

`initial(`*initial_values*`)` specifies the initial values for model parameters. You can specify a $1 \times k$ matrix, where k is the total number of parameters in the model, or you can specify a parameter name, its initial value, another parameter name, its initial value, and so on. For example, to initialize `{alpha}` to 1.23 and `{delta}` to 4.57, you would type

```
. menl ..., initial(alpha 1.23 delta 4.57) ...
```

To initialize multiple parameters that have the same group name, for example, `{y:x1}` and `{y:x2}`, with the same initial value, you can simply type

```
. menl ..., initial({y:} 1) ...
```

For the full specification, see *Specifying initial values*.

Residuals

`menl` provides two ways to model the within-group error covariance structure, sometimes also referred to as residual covariance structure in the literature. You can model the covariance directly by using the `rescovariance()` option or indirectly by using the `resvariance()` and `rescorrelation()` options.

`rescovariance(`*rescov* [, *rescovopts*]`)` specifies the within-group errors covariance structure or covariance structure of the residuals within the lowest-level group of the nonlinear mixed-effects model. For example, if you are modeling random effects for classes nested within schools, then `rescovariance()` refers to the residual variance–covariance structure of the observations within classes, the lowest-level groups.

rescov is one of the following: `identity`, `independent`, `exchangeable`, `ar` [#], `ma` [#], `ctar1`, `toeplitz` [#], `banded` [#], or `unstructured`. Below, we describe each *rescov* with its specific options *rescovopts*:

`identity` [, `by(`*byvar*`)`], the default, specifies that all within-group errors be independent and identically distributed (i.i.d.) with one common error variance σ^2_ϵ. When combined with `by(`*byvar*`)`, independence is still assumed, but you estimate a distinct variance for each category of *byvar*.

`independent, index(`*varname*`)` [`group(`*grpvar*`)`] specifies that within-group errors are independent with distinct variances for each value (index) of *varname*. `index(`*varname*`)` is required. `group(`*grpvar*`)` is required if there are no random effects in the model.

`exchangeable` [, `by(`*byvar*`)` `group(`*grpvar*`)`] assumes that within-group errors have equal variances and a common covariance.

`ar` [#], `t(`*timevar*`)` [`by(`*byvar*`)` `group(`*grpvar*`)`] assumes that within-group errors have an AR(#) structure. If # is omitted, `ar 1` is assumed. `t(`*timevar*`)` is required. For this structure, # + 1 parameters are estimated: # AR coefficients and one overall error variance, σ^2_ϵ.

`ma` [*#*], `t(`*timevar*`)` [`by(`*byvar*`)` `group(`*grpvar*`)`] assumes that within-group errors have an MA(*#*) structure. If *#* is omitted, `ma 1` is assumed. `t(`*timevar*`)` is required. For this structure, $\# + 1$ parameters are estimated: *#* MA coefficients and one overall error variance, σ^2_ϵ.

`ctar1`, `t(`*timevar*`)` [`by(`*byvar*`)` `group(`*grpvar*`)`] assumes that within-group errors have a continuous-time AR(1) structure. This is a generalization of the AR covariance structure that allows for unequally spaced and noninteger time values. `t(`*timevar*`)` is required. For this structure, two parameters are estimated: the correlation parameter, ρ, and one overall error variance, σ^2_ϵ. The correlation between two error terms is the parameter ρ raised to a power equal to the absolute value of the difference between the `t()` values for those errors.

`toeplitz` [*#*], `t(`*timevar*`)` [`by(`*byvar*`)` `group(`*grpvar*`)`] assumes that within-group errors have a Toeplitz structure of order *#*, for which correlations are constant with respect to time lags less than or equal to *#* and are 0 for lags greater than *#*. *#* is an integer between 1 and the maximum observed lag (the default). `t(`*timevar*`)` is required. For this structure, $\# + 1$ parameters are estimated: *#* correlations and one overall error variance, σ^2_ϵ.

`banded` [*#*], `index(`*varname*`)` [`group(`*grpvar*`)`] is a special case of `unstructured` that restricts estimation to the covariances within the first *#* off-diagonals and sets the covariances outside this band to 0. `index(`*varname*`)` is required. *#* is an integer between 0 and $L - 1$, where L is the number of levels of `index()`. By default, *#* is $L - 1$; that is, all elements of the covariance matrix are estimated. When *#* is 0, only the diagonal elements of the covariance matrix are estimated. `group(`*grpvar*`)` is required if there are no random effects in the model.

`unstructured`, `index(`*varname*`)` [`group(`*grpvar*`)`] assumes that within-group errors have distinct variances and covariances. This is the most general covariance structure in that no structure is imposed on the covariance parameters. `index(`*varname*`)` is required. When you have L levels of `index()`, then $L(L+1)/2$ parameters are estimated. `group(`*grpvar*`)` is required if there are no random effects in the model.

rescovopts are `index(`*varname*`)`, `t(`*timevar*`)`, `by(`*byvar*`)`, and `group(`*grpvar*`)`.

`index(`*varname*`)` is used within the `rescovariance()` option with *rescov* `independent`, `banded`, or `unstructured`. *varname* is a nonnegative-integer–valued variable that identifies the observations within the lowest-level groups (for example, `obsid`). The groups may be unbalanced in that different groups may have different `index()` values, but you may not have repeated `index()` values within any particular group.

`t(`*timevar*`)` is used within the `rescovariance()` option to specify a time variable for the `ar`, `ma`, `ctar1`, and `toeplitz` structures.

With *rescov* `ar`, `ma`, and `toeplitz`, *timevar* is an integer-valued time variable used to order the observations within the lowest-level groups and to determine the lags between successive observations. Any nonconsecutive time values will be treated as gaps.

With *rescov* `ctar1`, *timevar* is a real-valued time variable.

`by(`*byvar*`)` is for use within the `rescovariance()` option and specifies that a set of distinct within-group error covariance parameters be estimated for each category of *byvar*. In other words, you can use `by()` to model heteroskedasticity. *byvar* must be nonnegative-integer valued and constant within the lowest-level groups.

`group(`*grpvar*`)` is used to identify the lowest-level groups (panels) when modeling within-group error covariance structures. *grpvar* is a nonnegative-integer–valued group membership variable. This option lets you model within-group error covariance structures at the lowest level of your model hierarchy without having to include random effects at that level in your model. This is useful, for instance, when fitting nonlinear marginal or population-averaged models that model the dependence between error terms directly, without introducing random effects; see example 19. In the presence of random effects at other levels of hierarchy in your model, *grpvar* is assumed to be nested within those levels.

`resvariance(`*resvarfunc* [`,` *resvaropts*]`)` specifies a heteroskedastic variance structure of the within-group errors. It can be used with the `rescorrelation()` option to specify flexible within-group error covariance structures. The heteroskedastic variance structure is modeled as $\text{Var}\left(\epsilon_{ij}\right) = \sigma^2 g^2\left(\boldsymbol{\delta}, \upsilon_{ij}\right)$, where σ is an unknown scale parameter, $g(\cdot)$ is a function that models heteroskedasticity (also known as variance function in the literature), $\boldsymbol{\delta}$ is a vector of unknown parameters of the variance function, and υ_{ij}'s are the values of a fixed covariate x_{ij} or of the predicted mean $\widehat{\mu}_{ij}$.

resvarfunc, omitting the arguments, is one of the following: `identity`, `linear`, `power`, `exponential`, or `distinct`, and *resvaropts* are options specific to each variance function.

`identity`, the default, specifies a homoskedastic variance structure for the within-group errors; $g\left(\boldsymbol{\delta}, \upsilon_{ij}\right) = 1$, so that $\text{Var}\left(\epsilon_{ij}\right) = \sigma^2 = \sigma^2_\epsilon$.

`linear` *varname* specifies that the within-group error variance vary linearly with *varname*; that is, $g\left(\boldsymbol{\delta}, \upsilon_{ij}\right) = \sqrt{varname_{ij}}$, so that $\text{Var}\left(\epsilon_{ij}\right) = \sigma^2 varname_{ij}$. *varname* must be positive.

`power` *varname*| `_yhat` [`, strata(`*stratavar*`)` `noconstant`] specifies that the within-group error variance, or more precisely the variance function, be expressed in terms of a power of either *varname* or the predicted mean `_yhat`, plus a constant term; $g\left(\boldsymbol{\delta}, \upsilon_{ij}\right) = |\upsilon_{ij}|^{\delta_1} + \delta_2$. If `noconstant` is specified, the constant term δ_2 is suppressed. In general, three parameters are estimated: a scale parameter σ, the power δ_1, and the constant term δ_2. When `strata(`*stratavar*`)` is specified, the power and constant parameters (but not the scale) are distinctly estimated for each stratum. A total number of $2L + 1$ parameters are estimated (L power parameters, L constant parameters, and scale σ), where L is the number of strata defined by variable *stratavar*.

`exponential` *varname*| `_yhat` [`, strata(`*stratavar*`)`] specifies that the within-group error variance vary exponentially with *varname* or with the predicted mean `_yhat`; $g\left(\gamma, \upsilon_{ij}\right) = \exp(\gamma\upsilon_{ij})$. Two parameters are estimated: a scale parameter σ and an exponential parameter γ. When `strata(`*stratavar*`)` is specified, the exponential parameter γ (but not scale σ) is distinctly estimated for each stratum. A total number of $L + 1$ parameters are estimated (L exponential parameters and scale σ), where L is the number of strata defined by variable *stratavar*.

`distinct, index(`*varname*`)` [`group(`*grpvar*`)`] specifies that the within-group errors have distinct variances, σ^2_l, for each value (index), l, of *varname*, υ_{ij}; $g\left(\boldsymbol{\delta}, \upsilon_{ij}\right) = \delta_{\upsilon_{ij}}$ with $\delta_{\upsilon_{ij}} = \sigma_{\upsilon_{ij}}/\sigma_1$ ($\delta_1 = 1$ for identifiability purposes) such that $\text{Var}\left(\epsilon_{ij}\right) = \sigma^2_{\upsilon_{ij}} = \sigma^2_1\delta^2_{\upsilon_{ij}}$ for $l = 1, 2, \ldots, L$ and $\upsilon_{ij} \in \{1, 2, \ldots, L\}$. `index(`*varname*`)` is required. `group(`*grpvar*`)` is required if there are no random effects in the model. `resvariance(distinct)` in combination with `rescorrelation(identity)` is equivalent to `rescovariance(independent)`.

resvaropts are `strata(`*stratavar*`)`, `noconstant`, `index()`, and `group(`*grpvar*`)`.

`strata(`*stratavar*`)` is used within the `resvariance()` option with *resvarfunc* `power` and `exponential`. `strata()` specifies that the parameters of the variance function $g(\cdot)$ be distinctly estimated for each stratum. The scale parameter σ remains constant across strata. In contrast, `rescovariance()`'s `by(`*byvar*`)` suboption specifies that all covariance parameters, including σ (whenever applicable), be estimated distinctly for each category of *byvar*. *stratavar* must be nonnegative-integer valued and constant within the lowest-level groups.

noconstant is used within the resvariance() option with *resvarfunc* power. noconstant specifies that the constant parameter be suppressed in the expression of the variance function $g(\cdot)$.

index(*varname*) is used within the resvariance() option with *resvarfunc* distinct. *varname* is a nonnegative-integer–valued variable that identifies the observations within the lowest-level groups (for example, obsid). The groups may be unbalanced in that different groups may have different index() values, but you may not have repeated index() values within any particular group.

group(*grpvar*) is used within the resvariance() option with *resvarfunc* distinct. It identifies the lowest-level groups (panels) when no random effects are included in the model specification such as with nonlinear marginal models. *grpvar* is a nonnegative-integer–valued group membership variable.

rescorrelation(*rescorr* [, *rescorropts*]) specifies a correlation structure of the within-group errors. It can be used with the resvariance() option to specify flexible within-group error covariance structures.

rescorr is one of the following: identity, exchangeable, ar [*#*], ma [*#*], ctar1, toeplitz [*#*], banded [*#*], or unstructured.

identity, the default, specifies that all within-group error correlations be zeros.

exchangeable [, by(*byvar*) group(*grpvar*)] assumes that within-group errors have a common correlation.

ar [*#*], t(*timevar*) [by(*byvar*) group(*grpvar*)] assumes that within-group errors have an AR(*#*) correlation structure. If *#* is omitted, ar 1 is assumed. The t(*timevar*) option is required. For this structure, *#* AR coefficients are estimated.

ma [*#*], t(*timevar*) [by(*byvar*) group(*grpvar*)] assumes that within-group errors have an MA(*#*) correlation structure. If *#* is omitted, ma 1 is assumed. The t(*timevar*) option is required. For this structure, *#* MA coefficients are estimated.

ctar1, t(*timevar*) [by(*byvar*) group(*grpvar*)] assumes that within-group errors have a continuous-time AR(1) correlation structure. The t(*timevar*) option is required. The correlation between two errors is the parameter ρ raised to a power equal to the absolute value of the difference between the t() values for those errors.

toeplitz [*#*], t(*timevar*) [by(*byvar*) group(*grpvar*)] assumes that within-group errors have a Toeplitz correlation structure of order *#*, for which correlations are constant with respect to time lags less than or equal to *#* and are 0 for lags greater than *#*. *#* is an integer between 1 and the maximum observed lag (the default). t(*timevar*) is required. For this structure, *#* correlation parameters are estimated.

banded [*#*], index(*varname*) [group(*grpvar*)] is a special case of unstructured that restricts estimation to the correlations within the first *#* off-diagonals and sets the correlations outside this band to 0. index(*varname*) is required. *#* is an integer between 0 and $L-1$, where L is the number of levels of index(). By default, *#* is $L-1$; that is, all elements of the correlation matrix are estimated. When *#* is 0, the correlation matrix is assumed to be identity. group(*grpvar*) is required if there are no random effects in the model.

unstructured, index(*varname*) [group(*grpvar*)] assumes that within-group errors have distinct correlations. This is the most general correlation structure in that no structure is imposed on the correlation parameters. index(*varname*) is required. group(*grpvar*) is required if there are no random effects in the model.

rescorropts are `index(`*varname*`)`, `t(`*timevar*`)`, `by(`*byvar*`)`, and `group(`*grpvar*`)`.

`index(`*varname*`)` is used within the `rescorrelation()` option with *rescorr* `banded` or `unstructured`. *varname* is a nonnegative-integer–valued variable that identifies the observations within the lowest-level groups (for example, `obsid`). The groups may be unbalanced in that different groups may have different `index()` values, but you may not have repeated `index()` values within any particular group.

`t(`*timevar*`)` is used within the `rescorrelation()` option to specify a time variable for the `ar`, `ma`, `ctar1`, and `toeplitz` structures.

With *rescorr* `ar`, `ma`, and `toeplitz`, *timevar* is an integer-valued time variable used to order the observations within the lowest-level groups and to determine the lags between successive observations. Any nonconsecutive time values will be treated as gaps.

With *rescorr* `ctar1`, *timevar* is a real-valued time variable.

`by(`*byvar*`)` is used within the `rescorrelation()` option and specifies that a set of distinct within-group error correlation parameters be estimated for each category of *byvar*. *byvar* must be nonnegative-integer valued and constant within the lowest-level groups.

`group(`*grpvar*`)` is used to identify the lowest-level groups (panels) when modeling within-group error correlation structures. *grpvar* is a nonnegative-integer–valued group membership variable. This option lets you model within-group error correlation structures at the lowest level of your model hierarchy without having to include random effects at that level in your model. This is useful, for instance, when fitting nonlinear marginal or population-averaged models that model the dependence between error terms directly, without introducing random effects; see example 19. In the presence of random effects at other levels of hierarchy in your model, *grpvar* is assumed to be nested within those levels.

Time series

`tsorder(`*varname*`)` specifies the time variable that determines the time order for time-series operators used in expressions; see *Time-series operators*. When you use time-series operators with `menl`, you must either `tsset` your data prior to executing `menl` or specify option `tsorder()`. When you specify `tsorder()`, `menl` uses the time variable *varname* to create a new temporary variable that contains consecutive integers, which determine the sort order of observations within the lowest-level group. `menl` also creates and uses the appropriate panel variable based on the hierarchy of your model specification and the estimation sample; see example 17 and example 18.

`tsinit({`*name*`:}=<`*resubexpr*`>)` specifies an initial condition for the named expression *name* used with the one-period lag operator, `L.{`*name*`:}` or `L1.{`*name*`:}`, in the model specification. *name* can be the *depvar* or the name of a function of model parameters previously defined in, for instance, option `define()`. If you include the lagged predicted mean function `L.{`*depvar*`:}` or, equivalently, `L._yhat` in your model, you must specify its initial condition in `tsinit({`*depvar*`:}=...)`. The initial condition can be expressed as a random-effects substitutable expression, *<resubexpr>*. Option `tsinit()` may be repeated. Also see *Time-series operators*, example 17, and example 18.

`tsmissing` specifies that observations containing system missing values (`.`) in *depvar* be retained in the computation when a lagged named expression is used in the model specification. Extended missing values in *depvar* are excluded. Both missing and nonmissing observations are used to evaluate the predicted nonlinear mean function but only nonmissing observations are used to evaluate the likelihood. Observations containing missing values in variables used in the model other than the dependent variable are excluded. This option is often used when subjects have intermittent *depvar* measurements and the lagged predicted mean function, `L.{`*depvar*`:}` or `L._yhat`, is used in the model specification. Such models are common in pharmacokinetics; see example 17 and example 18.

Reporting

`level(#)`; see [R] **Estimation options**.

`variance`, the default, displays the random-effects and within-group error parameter estimates as variances and covariances.

`stddeviations` displays the random-effects and within-group error parameter estimates as standard deviations and correlations.

`noretable` suppresses the random-effects table from the output.

`nofetable` suppresses the fixed-effects table from the output.

`estmetric` displays all parameter estimates in one table using the metric in which they are stored in `e(b)`. Random-effects parameter estimates are stored as log standard-deviations and hyperbolic arctangents of correlations. Within-group error parameter estimates are stored as log standard-deviations and, when applicable, as hyperbolic arctangents of correlations. Note that fixed-effects estimates are always stored and displayed in the same metric.

`nolegend` suppresses the expression legend that appears before the fixed-effects estimation table when functions of parameters or named substitutable expressions are specified in the main equation or in the `define()` options.

`noheader` suppresses the output header, either at estimation or upon replay.

`nogroup` suppresses the display of group summary information (number of groups, average group size, minimum, and maximum) from the output header.

`nostderr` prevents `menl` from calculating standard errors for the estimated random-effects parameters, although standard errors are still provided for the fixed-effects parameters. Specifying this option will speed up computation times.

`lrtest` specifies to fit a reference nonlinear regression model and to use this model in calculating a likelihood-ratio test, comparing the nonlinear mixed-effects model with ordinary nonlinear regression.

`notsshow` prevents `menl` from showing the key `ts` variables; see [TS] **tsset**.

display_options: `noci`, `nopvalues`, `noomitted`, `vsquish`, `noemptycells`, `baselevels`, `allbaselevels`, `nofvlabel`, `fvwrap(#)`, `fvwrapon(`*style*`)`, `cformat(%`*fmt*`)`, `pformat(%`*fmt*`)`, `sformat(%`*fmt*`)`, and `nolstretch`; see [R] **Estimation options**.

EM options

These options control the EM iterations that occur before estimation switches to the Lindstrom–Bates method. EM is used to obtain starting values.

`emiterate(#)` specifies the number of EM iterations to perform. The default is `emiterate(25)`.

`emtolerance(#)` specifies the convergence tolerance for the EM algorithm. The default is `emtolerance(1e-10)`. EM iterations will be halted once the log (restricted) likelihood changes by a relative amount less than #. At that point, optimization switches to the Lindstrom–Bates method.

`emlog` specifies that the EM iteration log be shown. The EM iteration log is not displayed by default.

Maximization

menlmaxopts: iterate(#), tolerance(#), ltolerance(#), nrtolerance(#), nonrtolerance, pnlsopts(), lmeopts(), [no]log. The convergence is declared when either tolerance() or ltolerance() is satisfied; see *Stopping rules* for details.

menlmaxopts control the maximization process of the Lindstrom–Bates, the generalized nonlinear least-squares (GNLS), and the nonlinear least-squares (NLS) algorithms. The Lindstrom–Bates algorithm is the main optimization algorithm used for nonlinear models containing random effects. The GNLS algorithm is used for the models without random effects but with non-i.i.d. errors. The NLS algorithm is used for the models without random effects and with i.i.d. errors. The Lindstrom–Bates and GNLS algorithms are alternating algorithms—they alternate between two optimization steps and thus support options to control the overall optimization as well as the optimization of each step. The Lindstrom–Bates algorithm alternates between the penalized least-squares (PNLS) and the linear mixed-effects (LME) optimization steps. The GNLS algorithm alternates between the GNLS and ML or, if option reml is used, REML steps. Option pnlsopts() controls the PNLS and GNLS steps, and option lmeopts() controls the LME and ML/REML steps. The other *menlmaxopts* control the overall optimization of the alternating algorithms as well as the NLS optimization.

iterate(#) specifies the maximum number of iterations for the alternating algorithms and the NLS algorithm. One alternating iteration of the Lindstrom–Bates algorithm involves $\#_{\rm pnls}$ PNLS iterations as specified in pnlsopts()'s iterate() suboption and $\#_{\rm lme}$ LME iterations as specified in lmeopts()'s iterate() suboption. Similarly, one alternating iteration of the GNLS algorithm involves $\#_{\rm gnls}$ GNLS iterations and $\#_{\rm ml}$ ML/REML iterations. The default is the number set using set maxiter, which is 300 by default.

tolerance(#) specifies the tolerance for the parameter vector in the alternating algorithms and the NLS algorithm. When the relative change in the parameter vector from one (alternating) iteration to the next is less than or equal to tolerance(), the parameter convergence is satisfied. The default is tolerance(1e-6).

ltolerance(#) specifies the tolerance for the linearization log likelihood of the Lindstrom–Bates algorithm and for the log likelihood of the GNLS and NLS algorithms. The linearization log likelihood is the log likelihood from the LME optimization step in the last iteration. When the relative change in the log likelihood from one (alternating) iteration to the next is less than or equal to ltolerance(), the log-likelihood convergence is satisfied. The default is ltolerance(1e-7).

nrtolerance(#) and nonrtolerance control the tolerance for the scaled gradient.

nrtolerance(#) specifies the tolerance for the scaled gradient. Convergence is declared when $g(-H^{-1})g'$ is less than nrtolerance(#), where g is the gradient row vector and H is the approximated Hessian matrix from the current iteration. The default is nrtolerance(1e-5).

nonrtolerance specifies that the default nrtolerance() criterion be turned off.

nrtolerance(#) and nonrtolerance are allowed only with the NLS algorithm.

pnlsopts(*pnlsopts*) controls the PNLS optimization step of the Lindstrom–Bates alternating algorithm and the GNLS optimization step of the GNLS alternating algorithm. *pnlsopts* include any of the following: iterate(#), ltolerance(#), tolerance(#), nrtolerance(#), and *maximize_options*. The convergence of this step within each alternating iteration is declared when nrtolerance() and one of tolerance() or ltolerance() are satisfied. This option is not allowed with the NLS algorithm.

iterate(#) specifies the maximum number of iterations for the PNLS and GNLS optimization steps of the alternating algorithms. The default is iterate(5).

`ltolerance(#)` specifies the tolerance for the objective function in the PNLS and GNLS optimization steps. When the relative change in the objective function from one PNLS or GNLS iteration to the next is less than or equal to `ltolerance()`, the objective-function convergence is satisfied. The default is `ltolerance(1e-7)`.

`tolerance(#)` specifies the tolerance for the vector of fixed-effects parameters. When the relative change in the coefficient vector from one PNLS or GNLS iteration to the next is less than or equal to `tolerance()`, the parameter convergence criterion is satisfied. The default is `tolerance(1e-6)`.

`nrtolerance(#)` specifies the tolerance for the scaled gradient in the PNLS and GNLS optimization steps. Convergence is declared when $g(-H^{-1})g'$ is less than `nrtolerance(#)`, where g is the gradient row vector and H is the approximated Hessian matrix from the current iteration. The default is `nrtolerance(1e-5)`.

maximize_options are [`no`]`log`, `trace`, `showtolerance`, `nonrtolerance`; see [R] **Maximize**.

`lmeopts(`*lmeopts*`)` controls the LME optimization step of the Lindstrom–Bates alternating algorithm and the ML/REML optimization step of the GNLS alternating algorithm. *lmeopts* include any of the following: `iterate(#)`, `ltolerance(#)`, `tolerance(#)`, `nrtolerance(#)`, and *maximize_options*. The convergence of this step within each alternating iteration is declared when `nrtolerance()` and one of `tolerance()` or `ltolerance()` are satisfied. This option is not allowed with the NLS algorithm.

`iterate(#)` specifies the maximum number of iterations for the LME and ML/REML optimization steps of the alternating algorithms. The default is `iterate(5)`.

`ltolerance(#)` specifies the tolerance for the log likelihood in the LME and ML/REML optimization steps. When the relative change in the log likelihood from one LME or ML/REML iteration to the next is less than or equal to `ltolerance()`, the log-likelihood convergence is satisfied. The default is `ltolerance(1e-7)`.

`tolerance(#)` specifies the tolerance for the random-effects and within-group error covariance parameters. When the relative change in the vector of parameters from one LME or ML/REML iteration to the next is less than or equal to `tolerance()`, the convergence criterion for covariance parameters is satisfied. The default is `tolerance(1e-6)`.

`nrtolerance(#)` specifies the tolerance for the scaled gradient in the LME and ML/REML optimization steps. Convergence is declared when $g(-H^{-1})g'$ is less than `nrtolerance(#)`, where g is the gradient row vector and H is the approximated Hessian matrix from the current iteration. The default is `nrtolerance(1e-5)`.

maximize_options are [`no`]`log`, `trace`, `gradient`, `showstep`, `hessian`, `showtolerance`, `nonrtolerance`; see [R] **Maximize**.

[`no`]`log`; see [R] **Maximize**.

The following option is available with `menl` but is not shown in the dialog box:

`coeflegend`; see [R] **Estimation options**.

Remarks and examples

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Remarks are presented under the following headings:

Introduction

Nonlinear mixed-effects (NLME) models are models containing both fixed effects and random effects where some of, or all, the fixed and random effects enter the model nonlinearly. They can be viewed as a generalization of linear mixed-effects (LME) models (see [ME] **mixed**), in which the conditional mean of the outcome given the random effects is a nonlinear function of the coefficients and random effects. Alternatively, they can be considered as an extension of nonlinear regression models for independent data (see [R] **nl**), in which coefficients may incorporate random effects, allowing them to vary across different levels of hierarchy and thus inducing correlation within observations at the same level.

Why use NLME models? Can't we use higher-order polynomial LME models or generalized linear mixed-effects (GLME) models instead?

In principle, any smooth nonlinear function can be approximated by a higher-order polynomial. One may argue that we can use an LME (see [ME] **mixed**) polynomial model and increase the order of the polynomial until we get an accurate approximation of the desired nonlinear model. There are three problems with this approach. First, parameters in NLME models often have natural physical interpretations such as half-life and limiting growth. This is not the case in LME polynomial models. For example, what is the physical interpretation of the coefficient of `time`^{4}? Second, NLME models typically use fewer parameters than the corresponding LME polynomial model, which provides a more parsimonious summarization of the data. Third, NLME models usually provide better predictions outside the range of the observed data than predictions based on LME higher-order polynomial models.

GLME models (see [ME] **meglm**) are also nonlinear, but in the restricted sense that the conditional mean response given random effects is a nonlinear function of the linear predictor that contains both fixed and random effects, and only indirectly nonlinear in fixed and random effects themselves. That is, the nonlinear function must be an invertible function of the linear predictor. However, many estimation methods for GLME and NLME models are similar because random effects enter both models nonlinearly.

Population pharmacokinetics, bioassays, and studies of biological and agricultural growth processes are just a few areas that use NLME models to analyze multilevel data such as longitudinal or repeated-measures data. Comprehensive treatments of both methodology and history of NLME models may be found in Davidian and Giltinan (1995), Vonesh and Chinchilli (1997), Demidenko (2013), and Pinheiro and Bates (2000). Davidian and Giltinan (2003) provide an excellent summary.

Consider a sample of M subjects from a population of interest, where n_j measurements, $y_{1j}, \dots, y_{n_j j}$, are observed on subject j at times $t_{1j}, \dots, t_{n_j j}$. By "subject", we mean any distinct experimental unit, individual, panel, or cluster with two or more correlated observations. The basic nonlinear two-level model can be written as follows (in our terminology, a one-level NLME is just a nonlinear regression model for independent data),

$$y_{ij} = \mu\left(\mathbf{x}'_{ij},\, \boldsymbol{\beta},\, \mathbf{u}_j\right) + \epsilon_{ij} \qquad i = 1, \dots, n_j;\; j = 1, \dots, M \tag{1}$$

where $\mu(\cdot)$ is a real-valued function that depends on a $p \times 1$ vector of fixed effects $\boldsymbol{\beta}$, a $q \times 1$ vector of random effects $\mathbf{u}_j$, which are distributed as multivariate normal with mean $\mathbf{0}$ and variance–covariance matrix $\boldsymbol{\Sigma}$, and a covariate vector $\mathbf{x}_{ij}$ that contains both within-subject covariates $\mathbf{x}^w_{ij}$ and between-subject covariates $\mathbf{x}^b_j$. The $n_j \times 1$ vector of errors $\boldsymbol{\epsilon}_j = \left(\epsilon_{1j}, \dots, \epsilon_{n_j j}\right)'$ is assumed to be multivariate normal with mean $\mathbf{0}$ and variance–covariance matrix $\sigma^2 \boldsymbol{\Lambda}_j$, where depending on $\boldsymbol{\Lambda}_j$, σ^2 is either a within-group error variance σ^2_ϵ or a squared scale parameter σ^2.

Parameters of NLME models often have scientifically meaningful interpretations, and research questions are formed based on them. To allow parameters to reflect phenomena of interest, (1) can be equivalently formulated as a two-stage hierarchical model as follows:

$$\begin{aligned} \text{Stage 1: Individual-level model } y_{ij} &= m\left(\mathbf{x}^w_{ij},\, \boldsymbol{\phi}_j\right) + \epsilon_{ij} \qquad & i &= 1, \dots, n_j \\ \text{Stage 2: Group-level model } \boldsymbol{\phi}_j &= \boldsymbol{d}\left(\mathbf{x}^b_j,\, \boldsymbol{\beta},\, \mathbf{u}_j\right) \qquad & j &= 1, \dots, M \end{aligned} \tag{2}$$

In stage 1, we model the response by using a function $m(\cdot)$, which describes within-subject behavior. This function depends on subject-specific parameters $\boldsymbol{\phi}_j$'s, which have a natural physical interpretation, and a vector of within-subject covariates $\mathbf{x}^w_{ij}$. In stage 2, we use a known vector-valued function $\boldsymbol{d}(\cdot)$ to model between-subject behavior, that is, to model $\boldsymbol{\phi}_j$'s and to explain how they vary across subjects. The $\boldsymbol{d}(\cdot)$ function incorporates random effects and, optionally, a vector of between-subject covariates $\mathbf{x}^b_j$. The general idea is to specify a common functional form for each subject in stage 1 and then allow some parameters to vary randomly across subjects in stage 2.

To further illustrate (1) and (2), we consider the soybean plants data (Davidian and Giltinan 1995), in which we model the average leaf weight per soybean plant, y_{ij}, in plot j at t_{ij} days after planting. Let's first use (1):

$$\begin{aligned} y_{ij} &= \mu\left(\mathbf{x}'_{ij},\, \boldsymbol{\beta},\, \mathbf{u}_j\right) + \epsilon_{ij} \\ &= \frac{\beta_1 + u_{1j}}{1 + \exp\left[-\left\{t_{ij} - (\beta_2 + u_{2j})\right\} / (\beta_3 + u_{3j})\right]} + \epsilon_{ij} \end{aligned}$$

Here $\boldsymbol{\beta} = (\beta_1, \beta_2, \beta_3)'$, $\mathbf{u}_j = (u_{1j}, u_{2j}, u_{3j})'$, and $\mathbf{x}_{ij}$ is simply t_{ij}.

Equivalently, we can use (2) to define our model,

$$\begin{aligned}
\text{Stage 1: } y_{ij} &= m\left(\mathbf{x}_{ij}^{w},\, \boldsymbol{\phi}_j\right) + \epsilon_{ij} \\
&= \frac{\phi_{1j}}{1+\exp\left\{-\left(t_{ij}-\phi_{2j}\right)/\phi_{3j}\right\}} + \epsilon_{ij} \\
\text{Stage 2: } \phi_{1j} &= \beta_1 + u_{1j} \\
\phi_{2j} &= \beta_2 + u_{2j} \\
\phi_{3j} &= \beta_3 + u_{3j}
\end{aligned}$$

where $\mathbf{x}_{ij}^{w} = t_{ij}$, $\boldsymbol{\phi}_j = (\phi_{1j}, \phi_{2j}, \phi_{3j})' = \boldsymbol{d}\left(\mathbf{x}_j^{b},\, \boldsymbol{\beta},\, \mathbf{u}_j\right) = \boldsymbol{\beta} + \mathbf{u}_j$. A key advantage of (2) is the interpretability. $\boldsymbol{\phi}_j$'s are parameters that characterize features of the trajectory. For example, ϕ_{1j} can be interpreted as the asymptotic average leaf weight per soybean plant in plot j when $t_{ij} \to \infty$ and ϕ_{2j} as the time at which half of ϕ_{1j} is reached; that is, if we set $t_{ij} = \phi_{2j}$, then $E(y_{ij}) = \phi_{1j}/2$. `menl` provides both representations.

The random effects $\mathbf{u}_j$ are not directly estimated (although they may be predicted) but instead are characterized by the elements of $\boldsymbol{\Sigma}$, known as variance components, which are estimated together with the parameters of the within-group error variance–covariance matrix $\sigma^2\boldsymbol{\Lambda}_j$. Correlation among repeated measures is induced either indirectly through the subject-specific random effects $\mathbf{u}_j$ or directly through specification of the within-subject covariance matrix $\sigma^2\boldsymbol{\Lambda}_j$. Several covariance structures are available for $\boldsymbol{\Sigma}$, similar to those allowed in `mixed`. In contrast to `mixed`, `menl` provides more flexible modeling of the within-subject variance and correlation structures.

`menl` uses the following decomposition of the $\boldsymbol{\Lambda}_j$ matrix,

$$\boldsymbol{\Lambda}_j = \mathbf{S}_j\mathbf{C}_j\mathbf{S}_j \tag{3}$$

where $\mathbf{S}_j$ is diagonal with positive elements such that $\text{Var}\left(\epsilon_{ij}\right) = \sigma^2[\mathbf{S}_j]_{ii}^2$ and $\mathbf{C}_j$ is a correlation matrix such that $\text{corr}\left(\epsilon_{ij},\, \epsilon_{kj}\right) = [\mathbf{C}_j]_{ik}$; $[A]_{ij}$ denotes the ijth element of matrix A. Decomposition (3) of $\boldsymbol{\Lambda}_j$ allows us to separately model the variance structure (heteroskedasticity) and the correlation structure by using disjoint sets of parameters for $\mathbf{C}_j$ and $\mathbf{S}_j$. This is different from how `mixed` handles within-subject correlation, where heteroskedasticity and correlation are determined by the type of the chosen residual covariance structure. For convenience, `menl` accommodates the behavior of the `mixed` command for specifying residual covariance structures via the `rescovariance()` option. The more flexible modeling of the residual structures according to (3) is available via the `resvariance()` and `rescorrelation()` options.

For LME models, because the random effects $\mathbf{u}_j$'s are unobserved, inference about $\boldsymbol{\beta}$ and the covariance parameters are based on the marginal likelihood obtained after integrating out the random effects. Unlike LME models, no closed-form solution is available because the random effects enter the model nonlinearly, making the integration analytically intractable in all but the simplest situations. There are two principal methods proposed in the literature for fitting NLME models. One is to use an adaptive Gauss–Hermite (AGH) quadrature to approximate the integral that appears in the expression of the marginal likelihood. The other one is to use the linearization method of Lindstrom and Bates (1990), also known as a conditional first-order linearization method, which is based on a first-order Taylor-series approximation of the mean function and essentially linearizes the mean function with respect to fixed and random effects. With the AGH method, the level of accuracy increases as the number of quadrature points increases but at the expense of increasing computational burden. The linearization method is computationally efficient because it avoids the intractable integration, but the approximation cannot be made arbitrarily accurate. Despite its potential limiting accuracy, the linearization method has proven the most popular in practice (Fitzmaurice et al. 2009, sec. 5.4.8). The linearization method of Lindstrom and Bates (1990), with extensions from Pinheiro and Bates (1995), is the method of estimation in menl.

The linearization method uses a first-order Taylor-series expansion of the specified nonlinear mean function to approximate it with a linear function of fixed and random effects. Thus an NLME model is approximated by an LME model, in which the fixed-effects and random-effects design matrices involve derivatives of the nonlinear mean function with respect to fixed effects (coefficients) and random effects, respectively. As such, inference after the linearization method uses the computational machinery of the LME models. For example, estimates of random effects are computed as best linear unbiased predictors (BLUPs) of random effects from the approximating LME model. The accuracy of the inferential results will depend on the accuracy of the linearization method in approximating the original NLME model. In general, asymptotic inference for the NLME models based on the linearization method is only "approximately asymptotic", making it less accurate than the corresponding asymptotic inference for true LME models. In practice, however, the linearization method was found to perform well in many situations (for example, Pinheiro and Bates [1995]; Wolfinger and Lin [1997]; Plan et al. [2012]; and Harring and Liu [2016]).

Both ML and REML estimation are supported by menl. The ML estimates are based on the usual application of likelihood theory, given the distributional assumptions of the model. In small samples, ML estimation generally leads to small-sample bias in the estimated variance components. The REML method (Thompson 1962) reduces this bias by forming a set of linear contrasts of the response that do not depend on the fixed effects $\boldsymbol{\beta}$ but instead depend only on the variance components to be estimated. The likelihood is then formed based on the distribution of the linear contrasts, and standard ML methods are applied.

The next section describes how to specify nonlinear expressions containing random effects in menl.

Random-effects substitutable expressions

You define the nonlinear model to be fit by menl by using a random-effects substitutable expression, a substitutable expression that contains random effects. For example, exp({b}+{U[id]}), {b1}/({b2}+{b3}*x+{U[id]}), and ({b1}+{U1[id]})/(1+{b2}*x+{c.x#U2[id]}) are a few examples of such expressions. We describe them in more detail below.

Substitutable expressions

Let's first consider substitutable expressions without random effects. Substitutable expressions are just like any other mathematical expressions involving scalars and variables, such as those you would use with Stata's generate command, except that the parameters to be estimated are bound in braces. See **[U] 13.2 Operators** and **[U] 13.3 Functions** for more information on expressions.

For teaching purposes, we will start with simpler substitutable expressions that do not contain random effects. Suppose that we wish to fit the model

$$y_{ij} = \alpha\left(1 - e^{-(\beta_0+\beta_1 x_{1ij}+\beta_2 x_{2ij})}\right) + \epsilon_{ij}$$

where α, β_0, β_1, and β_2 are the parameters to be estimated and ϵ_{ij} is an error term. We could simply type

```
        . menl y = {a}*(1 - exp(-({b0}+{b1}*x1+{b2}*x2)))
```

Because a, b0, b1, and b2 are enclosed in braces, menl knows that they are parameters in the model.

You can group several parameters together by assigning a group name (or equation name) to them. Parameters with the same group name, `lc` in the example below, will be grouped together in the output table:

```
. menl y = {a}*(1 - exp(-({lc:b0}+{lc:b1}*x1+{lc:b2}*x2)))
```

That is, parameters `b0`, `b1`, and `b2` will appear together in the output table in the equation labeled `lc`. Parameters without equation names will appear at the bottom of the output table.

Sometimes, it may be convenient to define subexpressions within the main expression. This can be done inside the expression itself or by using the `define()` option. For example,

```
. menl y = {a}*(1 - exp(-{xb:})), define(xb: {lc:b0}+{lc:b1}*x1+{lc:b2}*x2)
```

defines the linear predictor of the exponent in the `define()` option with label `xb` and then refers to it inside the exponent as `{xb:}`. You can define as many subexpressions as you like by using the `define()` option repeatedly. Defining subexpressions is also useful for later predictions; see, for instance, example 13.

The above is equivalent to

```
. menl y = {a}*(1 - exp(-{xb: {lc:b0}+{lc:b1}*x1+{lc:b2}*x2}))
```

Parameters `{a}`, `{lc:b0}`, `{lc:b1}`, and `{lc:b2}` are what we call "free parameters", meaning that they are not defined by a linear form, which we describe in the next section. Free parameters are displayed with a forward slash in front of their names or their group names.

The general syntax for a free parameter is

{[*eqname*:] *name*}

Linear combinations

Nonlinear functions will often contain linear combinations of variables. Recall our nonlinear function from *Substitutable expressions*:

$$y_{ij} = \alpha\left(1 - e^{-(\beta_0+\beta_1 x_{1ij}+\beta_2 x_{2ij})}\right) + \epsilon_{ij}$$

Instead of explicitly specifying the linear combination that appears in the exponent, as we did in the previous section, we can use `menl`'s shorthand notation

```
. menl y = {a}*(1 - exp(-({lc: x1 x2})))
```

By specifying `{lc:x1 x2}`, you are telling `menl` that you are declaring a linear combination named `lc` that is a function of two variables, `x1` and `x2`. `menl` will create three parameters, named `{lc:_cons}`, `{lc:x1}`, and `{lc:x2}`.

Although both specifications produce the same results, the shorthand specification is more convenient.

The general syntax for defining a linear combination is

{ *eqname*: *varspec* [, xb noconstant] }

where *varspec* includes a list of variables (*varlist*), a list of random-effects terms, or both.

The xb option is used to distinguish between the linear combination that contains one variable and a free parameter that has the same name as the variable and the same group name as the linear combination. For example, {lc: x1, xb} is equivalent to {lc:_cons} + {lc:x1}*x1, whereas {lc:x1} refers to either a free parameter x1 with a group name lc or the coefficient of the x1 variable, if {lc:} has been previously defined in the expression as a linear combination that involves variable x1; see examples below. Thus the xb option indicates that the specification is a linear combination rather than a single parameter to be estimated.

When you define a linear combination, a constant term is included by default (a mathematician would argue that "affine combination" is the correct terminology!). The noconstant option suppresses the constant.

Having defined a linear combination such as {lc:x1 x2}, you can refer to its individual coefficients by using {lc:x1} and {lc:x2} or, more generally, {*eqname*:*varname*}. For example, suppose that we want to fit the following model, where the coefficient of x1, β_1, appears in two places in the expression:

$$y_{ij} = \frac{1}{(1+\beta_1 x_{1ij} + \beta_2 x_{2ij} + \beta_3 x_{3ij})} \exp\left\{-\left(\alpha_0 + \alpha_1 z_{ij}\right) / \left(1 + \beta_1 x_{4ij}\right)\right\} + \epsilon_{ij}$$

We use {lc1: x1 x2 x3, noconstant} to specify the first linear combination, which appears in the denominator outside the exponentiated expression, and then use {lc1:x1} to refer to β_1 in the denominator inside the exponentiated expression. We also use the xb option, when we specify the second linear combination that contains only one covariate z. Below is the full specification:

```
. menl y = 1/(1+{lc1: x1 x2 x3, noconstant})*exp(-{lc2: z, xb}/(1+{lc1:x1}*x4))
```

You may also refer to a "subset" of a previously defined linear combination. For example, let's modify our previous expression by substituting $\beta_1 x_{4ij}$ in the denominator in the exponent with the subset $\beta_1 x_{1ij} + \beta_3 x_{3ij}$ of the first linear combination:

$$y_{ij} = \frac{1}{(1+\beta_1 x_{1ij} + \beta_2 x_{2ij} + \beta_3 x_{3ij})} \exp\left\{-\left(\alpha_0 + \alpha_1 z_{ij}\right) / \left(1 + \beta_1 x_{1ij} + \beta_3 x_{3ij}\right)\right\} + \epsilon_{ij}$$

The coefficients for variables x1 and x3 are the same in the denominators inside and outside the exponent. We fit this model by typing

```
. menl y = 1/(1+{lc1: x1 x2 x3, nocons})*     ///
        exp(-{lc2: z, xb}/(1+{lc1: x1 x3, nocons}))
```

We used the same equation name, lc1, to constrain the coefficients to be the same between the two linear-combination specifications. If we used a different equation name, say, lc3, in the last linear combination, we would have specified $\beta_4 x_{1ij} + \beta_5 x_{3ij}$ instead of $\beta_1 x_{1ij} + \beta_3 x_{3ij}$ and estimated two extra parameters, β_4 named {lc3:x1} and β_5 named {lc3:x3}.

To refer to the entire linear combination that was already defined, you can simply refer to its name. For example, if both denominators included the same linear combination, $\beta_1 x_{1ij} + \beta_2 x_{2ij} + \beta_3 x_{3ij}$, the corresponding menl specification would be

```
. menl y = 1/(1+{lc1: x1 x2 x3, nocons})*exp(-{lc2: z, xb}/(1+{lc1:}))
```

Just like subexpressions, linear combinations can be defined in the define() option. For example, the above is equivalent to

```
. menl y = 1/(1+{lc1:})*exp(-{lc2:}/(1+{lc1:})), define(lc1: x1 x2 x3, nocons) ///
                                                  define(lc2: z, xb)
```

Linear forms versus linear combinations

As we mentioned in *Linear combinations*, the linear-combination specification is syntactically convenient. It can also be more computationally efficient when a linear combination is a linear form.

A linear combination is what we call a linear form as long as you do not refer to its coefficients or any subset of the linear combination anywhere in the expression. Linear forms are beneficial for some nonlinear commands such as `nl` because they make derivative computation faster and more accurate. Although `menl` does not fully utilize the linear-form specification in its computations, it is still important to learn to distinguish between linear forms and linear combinations.

For example, in *Linear combinations*, the first linear combination `{lc:}`, the linear combination `{lc2:}`, and the linear combination `{lc1:}` in the last example are all linear forms. The linear combination `{lc1:}` in the examples where we referred to `{lc1:x1}` and `{lc1:x1 x3}` is not a linear form.

In contrast to free parameters, parameters of a linear form are displayed without forward slashes in the output. Rather, they are displayed as parameters within an equation whose name is the linear combination name. Parameters of linear combinations that are not linear forms are considered free parameters.

Random effects

So far, we have restricted our discussion to substitutable expressions that do not contain random effects. Examples of random effects specified within the `menl` syntax are `{U1[id]}`, `{U2[id1>id2]}`, `{c.x1#U3[id]}`, and `{2.f1#U4[id]}`. These represent a random intercept at the `id` level, a random intercept at the `id2`-within-`id1` level, a random slope for the continuous variable `x1`, and a random slope associated with the second level of the factor variable `f1`, respectively.

The general syntax for specifying random effects, *respec*, is provided below.

respec	Description
`{`*rename*`[`*levelspec*`]}`	Random intercepts *rename* at hierarchy *levelspec*
`{c.`*varname*`#`*rename*`[`*levelspec*`]}`	Random coefficients *rename* for continuous variable *varname*
`{#.`*fvvarname*`#`*rename*`[`*levelspec*`]}`	Random coefficients *rename* for the #th level of factor variable *fvvarname*

rename is a random-effects name. It is a Stata name that starts with a capital letter. *levelspec* defines the level of hierarchy and is described below.

levelspec	Description
levelvar	variable identifying the group structure for the random effect at that level
lv2 > *lv1*	two-level nesting: levels of variable *lv1* are nested within *lv2*
lv3 > *lv2* > *lv1*	three-level nesting: levels of variable *lv1* are nested within *lv2*, which is nested within *lv3*
. . . > *lv3* > *lv2* > *lv1*	higher-level nesting

You can equivalently specify levels in the opposite order, from the lowest level to the highest; for example, *lv1* < *lv2* < *lv3*, but they will be displayed in the canonical order, from the highest level to the lowest.

Random effects can be specified within a linear-combination specification such as `{lc_u: x1 x2 U1[id1] U2[id2>id1]}`. In this case, the curly braces around each random effect are not needed.

Let us illustrate several random-effects specifications with `menl`. In this section, we concentrate on two-level nonlinear models; see *Multilevel specifications* for higher-level models.

Suppose that we want to fit the following model:

$$y_{ij} = \frac{\alpha z_{ij} + u_{0j}}{1 + \exp\left\{-\left(\beta_0 + \beta_1 x_{1ij}\right)\right\}} + \epsilon_{ij}$$

Compared with models we considered in previous sections, this model includes random effects or, specifically, random intercepts u_{0j}. Suppose that these random intercepts correspond to the levels of the `id` variable. Then, we can include them in our model by using `{U0[id]}`, where `U0` will be their name.

```
. menl y = ({a}*z+{U0[id]})/(1+exp(-({b0}+{b1}*x1)))
```

A more efficient specification is to use the linear-combination notation:

```
. menl y = {lc1: z U0[id], nocons}/(1+exp(-{lc2: x1, xb}))
```

The curly braces around `U0[id]` are removed when it is specified within a linear-combination specification.

If you need to refer to the random-effects term again in the expression, you can simply use its name. For example, suppose that our model includes the same random intercepts in both the numerator and the denominator.

$$y_{ij} = \frac{\alpha z_{ij} + u_{0j}}{1 + \exp\left\{-\left(\beta_0 + \beta_1 x_{1ij} + u_{0j}\right)\right\}} + \epsilon_{ij}$$

We include random intercepts u_{0j}'s in the second linear combination by simply referring to their name, `U0`:

```
. menl y = {lc1: z U0[id], nocons}/(1+exp(-{lc2: x1 U0}))
```

If instead of u_{0j}'s, we had a different set of random intercepts, v_{0j}'s, in the denominator, we would need to specify a new set of random intercepts, say, `V0[id]`, with `menl`:

```
. menl y = {lc1: z U0[id], nocons}/(1+exp(-{lc2: x1 V0[id]}))
```

The shorthand notation for referring to random effects only by name, that is, without the brackets and the *levelspec*, is also useful when specifying the `covariance()` option, especially for multilevel random effects with long-level specifications; see *Multilevel specifications*.

Let's now see how to include random slopes. Consider the following extension of the *first*, simpler model in this subsection:

$$y_{ij} = \frac{\alpha z_{ij} + u_{0j} + u_{1j} z_{ij}}{1 + \exp\left\{-\left(\beta_0 + \beta_1 x_{1ij}\right)\right\}} + \epsilon_{ij}$$

Here u_{1j} is a random slope for a continuous variable `z` and is specified as `{c.z#U1[id]}` directly or without curly braces within a linear-combination specification.

```
. menl y = {lc1: z U0[id] c.z#U1[id], nocons}/(1+exp(-{lc2: x1, xb}))
```

We can also include random slopes for factor variables. To demonstrate this, let's consider a different nonlinear model for variety. Consider the model below, where binary variables x_{1ij} and x_{2ij} correspond to the factor levels 1 and 2 of a factor variable x that takes on values 0, 1, and 2, with 0 being the base level.

$$y_{ij} = \alpha_0 + \alpha_1 z_{1ij} - \sqrt{w_{ij}^2 + \exp\left(\beta_0 + \beta_1 x_{1ij} + \beta_2 x_{2ij} + u_{0j} + u_{1j} x_{1ij} + u_{2j} x_{2ij}\right)} + \epsilon_{ij}$$

There are three random-effects terms in this model: random intercepts u_{0j}, random slopes u_{1j} for x_{1ij} (level 1 of x), and random slopes u_{2j} for x_{2ij} (level 2 of x). In Stata, for a factor variable `x`, we can use the factor-variable notation (**[U] 11.4.3 Factor variables**) to refer to its levels, `1.x` for level 1 and `2.x` for level 2. So, to include the three random-effects terms in `menl`, we will use `U0[id]`, `1.x#U1[id]`, and `2.x#U2[id]`, respectively.

```
. menl y = {lc1: z1, xb} - sqrt(c.w#c.w +  ///
      exp({lc2: i.x U0[id] 1.x#U1[id] 2.x#U2[id]}))
```

In the above specification, we used the factor-variable notations `i.x` to include fixed effects for all levels of `x`, except the base level, and `c.w#c.w` to include a square of `w`; see **[U] 11.4.3 Factor variables** for details. The factor-variable specification `i.` or any other specification that refers to multiple levels of a factor variable is not allowed when specifying random coefficients, because each level will typically require a different set of random effects. For example, if we had specified `i.x#U[id]` in the above example, we would have received an error.

Multilevel specifications

In *Random effects*, we focused on specifying substitutable expressions containing random effects for two-level nonlinear mixed-effects models. Here we will consider higher-level models.

Suppose that we want to fit the following three-level nonlinear mixed-effects model,

$$y_{ijk} = \beta_0 + u_{0k}^{(3)} + u_{0jk}^{(2)} + \cos\left\{\left(\beta_1 + u_{1k}^{(3)}\right) x_{1ijk}\right\} + \epsilon_{ijk}$$

where first-level observations, indexed by i, are nested within second-level groups, indexed by j, which are nested within third-level groups, indexed by k.

There are three random-effects terms in this model: random intercepts, $u_{0k}^{(3)}$, and random slopes for x_1, $u_{1k}^{(3)}$, at the third level (`idk`) and random intercepts $u_{0jk}^{(2)}$ at the second level (`idj`-nested-within-`idk`). We specify random intercepts and random slopes for x_1 at the highest hierarchical level just like we did in *Random effects* for two-level models. Specifically, we can use `U0[idk]` and `c.x1#U1[idk]`, respectively. To specify random intercepts $u_{0jk}^{(2)}$ at the `idj`-nested-within-`idk` level, we need to use one of the *levelspec* specifications for two nested levels. For example, we can use `UU0[idk>idj]`. Below is the full specification:

```
. menl y = {lc1: U0[idk] UU0[idk>idj]} + cos({lc2: x1 c.x1#U1[idk], noconstant})
```

We can also include a random slope of the `x1` variable at the `idj`-within-`idk` level in the cosine function by specifying `c.x1#UU1[idk>idj]` inside the `cos()` function.

```
. menl y = {lc1: U0[idk] UU0[idk>idj]} +   ///
      cos({lc2: x1 c.x1#U1[idk] c.x1#UU1[idk>idj], noconstant})
```

We can shorten the above specification by writing `c.x1#U1[idk] c.x1#UU1[idk>idj]` more compactly as `c.x1#(U1[idk] UU1[idk>idj])`,

```
. menl y = {lc1: U0[idk] UU0[idk>idj]} +   ///
      cos({lc2: x1 c.x1#(U1[idk] UU1[idk>idj]), noconstant})
```

Similarly, if we had a four-level model with, say, a random intercept at the idj-within-idk-within-idl level, we could specify it as W[idl>idk>idj]; see *levelspec* for other specifications.

Time-series operators

You can use time-series operators in the specification of your nonlinear model (see **[U] 11.4.4 Time-series varlists**) but with some exceptions described next. You can use time-series operators in the main nonlinear specification <*menlexpr*> or any random-effects substitutable expression <*resubexpr*>. The supported time-series operators include L. and L#., F. and F#., and D. and D#.. You cannot combine time-series operators or use them with a list of variables. Also, you cannot combine time-series operators with factor variables.

You can also include the lagged predicted mean function and lagged functions of model parameters in your expressions. For brevity, we will refer to both types of lagged functions as lagged named expressions. Lagged named expressions are useful, for instance, for fitting certain pharmacokinetic models; see example 17 and example 18.

To include the lagged predicted mean function, you can use the specification L.{*depvar*:} or, equivalently, L._yhat. (Do not confuse this with the lagged dependent variable specification L.*depvar*.) You can specify the lagged predicted mean function only in the main nonlinear specification *menlexpr*. To include a lagged function of model parameters, you can use the specification L.{*name*:}, where *name* is the name of the previously defined function of model parameters. Such functions are typically defined in the define() options. Only the one-period lag operator, L. or L1., is supported with named expressions.

To use time-series operators, you must either tsset your data prior to executing menl or specify the tsorder() option with menl. You must specify time and panel variables with tsset. When you use the tsorder(*varname*) option, menl uses the time variable *varname* to determine the ordering for time-series operators. menl creates a new temporary time variable that takes on values 1, 2, ... in each panel for the estimation sample. menl also creates the appropriate panel variable and uses the newly generated variables with tsset. For two-level models, menl uses the specified level variable as the panel variable. With more than two levels, menl creates the panel variable as a variable that takes on values 1, 2, ... for the groups formed by all level variables in the estimation sample. The generated panel and time variables are labeled as <panel> and <time> in the output of tsset as displayed by menl.

When you use time-series operators with variables in the dataset, some of the observations are used to initialize the series for those variables. For example, if you include a lagged variable $varname_{t-1}$ (L.*varname*) in your model, the value of *varname* in the first observation in each panel is used to initialize the series; see **[TS] tsset**. But what happens when you include a lagged named expression for which there is no existing variable in the dataset? If your named expression is a function of existing variables, the values of those variables in the first observation (in each panel) will be used to compute an initial value for the lagged named expression. For some models, a named expression can depend on its own lag; see example 17 and example 18. In this case, you must specify the initial condition for it in the tsinit() option. Note that you will always need to specify the tsinit() option for the lagged predicted mean function. The tsinit() option may be repeated and may contain functions of variables and model parameters. When you specify the tsinit() option, menl uses its value (or values in the first observation of each panel) to initialize the corresponding lagged named expression. Just like with regular time-series variables, the first observation in each panel will be excluded from the estimation sample whenever you use lagged named expressions in the model.

Summary

To summarize, here are a few rules to keep in mind when defining substitutable expressions.

1. Model parameters and random effects are bound in braces if specified directly in the expression: `{b0}`, `{U0[id]}`, etc.
2. Model parameters can be assigned group names: `{slopes:x1}`, `{slopes:x2}`, etc.
3. Random-effects names must start with a capital letter as in `{U0[id]}`, `{c.x#U1[id]}`, `{V0[id2>id1]}`, `{1.z#V1[id2>id1]}`, etc.
4. The factor-variable specification `i.`, as in `{i.z#V1[id2>id1]}`, or any other specification that refers to multiple levels of a factor variable, as in `{i(1/4).z#V1[id2>id1]}`, is not allowed when specifying random coefficients.
5. Linear combinations of variables can be included using the specification

   `{`*eqname*`:`*varlist* [`, xb` `noconstant`] `}`

   For example, `{price: mpg weight i.rep78}` and `{lc: x1 x2, noconstant}`.
6. Random effects can be specified within a linear combination, in which case they should be included without curly braces, for example, `{lc_u: x1 x2 U[id]}`.
7. To specify a linear combination that contains only one variable, use the `xb` option, for example, `{lc: x1, xb}`.
8. To refer to the previously defined linear combination again in the expression, simply use its name `{`*eqname*`:}`, for example, `{lc:}` and `{lc_u:}`.
9. You can refer to individual parameters of the linear combination by using `{`*eqname*`:_cons}` and `{`*eqname*`:`*varname*`}`, for example, `{price:_cons}` and `{price:weight}`.
10. You can refer to a "subset" of the previously defined linear combination by using `{`*eqname*`:`*subset*`}`, where *subset* is a subset of the variables from *varlist* used to define *eqname*, as in `{price: mpg weight}`. To refer to the subset containing only one variable, use the `xb` option, as in `{price: weight, xb}`. If a linear combination contains only one random-effects term, the `xb` option is implied.
11. To refer to the previously defined random effects again in the expression or in the `covariance()` option, simply use their names, such as `{U0}` and `{U1}`.
12. You can define subexpressions, including linear combinations, inside the main expression or in the `define()` option, which can be repeated. For example,

```
. menl y = {numer:}/{denom:}, define(numer: z U0[id]) ///
      define(denom:1+exp(-{lc: x1, xb}))
```

13. Specify linear forms whenever possible for faster and more accurate computation of derivatives; see *Linear forms versus linear combinations*.
14. Model parameters that are not defined by linear forms are considered free parameters. They are included in the output with a forward slash in front of their names or group names and displayed after linear forms in the estimation table.

Specifying initial values

By default, `menl` uses the EM algorithm to obtain initial values, but you may often need to specify your own. You specify your own initial values in the `initial()` option. For example, specifying the `initial(a 1.1 b -2)` option with `menl` initializes parameter `{a}` to 1.1 and parameter `{b}` to −2.

When you specify your own initial values, they are used for initialization, and the EM algorithm is not performed. When you specify initial values for only a subset of model parameters, the remaining parameters are initialized with some predetermined values such as zeros for fixed-effects parameters and correlations and ones for variances. You can specify the `iterate(0)` option to see the initial values that will be used by `menl` in the optimization.

Often, you may have good initial values for fixed-effects parameters but not for random-effects parameters. In this case, you can specify `initial()`'s `fixed` suboption to supply your own fixed-effects parameters, but use the EM algorithm to obtain initial values for the random-effects parameters.

There are three ways in which you can use the `initial(`*initial_values*`)` option: you can specify a vector of values, a list of values, or values for individual parameters and groups of parameters.

Specifically, *initial_values* is one of the following:

vectorname [`, skip copy fixed`]

# [\#] [...] `, copy`

paramlist[`=`]\# [*paramlist*[`=`]\# [...]] [`, fixed`]

`skip` specifies that any parameters found in the specified initialization vector, *vectorname*, that are not also found in the model be ignored. The default action is to issue an error message.

`copy` specifies that the initial values be copied into the initialization vector without checking for valid column names. `copy` must be specified when initial values are supplied as a list of numbers.

`fixed` specifies that initial estimates are being supplied for the fixed effects only and that `menl` should still perform the EM algorithm to refine initial values for variance components. The specified initial values are used for fixed-effects parameters during the EM algorithm. If you omit `fixed`, `menl` presumes that you are specifying starting values for all parameters in `e(b)`, and the EM algorithm will not be performed.

Examples of *paramlist* are `param`, `{param}`, `{param1} {param2}`, `{param1 param2}`, `{grp:param1} {grp:param2} {grp:param3}`, `{grp:param1 param2}`, and `{grp:}`.

Let's describe each specification in more detail. You can specify the name of a vector containing the initial values, say, `initial(b0)`. Vector `b0` should be properly labeled with labels found in column names of `e(b)`, unless you specify the `copy` option. A properly labeled vector can have fewer elements than `e(b)` or, if `skip` is specified, even more elements. A vector without labels must be of the same dimension as `e(b)`.

Alternatively, you can supply a list of numbers to `initial()`, in which case `copy` must be specified. The list of numbers should be of length equal to the dimension of `e(b)`. For example, if `e(b)` has four parameters and you type `initial(1.1 0 3 -2, copy)`, then the four coefficients in `e(b)` will be initialized to 1.1, 0, 3, and −2, respectively. If instead you specify, for example, only three initial values in your list, an error will be issued.

Finally, you can initialize parameters by referring to their names. You can specify a parameter name, its initial value, another parameter name, its initial value, and so on, for example, `initial(a 1.1 b -2)`. You can also assign the same initial value to a group of parameters. For example, `initial({a b c} 1)` will initialize parameters `{a}`, `{b}`, and `{c}` to 1 and `initial({lc:x1 x2 _cons} 0)` will initialize `{lc:x1}`, `{lc:x2}`, and `{lc:_cons}` to 0. You can assign the same initial value to all parameters with the same group name. For example, we can shorten the previous specification to `initial({lc:} 0)`.

Depending on the situation, it may also be beneficial to specify initial values for the NLS algorithm used by `menl` to obtain starting values for the EM algorithm. These initial values can be specified in the parameter definition such as `{a=0.5}`, in which case the NLS algorithm used during the initialization will use 0.5 as the starting value for parameter `a` instead of the default 0. Such initialization is particularly useful for parameters used in the denominators for which zero values may lead to an undefined value of the mean function.

See *Examples of specifying initial values* and *Obtaining initial values* for examples.

Two-level models

The sole purpose of this section and its examples is to highlight the syntax of `menl` and make you familiar with how to specify substitutable expressions in `menl` and with its output. Also see an introductory example in *Nonlinear models* in [ME] **me**.

We will use the data from the Longitudinal Study of Unicorn Health in Zootopia, which contain the brain weight (`weight`) of 30 newborn male unicorns and 30 newborn female unicorns. Measurements were collected at 13 occasions every 2 months over the first 2 years after birth (`time`). Based on previous studies, a model for unicorn brain shrinkage is believed to be

$$\texttt{weight}_{ij} = \beta_1 + (\beta_2 - \beta_1)\,\exp\left(-\beta_3 \texttt{time}_{ij}\right) + \epsilon_{ij} \quad i = 1, 2, \ldots, 13;\;\; j = 1, 2, \ldots, 60$$

Parameter β_1 represents the average brain weight of unicorns as $\texttt{time}_{ij}$ increases to infinity. Parameter β_2 is the average brain weight at birth (at $\texttt{time}_{ij} = 0$), and β_3 is a scale parameter that determines the rate at which the average brain weight of unicorns approaches the asymptotic weight β_1 (decay rate). This model can be fit with the `nl` command; see [R] **nl**.

We will start with a simple two-level model in which we allow the asymptote parameter β_1 to vary between unicorns by replacing β_1 in the above equation with $\beta_1 + u_{0j}$,

$$\texttt{weight}_{ij} = \beta_1 + u_{0j} + (\beta_2 - \beta_1 - u_{0j})\,\exp\left(-\beta_3 \texttt{time}_{ij}\right) + \epsilon_{ij} \tag{4}$$

where β_1, β_2, and β_3 are fixed-effects parameters to be estimated and u_{0j} is a random intercept at the unicorn, `id`, level that follows a normal distribution with mean 0 and variance σ_u^2.

Equivalently, the model defined by (4) can be written as a two-stage model,

$$\texttt{weight}_{ij} = \phi_{1j} + (\phi_{2j} - \phi_{1j})\,\exp\left(-\phi_{3j} \texttt{time}_{ij}\right) + \epsilon_{ij} \tag{5}$$

with the following stage 2 specification:

$$\begin{aligned} \phi_{1j} &= \beta_1 + u_{0j} \\ \phi_{2j} &= \beta_2 \\ \phi_{3j} &= \beta_3 \end{aligned} \tag{6}$$

Parameters ϕ_{1j}, ϕ_{2j}, and ϕ_{3j} now describe the behavior of the jth unicorn. For example, ϕ_{1j} represents the brain weight of the jth unicorn as $\texttt{time}_{ij}$ increases to infinity.

▷ Example 1: Simple two-level model

Let's use `menl` to first fit a single-equation model defined by (4), described above.

```
. use https://www.stata-press.com/data/r18/unicorn
(Brain shrinkage of unicorns in the land of Zootopia)
. menl weight = {b1}+{U0[id]}+({b2}-{b1}-{U0[id]})*exp(-{b3}*time)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood =  -56.97576
Computing standard errors:
Mixed-effects ML nonlinear regression            Number of obs     =        780
Group variable: id                               Number of groups  =         60
                                                 Obs per group:
                                                               min =         13
                                                               avg =       13.0
                                                               max =         13
Linearization log likelihood =  -56.97576

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
         /b1 |   4.707954   .1414511    33.28   0.000     4.430715    4.985193
         /b2 |   8.089432   .0260845   310.12   0.000     8.038307    8.140556
         /b3 |    4.13201   .0697547    59.24   0.000     3.995293    4.268726
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                     var(U0) |   1.189809   .2180073      .8308307    1.703891
-----------------------------+------------------------------------------------
               var(Residual) |   .0439199   .0023148      .0396095    .0486995
------------------------------------------------------------------------------
```

Notes:

1. The response variable `weight` is specified on the left-hand side of the equality sign, and parameters to be estimated are enclosed in curly braces `{b1}`, `{b2}`, and `{b3}` on the right-hand side.
2. By typing `{U0[id]}`, we specified a random intercept at the level identified by the group variable `id`, that is, the unicorn level (level two).
3. The estimation log consists of three parts:
   a. A set of EM iterations used to refine starting values. By default, the iterations themselves are not displayed, but you can display them by using the `emlog` option. NLME models may often have multiple solutions and converge to a local maximum. It is thus important to try different initial values to investigate the existence of multiple solutions and the convergence to a global maximum; see *Obtaining initial values*.

   b. A set of iterations displaying the value of the linearization log likelihood from the Lindstrom–Bates algorithm or alternating algorithm. The term "linearization" reflects the fact that the reported log likelihood corresponds to the linear mixed-effects model obtained after linearization of the specified nonlinear mean function with respect to fixed and random effects. See *Inference based on linearization* and *Stopping rules* for details about the algorithm.

   c. The message "Computing standard errors". This is just to inform you that `menl` has finished its iterative maximization and is now reparameterizing the variance components (see *Methods and formulas*) to their natural metric and computing their standard errors. If you are interested only in the fixed-effects estimates, you can use the `nostderr` option to bypass this step.

4. The output title, "Mixed-effects ML nonlinear regression", informs us that our model was fit using ML, the default. For REML estimates, use the `reml` option.
5. The header information is similar to that of the `mixed` command, but unlike `mixed`, `menl` in general does not report a model χ^2 statistic in the header because a test of the joint significance of all fixed-effects parameters (except the constant term) may not be relevant in a nonlinear model.
6. The first estimation table reports the fixed effects. We estimate $\beta_1 = 4.71$, $\beta_2 = 8.09$, and $\beta_3 = 4.13$. Although z tests against zeros are reported automatically for all fixed-effects parameters, as part of standard estimation output, they may not always be of interest or even appropriate for parameters of nonlinear models. You can use the `test` command ([R] **test**) to test hypotheses of interest or reparameterize your model so that the tests of parameters against zeros are meaningful.
7. The second estimation table shows the estimated variance components. The first section of the table is labeled `id: Identity`. In general, this means that our model includes random effects at the `id` (unicorn) level and that their variance–covariance matrix, $\mathbf{\Sigma}$, is the identity matrix (all random effects have the same variance). In our example, because we have only one random effect, u_{0j}, the random-effect covariance structure is irrelevant, and the variance of the random intercept, σ^2_u, labeled as `var(U0)` in the output, is estimated as 1.19 with standard error 0.22.
8. The row labeled `var(Residual)` displays the estimated overall error variance or variance of the error term; that is, $\widehat{\text{Var}}\,(\epsilon_{ij}) = \widehat{\sigma}^2_\epsilon = 0.044$.

◁

▷ Example 2: Two-level model as a two-stage model, using the define() option

The model from example 1 can also be specified as a two-stage model, as defined by (5) and (6), by using the `define()` option. The `define()` option is particularly useful when you have a complicated nonlinear expression, and you would like to break it down into smaller pieces. Parameters of interest that are functions of other parameters can be defined using the `define()` option. This will make it easier to predict them for each subject after estimation; see [ME] **menl postestimation**.

Below we specify the asymptote parameter, ϕ_{1j}, by using `define()`. The colon (`:`) in `{phi1:}` instructs `menl` that `phi1` will be specified as a substitutable expression within the `define()` option. Parameters `{phi2}` and `{phi3}` are simple free parameters and thus do not need to be specified in `define()`.

```
. menl weight = {phi1:}+({phi2}-{phi1:})*exp(-{phi3}*time),
> define(phi1: {b1}+{U0[id]})
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood =  -56.97576
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        780
Group variable: id                              Number of groups  =         60
                                                Obs per group:
                                                             min =         13
                                                             avg =       13.0
                                                             max =         13
Linearization log likelihood =  -56.97576
        phi1: {b1}+{U0[id]}

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
         /b1 |   4.707954   .1414511    33.28   0.000     4.430715    4.985193
       /phi2 |   8.089432   .0260845   310.12   0.000     8.038307    8.140556
       /phi3 |    4.13201   .0697547    59.24   0.000     3.995293    4.268726
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                     var(U0) |   1.189809   .2180059      .8308326    1.703888
-----------------------------+------------------------------------------------
               var(Residual) |   .0439199   .0023148      .0396095    .0486995
------------------------------------------------------------------------------
```

The results are identical to those obtained in example 1, but the estimation table now has a legend that lists the expression phi1 defined in the model. We can suppress this legend by specifying the nolegend option.

We could have defined phi1 directly in the main expression instead of in the define() option,

```
. menl weight = {phi1:{b1}+{U0[id]}}+({phi2}-{phi1:})*exp(-{phi3}*time)
  (output omitted )
```

but by using the define() option, we simplified the main expression.

◁

▷ Example 3: Two-level model containing covariates

Reducing brain weight loss has been an active research area in Zootopia for the past two decades, and scientists believe that consuming rainbow cupcakes right after birth may help slow down brain shrinkage. Recall that the scale parameter ϕ_{3j} determines the rate at which the brain weight of the jth unicorn decreases to its asymptotic value ϕ_{1j}. Hence, covariate cupcake, which represents the number of rainbow cupcakes consumed right after birth, is added to the equation of ϕ_{3j}. Also, we would like to investigate whether the asymptote, ϕ_{1j}, is gender specific, so we include the factor variable female in the equation for ϕ_{1j}. $\texttt{female}_j$ is 1 if the jth unicorn is a female and 0 otherwise.

The stage 2 specification of the model defined by (5) becomes

$$\begin{aligned}\phi_{1j} &= \beta_{10} + \beta_{11}\texttt{female}_j + u_{0j}\\ \phi_{2j} &= \beta_2 \\ \phi_{3j} &= \beta_{30} + \beta_{31}\texttt{cupcake}_j\end{aligned} \tag{7}$$

The `define()` option can be repeated, so we specify a separate `define()` option for ϕ_{1j}, ϕ_{2j}, and ϕ_{3j}. We could have left ϕ_{2j} as a free parameter `{phi2}` in our specification, but we wanted to closely match the stage 2 specification (7).

```
. menl weight = {phi1:}+({phi2:}-{phi1:})*exp(-{phi3:}*time),
> define(phi1: {b10}+{b11}*1.female+{U0[id]})
> define(phi2: {b2})
> define(phi3: {b30}+{b31}*cupcake)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -29.014988
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        780
Group variable: id                              Number of groups  =         60

                                                Obs per group:
                                                             min =         13
                                                             avg =       13.0
                                                             max =         13

Linearization log likelihood = -29.014988

               phi1: {b10}+{b11}*1.female+{U0[id]}
               phi2: {b2}
               phi3: {b30}+{b31}*cupcake

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        /b10 |   4.072752   .1627414    25.03   0.000     3.753785     4.39172
        /b11 |   1.264407   .2299723     5.50   0.000     .8136694    1.715144
         /b2 |   8.088102   .0255465   316.60   0.000     8.038032    8.138172
        /b30 |   4.706926   .1325714    35.50   0.000      4.44709    4.966761
        /b31 |  -.2007309   .0356814    -5.63   0.000    -.2706651   -.1307966
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Identity                 |
                     var(U0) |   .7840578   .1438924      .5471838    1.123474
-----------------------------+------------------------------------------------
               var(Residual) |   .0420763   .0022176      .0379468    .0466551
------------------------------------------------------------------------------
```

In the table legend, `/b10` and `/b11` correspond, respectively, to the constant term and coefficient of `1.female` in the equation for ϕ_{1j}. `/b2` is ϕ_{2j}, and `/b30` and `/b31` correspond, respectively, to the constant term and coefficient for `cupcake` in the equation for ϕ_{3j}.

Based on our results, consuming rainbow cupcakes after birth indeed slows down brain shrinkage: `/b31` is roughly -0.2 with a 95% CI of $[-0.271, -0.131]$.

◁

▷ Example 4: Specifying linear combinations

A more convenient way to specify the model in example 3 is to use linear-combination specifications; see *Random-effects substitutable expressions*.

For example, `define(phi1: {b10}+{b11}*1.female+{U0[id]})` can be replaced with `define(phi1: i.female U0[id])`. `menl` knows that we are defining ϕ_{1j} as a linear combination of `i.female` and `U0[id]` and thus will create a constant term and a coefficient for each level of factor variable `female` and will use a coefficient of 1 for any random effect. Because `female` has only two levels, `menl` will create two coefficients for `0b.female` and `1.female`, respectively, but will constrain the coefficient of the base level, level 0, to be 0.

We now fit our model by using linear-combination specifications within the `define()` options. We explain the use of the second and third `define()` specifications following estimation.

```
. menl weight = {phi1:}+({phi2:}-{phi1:})*exp(-{phi3:}*time),
> define(phi1: i.female U0[id])
> define(phi2: _cons, xb)
> define(phi3: cupcake, xb)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -29.014988
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        780
Group variable: id                              Number of groups  =         60
                                                Obs per group:
                                                              min =         13
                                                              avg =       13.0
                                                              max =         13
                                                Wald chi2(2)      =      61.78
Linearization log likelihood = -29.014988       Prob > chi2       =     0.0000
        phi1: i.female U0[id]
        phi3: cupcake, xb

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
      female |
     female  |   1.264407   .2299723     5.50   0.000     .8136694    1.715144
       _cons |   4.072752   .1627414    25.03   0.000     3.753785     4.39172
-------------+----------------------------------------------------------------
phi2         |
       _cons |   8.088102   .0255465   316.60   0.000     8.038032    8.138172
-------------+----------------------------------------------------------------
phi3         |
     cupcake |  -.2007309   .0356814    -5.63   0.000    -.2706651   -.1307966
       _cons |   4.706926   .1325714    35.50   0.000      4.44709    4.966761
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters |   Estimate   Std. err.     [95% conf. interval]
----------------------------+-------------------------------------------------
id: Identity                |
                    var(U0) |   .7840578   .1438935      .5471824    1.123477
----------------------------+-------------------------------------------------
              var(Residual) |   .0420763   .0022176      .0379468    .0466551
------------------------------------------------------------------------------
```

By using linear-combination specifications within the `define()` options, we improved the readability of the coefficient table. For example, it is now clear that `_cons` in the equation labeled `phi3` corresponds to the constant term in the equation for ϕ_{3j}. This term was labeled `/b30` previously.

Notes:

1. The `define()` option interprets its specification as a random-effects substitutable expression, so you do not need to specify the curly braces (`{}`) around the specification.
2. All rules for random-effects substitutable expressions apply to the specifications within `define()`.

3. Following one of the rules for random-effects substitutable expressions, we used the `xb` option within `define()`s for `phi2` and `phi3`, because their linear combinations contained only one term: `_cons` for `phi2` and `cupcake` for `phi3`.
4. Specification `define(phi2: _cons, xb)` is the same as `define(phi2:, xb)`. In other words, `_cons` is implied with any linear combination, unless the `noconstant` option is specified. We chose to include `_cons` directly for clarity.
5. We could have used a free parameter `{phi2}` instead of the linear combination `{phi2: _cons, xb}`, but we wanted to preserve the order in which `phi1`, `phi2`, and `phi3` appear in the estimation table. See example 5, where we specify ϕ_{2j} as a free parameter `{phi2}`.
6. In the presence of linear combinations, `menl` reports a joint test of significance of all coefficients (except the constant term) across all linear combinations.
7. Linear combinations containing only a constant such as `{phi2:}` are not listed in the table expression legend for brevity.

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▷ Example 5: Including random coefficients

In previous examples, we only illustrated how to specify random intercepts such as `{U0[id]}`, and it is bad karma to end a unicorn story without showing how to specify random coefficients or random slopes.

Continuing with our model as defined by (5) and (7), let's suppose that the equation for the brain-weight scale parameter, ϕ_{3j}, is as follows:

$$\phi_{3j} = \beta_{30} + (\beta_{31} + u_{1j})\texttt{cupcake}_j$$

We incorporated a unicorn-specific random slope for variable `cupcake`. The random slope, u_{1j}, for a continuous variable `cupcake` can be specified in `menl` as `c.cupcake#U1[id]`, and by default, `menl` assumes that it is independent of the random intercept, u_{0j}. (See example 9 for specifying other random-effects covariance structures.)

```
. menl weight = {phi1:}+({phi2}-{phi1:})*exp(-{phi3:}*time),
> define(phi1: i.female U0[id])
> define(phi3: cupcake c.cupcake#U1[id])
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood =  165.41751
Iteration 2:  Linearization log likelihood =  165.42008
Iteration 3:  Linearization log likelihood =  165.42011
Iteration 4:  Linearization log likelihood =   165.4201
Computing standard errors:
Mixed-effects ML nonlinear regression               Number of obs     =        780
Group variable: id                                  Number of groups  =         60
                                                    Obs per group:
                                                                  min =         13
                                                                  avg =       13.0
                                                                  max =         13
                                                    Wald chi2(2)      =      46.70
Linearization log likelihood =   165.4201           Prob > chi2       =     0.0000
        phi1: i.female U0[id]
        phi3: cupcake c.cupcake#U1[id]

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
      female |
     female  |   1.320623   .2215707     5.96   0.000     .8863522    1.754894
       _cons |   4.006823   .1568268    25.55   0.000     3.699448    4.314198
-------------+----------------------------------------------------------------
phi3         |
     cupcake |   -.219661   .0659984    -3.33   0.001    -.3490155   -.0903066
       _cons |   4.771466   .1128421    42.28   0.000       4.5503    4.992633
-------------+----------------------------------------------------------------
       /phi2 |   8.087655   .0179406   450.80   0.000     8.052492    8.122818
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
id: Independent              |
                     var(U0) |    .727464   .1337157      .5074012    1.042969
                     var(U1) |   .1258914   .0309569      .0777471    .2038487
-----------------------------+------------------------------------------------
               var(Residual) |   .0208202   .0011403       .018701    .0231795
------------------------------------------------------------------------------
```

In addition to the overall error variance and the random-intercept variance, we now have a random-slope variance, which is labeled `var(U1)` in the output. In this example, we also specified parameter ϕ_{2j} as a free parameter `{phi2}` instead of a linear combination as in example 4. As we mentioned in *Summary*, free parameters are displayed after linear combinations, so `phi2` is listed last in the estimation table.

Previous studies of unicorns considered a model that also incorporated gender-specific variation between unicorns in asymptotic weight ϕ_{1j},

$$\phi_{1j} = \beta_{10} + u_{0j} + (\beta_{11} + u_{2j})\texttt{female}_j$$

but found no statistical evidence of such variation.

If we wanted to verify this for our data, we could have fit the following model:

```
. menl weight = {phi1:}+({phi2}-{phi1:})*exp(-{phi3:}*time), ///
    define(phi1: i.female U0[id] 1.female#U2[id])          ///
    define(phi3: cupcake c.cupcake#U1[id])
```

Compared with our previous specification, we included a new term in the `define()` option for `phi1`—a random slope for level 1 of the factor variable `female`, `1.female#U2[id]`. To include random slopes for a factor variable, we must specify random effects for each level, except the base level, of the factor variable. The specification `i.`*fvvarname* for referring to all levels of a factor variable is not allowed in the context of random effects, because a different set of random effects must be defined for each level. For example, if we specified `i.female#U2[id]` in our example, we would have received an error.

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To summarize:

1. Use {*name*} to define free parameters such as `{b1}`.
2. Use, for example, `{U0[id]}` to define random intercepts at the `id` level, `{c.`*varname*`#U1[id]}` to define random slopes for continuous variable *varname* at the `id` level, and `{`*#*`.`*fvvarname*`#U1[id]}` for each level *#*, except the base level, of variable *fvvarname* to include random slopes for factor variable *fvvarname*. The specification `{i.`*fvvarname*`#U1[id]}` is not allowed.
3. Use linear-combination specifications whenever possible. Do not use `{}` around random effects when they are specified within a linear combination.
4. Use multiple `define()` options to specify parameters of interest that are functions of other parameters, and use linear-combination specifications within `define()` whenever possible.
5. Use the `xb` option within a linear combination or within `define()` whenever you specify one variable such as `define(phi1: cupcake, xb)`, one random effect such as `{phi2: U0[id], xb}`, or a constant-only linear combination such as `{phi2: _cons, xb}` or `{phi2: , xb}`. When you specify the `xb` option, the above specifications are interpreted by `menl`, respectively, as a linear combination `{phi1:_cons}+{phi1:cupcake}*cupcake`, a linear combination `{phi:_cons}+{U0[id]}`, and a constant term `{phi2:_cons}`.
6. Unicorns do exist in our world, they are just gray, fat, and called rhinos.

Testing variance components

Consider data on the intensity of 23 large earthquakes in western North America between 1940 and 1980 analyzed originally by Joyner and Boore (1981) and then also by Davidian and Giltinan (1995, sec. 11.4). The objective of the study was to model the maximum horizontal acceleration (in g units), `accel`, taken at the ith measuring station for the jth earthquake, as a function of the magnitude of the quake on the Richter scale, `richter`, and the distance (in km) of the measuring station from the quake epicenter, `distance`. We are also interested in the possible effect of the soil type `soil`, soil versus rock, at a given measuring station on acceleration. The results of this study are useful to understand the nature of the damage caused by a particular earthquake and to determine the location for sensitive installations such as nuclear facilities.

Let's consider one of the models studied by Davidian and Giltinan (1995) for these data,

$$\log_{10}(\texttt{accel}_{ij}) = \phi_{1j} - \log_{10}\sqrt{\texttt{distance}_{ij}^2 + \exp\left(\phi_{2j}\right)} - \phi_{3ij}\sqrt{\texttt{distance}_{ij}^2 + \exp\left(\phi_{2j}\right)} + \epsilon_{ij} \tag{8}$$

where

$$\begin{aligned}\phi_{1j} &= \beta_0 + \beta_1\texttt{richter}_j + u_{1j}\\ \phi_{2j} &= \beta_2\\ \phi_{3i} &= \beta_3 + u_{3j}\end{aligned} \tag{9}$$

and

$$\mathbf{u}_j = \begin{bmatrix} u_{1j} \\ u_{3j} \end{bmatrix} \sim N(\mathbf{0},\mathbf{\Sigma}),\ \text{diagonal } \mathbf{\Sigma} = \begin{bmatrix} \sigma^2_{u_1} & 0 \\ 0 & \sigma^2_{u_3} \end{bmatrix},\ \text{and } \epsilon_{ij} \sim N(0,\sigma^2_\epsilon) \tag{10}$$

▷ Example 6: Fitting an NLME model for the earthquake data

Let’s fit the model defined by (8), (9), and (10) by using `menl`.

```
. use https://www.stata-press.com/data/r18/earthquake
(Earthquake intensity (Joyner and Boore, 1981))

. menl laccel = {phi1:}-log10(sqrt(c.distance#c.distance+exp({phi2})))
> -{phi3:}*sqrt(c.distance#c.distance+exp({phi2})),
> define(phi1: richter U1[quake]) define(phi3: U3[quake], xb)

Obtaining starting values by EM:

Alternating PNLS/LME algorithm:

Iteration 1:  Linearization log likelihood =  2.4115811
Iteration 2:  Linearization log likelihood =  2.4075141
Iteration 3:  Linearization log likelihood =   2.407347
Iteration 4:  Linearization log likelihood =  2.4073424
Iteration 5:  Linearization log likelihood =  2.4073412
Iteration 6:  Linearization log likelihood =  2.4073411

Computing standard errors:

Mixed-effects ML nonlinear regression           Number of obs     =        182
Group variable: quake                           Number of groups  =         23

                                                Obs per group:
                                                             min =          1
                                                             avg =        7.9
                                                             max =         38

                                                Wald chi2(1)      =      26.26
Linearization log likelihood =  2.4073411       Prob > chi2       =     0.0000

        phi1: richter U1[quake]
        phi3: U3[quake], xb

------------------------------------------------------------------------------
      laccel | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
     richter |   .2310021   .0450804     5.12   0.000     .1426461     .319358
       _cons |  -.8836537   .2826255    -3.13   0.002    -1.437589    -.329718
-------------+----------------------------------------------------------------
phi3         |
       _cons |    .004575   .0014192     3.22   0.001     .0017935    .0073566
-------------+----------------------------------------------------------------
       /phi2 |   4.063075   .4023386    10.10   0.000     3.274506    4.851644
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
quake: Independent           |
                     var(U1) |   .0056676    .0073404      .0004477     .071752
                     var(U3) |    .000013    8.42e-06      3.66e-06    .0000463
-----------------------------+------------------------------------------------
               var(Residual) |   .0461647    .0054421      .0366409    .0581639
------------------------------------------------------------------------------
```

We also store our estimates for later use:

```
. estimates store E1
```

By default, `menl` assumes that the random effects u_{1j} and u_{3j} are independent, so there is no need to specify the `covariance()` option in this case. In other words, omitting the `covariance()` option is equivalent to specifying `covariance(U1 U3, independent)`.

◁

▷ Example 7: Likelihood-ratio test for variance components

Davidian and Giltinan (1995) did not include any random effects in the model for the ϕ_{2j} parameters. Let's check whether the random effects are needed in the equations for ϕ_{1j} and ϕ_{3j} parameters in (9).

One simple way to assess whether a random effect associated with a certain ϕ_j can be omitted, is to examine its coefficient of variation (CV), the ratio of the standard deviation to the mean. Let's compute the CV for ϕ_{3j}. For convenience, let's redisplay the results from example 6 as standard deviations for variance components.

```
. menl, stddeviations
Mixed-effects ML nonlinear regression               Number of obs     =        182
Group variable: quake                               Number of groups  =         23
                                                    Obs per group:
                                                                  min =          1
                                                                  avg =        7.9
                                                                  max =         38
                                                    Wald chi2(1)      =      26.26
Linearization log likelihood =  2.4073411           Prob > chi2       =     0.0000
        phi1: richter U1[quake]
        phi3: U3[quake], xb

      laccel   Coefficient  Std. err.      z    P>|z|     [95% conf. interval]

phi1
     richter     .2310021   .0450804     5.12   0.000     .1426461     .319358
       _cons    -.8836537   .2826255    -3.13   0.002    -1.437589    -.329718

phi3
       _cons      .004575   .0014192     3.22   0.001     .0017935    .0073566

       /phi2     4.063075   .4023386    10.10   0.000     3.274506    4.851644


  Random-effects parameters   Estimate   Std. err.     [95% conf. interval]

quake: Independent
                     sd(U1)   .0752832   .0487517      .0211582    .2678656
                     sd(U3)   .0036085   .0011673      .0019142    .0068026

              sd(Residual)   .2148596   .0126644      .1914181     .241172
```

The `stddeviations` option specifies that `menl` display random-effects and error standard deviations instead of variances. It will also display correlations instead of covariances whenever they are in the model. Because random-effects variances for these data are very small, we will use this option in all subsequent examples to display results in the standard deviation metric.

The interquake random variation in the ϕ_{3j} values about their mean is CV $=$ `sd(U3)`/`{phi3:_cons}` $= 0.0036/0.0046 \approx 78\%$, and it appears reasonable to keep it in the model. You can perform a formal likelihood-ratio (LR) test of H_0: $\sigma^2_{u_3} = 0$ to verify this, as we show below for the test of H_0: $\sigma^2_{u_1} = 0$.

Let's check whether we need random intercept u_{1j} to model ϕ_{1j}. Computing CV in this case to get an initial assessment is not simple because the mean of ϕ_{1j} depends on the jth quake through variable `richter`. Given the same main equation (8), we will use the LR test to compare the restricted model, with u_{1j} excluded, which is defined by (11) and (12) below, with the full model defined by (9) and (10).

The stage 2 specification of the restricted model is

$$\begin{aligned}\phi_{1j} &= \beta_0 + \beta_1 \texttt{richter}_j \\ \phi_{2j} &= \beta_2 \\ \phi_{3ij} &= \beta_3 + u_{3j}\end{aligned} \tag{11}$$

where

$$u_{3j} \sim N(0, \sigma^2_{u_3}) \quad \text{and} \quad \epsilon_{ij} \sim N(0, \sigma^2_\epsilon) \tag{12}$$

We now fit the restricted model:

```
. menl laccel = {phi1:}-log10(sqrt(c.distance#c.distance+exp({phi2})))
> -{phi3:}*sqrt(c.distance#c.distance+exp({phi2})),
> define(phi1: richter, xb) define(phi3: U3[quake], xb)
> stddeviations
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood =  2.1262862
Iteration 2:  Linearization log likelihood =   2.126043
Iteration 3:  Linearization log likelihood =  2.1260328
Iteration 4:  Linearization log likelihood =    2.12603
Iteration 5:  Linearization log likelihood =  2.1260297
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        182
Group variable: quake                           Number of groups  =         23
                                                Obs per group:
                                                              min =          1
                                                              avg =        7.9
                                                              max =         38
                                                Wald chi2(1)      =      32.22
Linearization log likelihood =  2.1260297       Prob > chi2       =     0.0000
        phi1: richter, xb
        phi3: U3[quake], xb

------------------------------------------------------------------------------
      laccel | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
     richter |   .2208878   .0389144     5.68   0.000     .1446169    .2971586
       _cons |  -.7863293   .2503442    -3.14   0.002    -1.276995   -.2956637
-------------+----------------------------------------------------------------
phi3         |
       _cons |   .0054348   .0015661     3.47   0.001     .0023653    .0085044
-------------+----------------------------------------------------------------
       /phi2 |   4.228431   .3702251    11.42   0.000     3.502803    4.954059
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
quake: Identity              |
                      sd(U3) |   .0042144   .0011309      .0024907    .0071309
-----------------------------+------------------------------------------------
               sd(Residual) |   .2170084   .0122821      .1942231    .2424668
------------------------------------------------------------------------------
. estimates store E2
```

Next, we use `lrtest` to perform an LR test of the hypothesis:

$$H_0\colon \sigma^2_{u_1} = 0 \qquad \text{versus} \qquad H_1\colon \sigma^2_{u_1} \neq 0$$

```
. lrtest E1 E2, stats
Likelihood-ratio test
Assumption: E2 nested within E1
 LR chi2(1) =   0.56
Prob > chi2 = 0.4532
Note: The reported degrees of freedom assumes the null hypothesis is not on
      the boundary of the parameter space. If this is not true, then the
      reported test is conservative.
Akaike's information criterion and Bayesian information criterion

       Model │          N   ll(null)  ll(model)      df         AIC        BIC
─────────────┼──────────────────────────────────────────────────────────────
          E2 │        182          .    2.12603       6    7.747941   26.97198
          E1 │        182          .   2.407341       7    9.185318   31.61336
─────────────┴──────────────────────────────────────────────────────────────
Note: BIC uses N = number of observations. See [R] IC note.
```

Because testing of H_0: $\sigma^2_{u_1} = 0$ is on the boundary of the parameter space, `lrtest` reports a note that the provided LR test is conservative; that is, the actual p-value is smaller than the one reported. For a test of H_0: $\sigma^2_{u_1} = 0$ in a two-level model, the true asymptotic distribution is not $\chi^2(1)$ but a mixture of $\chi^2(0)$ and $\chi^2(1)$ with equal weights, $0.5\chi^2(0) + 0.5\chi^2(1)$; thus the p-value is actually $0.4532/2 = 0.2266$ (see Rabe-Hesketh and Skrondal 2022, sec 8.8). We do not have sufficient evidence to reject the null hypothesis, so we can omit random effect u_{1j} from the full model. AIC and BIC also favor a simpler, reduced model.

◁

▷ Example 8: Including within-subject covariates

One of the questions of interest in the earthquake study was the potential effect of the soil type on acceleration. Variable `soil` is a within-subject covariate because the values $\texttt{soil}_{ij}$ may vary within a subject (earthquake). We include variable `soil` in the equation for ϕ_{3ij} in (11),

$$\begin{aligned}
\phi_{1j} &= \beta_0 + \beta_1 \texttt{richter}_j \\
\phi_{2j} &= \beta_2 \\
\phi_{3ij} &= \beta_3 + \beta_4 \texttt{soil}_{ij} + u_{3j}
\end{aligned}$$

and fit the corresponding model:

```
. menl laccel = {phi1:}-log10(sqrt(c.distance#c.distance+exp({phi2})))
> -{phi3:}*sqrt(c.distance#c.distance+exp({phi2})),
> define(phi1: richter, xb) define(phi3: i.soil U3[quake]) stddeviations
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood =  3.5634779
Iteration 2:  Linearization log likelihood =  3.5632472
Iteration 3:  Linearization log likelihood =  3.5632339
Iteration 4:  Linearization log likelihood =  3.5632304
Iteration 5:  Linearization log likelihood =  3.5632298
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        182
Group variable: quake                           Number of groups  =         23
                                                Obs per group:
                                                              min =          1
                                                              avg =        7.9
                                                              max =         38
                                                Wald chi2(2)      =      34.20
Linearization log likelihood =  3.5632298       Prob > chi2       =     0.0000

        phi1: richter, xb
        phi3: i.soil U3[quake]

------------------------------------------------------------------------------
      laccel | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
     richter |   .2275944   .0395549     5.75   0.000     .1500683    .3051206
       _cons |  -.8079826   .2548833    -3.17   0.002    -1.307545   -.3084205
-------------+----------------------------------------------------------------
phi3         |
        soil |
       soil  |  -.0011041   .0006441    -1.71   0.087    -.0023665    .0001583
       _cons |   .0067347   .0017416     3.87   0.000     .0033213    .0101481
-------------+----------------------------------------------------------------
       /phi2 |     4.3212   .3653809    11.83   0.000     3.605067    5.037334
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
quake: Identity              |
                      sd(U3) |   .0043088   .0011285      .0025788    .0071992
-----------------------------+------------------------------------------------
                sd(Residual) |   .2147101   .0121424      .1921829    .2398779
------------------------------------------------------------------------------
```

The estimated coefficient for the soil type is −0.0011 with a 95% CI of [−0.0024, 0.0002]. The knowledge of the soil type at a particular site does not appear to add explanatory power to our model.

◁

Random-effects covariance structures

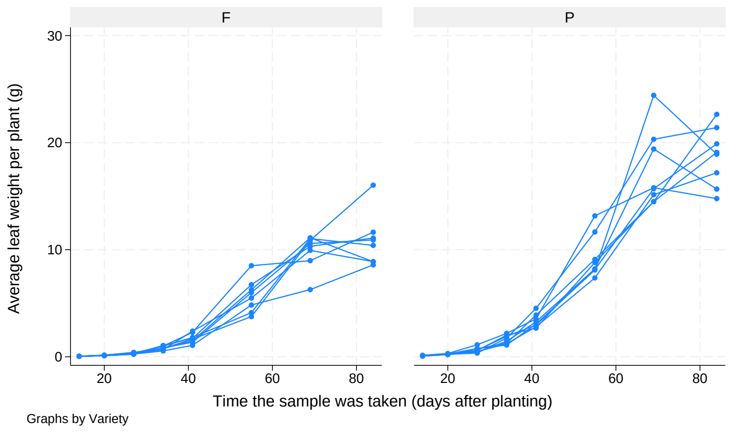
`menl` supports various covariance structures to model the random-effects covariance matrix. They are specified using the `covariance()` option. The `covariance()` option may be repeated. This is necessary to accommodate multilevel NLME models, where you may need to specify different covariance matrices for the random effects at different levels. Repeating this option may also be useful if you want to specify a block-diagonal covariance structure. See example 23 for details.

▷ Example 9: Two-level model with correlated random effects

Davidian and Giltinan (1995, sec. 1.1.3 and 11.2) discuss a study of soybean plants that started in 1988 and spanned over three growing seasons, `year`. The central objective of the study was to compare the growth patterns of two genotypes of soybean plants, `variety`: a commercial variety of soybean, denoted by F, and an experimental variety, denoted by P. In each season, eight plots were planted using F variety and eight using P variety. To assess growth, researchers sampled each plot 8 to 10 times ($8 \le n_j \le 10$) at approximately weekly intervals, `time`. At each sampling time, six plants were taken from each plot at random. Leaves from the plants were weighed, and the resulting total weight was divided by six to yield a measure of the average leaf weight per plant (in g) for the plot for that week, `weight`. Plots are identified by the `plot` variable.

Let's plot the data first.

```
. use https://www.stata-press.com/data/r18/soybean
(Growth of soybean plants (Davidian and Giltinan, 1995))
. twoway connected weight time if year==2, connect(L) by(variety)
```



The graph shows the average leaf weights per plant over time for the eight plots with plants of each genotype in the 1989 growing season. Longitudinal growth measures for each plot are connected with solid lines. Apart from some intraplot variation, the growth profile of each plot follows roughly an S shape, according to which growth begins slowly, then shows a linear trend during the middle of the growing season, and then "levels off" at the end. Such pattern is typical for many growth studies.

The main goal of the study was to compare growth patterns over the growing season for the two soybean genotypes. Because the three growing seasons differed markedly in terms of precipitation—1988 was unusually dry, 1989 was wet, and 1990 was normal—contrasting these growth patterns across years was also of interest. The results of this study are useful, for example, for harvesting purposes.

A popular model for individual profiles that resemble an S shape is the logistic growth model:

$$\texttt{weight}_{ij} = \frac{\phi_{1j}}{1 + \exp\left\{-\left(\texttt{time}_{ij} - \phi_{2j}\right)/\phi_{3j}\right\}} + \epsilon_{ij} \tag{13}$$

ϕ_{1j} is the asymptotic average leaf weight per soybean plant in plot j as $\texttt{time}_{ij} \to \infty$. ϕ_{2j} is the time at which half of ϕ_{1j} is reached; that is, if $\texttt{time}_{ij} = \phi_{2j}$, then $E(\texttt{weight}_{ij}) = 0.5\phi_{1j}$. ϕ_{1j} and ϕ_{2j} will henceforth be referred to as "the limiting growth" and "half-life", respectively. ϕ_{3j} is a scale parameter, and it represents the number of days it takes for average leaf weight to grow from 50% (half-life) to about 73% of its limiting growth. That is, if we set $\texttt{time}_{ij} = t_{0.73} = \phi_{2j} + \phi_{3j}$, the right-hand side of (13), ignoring the error term, reduces to $\phi_{1j}/\{1 + \exp(-1)\} = 0.73\phi_{1j}$, and then $\phi_{3j} = t_{0.73} - \phi_{2j}$.

We will start with a simple stage 2 specification that does not contain any covariates. Also, because the number of soybean plots, 48, is large compared with the number of random effects, 3, we consider a general positive-definite, unstructured, random-effects covariance matrix:

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix} + \begin{bmatrix} u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \tag{14}$$

$$\mathbf{u}_j = \begin{bmatrix} u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N\left(\mathbf{0}, \boldsymbol{\Sigma}\right), \boldsymbol{\Sigma} = \begin{bmatrix} \sigma_{11} & \sigma_{12} & \sigma_{13} \\ \sigma_{12} & \sigma_{22} & \sigma_{23} \\ \sigma_{13} & \sigma_{23} & \sigma_{33} \end{bmatrix}, \epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$$

To specify this covariance structure in `menl`, we specify `unstructured` in the `covariance()` option. The `covariance()` option also requires that we list the names of random effects to be correlated.

```
. menl weight = {phi1:}/(1+exp(-(time-{phi2:})/{phi3:})),
> define(phi1: U1[plot], xb) define(phi2: U2[plot], xb) define(phi3: U3[plot], xb)
> covariance(U1 U2 U3, unstructured)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -739.90142
Iteration 2:  Linearization log likelihood = -739.84929
  (iteration log omitted)
Iteration 39: Linearization log likelihood = -739.83452
Iteration 40: Linearization log likelihood = -739.83445
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        412
Group variable: plot                            Number of groups  =         48
                                                Obs per group:
                                                              min =          8
                                                              avg =        8.6
                                                              max =         10
Linearization log likelihood = -739.83445
        phi1: U1[plot], xb
        phi2: U2[plot], xb
        phi3: U3[plot], xb

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |   19.25314   .8031811    23.97   0.000     17.67893    20.82734
-------------+----------------------------------------------------------------
phi2         |
       _cons |   55.01999   .7272491    75.65   0.000     53.59461    56.44537
-------------+----------------------------------------------------------------
phi3         |
       _cons |   8.403468   .3152551    26.66   0.000      7.78558    9.021357
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
plot: Unstructured           |
                     var(U1) |   27.05081   6.776526       16.5556    44.19932
                     var(U2) |   17.61605   5.317903      9.748762    31.83229
                     var(U3) |   1.972036   .9849788      .7409048    5.248885
                  cov(U1,U2) |   15.73304   5.413377      5.123017    26.34307
                  cov(U1,U3) |   5.193819   2.165588      .9493435    9.438294
                  cov(U2,U3) |   5.649306   2.049457      1.632445    9.666168
-----------------------------+------------------------------------------------
               var(Residual) |   1.262237   .1111685      1.062119    1.500059
------------------------------------------------------------------------------
```

The expected limiting growth or expected maximum average weight, $\beta_1 = E(\phi_{1j})$, of soybean leaves is estimated to be around 19.25 grams. The expected half-life or the time at which the leaves reach half of their expected maximum average weight, $\beta_2 = E(\phi_{2j})$, is estimated to be around 55 days after planting. The expected time needed for the average leaf weight per plant to grow from 50% to 73% of the limiting growth, $\beta_3 = E(\phi_{3j})$, is about 8.4 days.

The estimates of the six random-effects variance–covariance parameters σ_{11}, σ_{22}, σ_{33}, σ_{12}, σ_{13}, and σ_{23} are displayed in the upper part of the random-effects parameters table. There is a plot-to-plot variation in the estimates of all three parameters of interest: β_1, β_2, and β_3. Also, the plot-specific effects associated with the parameters of interest are positively correlated. For example, based on the estimate of 5.19 of `cov(U1,U3)`, plants with larger maximum weights tend to grow faster.

We store our estimates for later use:

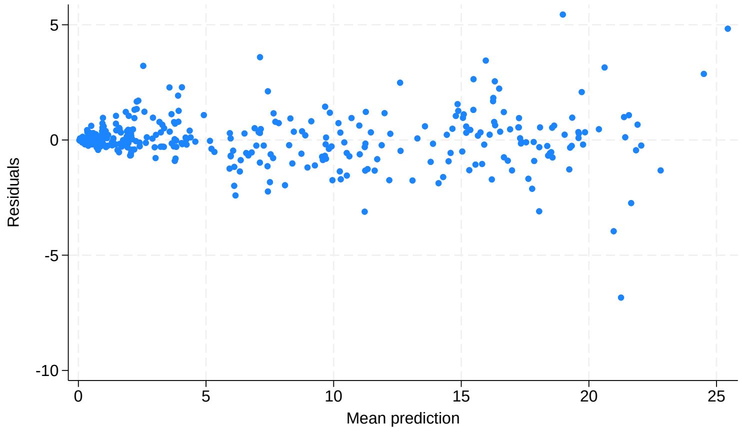
```
. estimates store S1
```

◁

▷ Example 10: Residuals-vs-fitted plot to check for heteroskedasticity

A popular tool for investigating within-cluster heteroskedasticity is the plot of residuals against the predicted values and other candidate variance covariates. For growth models, variance is often a function of the mean (predicted values). Below we construct the plot of residuals versus predicted values to evaluate the assumption of homoskedastic errors in example 9.

```
. predict fitweight, yhat
. predict res, residuals
. scatter res fitweight
```



The plot reveals increasing variability with the predicted average leaf weights, which indicates that our within-cluster variance model is misspecified. In *Heteroskedastic within-group errors*, we will show how to account for within-cluster heteroskedasticity by using the `resvariance()` option.

◁

Heteroskedastic within-group errors

Until now, we assumed that the within-group errors—the ϵ's in the considered models—are i.i.d. Gaussian with common variance σ^2_ϵ, labeled as `var(Residual)` by `menl` in the output.

To relax the assumptions of homoskedasticity and the independence of errors, `menl` provides two alternatives. You can model the within-group error variance–covariance matrix, $\sigma^2\mathbf{\Lambda}_j$, directly by using the `rescovariance()` option. If you used the `mixed` command and its `residuals()` option before, you should be familiar with this approach. Alternatively, you can model the error variance–covariance matrix indirectly by modeling the heteroskedasticity structure with the `resvariance()` option and the correlation structure with the `rescorrelation()` option; see *Variance-components parameters*. The latter approach offers more flexibility, particularly in modeling the heteroskedasticity structure. For example, many NLME models exhibit within-subject heterogeneity that is a power function of the mean. The `rescovariance()` option cannot model this, but `resvariance(power _yhat)` can.

If your error structure is simple and is similar to those encountered in `mixed`, you can use the `rescovariance()` option. Otherwise, use `resvariance()`, `rescorrelation()`, or both to model more flexible within-group error covariance structures.

▷ Example 11: Heteroskedastic power structure

Continuing with example 9, for these types of growth data, we find it is common for the intraplot variance to increase systematically with the average leaf weight, as we saw in example 10 from the residuals-versus-fitted plot. Davidian and Giltinan (1995) proposed a variance structure that models the within-group error variance as a power function of the mean to account for the intraplot variability. To reduce the number of parameters to be estimated, the authors assume that the random effects are independent.

Stage 2 specification of the model defined by (13) becomes

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \beta_2 \\ \beta_3 \end{bmatrix} + \begin{bmatrix} u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \tag{15}$$

where

$$\mathbf{u}_j = \begin{bmatrix} u_{1j} \\ u_{2j} \\ u_{3j} \end{bmatrix} \sim N\left(\mathbf{0}, \boldsymbol{\Sigma}\right), \text{ diagonal } \boldsymbol{\Sigma} = \begin{bmatrix} \sigma^2_{u_1} & 0 & 0 \\ 0 & \sigma^2_{u_2} & 0 \\ 0 & 0 & \sigma^2_{u_3} \end{bmatrix}$$

and

$$\text{Var}\left(\epsilon_{ij}\right) = \sigma^2 (\widehat{\texttt{weight}}_{ij})^{2\delta}$$

Parameter σ^2 in the above is no longer an overall error variance σ^2_ϵ but a common multiplier or a (squared) scale parameter.

In `menl`, this type of heteroskedasticity is modeled by specifying `resvariance(power _yhat, noconstant)`. `_yhat` designates that the variance should be modeled as a function of predicted values, $\widehat{\texttt{weight}}_{ij}$. By default, variance function `power` includes a constant, which we suppress by specifying the `noconstant` option.

```
. menl weight = {phi1:}/(1+exp(-(time-{phi2:})/{phi3:})),
> define(phi1: U1[plot], xb) define(phi2: U2[plot], xb) define(phi3: U3[plot], xb)
> resvariance(power _yhat, noconstant)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -364.02249
Iteration 2:  Linearization log likelihood = -364.22838
Iteration 3:  Linearization log likelihood = -364.43168
Iteration 4:  Linearization log likelihood = -364.38319
Iteration 5:  Linearization log likelihood = -364.38964
Iteration 6:  Linearization log likelihood = -364.38915
Iteration 7:  Linearization log likelihood =  -364.3892
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        412
Group variable: plot                            Number of groups  =         48
                                                Obs per group:
                                                              min =          8
                                                              avg =        8.6
                                                              max =         10
```

```
Linearization log likelihood =  -364.3892

        phi1: U1[plot], xb
        phi2: U2[plot], xb
        phi3: U3[plot], xb

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |   16.82289   .6030531    27.90   0.000     15.64093    18.00485
-------------+----------------------------------------------------------------
phi2         |
       _cons |   51.74669   .4579632   112.99   0.000      50.8491    52.64429
-------------+----------------------------------------------------------------
phi3         |
       _cons |   7.545371   .0856321    88.11   0.000     7.377535    7.713206
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
plot: Independent            |
                     var(U1) |   11.32134    2.83114      6.934848    18.48242
                     var(U2) |    2.68911   .9344038       1.36093     5.31351
                     var(U3) |   4.88e-11   2.67e-07             0           .
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                      sigma2 |   .0509223    .004422      .0429527    .0603706
                       delta |   .9339856   .0244477       .886069    .9819023
------------------------------------------------------------------------------
```

The near-zero estimate of the variance component of u_{3j}, `var(U3)`, suggests that the random-effects model is overparameterized. The within-group heteroskedasticity structure appears to explain enough variability in our data, and we no longer need random effects specific to ϕ_{3j}. This is quite common in mixed-effects models: the random-effects covariance structure and the within-group error covariance structure compete with each other, in the sense that fewer random effects are needed when the within-group error covariance structure is present, and vice versa.

Let's omit u_{3j} from (15) but now assume an unstructured covariance matrix for u_{1j} and u_{2j}. The EM algorithm used by `menl` to obtain initial values produces the starting values for variance components that are, in general, close to the final estimates upon convergence. Thus it can be used as a tool to help us detect potential convergence problems because of an overparameterized random-effects structure at an earlier stage. For example, we can check whether an unstructured covariance matrix is a reasonable choice for the random effects u_{1j} and u_{2j} for these data by displaying estimates after a few iterations. This can be done by specifying the `iterate(#)` option, where # is a small number of iterations, say, between 1 and 4. Below we specify `iterate(3)` to perform only three iterations and the `stddeviations` option to obtain standard deviations and correlations instead of variances and covariances for easier interpretability:

```
. menl weight = {phi1:}/(1+exp(-(time-{phi2:})/{phi3})),
> define(phi1: U1[plot], xb) define(phi2: U2[plot], xb)
> covariance(U*, unstructured) resvariance(power _yhat, noconstant)
> iterate(3) stddeviations
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -379.66343
Iteration 2:  Linearization log likelihood = -362.90921
Iteration 3:  Linearization log likelihood = -361.92335
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        412
Group variable: plot                            Number of groups  =         48

                                                Obs per group:
                                                              min =          8
                                                              avg =        8.6
                                                              max =         10

Linearization log likelihood = -361.94037

        phi1: U1[plot], xb
        phi2: U2[plot], xb

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |   16.92772   .5677148    29.82   0.000     15.81502    18.04042
-------------+----------------------------------------------------------------
phi2         |
       _cons |   51.81715   .4484351   115.55   0.000     50.93823    52.69606
-------------+----------------------------------------------------------------
       /phi3 |    7.54089   .0869059    86.77   0.000     7.370557    7.711223
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
plot: Unstructured           |
                      sd(U1) |   2.904856   .4070788      2.207188    3.823047
                      sd(U2) |   1.282287    .255515      .8677018     1.89496
                 corr(U1,U2) |    -.99999   .0034198            -1           1
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                       sigma |   .2255029   .0095093      .2076144    .2449327
                       delta |   .9553162   .0230654      .9101088    1.000524
------------------------------------------------------------------------------
Warning: Convergence not achieved.
```

The `U*` in `covariance(U*, unstructured)` is a shorthand notation to reference all random effects starting with `U`, that is, `U1` and `U2` in this example. The correlation between u_{1j} and u_{2j} is near -1 with a 95% CI of $[-1, 1]$, which indicates that the random-effects model may still be overparameterized. If you try to fit this model without the `iteration(3)` option, it would keep iterating without convergence.

Therefore, we further simplify the random-effects covariance structure by assuming independence between u_{1j} and u_{2j}. Stage 2 specification of the model defined by (13) is now

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \end{bmatrix} = \begin{bmatrix} \beta_1 + u_{1j} \\ \beta_2 + u_{2j} \\ \beta_3 \end{bmatrix} \tag{16}$$

where

$$\mathbf{u}_j = \begin{bmatrix} u_{1j} \\ u_{2j} \end{bmatrix} \sim N(\mathbf{0}, \boldsymbol{\Sigma}), \text{ diagonal } \boldsymbol{\Sigma} = \begin{bmatrix} \sigma^2_{u_1} & 0 \\ 0 & \sigma^2_{u_2} \end{bmatrix}$$

and

$$\text{Var}(\epsilon_{ij}) = \sigma^2 (\widehat{\texttt{weight}}_{ij})^{2\delta}$$

We fit this model and store its results as S2:

```
. menl weight = {phi1:}/(1+exp(-(time-{phi2:})/{phi3})),
> define(phi1: U1[plot], xb) define(phi2: U2[plot], xb)
> resvariance(power _yhat, noconstant)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -402.76182
Iteration 2:  Linearization log likelihood = -372.91627
Iteration 3:  Linearization log likelihood = -363.87814
Iteration 4:  Linearization log likelihood = -364.41042
Iteration 5:  Linearization log likelihood = -364.38112
Iteration 6:  Linearization log likelihood = -364.39023
Iteration 7:  Linearization log likelihood = -364.38915
Iteration 8:  Linearization log likelihood = -364.38921
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        412
Group variable: plot                            Number of groups  =         48
                                                Obs per group:
                                                              min =          8
                                                              avg =        8.6
                                                              max =         10
Linearization log likelihood = -364.38921
               phi1: U1[plot], xb
               phi2: U2[plot], xb

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |   16.82289   .6030524    27.90   0.000     15.64093    18.00485
-------------+----------------------------------------------------------------
phi2         |
       _cons |   51.74669   .4579626   112.99   0.000      50.8491    52.64428
-------------+----------------------------------------------------------------
       /phi3 |   7.545369    .085632    88.11   0.000     7.377533    7.713205
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
plot: Independent            |
                     var(U1) |   11.32134   2.831139      6.934846    18.48241
                     var(U2) |   2.689111    .934404       1.36093    5.313511
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                      sigma2 |   .0509223    .004422      .0429527    .0603706
                       delta |   .9339856   .0244477       .886069    .9819023
------------------------------------------------------------------------------
. estimates store S2
```

Because (16) is not nested in (14), we assess the adequacy of the heteroskedastic model by using information criteria. We use `estimates stats` to display the AIC and BIC values for the three models.

```
. estimates stats S1 S2
Akaike's information criterion and Bayesian information criterion

-----------------------------------------------------------------------------
       Model |          N   ll(null)  ll(model)      df        AIC        BIC
-------------+---------------------------------------------------------------
          S1 |        412          .  -739.8344      10   1499.669   1539.879
          S2 |        412          .  -364.3892       7   742.7784   770.9256
-----------------------------------------------------------------------------
Note: BIC uses N = number of observations. See [R] IC note.
```

The heteroskedastic model defined by (16) has smaller AIC and BIC values and thus provides a much better representation of the data than (14).

◁

▷ Example 12: Heteroskedastic model with interactions

The main goal of the soybean study was to compare growth patterns of the two genotypes of soybean over the three growing seasons, represented by calendar years 1988 through 1990. More specifically, we would like to compare the limiting growth, the half-life, and the growth rate of soybeans across growing seasons and genotypes.

Let $P_j = I\left(\texttt{variety}_j = \texttt{P}\right)$ be the indicator for genotype variety P, $S_{89,j} = I\left(\texttt{year}_j = 1989\right)$ be the indicator for growing season 1989, and $S_{90,j} = I\left(\texttt{year}_j = 1990\right)$ be the indicator for growing season 1990. Genotype variety F and growing season 1988 are baselines.

Consider an extension of the model defined by (13) and (16), where, in addition to random effects, ϕ_{1j} includes main and interaction effects of growing seasons and genotype variety, ϕ_{2j} includes main effects of growing seasons and genotype variety, and ϕ_{3j} contains main effects of growing seasons only.

$$\boldsymbol{\phi}_j = \begin{bmatrix}\phi_{1j}\\ \phi_{2j}\\ \phi_{3j}\end{bmatrix} = \begin{bmatrix}\beta_{11}+\beta_{12}S_{89,j}+\beta_{13}S_{90,j}+\beta_{14}P_j+\beta_{15}S_{89,j}\times P_j+\beta_{16}S_{90,j}\times P_j+u_{1j}\\ \beta_{21}+\beta_{22}S_{89,j}+\beta_{23}S_{90,j}+\beta_{24}P_j+u_{2j}\\ \beta_{31}+\beta_{32}S_{89,j}+\beta_{33}S_{90,j}\end{bmatrix} \tag{17}$$

To fit the model defined by (13) and (17) by using `menl`, we extend `menl`'s specification from example 11 by including the full-factorial interaction `i.year##i.variety` in the expression `{phi1:}`, main effects `i.year` and `i.variety` in the expression `{phi2:}`, and main effects `i.year` in the expression `{phi3:}`.

```
. menl weight = {phi1:}/(1+exp(-(time-{phi2:})/{phi3:})),
> define(phi1: i.year##i.variety U1[plot])
> define(phi2: i.year i.variety U2[plot])
> define(phi3: i.year, xb)
> resvariance(power _yhat, noconstant)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -292.62615
Iteration 2:  Linearization log likelihood = -290.24389
  (iteration log omitted)
Iteration 10: Linearization log likelihood = -290.90729
Iteration 11: Linearization log likelihood =  -290.9073
```

```
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        412
Group variable: plot                            Number of groups  =         48
                                                Obs per group:
                                                             min =          8
                                                             avg =        8.6
                                                             max =         10
                                                Wald chi2(10)     =     413.88
Linearization log likelihood =  -290.9073       Prob > chi2       =     0.0000
        phi1: i.year i.variety i.year#i.variety U1[plot]
        phi2: i.year i.variety U2[plot]
        phi3: i.year

------------------------------------------------------------------------------
      weight | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
        year |
       1989  |  -8.837933   1.056113    -8.37   0.000    -10.90788    -6.76799
       1990  |  -3.666206   1.165969    -3.14   0.002    -5.951463    -1.38095
             |
     variety |
          P  |   1.648139   1.033433     1.59   0.111    -.3773532    3.673631
             |
year#variety |
     1989#P  |   5.563008   1.167782     4.76   0.000     3.274196    7.851819
     1990#P  |   .0974815   1.178054     0.08   0.934    -2.211462    2.406425
             |
       _cons |   19.42734   .9445749    20.57   0.000     17.57601    21.27867
-------------+----------------------------------------------------------------
phi2         |
        year |
       1989  |  -2.253227   .9746495    -2.31   0.021    -4.163505   -.3429494
       1990  |  -4.970736   .9778317    -5.08   0.000    -6.887251   -3.054221
             |
     variety |
          P  |  -1.294058   .4255317    -3.04   0.002    -2.128085   -.4600314
       _cons |   54.81257   .7587239    72.24   0.000      53.3255    56.29964
-------------+----------------------------------------------------------------
phi3         |
        year |
       1989  |  -.9023768   .1992358    -4.53   0.000    -1.292872   -.5118818
       1990  |  -.6805314   .2100799    -3.24   0.001     -1.09228   -.2687823
             |
       _cons |   8.060677   .1459662    55.22   0.000     7.774588    8.346765
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
plot: Independent            |
                     var(U1) |   .8643052   .5271147      .2615435    2.856211
                     var(U2) |   .1341755   .2306869      .0046154    3.900652
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                      sigma2 |   .0467091   .0039176      .0396286    .0550546
                       delta |   .9451193   .0227608      .9005089    .9897297
------------------------------------------------------------------------------

. estimates store S3
```

By including more fixed effects in the model, which explain some of the variability in the average leaf weight, we substantially reduced the estimates of variance components. Compared with example 11, `var(U1)` decreased from 11.32 to 0.86, and `var(U2)` decreased from 2.69 to 0.13. It often happens that specifying a better-fitting model for the fixed effects reduces the need for random effects in the model.

We can compare model `S3` or the model defined by (17) with model `S2` or the one defined by (16) by using, for example, information criteria.

```
. estimates stats S2 S3
Akaike's information criterion and Bayesian information criterion

-----------------------------------------------------------------------------
       Model |          N   ll(null)  ll(model)      df        AIC        BIC
-------------+---------------------------------------------------------------
          S2 |        412          .  -364.3892       7   742.7784   770.9256
          S3 |        412          .  -290.9073      17   615.8146    684.172
-----------------------------------------------------------------------------
Note: BIC uses N = number of observations. See [R] IC note.
```

Even though `S3` has many more parameters, it fits the soybean data better than `S2`.

By inspecting the fixed-effects estimates from the output of model `S3`, we see that both the type of year and genotype variety affect all three parameters: the expected maximum leaf weight, half-life, and scale. For example, all three parameters achieve their highest values in the dry year, baseline year 1988, because coefficient estimates for the other years are negative. Also, the genotype variety F reaches its half-life roughly a day later ($\beta_{24} = -1.29$) than genotype variety P.

◁

▷ Example 13: Obtaining predictions

After estimation, we may want to obtain predicted values for the outcome or for the parameters of interest. Continuing with example 12, we want to predict the asymptotic average leaf weight per soybean plant in each plot, $\widehat{\phi_{1j}}$. The ϕ_{1j} parameter is not constant but varies for each plot, growing season, and genotype variety. We can use `predict` after `menl` to obtain predicted values for ϕ_{1j}; see [ME] **menl postestimation**.

First, we create a new grouping variable for growing seasons, genotype variety, and plot types. We also create the `tolist` variable to mark the first observation in each group.

```
. egen group = group(year variety plot)
. by group, sort: generate byte tolist=(_n==1)
```

Next, we use `predict` to compute predicted values for the expression `{phi1:}` and store them in the new variable `phi1`. We store only unique values in `phi1`, one for each `group`; the remaining observations are replaced with missing values.

```
. predict double (phi1 = {phi1:})
. quietly replace phi1 = . if tolist!=1
```

We now list the five smallest and the five largest values of the asymptotic average leaf weight.

```
. sort phi1
. list plot year variety phi1 if (_n<=5 | _n>43) & phi1<., sep(5)

     +-----------------------------------+
     |   plot   year   variety      phi1 |
     |-----------------------------------|
  1. | 1989F6   1989         F   8.8421451 |
  2. | 1989F4   1989         F   10.449521 |
  3. | 1989F5   1989         F   10.473849 |
  4. | 1989F1   1989         F   10.721364 |
  5. | 1989F7   1989         F   10.810197 |
     |-----------------------------------|
 44. | 1988P8   1988         P    20.86739 |
 45. | 1988P2   1988         P   21.237692 |
 46. | 1988P4   1988         P   21.310511 |
 47. | 1988P3   1988         P   21.506007 |
 48. | 1988P6   1988         P   21.581873 |
     +-----------------------------------+
```

Soybean plants with genotype variety P have substantially larger asymptotic average leaf weight in the dry year, 1988, than soybean plants with genotype variety F in the wet year, 1989.

◁

▷ Example 14: Within-group error correlation structure

Pinheiro and Bates (2000, chap. 8) analyzed data from a study of the estrus cycles of mares. Originally analyzed in Pierson and Ginther (1987), the data contain daily records of the number of ovarian follicles larger than 10 mm over a period ranging from 3 days before ovulation to 3 days after the subsequent ovulation. The measurement times for each mare are scaled so that the ovulations for each mare occur at times 0 and 1 and are recorded in `stime`.

The considered model is

$$\texttt{follicles}_{ij} = \phi_{1j} + \phi_{2j}\sin\left(2\pi\phi_{3j}\texttt{stime}_{ij}\right) + \phi_{4j}\cos\left(2\pi\phi_{3j}\texttt{stime}_{ij}\right) + \epsilon_{ij}$$

where ϕ_{1j} is an intercept, ϕ_{3j} is the frequency of the sine wave for the jth mare, and ϕ_{2j} and ϕ_{4j} are terms determining the amplitude and phase of the sine wave for the jth mare. If a_j and p_j are the amplitude and phase for mare j, then $\phi_{2j} = a_j\cos(p_j)$ and $\phi_{4j} = a_j\sin(p_j)$.

This model was fit in example 8 of [ME] **mixed** in the context of a linear mixed-effects model, where the number of ovarian follicles was a periodic function of time with known frequency ϕ_{3j} equal to 1. If we want to estimate frequency, we cannot use the `mixed` command, because ϕ_{3j} enters the model nonlinearly.

Pinheiro and Bates (2000) suggested an AR(1) correlation structure for modeling the within-group error correlation. This structure can be specified by using the `rescorrelation()` option as `rescorrelation(ar 1, t(time))`, where `time` is an integer-valued time variable used to order the observations within mares and to determine the lags between successive observations.

We also considered several random-effects structures and found that we need only one random intercept to model ϕ_{1j}.

The full specification for the stage 2 model is

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \\ \phi_{4j} \end{bmatrix} = \begin{bmatrix} \beta_1 + u_{1j} \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{bmatrix}$$

where

$$\mathbf{u}_j = u_{1j} \sim N\left(0, \sigma_u^2\right), \; \boldsymbol{\epsilon}_j \sim N(\mathbf{0}, \sigma_\epsilon^2 \boldsymbol{\Lambda}_j)$$

and

$$\sigma_\epsilon^2 \boldsymbol{\Lambda}_j = \sigma_\epsilon^2 \begin{bmatrix} 1 & \rho & \rho^2 & \dots & \rho^{n_j-1} \\ \rho & 1 & \rho & \dots & \rho^{n_j-2} \\ \rho^2 & \rho & 1 & \dots & \rho^{n_j-3} \\ \vdots & \vdots & \vdots & \ddots & \vdots \\ \rho^{n_j-1} & \rho^{n_j-2} & \rho^{n_j-3} & \dots & 1 \end{bmatrix}$$

We fit this model by using `menl` as follows:

```
. use https://www.stata-press.com/data/r18/ovary, clear
(Ovarian follicles in mares)

. menl follicles = {phi1: U1[mare], xb} + {phi2}*sin(2*_pi*stime*{phi3}) +
> {phi4}*cos(2*_pi*stime*{phi3}), rescorrelation(ar 1, t(time))

Obtaining starting values by EM:

Alternating PNLS/LME algorithm:

Iteration 1:  Linearization log likelihood = -789.43415
Iteration 2:  Linearization log likelihood = -789.43439
Iteration 3:  Linearization log likelihood = -789.43439

Computing standard errors:

Mixed-effects ML nonlinear regression           Number of obs     =        308
Group variable: mare                            Number of groups  =         11

                                                Obs per group:
                                                              min =         25
                                                              avg =       28.0
                                                              max =         31

Linearization log likelihood = -789.43439

        phi1: U1[mare], xb

------------------------------------------------------------------------------
   follicles | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |   11.98929   .9055946    13.24   0.000     10.21436    13.76422
-------------+----------------------------------------------------------------
       /phi2 |   .2226033   .3290159     0.68   0.499    -.4222559    .8674626
       /phi3 |    4.18747   .2746499    15.25   0.000     3.649166    4.725774
       /phi4 |    .279653   .3223277     0.87   0.386    -.3520977    .9114036
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
mare: Identity               |
                     var(U1) |   4.935352   3.967849      1.020897    23.85911
-----------------------------+------------------------------------------------
Residual: AR(1),             |
    time time                |
                      var(e) |   20.14587    3.49294      14.34176    28.29889
                        corr |   .7332304   .0463231      .6287332    .8117158
------------------------------------------------------------------------------
```

By using estimates of ϕ_{2j} and ϕ_{4j}, we can compute the amplitude and phase for the sine wave for mare j. The amplitude and the phase are the same for all the mares because ϕ_{2j} and ϕ_{4j} are constant and not mare specific.

For example, the amplitude a_j can be computed as $\sqrt{\phi_{2j}^2 + \phi_{4j}^2}$ by using the relationship $\phi_{2j}^2 + \phi_{4j}^2 = a_j^2 \left\{\sin^2(p_j) + \cos^2(p_j)\right\} = a_j^2$. The phase p_j can be computed as $p_j = \text{atan}(\phi_{4j}/\phi_{2j})$ by using the relationship $\phi_{4j}/\phi_{2j} = \{a_j \sin(p_j)\} / \{a_j \cos(p_j)\} = \tan(p_j)$.

We can use `nlcom` to compute the amplitude and the phase.

```
. nlcom (amplitude: sqrt(_b[/phi2]^2 + _b[/phi4]^2))
> (phase: atan(_b[/phi4]/_b[/phi2]))

   amplitude: sqrt(_b[/phi2]^2 + _b[/phi4]^2)
       phase: atan(_b[/phi4]/_b[/phi2])

------------------------------------------------------------------------------
   follicles | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
   amplitude |   .3574325   .2451183     1.46   0.145    -.1229904    .8378555
       phase |   .8985001   1.090985     0.82   0.410     -1.23979     3.03679
------------------------------------------------------------------------------
```

As we mentioned in example 1, it is important to try different initial values when fitting NLME models to investigate potential convergence to a local maximum, especially for models containing periodic functions, as in our example. We explore different initial values for this model in *Linearization approach to finding initial values* by considering the functional form of the mean function and arrive at a different solution with a larger log likelihood.

◁

Restricted maximum likelihood

Like `mixed`, `menl` provides estimation by using ML or REML. The difference between the two approaches is described in detail in *Likelihood versus restricted likelihood* in [ME] **mixed**. Briefly, REML is preferable when you have a small number of groups because it produces unbiased, at least for balanced data, estimates of variance components. In large samples, there is little difference between ML and REML. One disadvantage of REML, however, is that LR tests based on REML are inappropriate for comparing models with different fixed-effects specifications. See example 15 for an example of REML estimation.

Pharmacokinetic modeling

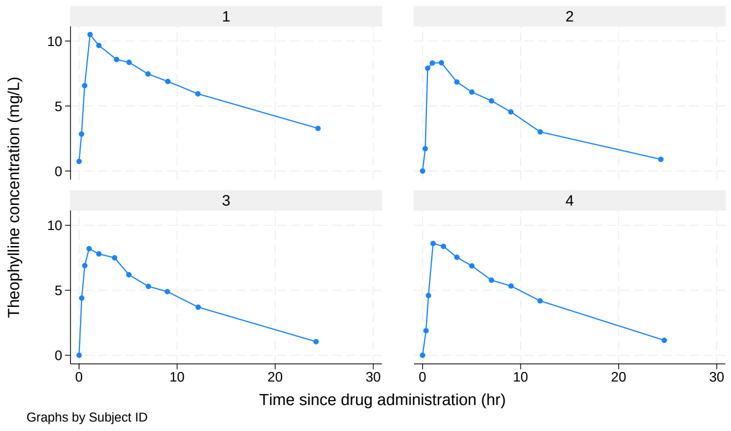
Pharmacokinetics (PKs) is the study of drug absorption, distribution, metabolism, and excretion. It is often referred to as the study of "what the body does with a drug". The goal of PK modeling is to summarize the concentration-time measurements using a model that relates drug input to drug response, to relate the parameters of this model to patient characteristics, and to provide individual dose–response predictions to optimize individual doses. In other words, by understanding between-subject variation in drug disposition, we can individualize the dosage regimen for a particular patient based on relevant physiological information identified by our PK model.

Single-dose pharmacokinetic modeling

▷ Example 15: Single-oral-dose model

Consider a PK study of the antiasthmatic agent theophylline that was reported by Boeckmann, Sheiner, and Beal (2011) and analyzed by Davidian and Giltinan (1995). The drug was administered orally to 12 subjects, where dosage `dose` (mg/kg) was given on a per weight basis. Serum concentrations (in mg/L) were obtained at 11 time points per subject over 25 hours following administration. The graph below shows the resulting concentration-time profiles for four subjects.

```
. use https://www.stata-press.com/data/r18/theoph
(Theophylline kinetics (Boeckmann et al., [1994] 2011))
. twoway connected conc time if subject<=4, connect(L) by(subject)
```



In PKs, the pattern of rapid rise to a peak concentration followed by an apparent exponential decay may be described by a so-called one-compartment open model with first-order absorption and elimination. The model corresponds roughly to viewing the body as one "blood compartment" and is particularly useful for the PK analysis of drugs that distribute relatively rapidly throughout the body, which makes it a reasonable model for the kinetics of theophylline after oral administration. Further details about compartmental modeling may be found in Gibaldi and Perrier (1982). The one-compartment open model for theophylline kinetics may be expressed as

$$\texttt{conc}_{ij} = \frac{\texttt{dose}_j k_{e_j} k_{a_j}}{\text{Cl}_j \left(k_{a_j} - k_{e_j}\right)} \left\{ \exp\left(-k_{e_j}\texttt{time}_{ij}\right) - \exp\left(-k_{a_j}\texttt{time}_{ij}\right)\right\} + \epsilon_{ij} \tag{18}$$

for $i = 1, \ldots, 11$ and $j = 1, \ldots, 12$. Model parameters are the elimination rate constant k_{e_j}, the absorption rate constant k_{a_j}, and the clearance Cl_j for each subject j.

Because each of the model parameters must be positive to be meaningful, we write

$$\begin{aligned} \mathrm{Cl}_j &= \exp\left(\beta_0 + u_{0j}\right) \\ k_{a_j} &= \exp\left(\beta_1 + u_{1j}\right) \\ k_{e_j} &= \exp\left(\beta_2\right) \end{aligned}$$

where u_{0j} and u_{1j} are assumed independent and normally distributed with means zero and variance $\sigma^2_{u_0}$ and $\sigma^2_{u_1}$, respectively.

The model defined by (18) implies that the predicted value for the concentration at time $\texttt{time}_{ij} = 0$ is $\widehat{\texttt{conc}}_{ij} = 0$. Therefore, a power variance function, a natural candidate for this type of heteroskedastic pattern, cannot be used in this example because error variance will be 0 at $\texttt{time}_{ij} = 0$. So the constant plus power variance function, which adds a constant to the power term, is used instead to model the within-group error variance:

$$\mathrm{Var}\left(\epsilon_{ij}\right) = \sigma^2 \{ (\widehat{\texttt{conc}}_{ij})^{\delta} + c \}^2$$

In `menl`, we use the `resvariance(power _yhat)` option to specify the constant plus power variance function and the following model specification:

```
. menl conc = (dose*{ke:}*{ka:}/({cl:}*({ka:}-{ke:})))*
> (exp(-{ke:}*time)-exp(-{ka:}*time)), define(cl: exp({b0}+{U0[subject]}))
> define(ka: exp({b1}+{U1[subject]})) define(ke: exp({b2}))
> resvariance(power _yhat)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -167.51953
Iteration 2:  Linearization log likelihood = -167.65729
  (iteration log omitted)
Iteration 26: Linearization log likelihood = -167.67966
Iteration 27: Linearization log likelihood = -167.67964
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        132
Group variable: subject                         Number of groups  =         12

                                                Obs per group:
                                                              min =         11
                                                              avg =       11.0
                                                              max =         11

Linearization log likelihood = -167.67964

          cl: exp({b0}+{U0[subject]})
          ka: exp({b1}+{U1[subject]})
          ke: exp({b2})

------------------------------------------------------------------------------
        conc | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
         /b0 |  -3.227479   .0598389   -53.94   0.000    -3.344761   -3.110197
         /b1 |    .432931   .1980835     2.19   0.029     .0446945    .8211674
         /b2 |  -2.453742   .0514567   -47.69   0.000    -2.554595   -2.352889
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
subject: Independent         |
                     var(U0) |   .0288787   .0127763      .0121337    .0687323
                     var(U1) |   .4075667   .1948715      .1596652    1.040368
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                      sigma2 |   .0976905   .0833035      .0183658    .5196322
                       delta |   .3187133   .2469532     -.1653061    .8027327
                       _cons |   .7288982   .3822983      .2607486    2.037567
------------------------------------------------------------------------------
```

The number of groups, 12, is fairly small in these data, so we now refit the model by using REML estimation.

```
. menl conc = (dose*{ke:}*{ka:}/({cl:}*({ka:}-{ke:})))*
> (exp(-{ke:}*time)-exp(-{ka:}*time)), define(cl: exp({b0}+{U0[subject]}))
> define(ka: exp({b1}+{U1[subject]})) define(ke: exp({b2}))
> resvariance(power _yhat) reml
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log restricted-likelihood = -172.31734
Iteration 2:  Linearization log restricted-likelihood = -172.42325
  (iteration log omitted)
Iteration 23: Linearization log restricted-likelihood = -172.44383
Iteration 24: Linearization log restricted-likelihood = -172.44384
Computing standard errors:
Mixed-effects REML nonlinear regression         Number of obs     =        132
Group variable: subject                         Number of groups  =         12

                                                Obs per group:
                                                              min =         11
                                                              avg =       11.0
                                                              max =         11

Linear. log restricted-likelihood = -172.44384

          cl: exp({b0}+{U0[subject]})
          ka: exp({b1}+{U1[subject]})
          ke: exp({b2})

------------------------------------------------------------------------------
        conc | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
         /b0 |  -3.227295   .0619113   -52.13   0.000    -3.348639   -3.105951
         /b1 |   .4354519   .2072387     2.10   0.036     .0292716    .8416322
         /b2 |  -2.453743   .0517991   -47.37   0.000    -2.555267   -2.352218
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
subject: Independent         |
                      var(U0)|   .0316416    .014531      .0128634    .0778326
                      var(U1)|   .4500585   .2228208      .1705474    1.187662
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                       sigma2|   .1015759    .086537      .0191255      .53947
                        delta|   .3106636   .2466593     -.1727797     .794107
                        _cons|   .7150935   .3745351       .256177    1.996114
------------------------------------------------------------------------------
```

As expected, the estimates of the random-effects variances are slightly larger than the corresponding ML estimates, but we arrive at similar inferential conclusions based on our REML estimates.

◁

▷ Example 16: Nonlinear functions of parameters

A distinctive feature of example 15 is that parameters of interest are nonlinear functions of the estimated parameters and random effects. To interpret parameters that depend on random effects, we can either integrate random effects out of the parameter expression or condition on them. The former parameter estimates are often referred to as population-based estimates. The latter parameter estimates are referred to as conditional estimates and, when conditioning on zero random effects, $\mathbf{u}_j = 0$, as estimates for an "average" or typical subject. For linear functions, the population-based estimates coincide with the conditional estimates. This is no longer true for nonlinear functions.

In PK modeling, the parameters of interest are clearance, elimination rate, and absorption rate. These are nonlinear functions of the estimated parameters β_0, β_1, β_2, and subject-specific random effects. Depending on the context, we may be interested in their population-based estimates or in their conditional estimates.

In general, obtaining population-based estimates would require numerical integration to integrate the subject-specific random effects out of the expression. In our example, we can compute population-based estimates directly by using the fact that $\exp(u_{0j})$'s and $\exp(u_{1j})$'s are lognormally distributed.

Thus the population-based clearance Cl^P can be computed as $E\left(\mathrm{Cl}_j\right) = E\left\{\exp\left(\beta_0 + u_{0j}\right)\right\} = \exp\left(\beta_0 + \sigma^2_{u_0}/2\right)$ and the population-based absorption rate k_a^P as $E\left\{\exp\left(\beta_1 + u_{1j}\right)\right\} = \exp\left(\beta_1 + \sigma^2_{u_1}/2\right)$. The elimination rate k_e does not depend on subject-specific effects and can thus be computed simply as $k_e^P = k_e = \exp\left(\beta_2\right)$.

Alternatively, if we want parameters to represent a typical subject, we can simply set $u_{0j} = 0$ and $u_{1j} = 0$ in their expressions. Thus we can compute clearance and absorption rate for a typical subject simply as $\mathrm{Cl} = \exp\left(\beta_0\right)$ and $k_a = \exp\left(\beta_1\right)$. These formulas can also be viewed as a result of exponentiating population-based log-clearance and log-absorption rate; that is, $\mathrm{Cl} = \exp\left[E\left\{\log(\mathrm{Cl}_j)\right\}\right] = \exp\left(\beta_0\right)$ and $k_a = \exp\left[E\left\{\log(k_{a_j})\right\}\right] = \exp\left(\beta_1\right)$.

If we compare the formulas for, say, Cl^P and Cl, the former considers variation in clearances across subjects, whereas the latter ignores such variation and instead reflects what the clearance would be for a typical subject with $u_{0j} = 0$.

Both approaches have merit, and here we will compute, for example, $\mathrm{Cl}^P = \exp(\widehat{\beta}_0 + \widehat{\sigma}^2_{u_0}/2) = \exp(-3.23 + 0.032/2) = 0.04$. That is, 0.04 liters of serum concentration are cleared of the theophylline drug per hour per kg body weight in the considered population. In other words, for the population of subjects that weigh 75 kg, an average of $75 \times 0.04 \approx 3$ liters of serum concentration are cleared of theophylline every hour.

We can also use `nlcom` to compute the estimates of Cl^P and Cl. To use `nlcom`, we need to know how parameters are labeled by `menl` for postestimation. We can use `menl`'s option `coeflegend` to display parameter names. We also specify `noheader` to suppress the table header.

```
. menl, coeflegend noheader

------------------------------------------------------------------------------
        conc |  Coefficient  Legend
-------------+----------------------------------------------------------------
         /b0 |   -3.227295  _b[/b0]
         /b1 |    .4354519  _b[/b1]
         /b2 |   -2.453743  _b[/b2]
-------------+----------------------------------------------------------------
/subject     |
    lnsd(U0) |   -1.726641  _b[/subject:lnsd(U0)]
    lnsd(U1) |   -.3991888  _b[/subject:lnsd(U1)]
-------------+----------------------------------------------------------------
/Residual    |
     lnsigma |   -1.143475  _b[/Residual:lnsigma]
       delta |    .3106636  _b[/Residual:delta]
     ln_cons |    -.335342  _b[/Residual:ln_cons]
------------------------------------------------------------------------------
```

If we examine the output carefully, we will notice that `menl, coeflegend` displayed results in the estimation metric—as log standard-deviations instead of variances. Although by default `menl` displays parameters in their original metric, it stores them in the estimation metric, the metric that was used during optimization; see *Examples of specifying initial values* and *Methods and formulas* for more details about the estimation metric.

The parameters we need to compute Cl^P and Cl are coefficient `_b[/b0]` and the variance of `U0`, which can be obtained as `exp(2*_b[/subject:lnsd(U0)])` based on the stored estimate of the log standard-deviation of `U0`. We now use `nlcom` to compute our nonlinear estimates.

```
. nlcom (Cl_P: exp(_b[/b0]+0.5*exp(2*_b[/subject:lnsd(U0)]))) (Cl: exp(_b[/b0]))

        Cl_P: exp(_b[/b0]+0.5*exp(2*_b[/subject:lnsd(U0)]))
          Cl: exp(_b[/b0])

------------------------------------------------------------------------------
        conc | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Cl_P |   .0402972    .002512    16.04   0.000     .0353738    .0452205
          Cl |   .0396646   .0024557    16.15   0.000     .0348516    .0444777
------------------------------------------------------------------------------
```

Working with parameters in the estimation metric can be tedious, especially when nonlinear expressions contain multiple variance components. In that case, you may consider using `estat sd` after `menl` to obtain results in the standard deviation metric or, if you also specify the `variance` option, in the variance metric; see [ME] **menl postestimation**. If you specify the `post` option with `estat sd`, the results will also be stored in the standard deviation or variance metrics, which you can use for further postestimation analysis.

```
. estat sd, post variance coeflegend

------------------------------------------------------------------------------
        conc | Coefficient  Legend
-------------+----------------------------------------------------------------
         /b0 |  -3.227295  _b[/b0]
         /b1 |   .4354519  _b[/b1]
         /b2 |  -2.453743  _b[/b2]
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Legend
-----------------------------+------------------------------------------------
subject: Independent         |
                     var(U0) |   .0316416  _b[/subject:var(U0)]
                     var(U1) |   .4500585  _b[/subject:var(U1)]
-----------------------------+------------------------------------------------
Residual variance:           |
  Power _yhat                |
                      sigma2 |   .1015759  _b[/Residual:sigma2]
                       delta |   .3106636  _b[/Residual:delta]
                       _cons |   .7150935  _b[/Residual:_cons]
------------------------------------------------------------------------------
```

In addition to results being displayed in the variance metric, because of the `post` option, they are stored in that metric. We also specified the `coeflegend` option with `estat sd` to see how parameters are labeled so that we could refer to them in other postestimation commands such as `nlcom`.

Now, we can simply refer to the variance of `U0` as `_b[/subject:var(U0)]` in our `nlcom` command.

```
. nlcom (Cl_P: exp(_b[/b0]+0.5*_b[/subject:var(U0)]))
        Cl_P: exp(_b[/b0]+0.5*_b[/subject:var(U0)])

------------------------------------------------------------------------------
             | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        Cl_P |   .0402972    .002512    16.04   0.000     .0353738    .0452205
------------------------------------------------------------------------------
```

estat sd's post option should be used with caution because it clears all estimation results except the parameter estimates in e(b) and their VCE in e(V). Thus the only postestimation features that will work after estat sd, post are those that need only e(b) and e(V), such as lincom and nlcom. Other postestimation features will not be available, and you will need to refit your model to run them. To avoid refitting your model, you may consider storing your estimation results in memory (see [R] **estimates store**) or saving them on disk (see [R] **estimates save**) before using estat sd, post. We no longer needed the estimation results from menl, so we did not mind clearing them.

◁

Multiple-dose pharmacokinetic modeling

In example 15, a single dose of the analgesic theophylline was administered to each subject followed by multiple serum concentration measurements per subject. For long-duration illnesses, multiple doses are often given to each subject, with multiple serum concentration measurements interspersed. After a single-dose drug administration, the plasma drug level rises above and then falls below the minimum effective concentration, resulting in a decline in therapeutic effect. To treat chronic diseases, multiple-dosage or intravenous infusion regimens are used to maintain the plasma drug levels within the narrow limits of the therapeutic window to achieve optimal clinical effectiveness.

▷ Example 17: Multiple-intravenous-doses model

Grasela and Donn (1985) report a study of the neonatal PKs of phenobarbital. Data were collected on 59 preterm infants given phenobarbital for prevention of seizures during the first 16 days after birth. Each infant received one or more intravenous doses, dose (mg/kg). One to six blood serum phenobarbital concentration measurements, conc (mg/L), were obtained from each infant, subject, for a total of 155 measurements. The birthweight, in kilograms, and a five-minute Apgar score, a measure of the physical condition, were also obtained on each infant. The Apgar score is obtained by adding points (2, 1, or 0) for heart rate, respiratory effort, muscle tone, response to stimulation, and skin coloration; a score of 10 represents the best possible condition. time is measured in hours. Davidian and Giltinan (1995) and Pinheiro and Bates (2000) also analyze this dataset.

A one-compartment open model with intravenous administration and first-order elimination was used to model the PKs of this phenobarbital study

$$\texttt{conc}_{ij} = \sum_{t \le i} \frac{\texttt{dose}_{ik}}{V_j} \exp\left\{-\frac{\text{Cl}_j}{V_j}\left(\texttt{time}_{ij} - \texttt{time}_{tj}\right)\right\} + \epsilon_{ij} \qquad (19)$$

for $i = 1, \ldots, n_j$ and $j = 1, \ldots, 59$. Model parameters are the clearance Cl_j (L/h) and volume of distribution V_j (L) for each subject j. Clearance is the volume of blood or plasma that is totally cleared of its content of drug per unit time. It is the proportionality factor between the rate of elimination and concentration, $dC/dt = -k_e C = -(\text{Cl}/V)\,C$, where C is the plasma concentration and k_e is the elimination rate (h^{-1}). The volume of distribution, V, is defined as the apparent space or volume into which a drug distributes.

To fit this model using `menl`, we consider an alternative recursive formulation of model (19)

$$\texttt{conc}_{ij} = \mu\left(\mathbf{x}'_{ij},\, \boldsymbol{\beta},\, \mathbf{u}_j\right) = \frac{\texttt{dose}_{ij}}{V_j} + \mu\left(\mathbf{x}'_{i-1,j},\, \boldsymbol{\beta},\, \mathbf{u}_j\right) \exp\left\{-\frac{\mathrm{Cl}_j}{V_j}\left(\texttt{time}_{ij} - \texttt{time}_{i-1,j}\right)\right\} + \epsilon_{ij}$$

Here, $\mathbf{x}'_{ij} = \left(\texttt{time}_{ij}, \texttt{dose}_{ij}, \texttt{fapgar}_j, \texttt{weight}_j\right)$ is the vector of covariates corresponding to subject j at $\texttt{time}_{ij}$. Notice that concentration $\texttt{conc}_{ij} = \mu\left(\mathbf{x}'_{ij},\, \boldsymbol{\beta},\, \mathbf{u}_j\right)$ depends on its previous expected value, $\mu\left(\mathbf{x}'_{i-1,j},\, \boldsymbol{\beta},\, \mathbf{u}_j\right)$, and on the time difference, $\texttt{time}_{ij} - \texttt{time}_{i-1,j}$. In Stata, we can use the lag operator, `L.`, to refer to previous values and the difference operator, `D.`, to refer to the difference between the two successive values. `menl` supports time-series operators in the model specification; see *Time-series operators*. We can use `D.time` to include the time difference in the model. However, we cannot simply use `L.conc`, because this would include the previous observed value of `conc` in the model, and we need the previous (predicted) value of the mean function. `menl` provides a special syntax `L._yhat` to include lagged predicted values or, equivalently, a special syntax `L.{conc:}` to include the lagged predicted mean function. `{conc:}` refers to the nonlinear expression for the mean function of the `conc` variable. Thus, our `menl` main specification of the recursive model would be

```
. menl conc = dose/{V:} + L.{conc:}*exp(-{Cl:}/{V:}*D.time), ...
```

where expressions for `{V:}` and `{Cl:}` will be defined later.

Because we are using time-series operators in the expression, we need to declare our data to be time-series data. There are two ways to do this: you can specify `tsset` prior to calling `menl` or you can specify the time variable in `menl`'s option `tsorder()`; see *Time-series operators* for details. In this example, we will use the `tsorder()` option; see the technical note below for an example using `tsset`.

```
. menl conc = dose/{V:} + L.{conc:}*exp(-{Cl:}/{V:}*D.time), ... tsorder(time)
```

Let's take a quick look at our data by listing the observations for the first subject.

```
. use https://www.stata-press.com/data/r18/phenobarb
(Pharmacokinetics study of phenobarbital in neonatal infants)
. list if subject==1, sepby(subject)

     +---------------------------------------------------------------+
     | subject   weight   apgar    time   dose   conc   fapgar |
     |---------------------------------------------------------------|
  1. |       1      1.4       7       0     25      .     >= 5 |
  2. |       1      1.4       7       2      0   17.3     >= 5 |
  3. |       1      1.4       7    12.5    3.5      .     >= 5 |
  4. |       1      1.4       7    24.5    3.5      .     >= 5 |
  5. |       1      1.4       7      37    3.5      .     >= 5 |
  6. |       1      1.4       7      48    3.5      .     >= 5 |
  7. |       1      1.4       7    60.5    3.5      .     >= 5 |
  8. |       1      1.4       7    72.5    3.5      .     >= 5 |
  9. |       1      1.4       7    85.3    3.5      .     >= 5 |
 10. |       1      1.4       7    96.5    3.5      .     >= 5 |
 11. |       1      1.4       7   108.5    3.5      .     >= 5 |
 12. |       1      1.4       7   112.5      0     31     >= 5 |
     +---------------------------------------------------------------+
```

The most noticeable feature of our PK data is the presence of many missing values for the concentration. In fact, this is a common structure of PK data in the presence of multiple doses. Notice that the `conc` variable contains missing values for each nonzero `dose`. It is typical to measure concentration only after a dose or multiple doses are administered, which gives rise to missing concentration at some time points. By default, Stata commands omit all observations containing missing values in variables used with the command. In this example, we need to retain missing `conc` observations. We can use `menl`'s option `tsmissing` to do so.

```
. menl conc = dose/{V:} + L.{conc:}*exp(-{Cl:}/{V:}*D.time), ... tsmissing tsorder(time)
```

When you specify the `tsmissing` option, `menl` uses predicted values in place of system missing `conc` values in the computation. (Observations with extended missing values `.a`, `.b`, and so on in `conc`, if there were any, would have been omitted from the computation.) These predicted values are used to compute predicted values for the observed concentrations but are not used to compute the log likelihood. Only observed concentrations contribute to the log-likelihood calculation.

Another aspect of our data is that they are time-series data. Thus, the first observation in each panel provides starting values for the time-series operators. For example, from the data, the initial time value used by `D.time` for the first subject is $\texttt{time}_{i-1,j} = \texttt{time}_{0,1} = 0$. But how do we initialize `L.{conc:}` given that `{conc:}` does not exist as a variable in our dataset? We use `menl`'s option `tsinit()`.

```
. menl conc = dose/{V:} + L.{conc:}*exp(-{Cl:}/{V:}*D.time), ...
> tsinit({conc:}=dose/{V:}) tsmissing tsorder(time)
```

The `tsinit()` option allows us to specify initial conditions for the lagged predicted mean functions as expressions. In our example, the initial condition for the mean concentration for each subject j at time 0 is $\texttt{dose}_{0,j}/V_j$, which we specified in `tsinit()`.

Let's now return to our nonlinear model specification and provide expressions for `{V:}` and `{Cl:}`. One of the model parameterizations that Davidian and Giltinan (1995) consider for these data use `weight` as a covariate for clearance and volume. They also include a dichotomized Apgar score, factor variable `fapgar` in our dataset, to model volume. They express clearance and volume as

$$\begin{aligned} \mathrm{Cl}_j &= \beta_1 \texttt{weight}_j \times \exp(u_{1j}) \\ V_j &= \beta_2 \texttt{weight}_j (1 + \beta_3 \texttt{fapgar}_j) \exp(u_{2j}) \end{aligned}$$

where u_{1j}'s and u_{2j}'s are two independent sets of random effects that follow $N\left(0, \sigma^2_{u1}\right)$ and $N\left(0, \sigma^2_{u2}\right)$, respectively.

We specify the above expressions for subject-specific volume and clearance in `menl` using the `define()` options and fit the model:

```
. menl conc = dose/{V:} + L.{conc:}*exp(-{Cl:}/{V:}*D.time),
> define(Cl: {cl:weight}*weight*exp({U1[subject]}))
> define(V: {v:weight}*weight*(1+{v:apgar}*1.fapgar)*exp({U2[subject]}))
> tsinit({conc:} = dose/{V:})
> tsmissing tsorder(time)

Panel variable: subject (unbalanced)
 Time variable: <time>, 1 to 20
         Delta: 1 unit
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -432.58887
Iteration 2:  Linearization log likelihood = -436.35525
Iteration 3:  Linearization log likelihood = -436.36735
Iteration 4:  Linearization log likelihood = -436.36894
Iteration 5:  Linearization log likelihood =   -436.369
Iteration 6:  Linearization log likelihood = -436.36896
Computing standard errors:
Mixed-effects ML nonlinear regression              Number of obs =        685
                                                      Nonmissing =        155
                                                         Missing =        530

      Grouping information
      ───────────────────────────────────────────────────────────────────
                      │     No. of       Observations per group
                 Path │     groups    Minimum    Average    Maximum
      ────────────────┼──────────────────────────────────────────────────
              subject │         59          1       11.6         19
                 conc │         59          1        2.6          6
      ───────────────────────────────────────────────────────────────────

Linearization log likelihood = -436.36896
          Cl: {cl:weight}*weight*exp({U1[subject]})
           V: {v:weight}*weight*(1+{v:apgar}*1.fapgar)*exp({U2[subject]})

────────────────────────────────────────────────────────────────────────────────
        conc │ Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
─────────────┼──────────────────────────────────────────────────────────────────
/cl          │
      weight │    .004705   .0002219    21.20   0.000     .0042701      .00514
─────────────┼──────────────────────────────────────────────────────────────────
/v           │
      weight │   .9657032   .0294438    32.80   0.000     .9079945    1.023412
       apgar │   .1749755   .0845767     2.07   0.039     .0092082    .3407429
────────────────────────────────────────────────────────────────────────────────

────────────────────────────────────────────────────────────────────────────────
  Random-effects parameters  │  Estimate   Std. err.     [95% conf. interval]
─────────────────────────────┼──────────────────────────────────────────────────
subject: Independent         │
                     var(U1) │  .0404098   .0187133      .0163044    .1001537
                     var(U2) │   .030259   .0078857      .0181562    .0504295
─────────────────────────────┼──────────────────────────────────────────────────
               var(Residual) │  7.469354   1.280411      5.337875    10.45196
────────────────────────────────────────────────────────────────────────────────
Note: Lagged predicted mean function L.{conc:} is used in the model.
```

From the coefficient table, we see that heavier babies have a higher clearance and volume of distribution. There is a positive association between the volume of distribution and the Apgar score: healthier babies have a better ability to eliminate the drug.

Because we specified the tsmissing option, the header reported the number of missing and nonmissing concentration values used in the computation. Also, the table containing the information about the number of groups has an additional entry for conc providing the group information for nonmissing observations of conc.

When we specified the time variable in the tsorder() option, menl generated the corresponding consecutive integer-valued time variable and used it with tsset. From the output of tsset, as displayed by menl, we see that menl also identified the panel variable, subject, from our model specification and used it with tsset. The generated time variable used with tsset is labeled as <time> in the output.

◁

❑ Technical note

In example 17, we used the tsorder() option to specify the ordering for time-series operators. We could have used tsset instead, but we would need to create the appropriate time variable first. Here, we demonstrate how to do this.

We must specify the panel and time variables with tsset. Intuitively, we would want to type

```
. tsset subject time
```

but that would not produce the intended results. First, tsset requires an integer time variable, which the time variable is not. Second, even if time contained integers, it is not equally spaced, which would lead to gaps in the time series and thus missing values for time-series operators.

In our example, we are concerned only with the ordering of observations within a subject with respect to the time variable for the purpose of time-series operators. So, we create a new variable, tsorder, to contain consecutive integers based on time and use it with tsset.

```
. sort subject time
. by subject (time): generate long tsorder = _n
. tsset subject tsorder
Panel variable: subject (unbalanced)
 Time variable: tsorder, 1 to 20
         Delta: 1 unit
```

You can verify that the following specification of menl will produce the same results as in example 17.

```
. menl conc = dose/{V:} + L.{conc:}*exp(-{Cl:}/{V:}*D.time),
> define(Cl: {cl:weight}*weight*exp({U1[subject]}))
> define(V: {v:weight}*weight*(1+{v:apgar}*1.fapgar)*exp({U2[subject]}))
> tsinit({conc:} = dose/{V:})
> tsmissing
  (output omitted)
```

Note that we still use the time variable with the difference operator, D., in the model specification.

❑

▷ Example 18: Multiple-oral-doses model

Verme et al. (1992) evaluated the PK behavior of quinidine, a pharmaceutical agent used to prevent cardiac arrhythmias, in a study of 136 subjects receiving oral quinidine therapy. A total of 361 serum quinidine concentrations (variable conc, mg/L) were measured over time (variable time, hours), ranging from 1 to 11 observations per subject. Multiple doses (variable dose, mg) of quinidine, in two different forms, were administrated to each subject. The doses were adjusted for differences in salt content by conversion into milligrams of quinidine base. These data are also presented as examples in Davidian and Giltinan (1995) and Pinheiro and Bates (2000).

A one-compartment open model with first-order absorption and elimination is assumed for serum quinidine concentrations. This model, expressed in a compact recursive form, is

$$\texttt{conc}_{ij} = \mu_1\left(\mathbf{x}'_{ij},\,\boldsymbol{\beta},\,\mathbf{u}_j\right) = \mu_1\left(\mathbf{x}'_{i-1,j},\,\boldsymbol{\beta},\,\mathbf{u}_j\right)Q_{e_{ij}} + \mathrm{Ca}_{i-1,j}\frac{k_{a_j}}{k_{a_j}-k_{e_j}}\left(Q_{e_{ij}}-Q_{a_{ij}}\right)+\epsilon_{ij} \tag{20}$$

where

$$\begin{aligned}
\mathrm{Ca}_{ij} &= \mu_2\left(\mathbf{z}'_{ij},\,\boldsymbol{\beta},\,\mathbf{u}_j\right) = \mu_2\left(\mathbf{z}'_{i-1,j},\,\boldsymbol{\beta},\,\mathbf{u}_j\right)Q_{a_{ij}} + \frac{\texttt{dose}_{ij}}{V_j}\\
Q_{e_{ij}} &= \exp\left\{-k_{e_j}\left(\texttt{time}_{ij}-\texttt{time}_{i-1,j}\right)\right\}\\
Q_{a_{ij}} &= \exp\left\{-k_{a_j}\left(\texttt{time}_{ij}-\texttt{time}_{i-1,j}\right)\right\}
\end{aligned}$$

for subject $j = 1,\ldots,136$ and subject observation $i = 1,\ldots,n_j$, $n_j \in [1,11]$. The quantities $Q_{a_{ij}}$ and $Q_{e_{ij}}$ are defined for notational convenience to simplify the model expression. $\mathbf{z}'_{ij} = \left(\texttt{time}_{ij}, \texttt{dose}_{ij}\right)$ and $\mathbf{x}'_{ij} = \left(\mathbf{z}'_{ij}, \texttt{glyco}_{ij}, \texttt{creatinine}_j, \texttt{weight}_j\right)$ are vectors of covariates, which we describe later, corresponding to subject j at $\texttt{time}_{ij}$. Because the drug administration is extravascular, the quinidine concentration in the body over time is a function of both the absorption rate, k_{a_j}, and the elimination rate, k_{e_j}, for subject j. The function Ca_{ij} is the apparent concentration of quinidine in the absorption depot over time (indexed by i) for subject j.

From example 17, we know that $k_{e_j} = \mathrm{Cl}_j/V_j$, where Cl_j is the clearance, defined as the volume of plasma or blood that is totally cleared from its content of drug per unit time, and V_j is the apparent volume of distribution, defined as theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that is observed in the blood plasma.

The `menl` specification corresponding to model (20) is

```
. menl conc = L.{conc:}*{Qe:}+L.{Ca:}*({ka:}/({ka:}-{ke:}))*({Qe:}-{Qa:}),
> define(Ca: L.{Ca:}*{Qa:}+dose/{V:})
> define(Qe: exp(-{ke:}*D.time))
> define(Qa: exp(-{ka:}*D.time))
> define(ke: {Cl:}/{V:})
> define(ka: exp({lka}))
> ...
```

where expressions for `{Cl:}` and `{V:}` will be defined later. Similarly to example 17, we use `D.time` to specify differences between two successive time values and `L.{conc:}` to specify the lagged predicted mean function; also see *Time-series operators*. New in this specification is the inclusion of the lagged function of model parameters or lagged named expression `L.{Ca:}`. Expression `Ca` is defined in the `define()` option and is a function of its own lag, `L.{Ca:}`. Finally, parameter `{ka}` is reparameterized as `exp({lka})` to ensure that it is positive.

When a patient receives the same dosage at regular time intervals (variable `interval`), model (20) simplifies to the steady-state model

$$\texttt{conc}^{ss}_{ij} = \frac{\texttt{dose}_{ij}k_{a_j}}{V_j\left(k_{a_j}-k_{e_j}\right)}\left(Q^{ss}_{e_{ij}} - Q^{ss}_{a_{ij}}\right) \tag{21}$$

and

$$\text{Ca}_{ij}^{ss} = \frac{\texttt{dose}_{ij}}{V_j} Q_{a_{ij}}^{ss}$$

where

$$Q_{e_{ij}}^{ss} = \frac{1}{1 - \exp\left(-k_{e_j}\texttt{interval}_{ij}\right)}$$
$$Q_{a_{ij}}^{ss} = \frac{1}{1 - \exp\left(-k_{a_j}\texttt{interval}_{ij}\right)}$$

The quantities $Q_{e_{ij}}^{ss}$ and $Q_{a_{ij}}^{ss}$ are also defined for notational convenience.

The menl specification corresponding to model (21) is

```
. menl conc = dose*{ka:}/({V:}*({ka:}-{ke:}))*({Qe_ss:} - {Qa_ss:}),
> define(Qe_ss: 1/(1-exp(-{ke:}*interval))
> define(Qa_ss: 1/(1-exp(-{ka:}*interval))
> define(ke: {Cl:}/{V:})
> define(ka: exp({lka}))
> ...
```

For the quinidine model, the steady-state model (21) is assumed whenever $\texttt{interval}_{ij}$ is nonzero and the nonsteady-state model (20) is assumed otherwise. Thus, we need to switch back and forth between these two models in our menl specification. We can use the Stata function cond(*condition*,*expr_if_condition_true*,*expr_if_condition_false*).

For example, the menl specification becomes

```
. menl conc = cond(interval==0,
>                  L.{conc:}*{Qe:}+L.{Ca:}*({ka:}/({ka:}-{ke:}))*({Qe:}-{Qa:}),
>                  dose*{ka:}/({V:}*({ka:}-{ke:}))*({Qe_ss:} - {Qa_ss:})),
> define(Ca: cond(interval==0, L.{Ca:}*{Qa:}+dose/{V:}, dose/{V:}*{Qa_ss:})
> ...
```

where other expressions such as {Qe:} and {Qa_ss:} are as defined earlier. We used cond() for the main menl specification and for the definition of the {Ca:} function.

Recall from example 17 that when we specify the lagged predicted mean function, we need to specify an initial condition for it in the tsinit() option. Just like the main nonlinear specification, the initial condition for L.{conc:} will depend on the value of interval. The mean concentration at time 0 will be 0 for observations with zero interval values and will be equal to the expression for the steady-state model otherwise: tsinit({conc:}=cond(interval==0,0,dose*{ka:}/({V:}*({ka:}-{ke:}))*({Qe_ss:}-{Qa_ss:}))). Similarly, we need to provide an initial condition for the lagged function of model parameters L.{Ca:}. It also depends on interval: tsinit({Ca:} = cond(interval==0,dose/{V:},dose/{V:}*{Qa_ss:})). Because we are using the same expressions in the function definitions and the initial conditions, we can define additional functions to minimize typing:

```
. menl conc = cond(interval==0,
>                  L.{conc:}*{Qe:}+L.{Ca:}*({ka:}/({ka:}-{ke:}))*({Qe:}-{Qa:}),
>                  {Css:}),
> define(Ca: cond(interval==0,L.{Ca:}*{Qa:}+dose/{V:}, {Ca_ss:})
> define(Css: cond(interval==0,0,dose*{ka:}/({V:}*({ka:}-{ke:}))*({Qe_ss:}-{Qa_ss:})))
> define(Ca_ss: dose/{V:}*{Qa_ss:})
> ...
> tsinit({conc:} = cond(interval==0, 0, {Css:})
> tsinit({Ca:} = cond(interval==0, dose/{V:}, {Ca_ss:})
```

`{Css:}` contains the expression for the steady-state model (or 0 for observations in a nonsteady state), and `{Ca_ss:}` contains the expression for the `Ca` function in the steady state.

Let's now finalize our `menl` specification by defining expressions for `{Cl:}` and `{V:}`. The goal of the study from Verme et al. (1992) was to examine the relationship between quinidine PKs and several potential covariates: body `weight` (kg); `age` (years); `height` (in); `glyco`, α_1-acid glycoprotein concentration (mg/dL); `creatinine`, creatinine clearance ($\geq$ 50 or $<$ 50 ml/min); `race` (Caucasian, Latin, black); `smoke`, smoking status (yes, no); `ethanol`, alcohol abuse (former, none, current); and `heart`, congestive heart failure (no or mild, moderate, severe). We provide more details about covariates `creatinine` and `glyco` below.

Creatinine is a waste product from the normal breakdown of muscle tissue. As creatinine is produced, it is filtered through the kidneys and excreted in urine. Doctors use creatinine and creatinine clearance tests to check renal function (kidney function). Testing the rate of creatinine clearance shows the kidneys' ability to filter the blood. As renal function declines, creatinine clearance also goes down. Creatinine clearance in a healthy young person is about 95 ml/min for women and 120 ml/min for men.

α_1-acid glycoprotein (also known as AAG) is an important plasma protein involved in the binding and transport of many drugs, including quinidine. A healthy range is 50–120 mg/dl. Changes in AAG concentration could potentially alter the free fraction of drugs in plasma or at their target sites and eventually affect their PK disposition and pharmacological action. Because AGG levels are increased in response to stress, serum levels of total quinidine may be greatly increased in settings such as acute myocardial infarction. Protein binding is also increased in chronic renal failure. There tends to be a small increase in AAG with age.

For the purpose of illustration, we fit a modified version of model 2 from pages 248–249 of Davidian and Giltinan (1995). The clearance, Cl_j, is modeled on the log scale as a linear combination `{lCl:}` of `glyco`, `ib1.creatinine`, `weight`, and a random intercept, `U1`, at the `subject` level. The apparent volume, V_j, is modeled on the log scale using a fixed-effect intercept and `weight`. The absorption rate, k_a, is modeled on the log scale as a free parameter `{lka}`, and is assumed fixed for all subjects. The full second-stage specification is as follows:

$$\begin{aligned}
\mathrm{Cl}_{ij} &= \exp\left(\beta_1 + \beta_2 \texttt{glyco}_{ij} + \beta_3 \texttt{creatinine}_j + \beta_4 \texttt{weight}_j + u_{1j}\right)\\
V_j &= \exp\left(\beta_5 + \beta_6 \texttt{weight}_j\right)\\
k_{a_j} &= \exp\left(\beta_7\right)\\
k_{e_{ij}} &= \frac{\mathrm{Cl}_{ij}}{V_j}
\end{aligned}$$

where u_{1j}'s are random effects that follow $N\left(0, \sigma^2_{u1}\right)$.

Similarly to the phenobarbital data from example 17, the quinidine data also contain missing concentration values, so we specify the tsmissing option to retain them in the computation. Again, we will specify the time variable in the tsorder() option and let menl tsset the data for us.

```
. use https://www.stata-press.com/data/r18/quinidine

. menl conc = cond(interval==0,
>                  L.{conc:}*{Qe:}+L.{Ca:}*({ka:}/({ka:}-{ke:}))*({Qe:}-{Qa:}),
>                  {Css:}),
> define(Ca: cond(interval==0, L.{Ca:}*{Qa:}+dose/{V:}, {Ca_ss:}))
> define(Qe: exp(-{ke:}*D.time))
> define(Qa: exp(-{ka:}*D.time))
> define(Css: cond(interval==0,0,{ka:}*dose/({V:}*({ka:}-{ke:}))*({Qe_ss:}-{Qa_ss:})))
> define(Ca_ss: cond(interval==0,0,dose/{V:}*{Qa_ss:}))
> define(Qe_ss: 1/(1-exp(-{ke:}*interval)))
> define(Qa_ss: 1/(1-exp(-{ka:}*interval)))
> define(ke: {Cl:}/{V:})
> define(ka: exp({lka}))
> define(Cl: exp({lCl:glyco ib1.creatinine weight U1[subject], xb}))
> define(V: exp({lV: weight, xb}))
> tsinit({conc:} = cond(interval==0, 0, {Css:}))
> tsinit({Ca:} = cond(interval==0, dose/{V:}, {Ca_ss:}))
> tsorder(time) tsmissing

Panel variable: subject (unbalanced)
 Time variable: <time>, 1 to 47
         Delta: 1 unit

Obtaining starting values by EM:

Alternating PNLS/LME algorithm:

Iteration 1:  Linearization log likelihood = -423.26688
Iteration 2:  Linearization log likelihood = -425.82312
Iteration 3:  Linearization log likelihood = -425.81124
Iteration 4:  Linearization log likelihood =  -425.8119
Iteration 5:  Linearization log likelihood = -425.81241
Iteration 6:  Linearization log likelihood = -425.81223
Iteration 7:  Linearization log likelihood = -425.81233
Iteration 8:  Linearization log likelihood = -425.81228
Iteration 9:  Linearization log likelihood = -425.81231

Computing standard errors:

Mixed-effects ML nonlinear regression               Number of obs =      1,335
                                                       Nonmissing =        361
                                                          Missing =        974

      Grouping information
      ──────────────────────────────────────────────────────────────────
                      │     No. of       Observations per group
                 Path │     groups    Minimum    Average    Maximum
      ────────────────┼─────────────────────────────────────────────────
              subject │        136          1        9.8         46
                 conc │        136          1        2.7         11
      ──────────────────────────────────────────────────────────────────
```

```
                                                Wald chi2(4)      =     169.94
Linearization log likelihood = -425.81231       Prob > chi2       =     0.0000
          Ca: cond(interval==0,L.{Ca:}*{Qa:}+dose/{V:},{Ca_ss:})
       Ca_ss: cond(interval==0,0,dose/{V:}*{Qa_ss:})
          Cl: exp({lCl:})
         Css: cond(interval==0,0,{ka:}*dose/({V:}*({ka:}-{ke:}))*({Qe_ss:}-{
              Qa_ss:}))
          Qa: exp(-{ka:}*D.time)
       Qa_ss: 1/(1-exp(-{ka:}*interval))
          Qe: exp(-{ke:}*D.time)
       Qe_ss: 1/(1-exp(-{ke:}*interval))
           V: exp({lV:})
          ka: exp({lka})
          ke: {Cl:}/{V:}
         lCl: glyco ib1.creatinine weight U1[subject], xb
          lV: weight, xb

------------------------------------------------------------------------------
        conc | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
lCl          |
       glyco |  -.4689097   .0416876   -11.25   0.000    -.5506159   -.3872035
             |
  creatinine |
       >= 50 |   .1851334   .0464825     3.98   0.000     .0940294    .2762373
      weight |   .0036181   .0018213     1.99   0.047     .0000485    .0071877
       _cons |   2.668191   .1524726    17.50   0.000      2.36935    2.967031
-------------+----------------------------------------------------------------
lV           |
      weight |   .0087346   .0058603     1.49   0.136    -.0027514    .0202206
       _cons |   4.572762     .47765     9.57   0.000     3.636585    5.508939
-------------+----------------------------------------------------------------
        /lka |  -.8956278       .301    -2.98   0.003    -1.485577   -.3056787
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
subject: Identity            |
                     var(U1) |   .0589024   .0108271      .0410838    .0844492
-----------------------------+------------------------------------------------
               var(Residual) |   .4122599   .0364831       .346612    .4903413
------------------------------------------------------------------------------
Note: Lagged predicted mean function L.{conc:} is used in the model.
Note: Lagged named expression L.{Ca:} is used in the model.
```

From the coefficient table, we see that the clearance decreases with increase of AAG (glyco) as would be expected with the greater protein binding. The clearance is greater for creatinine clearance ≥ 50 as would be expected with better renal function. Both clearance and volume increase with weight; although, the effect of weight on volume is not statistically significant at the 5% level. The subject variability for clearance contributes to the model as seen by the confidence interval for the random-effects variance var(U1).

◁

Nonlinear marginal models

The variance–covariance matrix of the response vector $\mathbf{y}_j = \left(y_{1j}, \ldots, y_{n_j j}\right)$ involves two components to model heteroskedasticity and correlation: A random-effects component $\boldsymbol{\Sigma}$ and a within-group error component $\boldsymbol{\Lambda}_j$. In some applications, one may wish to directly model the covariance structure of the response by choosing the appropriate within-group error component $\boldsymbol{\Lambda}_j$ without introducing random effects. This results in the so-called nonlinear marginal model (for example, Pinheiro and Bates [2000, sec. 7.5.1]):

$$\begin{aligned} &\text{Stage 1: Individual-level model } \mathbf{y}_j = m\left(\mathbf{x}_j^w, \boldsymbol{\phi}_j\right) + \boldsymbol{\epsilon}_j && \boldsymbol{\epsilon}_j \sim N\left(\mathbf{0}, \sigma^2 \boldsymbol{\Lambda}_j\right) \\ &\text{Stage 2: Group-level model } \boldsymbol{\phi}_j = \boldsymbol{d}\left(\mathbf{x}_j^b, \boldsymbol{\beta}\right) && j = 1, \ldots, M \end{aligned}$$

The above is essentially a vector representation of (2) after excluding the random effects $\mathbf{u}_j$. Random effects are used in NLME models to explain the between-subject or between-group variation, but they are not used in the specification of nonlinear marginal models. This key difference implies that mixed-effects models allow for subject-specific inference, whereas marginal models do not. For this reason, mixed-effects models are often called subject-specific models, while marginal models are called population-averaged models.

`menl` provides the `group()` suboption within the `rescovariance()` and `rescorrelation()` options to model the dependence between within-group observations without introducing random effects. Below, we show an example of fitting a nonlinear marginal model, without random effects, using the `group()` suboption. See example 22 for the usage of the `group()` suboption in the presence of random effects.

▷ Example 19: Nonlinear marginal model

Vonesh and Carter (1992) analyzed data on 20 high-flux hemodialyzers to assess their in-vitro ultrafiltration performance. Dialyzers are used in hemodialysis, a treatment that replaces the work of kidneys, to filter harmful wastes out of blood for patients with kidney failure. High-flux dialyzers do this more efficiently than conventional dialyzers—they are composed of membranes with larger pores, which allows them to remove larger molecules and water during blood filtration. A dialyzer's ultrafiltration performance, or ability to filter blood, is controlled by so-called transmembrane pressure and also depends on the blood flow rate used during hemodialysis. In these data, the response variable, `rate`, is the dialyzer's ultrafiltration rate in mL/hr measured at 7 different transmembrane pressures, `pressure`, in dmHg. Ten dialyzers were evaluated using bovine blood at a blood flow rate, `qb`, of 200 mL/min, whereas the other 10 dialyzers were evaluated at 300 mL/min.

The ultrafiltration rate, $\texttt{rate}_{ij}$, at the ith transmembrane pressure, $\texttt{pressure}_{ij}$, for the jth subject is represented by the nonlinear model

$$\texttt{rate}_{ij} = \phi_{1j}\left[1 - \exp\left\{-\exp(\phi_{2j})\left(\texttt{pressure}_{ij} - \phi_3\right)\right\}\right] + \epsilon_{ij}$$

The parameters ϕ_1, ϕ_2, and ϕ_3 have physiological interpretation: ϕ_1 is the maximum attainable ultrafiltration rate, ϕ_2 is the logarithm of the hydraulic permeability transport rate of the membrane (rate at which water and molecules pass through the dialyzer membrane), and ϕ_3 is the transmembrane pressure required to offset the oncotic pressure (the transmembrane pressure at which the ultrafiltration rate is 0).

One of the models proposed in Vonesh and Carter (1992) included no random effects and used an exchangeable (also known as compound symmetry) covariance structure to model the within-dialyzer error covariance structure. The full description of the second stage of the model is

$$\phi_{1j} = \beta_{10} + \beta_{11}\texttt{qb}_j$$
$$\phi_{2j} = \beta_{20} + \beta_{21}\texttt{qb}_j$$
$$\phi_{3j} = \beta_3$$

and

$$\boldsymbol{\epsilon}_j \sim N(\mathbf{0}, \sigma^2_\epsilon \boldsymbol{\Lambda}_j), \quad \boldsymbol{\Lambda}_j = \begin{bmatrix} 1 & \rho & \dots & \rho \\ & 1 & \dots & \rho \\ & & \ddots & \vdots \\ & & & 1 \end{bmatrix}$$

Below, we use `rescovariance(exchangeable, group(dialyzer))` to request an exchangeable within-group error covariance structure where groups are identified by the `dialyzer` variable.

```
. use https://www.stata-press.com/data/r18/dialyzer
(High-flux hemodialyzers (Vonesh and Carter, 1992))
. menl rate = {phi1:}*(1-exp(-exp({phi2:})*(pressure - {phi3}))),
> define(phi1: i.qb, xb) define(phi2: i.qb, xb)
> rescovariance(exchangeable, group(dialyzer)) stddev
Obtaining starting values:
Alternating GNLS/ML algorithm:
Iteration 1:  Log likelihood = -365.34244
Iteration 2:  Log likelihood = -365.32697
Iteration 3:  Log likelihood = -365.32697
Iteration 4:  Log likelihood = -365.32697
Iteration 5:  Log likelihood = -365.32697
Iteration 6:  Log likelihood = -365.32697
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        140
Group variable: dialyzer                        Number of groups  =         20
                                                Obs per group:
                                                              min =          7
                                                              avg =        7.0
                                                              max =          7
                                                Wald chi2(2)      =     194.77
Log likelihood = -365.32697                     Prob > chi2       =     0.0000
        phi1: i.qb
        phi2: i.qb

------------------------------------------------------------------------------
        rate | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
          qb |
        300  |   17.23062    1.24589    13.83   0.000     14.78872    19.67252
       _cons |   44.95795   .8841506    50.85   0.000     43.22505    46.69086
-------------+----------------------------------------------------------------
phi2         |
          qb |
        300  |  -.5034708   .0763513    -6.59   0.000    -.6531166   -.353825
       _cons |   .7626986   .0630914    12.09   0.000     .6390417    .8863555
-------------+----------------------------------------------------------------
       /phi3 |   .2249104   .0102113    22.03   0.000     .2048965    .2449243
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
Residual: Exchangeable       |
                          sd |   3.722521   .3064517      3.167839    4.374326
                        corr |   .3867847   .0993617      .1771207    .5628661
------------------------------------------------------------------------------
```

The estimated values of ρ and σ_ϵ are $\widehat{\rho} = 0.39$ and $\widehat{\sigma}_e = 3.72$, respectively. The 95% confidence interval [0.18, 0.56] for ρ suggests a positive correlation within dialyzer measurements. The maximum ultrafiltration rate, ϕ_1, and the logarithm of the hydraulic permeability transport rate, ϕ_2, appear to be affected by the blood flow rate.

◁

Three-level models

Representation of (1) can be extended to, for example, two-nested levels of clustering, to form the following three-level model, with observations composing the first level,

$$\mathbf{y}_{jk} = \boldsymbol{\mu}\left(\mathbf{X}_{jk}, \boldsymbol{\beta}, \mathbf{u}_k^{(3)}, \mathbf{u}_{jk}^{(2)}\right) + \boldsymbol{\epsilon}_{jk}$$

where the first-level observations $i = 1, \ldots, n_{jk}$ are nested within the second-level groups $j = 1, \ldots, M_k$, which are nested within the third-level groups $k = 1, \ldots, M$. Group j nested within group k consists of n_{jk} observations, so $\mathbf{y}_{jk}$, $\mathbf{X}_{jk}$, and $\boldsymbol{\epsilon}_{jk}$ each have row dimension n_{jk}.

Also, assume that

$$\mathbf{u}_k^{(3)} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_3) \qquad \mathbf{u}_{jk}^{(2)} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_2) \qquad \boldsymbol{\epsilon}_{jk} \sim N(\mathbf{0}, \sigma^2 \boldsymbol{\Lambda}_{jk})$$

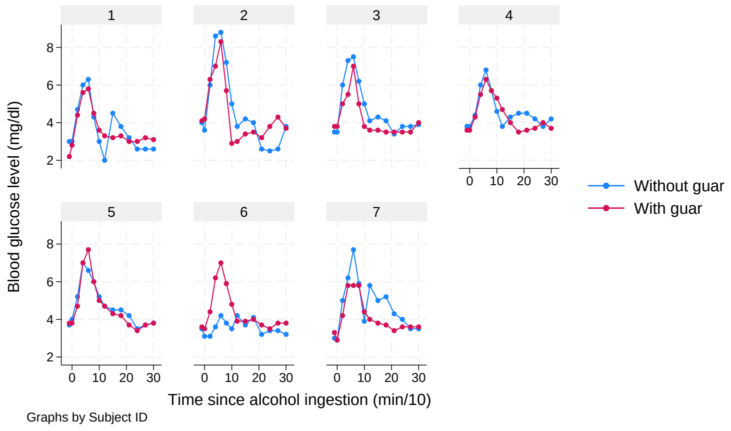
and that $\mathbf{u}_k^{(3)}$, $\mathbf{u}_{jk}^{(2)}$, and $\boldsymbol{\epsilon}_{jk}$ are independent.

▷ Example 20: Three-level model

Hand and Crowder (1996, 118–120) analyzed a study where the blood glucose levels `glucose` of 7 volunteers, `subject`, who took alcohol at time 0 were measured 14 times, `time`, over a period of 5 hours after alcohol consumption. The same experiment was repeated at a later date with the same subjects but with a dietary additive, guar, used for all subjects. Variable `guar` is a binary variable that identifies whether a subject received a dietary additive. It also identifies each experiment, with 0 corresponding to the experiment without guar and 1 corresponding to the experiment with guar. Thus we will use the `guar` variable both as the level indicator and, later, as a fixed-effects variable.

Here is a plot of the whole dataset.

```
. use https://www.stata-press.com/data/r18/glucose
(Glucose levels following alcohol ingestion (Hand and Crowder, 1996))
. twoway connected glucose time if guar==0 ||
> connected glucose time if guar==1 ||, by(subject, rows(2))
> legend(order(1 "Without guar" 2 "With guar"))
```



Our preliminary assessment based on the above graph is that, except for subject 6, the effect of the dietary additive guar on the temporal trajectory of the blood glucose levels does not seem to be important. The effect of guar will be formally tested in example 21.

Hand and Crowder (1996) proposed the following empirical model relating the expected glucose level to time,

$$\texttt{glucose}_{ijk} = \phi_{1jk} + \phi_{2jk}\texttt{time}^3 \exp\left(-\phi_{3jk}\texttt{time}\right) + \epsilon_{ijk} \tag{22}$$

where $k = 1, \ldots, 7$, $j = 1, 2$, and $i = 1, \ldots, 14$. The blood glucose level is ϕ_1 at $\texttt{time} = 0$ and as $\texttt{time} \to \infty$. This is intentional, so that ϕ_1 can be interpreted as both the blood glucose level before ingesting alcohol and the blood glucose level after the effect of alcohol ingestion has washed out.

Pinheiro and Bates (2000, exercise 3, 412) analyzed this dataset in the context of a three-level NLME model. They initially proposed the following stage 2 specification,

$$\begin{aligned} \phi_{1jk} &= \beta_1 + u_{1k}^{(3)} + u_{1j,k}^{(2)} \\ \phi_{2jk} &= \beta_2 + u_{2k}^{(3)} + u_{2j,k}^{(2)} \\ \phi_{3jk} &= \beta_3 \end{aligned} \tag{23}$$

$$\mathbf{u}_k^{(3)} = \begin{bmatrix} u_{1k}^{(3)} \\ u_{2k}^{(3)} \end{bmatrix} \sim N\left(\mathbf{0}, \boldsymbol{\Sigma}_3\right) \qquad \mathbf{u}_{j,k}^{(2)} = \begin{bmatrix} u_{1j,k}^{(2)} \\ u_{2j,k}^{(2)} \end{bmatrix} \sim N\left(\mathbf{0}, \boldsymbol{\Sigma}_2\right) \qquad \epsilon_{ijk} \sim N\left(0, \sigma_\epsilon^2\right)$$

where $\boldsymbol{\Sigma}_2$ and $\boldsymbol{\Sigma}_3$ are general symmetric covariance matrices. $u_{1j,k}^{(2)}$ and $u_{2j,k}^{(2)}$ are random intercepts at the `guar-within-subject` level and can be specified in `menl` as `UU1[subject>guar]` and `UU2[subject>guar]`.

The full model defined by (22) and (23) contains many parameters. We will follow our own advice from example 11 and specify the iterate() option to check how reasonable our model is for the data we have.

```
. menl glucose = {phi1:} + {phi2:}*c.time#c.time#c.time*exp(-{phi3}*time),
> define(phi1: U1[subject] UU1[subject>guar])
> define(phi2: U2[subject] UU2[subject>guar])
> covariance(U1 U2, unstructured) covariance(UU*, unstructured)
> stddeviations iterate(3)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -189.44711
Iteration 2:  Linearization log likelihood = -189.44116
Iteration 3:  Linearization log likelihood = -189.44113
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        196
            Grouping information

            ─────────────────────────────────────────────────────────────
                                    No. of       Observations per group
                          Path      groups    Minimum    Average    Maximum
            ─────────────────────────────────────────────────────────────
                       subject           7         28       28.0         28
                  subject>guar          14         14       14.0         14
            ─────────────────────────────────────────────────────────────

Linearization log likelihood = -189.44113

                phi1: U1[subject] UU1[subject>guar]
                phi2: U2[subject] UU2[subject>guar]

─────────────────────────────────────────────────────────────────────────────────
     glucose   Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
─────────────────────────────────────────────────────────────────────────────────
phi1
       _cons     3.661565   .1160346    31.56   0.000     3.434142    3.888989
─────────────────────────────────────────────────────────────────────────────────
phi2
       _cons     .4283296   .0530026     8.08   0.000     .3244465    .5322127
─────────────────────────────────────────────────────────────────────────────────
       /phi3     .5896813    .013861    42.54   0.000     .5625143    .6168482
─────────────────────────────────────────────────────────────────────────────────

─────────────────────────────────────────────────────────────────────────────────
  Random-effects parameters       Estimate   Std. err.     [95% conf. interval]
─────────────────────────────────────────────────────────────────────────────────
subject: Unstructured
                        sd(U1)    .2624564   .0926845     .1313596    .5243879
                        sd(U2)     .059842   .0724603      .005576    .6422312
                   corr(U1,U2)   -.1489817   .9201217    -.9636327    .9346854
─────────────────────────────────────────────────────────────────────────────────
subject>guar: Unstructured
                       sd(UU1)    .0919522   .0764226     .0180351      .46882
                       sd(UU2)    .1227068    .041288      .063454    .2372893
                 corr(UU1,UU2)      .99999   .0044367           -1           1
─────────────────────────────────────────────────────────────────────────────────
                  sd(Residual)    .5712263   .0305339     .5144091    .6343189
─────────────────────────────────────────────────────────────────────────────────
Warning: Convergence not achieved.
```

The estimated correlation corr(UU1,UU2) is near one with the confidence interval spanning the entire range for the correlation parameter, which indicates that the random-effects structure is overparameterized. The confidence interval for corr(U1,U2) contains zero, which suggests that this term does not contribute much to explaining between-subject variability. If we try to fit this model without the `iterate()` option, it will continue iterating without convergence.

We simplify our model by assuming independence between random effects; that is, we assume that random-effects covariance matrices Σ_2 and Σ_3 are diagonal.

Recall that `covariance(, independent)` is assumed by default, so we do not need to explicitly specify the `covariance()` option:

```
. menl glucose = {phi1:} + {phi2:}*c.time#c.time#c.time*exp(-{phi3}*time),
> define(phi1: U1[subject] UU1[subject>guar])
> define(phi2: U2[subject] UU2[subject>guar]) stddeviations
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -190.35529
Iteration 2:  Linearization log likelihood = -190.36034
Iteration 3:  Linearization log likelihood =  -190.3633
Iteration 4:  Linearization log likelihood = -190.36418
Iteration 5:  Linearization log likelihood = -190.36375
Iteration 6:  Linearization log likelihood = -190.36397
Iteration 7:  Linearization log likelihood = -190.36386
Iteration 8:  Linearization log likelihood = -190.36391
Iteration 9:  Linearization log likelihood = -190.36389
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        196
      Grouping information

      ─────────────────────────────────────────────────────────────────
                          │    No. of       Observations per group
                     Path │    groups    Minimum     Average    Maximum
      ────────────────────┼────────────────────────────────────────────
                  subject │         7         28        28.0         28
             subject>guar │        14         14        14.0         14
      ─────────────────────────────────────────────────────────────────

Linearization log likelihood = -190.36389
        phi1: U1[subject] UU1[subject>guar]
        phi2: U2[subject] UU2[subject>guar]

─────────────────────────────────────────────────────────────────────────────
     glucose │ Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
─────────────┼───────────────────────────────────────────────────────────────
phi1         │
       _cons │   3.658712   .1168642    31.31   0.000     3.429662    3.887762
─────────────┼───────────────────────────────────────────────────────────────
phi2         │
       _cons │   .4239173   .0526333     8.05   0.000      .320758    .5270766
─────────────┼───────────────────────────────────────────────────────────────
       /phi3 │   .5876636   .0137214    42.83   0.000     .5607701    .6145571
─────────────────────────────────────────────────────────────────────────────

─────────────────────────────────────────────────────────────────────────────
  Random-effects parameters │  Estimate   Std. err.     [95% conf. interval]
────────────────────────────┼────────────────────────────────────────────────
subject: Independent        │
                     sd(U1) │  .2685609    .092104      .1371261    .5259756
                     sd(U2) │  .0422075   .1078497      .0002821    6.315441
────────────────────────────┼────────────────────────────────────────────────
subject>guar: Independent   │
                    sd(UU1) │  .0666034   .1527522      .0007435    5.966149
                    sd(UU2) │  .1362263   .0433547      .0730066    .2541909
────────────────────────────┼────────────────────────────────────────────────
               sd(Residual) │  .5732488   .0309928      .5156118    .6373288
─────────────────────────────────────────────────────────────────────────────
```

The random-effects structure may still be overparameterized, given small estimates for sd(U2) and sd(UU1). If we were to perform an LR test of the corresponding variance components being zero, we would have no statistical evidence to reject this null hypothesis; see example 7 for an instance of performing an LR test.

◁

▷ Example 21: Three-level model with continuous-time AR(1) error structure

The main objective of the study from example 20 was to determine whether the use of the dietary additive guar significantly affected time profiles of the blood glucose levels of subjects.

We continue with the model without random effects U2[subject] and UU1[subject>guar] and include covariate **guar** for all ϕ_{jk}'s. Hand and Crowder (1996) also suggested to use a continuous-time AR(1) correlation structure for the **guar**-within-**subject** errors, which is specified in **menl** as **rescorrelation(ctar1, t(time))**:

```
. menl glucose = {phi1:} + {phi2:}*c.time#c.time#c.time*exp(-{phi3:}*time),
> define(phi1: i.guar U1[subject]) define(phi2: i.guar UU2[subject>guar])
> define(phi3: i.guar, xb) rescorrelation(ctar1, t(time)) stddeviations
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -180.62304
  (iteration log omitted)
Iteration 25: Linearization log likelihood = -181.18699
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        196
      Grouping information

      -------------------------------------------------------------
                   |     No. of       Observations per group
              Path |     groups    Minimum     Average    Maximum
      -------------+-----------------------------------------------
           subject |          7         28        28.0         28
      subject>guar |         14         14        14.0         14
      -------------------------------------------------------------

                                                Wald chi2(3)      =       0.66
Linearization log likelihood = -181.18699       Prob > chi2       =     0.8814

        phi1: i.guar U1[subject]
        phi2: i.guar UU2[subject>guar]
        phi3: i.guar

------------------------------------------------------------------------------
     glucose | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
        guar |
   with guar |  -.0814355   .1532735    -0.53   0.595     -.381846     .218975
       _cons |   3.685365   .1433368    25.71   0.000      3.40443      3.9663
-------------+----------------------------------------------------------------
phi2         |
        guar |
   with guar |   .0109469   .0883807     0.12   0.901     -.162276    .1841698
       _cons |    .344372   .0606914     5.67   0.000     .2254191    .4633248
-------------+----------------------------------------------------------------
phi3         |
        guar |
   with guar |   .0103743   .0330196     0.31   0.753     -.054343    .0750916
       _cons |   .5514012    .022009    25.05   0.000     .5082642    .5945381
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
subject: Identity            |
                       sd(U1)|   .2453634   .1013233      .1092206    .5512074
-----------------------------+------------------------------------------------
subject>guar: Identity       |
                      sd(UU2)|   .1011852   .0276419      .0592358    .1728421
-----------------------------+------------------------------------------------
Residual: CTAR1,             |
    time time                |
                        sd(e)|   .6208598   .0412948       .544977    .7073086
                         corr|   .6547722   .0564848       .544064    .7654804
------------------------------------------------------------------------------
```

The dietary additive guar does not seem to affect the blood-glucose-level profiles over time. This actually conforms with the plot of the data from example 20, where, except for subject 6, the profiles with and without guar are similar.

◁

▷ Example 22: Using group() in the presence of random effects

The actual NLME model presented in Hand and Crowder (1996) for these glucose data included random effects for ϕ_1 and ϕ_2 only at the `subject` level and used a continuous-time AR(1) correlation structure on `time` for the `guar`-within-`subject` errors, with errors from different `guar`-within-`subject` clusters assumed to be independent. This model can be specified in `menl` using `rescorrelation()`'s `group()` suboption:

```
. menl glucose = {phi1:} + {phi2:}*c.time#c.time#c.time*exp(-{phi3:}*time),
>         define(phi1: i.guar U1[subject])
>         define(phi2: i.guar U2[subject])
>         define(phi3: i.guar, xb)
>         rescorrelation(ctar1, t(time) group(guar)) stddeviations
note: group variable guar nested in subject assumed.

Obtaining starting values by EM:

Alternating PNLS/LME algorithm:

Iteration 1:  Linearization log likelihood =  -183.7208
Iteration 2:  Linearization log likelihood = -183.91698
  (iteration log omitted)
Iteration 13: Linearization log likelihood = -183.90513
Iteration 14: Linearization log likelihood = -183.90511

Computing standard errors:

Mixed-effects ML nonlinear regression           Number of obs     =        196

      Grouping information
      -------------------------------------------------------------
                      |     No. of       Observations per group
                 Path |     groups    Minimum    Average    Maximum
      ----------------+--------------------------------------------
              subject |          7         28       28.0         28
                 guar |         14         14       14.0         14
      -------------------------------------------------------------
```

```
                                                Wald chi2(3)      =       1.01
Linearization log likelihood = -183.90511       Prob > chi2       =     0.7978

        phi1: i.guar U1[subject]
        phi2: i.guar U2[subject]
        phi3: i.guar

------------------------------------------------------------------------------
     glucose | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
        guar |
  with guar  |  -.0557508   .1714288    -0.33   0.745     -.391745    .2802434
       _cons |   3.682235   .1503694    24.49   0.000     3.387517    3.976954
-------------+----------------------------------------------------------------
phi2         |
        guar |
  with guar  |    .032163   .0721232     0.45   0.656    -.1091958    .1735219
       _cons |   .3349061   .0577129     5.80   0.000     .2217908    .4480214
-------------+----------------------------------------------------------------
phi3         |
        guar |
  with guar  |   .0232717   .0346187     0.67   0.501    -.0445798    .0911232
       _cons |   .5464887   .0243374    22.45   0.000     .4987883    .5941891
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
subject: Independent         |
                      sd(U1) |   .2288441   .1103908      .0889065    .5890417
                      sd(U2) |   .0774363   .0306965      .0356058    .1684104
-----------------------------+------------------------------------------------
Residual: CTAR1,             |
    time time                |
                       sd(e) |   .6663828   .0439279      .5856156    .7582893
                        corr |   .7018854   .0468263      .6101075    .7936633
------------------------------------------------------------------------------
```

The fixed-effects estimates are similar to those in example 21, and the same conclusion is reached regarding the effect of the dietary additive `guar` on the blood-glucose-levels profiles over time. AIC and BIC may be used to decide on which model is better.

Notice the note displayed by `menl` following the command specification about the group variable `guar` being nested within variable `subject`. When you specify `group(`*grpvar*`)` within the `rescorrelation()` (or `rescovariance()`) option in the presence of random effects, *grpvar* is assumed to represent the lowest level of hierarchy and is thus assumed to be nested within other hierarchical levels.

◁

▷ Example 23: Three-level model with block-diagonal covariance matrix

Pinheiro and Bates (2000) report the data from the experiment conducted by Microelectronics Division of Lucent Technologies to study the variability in the manufacturing of analog MOS circuits. The intensities of the `current` (in mA) were collected on n-channel devices at five ascending `voltages`: 0.8, 1.2, 1.6, 2.0, and 2.4 V. Measurements were made on 8 `sites` of each of 10 `wafers`. The main objective of the study was to build an empirical model to simulate the behavior of similar circuits.

The intensity of the current at the ith level of `voltage` in the jth `site` within the kth `wafer` is expressed as

$$\texttt{current}_{ijk} = \phi_{1jk} + \phi_{2jk}\cos\left(\phi_{3jk}\texttt{voltage}_i + \pi/4\right) + \epsilon_{ijk}$$

where

$$\begin{aligned}
\phi_{1jk} &= \beta_0 + u_{0k}^{(3)} + u_{0j,k}^{(2)} + \left(\beta_1 + u_{1k}^{(3)} + u_{1j,k}^{(2)}\right)\texttt{voltage}_i + \left(\beta_2 + u_{2k}^{(3)} + u_{2j,k}^{(2)}\right)\texttt{voltage}_i^2\\
\phi_{2jk} &= \beta_3 + u_{3k}^{(3)} + u_{3j,k}^{(2)}\\
\phi_{3jk} &= \beta_4 + u_{4k}^{(3)}
\end{aligned}$$

$$\mathbf{u}_k^{(3)} = \begin{bmatrix} u_{0k}^{(3)}\\ u_{1k}^{(3)}\\ u_{2k}^{(3)}\\ u_{3k}^{(3)}\\ u_{4k}^{(3)} \end{bmatrix} \sim N\left(\mathbf{0},\boldsymbol{\Sigma}_3\right) \qquad \mathbf{u}_{j,k}^{(2)} = \begin{bmatrix} u_{0j,k}^{(2)}\\ u_{1j,k}^{(2)}\\ u_{2j,k}^{(2)}\\ u_{3j,k}^{(2)} \end{bmatrix} \sim N\left(\mathbf{0},\boldsymbol{\Sigma}_2\right) \qquad \epsilon_{ijk} \sim N\left(0,\sigma_\epsilon^2\right)$$

Parameters β_0, β_1, and β_2 characterize the quadratic component of the model, and amplitude β_3 and frequency β_4 characterize the periodic component represented by the cosine wave.

For illustration, consider the following random-effects covariance structures:

$$\boldsymbol{\Sigma}_3 = \begin{bmatrix} \sigma_{11}^{(3)} & & & & \\ & \sigma_{22}^{(3)} & & & \\ & & \sigma_{33}^{(3)} & & \\ & & & \sigma_{44}^{(3)} & \\ & & & & \sigma_{55}^{(3)} \end{bmatrix} \qquad \boldsymbol{\Sigma}_2 = \begin{bmatrix} \sigma_{11}^{(2)} & \sigma_{12}^{(2)} & 0 & 0\\ \sigma_{12}^{(2)} & \sigma_{22}^{(2)} & 0 & 0\\ 0 & 0 & \sigma_{33}^{(2)} & \sigma_{34}^{(2)}\\ 0 & 0 & \sigma_{34}^{(2)} & \sigma_{44}^{(2)} \end{bmatrix}$$

If we were to fit this model by using `menl`, we would type

```
. use https://www.stata-press.com/data/r18/wafer
(Modeling of analog MOS circuits)
. menl current = {phi1:}+{phi2:}*cos({phi3:}*voltage + _pi/4),
> define(phi1: voltage c.voltage#c.voltage W0[wafer] S0[wafer>site]
>              c.voltage#(W1[wafer] S1[wafer>site])
>              c.voltage#c.voltage#(W2[wafer] S2[wafer>site]))
> define(phi2: W3[wafer] S3[wafer>site]) define(phi3: W4[wafer], xb)
> covariance(S0 S1, unstructured) covariance(S2 S3, unstructured)
> covariance(W*, independent) stddeviations
```

In the specification above, $\boldsymbol{\Sigma}_3$ is specified as `covariance(W*, independent)`, although this specification could have been omitted because `independent` is `menl`'s default random-effects covariance structure. The block-diagonal matrix $\boldsymbol{\Sigma}_2$ is specified by using repeated `covariance()` options: `covariance(S0 S1, unstructured)` and `covariance(S2 S3, unstructured)`. If we tried to run this model, we would find out that it is overparameterized.

Because of the large number of random effects at each grouping level, to avoid numerically unstable estimates, we will further simplify our model by assuming independence between $u^{(2)}_{2j,k}$ and $u^{(2)}_{3j,k}$, which implies that $\sigma^{(2)}_{34} = 0$:

$$\boldsymbol{\Sigma}_3 = \begin{bmatrix} \sigma^{(3)}_{11} & & & & \\ & \sigma^{(3)}_{22} & & & \\ & & \sigma^{(3)}_{33} & & \\ & & & \sigma^{(3)}_{44} & \\ & & & & \sigma^{(3)}_{55} \end{bmatrix} \qquad \boldsymbol{\Sigma}_2 = \begin{bmatrix} \sigma^{(2)}_{11} & \sigma^{(2)}_{12} & 0 & 0 \\ \sigma^{(2)}_{12} & \sigma^{(2)}_{22} & 0 & 0 \\ 0 & 0 & \sigma^{(2)}_{33} & 0 \\ 0 & 0 & 0 & \sigma^{(2)}_{44} \end{bmatrix}$$

We now try to fit the above simpler model. Note that given the complexity of this model, it takes some time to execute.

```
. use https://www.stata-press.com/data/r18/wafer
(Modeling of analog MOS circuits)

. menl current = {phi1:}+{phi2:}*cos({phi3:}*voltage + _pi/4),
> define(phi1: voltage c.voltage#c.voltage W0[wafer] S0[wafer>site]
>              c.voltage#(W1[wafer] S1[wafer>site])
>              c.voltage#c.voltage#(W2[wafer] S2[wafer>site]))
> define(phi2: W3[wafer] S3[wafer>site]) define(phi3: W4[wafer], xb)
> covariance(S0 S1, unstructured) covariance(S2 S3, independent)
> covariance(W*, independent) stddeviations

Obtaining starting values by EM:

Alternating PNLS/LME algorithm:

Iteration 1:  Linearization log likelihood =  733.68089
Iteration 2:  Linearization log likelihood =  754.60617
Iteration 3:  Linearization log likelihood =  826.10124
Iteration 4:  Linearization log likelihood =   825.9171
Iteration 5:  Linearization log likelihood =   825.9171

Computing standard errors:

Mixed-effects ML nonlinear regression           Number of obs     =        400

      Grouping information
      ─────────────────────────────────────────────────────────────────
                           │    No. of       Observations per group
                      Path │    groups    Minimum    Average    Maximum
      ─────────────────────┼───────────────────────────────────────────
                     wafer │        10         40       40.0         40
                wafer>site │        80          5        5.0          5
      ─────────────────────────────────────────────────────────────────
```

```
                                                 Wald chi2(2)      =    8763.94
Linearization log likelihood =   825.9171        Prob > chi2       =     0.0000
        phi1: voltage c.voltage#c.voltage W0[wafer] S0[wafer>site]
              c.voltage#W1[wafer] c.voltage#S1[wafer>site]
              c.voltage#c.voltage#W2[wafer]
              c.voltage#c.voltage#S2[wafer>site]
        phi2: W3[wafer] S3[wafer>site]
        phi3: W4[wafer], xb

------------------------------------------------------------------------------
     current | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
     voltage |   6.046937   .1022632    59.13   0.000     5.846504    6.247369
             |
   c.voltage#|
   c.voltage |   1.158782   .0159669    72.57   0.000     1.127487    1.190076
             |
       _cons |  -4.658034   .0361763  -128.76   0.000    -4.728938    -4.58713
-------------+----------------------------------------------------------------
phi2         |
       _cons |   .1684428    .002054    82.01   0.000     .1644171    .1724686
-------------+----------------------------------------------------------------
phi3         |
       _cons |   6.449391   .0019631  3285.32   0.000     6.445543    6.453238
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
wafer: Independent           |
                       sd(W0)|   .1107108   .0262518      .0695589    .1762087
                       sd(W1)|   .3041975   .0764653      .1858624    .4978743
                       sd(W2)|   .0449994   .0125441       .026057    .0777121
                       sd(W3)|   .0057862   .0016144      .0033489    .0099974
                       sd(W4)|   .0061349   .0013878      .0039377    .0095579
-----------------------------+------------------------------------------------
wafer>site: Unstructured     |
                       sd(S0)|   .0729495    .006297      .0615952    .0863969
                       sd(S1)|   .2930062   .0252424      .2474834    .3469025
                  corr(S0,S1)|  -.8113227   .0413362     -.8782242   -.7132776
-----------------------------+------------------------------------------------
wafer>site: Independent      |
                       sd(S2)|   .0627587   .0053067      .0531738    .0740712
                       sd(S3)|   .0080611   .0006861      .0068227    .0095244
-----------------------------+------------------------------------------------
                 sd(Residual)|   .0008407   .0000711      .0007122    .0009922
------------------------------------------------------------------------------
```

In this example, our primary focus was to demonstrate how to use `menl` to fit a block-diagonal random-effects covariance structure. But if we were to interpret our fixed-effects estimates, the average frequency of the cosine wave, $\beta_4 = E\left(\phi_{3jk}\right)$, for example, is estimated to be $6.45V^{-1}$, with a corresponding estimated period of $2\pi/\widehat{\beta}_4 \approx 0.97V$. Also, some of the estimates of standard deviations such as `sd(W2)`, `sd(W3)`, and `sd(W4)` are very small, which suggests that this model may still be too rich for the observed data. If we proceeded to further analyze these data, we would consider simpler models. For example, at the very least, we would have omitted the term `W3[wafer]` from this model.

◁

Obtaining initial values

Obtaining good starting or initial values is important for the estimation of many statistical models, but it is often crucial for the estimation of NLME models. NLME models are known to be sensitive to the initial values and to have difficulty converging. Highly nonlinear mean specification or complicated variance–covariance structures for random effects and errors can often lead to multiple solutions, which requires considering different sets of initial values.

By default, `menl` uses the EM algorithm to obtain initial values. This default routine works well in many cases but cannot be guaranteed to provide good initial values in all situations. Sometimes, you may need to specify your own initial values. Trying different initial values can also be useful to investigate the existence of multiple solutions and to verify convergence to a global maximum.

So far we have been "lucky" that all the examples worked without us having to specify initial estimates. You may not be that lucky with your data and model. So, in this section, we provide some guidance on how to find good initial values when the default initial values do not work well.

We present three approaches that you may choose to explore to find good initial estimates for the fixed effects. In some cases, you may also be able to obtain initial estimates for covariance parameters; see *Linearization approach to finding initial values*.

Linearization approach to finding initial values

Sometimes, we can use an LME model to obtain initial values of the NLME model by holding some of the parameters fixed at specific values. We can then fit the resulting LME model by using the `mixed` command and use the corresponding estimates as initial values for the NLME model. We refer to this initialization method as the linearization method.

We could have used this method in example 14 and example 23, if the default EM method did not provide reasonable initial estimates. In any case, it is good practice to specify different initial values to investigate potential convergence of the algorithm to a local maximum.

For instance, in example 14, we fit

$$\texttt{follicles}_{ij} = \phi_{1j} + \phi_{2j}\sin\left(2\pi\phi_{3j}\texttt{stime}_{ij}\right) + \phi_{4j}\cos\left(2\pi\phi_{3j}\texttt{stime}_{ij}\right) + \epsilon_{ij}$$

where

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \\ \phi_{4j} \end{bmatrix} = \begin{bmatrix} \beta_1 + u_{1j} \\ \beta_2 \\ \beta_3 \\ \beta_4 \end{bmatrix}$$

This model is nonlinear because of the parameter ϕ_{3j}. To obtain initial values, we can hold ϕ_{3j} (or β_3) fixed at a specific value, say, $\beta_3 = 1$, thus making the above model linear,

$$\texttt{follicles}_{ij} = \phi_{1j} + \phi_{2j}\sin\left(2\pi\phi_{3j}\texttt{stime}_{ij}\right) + \phi_{4j}\cos\left(2\pi\phi_{3j}\texttt{stime}_{ij}\right) + \epsilon_{ij}$$

where

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \\ \phi_{4j} \end{bmatrix} = \begin{bmatrix} \beta_1 + u_{1j} \\ \beta_2 \\ 1 \\ \beta_4 \end{bmatrix}$$

Or, more compactly,

$$\texttt{follicles}_{ij} = \beta_1 + u_{1j} + \beta_2\sin\left(2\pi\texttt{stime}_{ij}\right) + \beta_4\cos\left(2\pi\texttt{stime}_{ij}\right) + \epsilon_{ij}$$

Now that the model is linear, we can use the `mixed` command to obtain initial values for β_1, β_2, and β_4 to be used in `menl`. In the code below, variables `sin1` and `cos1` are $\sin\left(2\pi\texttt{stime}_{ij}\right)$ and $\cos\left(2\pi\texttt{stime}_{ij}\right)$, respectively, and `|| mare:` specifies a random intercept at the `mare` level (see [ME] **mixed**). Also, for consistency with example 13, we assume an AR(1) within-group error correlation structure:

```
. mixed follicles sin1 cos1 || mare:, residuals(ar 1, t(time)) nolog
Mixed-effects ML regression                         Number of obs     =    308
Group variable: mare                                Number of groups =     11
                                                    Obs per group:
                                                                 min =     25
                                                                 avg =   28.0
                                                                 max =     31
                                                    Wald chi2(2)      =  39.00
Log likelihood = -776.51731                         Prob > chi2       = 0.0000

------------------------------------------------------------------------------
   follicles | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
        sin1 |  -2.958619   .4935054    -6.00   0.000    -3.925872   -1.991366
        cos1 |  -.8798847   .5031763    -1.75   0.080    -1.866092    .1063228
       _cons |   12.18963   .9017441    13.52   0.000     10.42224    13.95701
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
mare: Identity               |
                  var(_cons) |   7.095514    3.76488      2.508051    20.07388
-----------------------------+------------------------------------------------
Residual: AR(1)              |
                         rho |   .5974664   .0547217      .4795551    .6941854
                      var(e) |   13.08097   1.765325      10.04078     17.0417
------------------------------------------------------------------------------
LR test vs. linear model: chi2(2) = 242.63                Prob > chi2 = 0.0000
Note: LR test is conservative and provided only for reference.
```

We will now use the estimates of the fixed effects shown in the output table as initial values for `menl` by specifying the `initial()` option. We use 1 as the initial value for `/phi3`. There are three ways to specify initial values in the `initial()` option; see *Specifying initial values*. Here we will use the specification where we repeatedly list a parameter name followed by its initial value; also see *Examples of specifying initial values*.

```
. local xb phi1:_cons 12.2 /phi2 -3.0 /phi3 1 /phi4 -.88
. menl follicles = {phi1: U1[mare], xb} + {phi2}*sin(2*_pi*stime*{phi3}) +
> {phi4}*cos(2*_pi*stime*{phi3}), rescorrelation(ar 1, t(time)) init('xb')
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -775.62937
Iteration 2:  Linearization log likelihood = -775.62433
Iteration 3:  Linearization log likelihood = -775.62433
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        308
Group variable: mare                            Number of groups  =         11
                                                Obs per group:
                                                              min =         25
                                                              avg =       28.0
                                                              max =         31
Linearization log likelihood = -775.62433
        phi1: U1[mare], xb

   follicles   Coefficient  Std. err.      z    P>|z|     [95% conf. interval]

phi1
       _cons     12.18125   .9055128    13.45   0.000     10.40647    13.95602

       /phi2    -2.874413   .5389583    -5.33   0.000    -3.930751   -1.818074
       /phi3      .919114   .0512333    17.94   0.000     .8186986    1.019529
       /phi4    -1.675314   .6766091    -2.48   0.013    -3.001444   -.3491848


  Random-effects parameters     Estimate   Std. err.     [95% conf. interval]

mare: Identity
                     var(U1)    7.207072   3.755606      2.595361    20.01336

Residual: AR(1),
    time time
                      var(e)    12.63377   1.646897      9.785276    16.31146
                        corr    .5823733   .0544508      .4656903     .679153
```

In the above, we initialized only fixed-effects parameters and used naïve initial estimates of 1 for random-intercept and error variances and 0 for the correlation. We could have specified `initial()`'s `fixed` suboption to use the EM algorithm to compute initial estimates for the random-effects parameters; see *Examples of specifying initial values* for details.

With the linearization approach, we can also use estimates of the random-effects parameters from the `mixed` command to initialize the corresponding parameters of `menl`. This is an advantage of the linearization approach over the other two approaches we discuss in subsequent sections. One complication with the initialization of random-effects parameters is that the initial values must be supplied in the estimation metric, the metric used during estimation, instead of the parameter original metric. For example, instead of variances, we must supply estimates of log standard-deviations, and instead of covariances or correlations, we must supply inverse hyperbolic tangents of correlation parameters. Luckily for us, `mixed` stores results using the same metric as `menl` and provides the `estmetric` option to display parameters in that metric.

In our example, the random-effects parameters are the random-intercept variance, the within-group error variance, and the correlation between error terms. We refit the earlier `mixed` command but now with the `estmetric` option to obtain the estimates of the random-effects parameters as they are stored in `e(b)`.

```
. mixed follicles sin1 cos1 || mare:, residuals(ar 1, t(time)) nolog estmetric
Mixed-effects ML regression                          Number of obs     =    308
Group variable: mare                                 Number of groups =     11
                                                     Obs per group:
                                                                  min =     25
                                                                  avg =   28.0
                                                                  max =     31
                                                     Wald chi2(2)      =  39.00
Log likelihood = -776.51731                          Prob > chi2       = 0.0000

------------------------------------------------------------------------------
   follicles | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
follicles    |
        sin1 |  -2.958619   .4935054    -6.00   0.000    -3.925872   -1.991366
        cos1 |  -.8798847   .5031763    -1.75   0.080    -1.866092    .1063228
       _cons |   12.18963   .9017441    13.52   0.000     10.42224    13.95701
-------------+----------------------------------------------------------------
lns1_1_1     |
       _cons |   .9797314      .2653                        .5762507    1.665722
-------------+----------------------------------------------------------------
lnsig_e      |
       _cons |   1.285579   .0674768    19.05   0.000     1.153327    1.417832
-------------+----------------------------------------------------------------
r_atr1       |
       _cons |   .6891978   .0850992     8.10   0.000     .5224064    .8559891
------------------------------------------------------------------------------
```

menl uses the same ordering of the parameters as mixed does, so we can simply list all the estimates directly in the initial() option. When we list the values without parameter names, we must specify initial()'s copy suboption and specify the values for all parameters. In our example, we specify four fixed-effects coefficients and three random-effects parameters.

```
. menl follicles = {phi1: U1[mare], xb} + {phi2}*sin(2*_pi*stime*{phi3}) +
> {phi4}*cos(2*_pi*stime*{phi3}), rescorrelation(ar 1, t(time))
> initial(12.2 -3.0 1 -.88 .98 1.29 .69, copy)
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -775.62433
Iteration 2:  Linearization log likelihood = -775.62433
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        308
Group variable: mare                            Number of groups  =         11
                                                Obs per group:
                                                              min =         25
                                                              avg =       28.0
                                                              max =         31
Linearization log likelihood = -775.62433
        phi1: U1[mare], xb

------------------------------------------------------------------------------
   follicles | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |   12.18125   .9055135    13.45   0.000     10.40647    13.95602
-------------+----------------------------------------------------------------
       /phi2 |  -2.874434   .5389241    -5.33   0.000    -3.930706   -1.818162
       /phi3 |    .919119   .0512356    17.94   0.000      .818699    1.019539
       /phi4 |  -1.675261   .6766409    -2.48   0.013    -3.001452   -.3490689
------------------------------------------------------------------------------
```

```
------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
mare: Identity               |
                     var(U1) |   7.207072   3.755606       2.59536    20.01337
-----------------------------+------------------------------------------------
Residual: AR(1),             |
    time time                |
                      var(e) |   12.63377   1.646898      9.785276    16.31146
                        corr |   .5823733   .0544508      .4656902     .679153
------------------------------------------------------------------------------
```

The results are different from those in example 14. The value of the linearization log likelihood in this example, −775.62, is larger than that from example 14, −789.43. So it appears that we have converged to a local maximum of the linearization log likelihood in example 14.

Our initial values based on `mixed` turned out to be better than those computed by default by `menl`. This is not surprising. In general, `menl`'s EM algorithm should produce reasonable initial values for many nonlinear models, but the initial values may not necessarily be optimal for all of those models. In this example, our initial values were tailored to the ovary data and the model.

In general, sensitivity to initial values is one of the key issues in NLME models, especially for models that involve periodic functions. Therefore, it is important to try different sets of initial values to verify global convergence before reporting your final results. Sometimes, you may even have to rely on your knowledge of the science behind the problem to decide which set of results is more reasonable.

Graphical approach to finding initial values

If your model has parameters that have natural physical interpretations, you may be able to obtain starting values from a graph of the data.

Draper and Smith (1998) presented a dataset in which the trunk circumference `circumf` (in mm) of five different orange trees was measured over seven different time points, stored in `age`. Pinheiro and Bates (2000) suggested the following model for these data:

$$\texttt{circumf}_{ij} = \frac{\phi_{1j}}{1 + \exp\left\{-\left(\texttt{age}_{ij} - \phi_{2j}\right)/\phi_{3j}\right\}} + \epsilon_{ij} \tag{24}$$

In this model, ϕ_{1j} is the asymptotic trunk circumference for the jth tree as $\texttt{age}_{ij} \to \infty$, ϕ_{2j} is the age at which the jth tree attains half of its asymptotic trunk circumference ϕ_{1j}, and ϕ_{3j} is a scale parameter; see the graph below.

The stage 2 specification of this model is

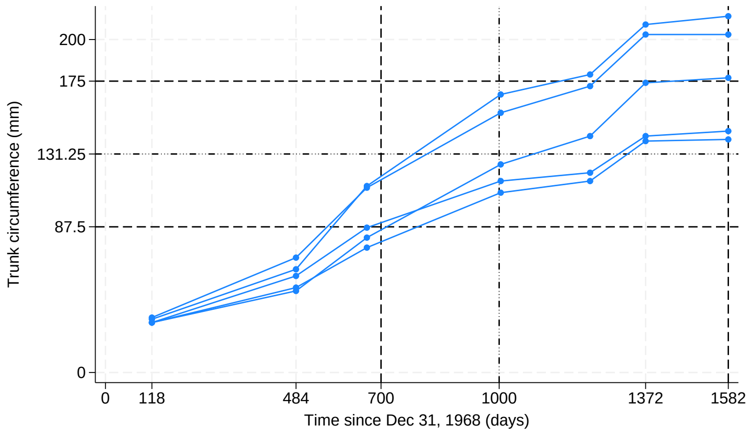
$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \end{bmatrix} = \begin{bmatrix} \beta_1 + u_{1j} \\ \beta_2 \\ \beta_3 \end{bmatrix}$$

where

$$u_{1j} \sim N\left(0, \sigma^2_{u_1}\right), \; \epsilon_{ij} \sim N\left(0, \sigma^2_{\epsilon}\right)$$

Because the model parameters have graphical interpretations, we can plot our data and obtain initial values from the graph.

```
. use https://www.stata-press.com/data/r18/orange
(Growth of orange trees (Draper and Smith, 1998))
. twoway connected circumf age, connect(L) yline(175) xline(1582)
> yline(87.5, lpattern(dash)) xline(700, lpattern(dash))
> yline(131.25, lpattern("-...")) xline(1000, lpattern("-..."))
> xlabel(0 118 484 700 1000 1372 1582) ylabel(#5 87.5 131.25 175)
```



From the above graph, the mean asymptotic trunk circumference can be estimated as 175 mm, which is roughly the mean of the circumference values at age 1,582 (in days). The trees attain half of their asymptotic trunk circumference, $175/2 = 87.5$, at about age 700 (in days). Therefore, we use the initial estimates $\beta_1 = 175$ for the asymptotic trunk circumference and $\beta_2 = 700$ for the location of the inflection point. To obtain an initial estimate for β_3, we note that when age $= \beta_2 + \beta_3$ in (24), $E(\texttt{circumf}_{ij}) = \beta_1/\{1 + \exp(-1)\} = 0.73\beta_1$, which we will approximate as $0.75\beta_1$ for the purpose of the graph. That is, the logistic curve reaches approximately 3/4 of its asymptotic value, $0.75 \times 175 = 131.25$, at age $= \beta_2 + \beta_3$. The above graph suggests that the trees attain 3/4 of their final trunk circumference at about 1,000 days ($= \beta_2 + \beta_3$), giving an initial estimate of $\beta_3 = 1000 - 700 = 300$. We can now supply these values to `menl` in the `initial()` option.

Unfortunately, the graph does not provide us with the estimates for variance components. In this case, we can use `initial()`'s `fixed` suboption to specify that the EM algorithm still be used to initialize variance components, while the supplied values be used to initialize fixed effects. If we do not specify `fixed`, `menl` will use naïve initial estimates for variance components such as ones for variances and zeros for covariances.

We now fit the model using our own initial estimates for fixed effects:

```
. menl circumf = {phi1: U1[tree], xb}/(1+exp(-(age-{phi2})/{phi3})),
> initial(phi1:_cons 175 /phi2 700 /phi3 300, fixed)
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -131.58494
Iteration 2:  Linearization log likelihood = -131.58458
Iteration 3:  Linearization log likelihood = -131.58458
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =         35
Group variable: tree                            Number of groups  =          5

                                                Obs per group:
                                                              min =          7
                                                              avg =        7.0
                                                              max =          7

Linearization log likelihood = -131.58458
        phi1: U1[tree], xb

------------------------------------------------------------------------------
     circumf | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |    191.049   16.15403    11.83   0.000     159.3877    222.7103
-------------+----------------------------------------------------------------
       /phi2 |    722.556   35.15082    20.56   0.000     653.6616    791.4503
       /phi3 |   344.1624   27.14739    12.68   0.000     290.9545    397.3703
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tree: Identity               |
                     var(U1) |   991.1514   639.4637      279.8776    3510.038
-----------------------------+------------------------------------------------
               var(Residual) |   61.56371   15.89568      37.11466    102.1184
------------------------------------------------------------------------------
```

For comparison, we fit the same model but now using the default initial values for fixed effects:

```
. menl circumf = {phi1: U1[tree], xb}/(1+exp(-(age-{phi2})/{phi3}))
Obtaining starting values by EM:
Alternating PNLS/LME algorithm:
Iteration 1:  Linearization log likelihood = -131.58458
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =         35
Group variable: tree                            Number of groups  =          5

                                                Obs per group:
                                                              min =          7
                                                              avg =        7.0
                                                              max =          7

Linearization log likelihood = -131.58458
      phi1: U1[tree], xb

------------------------------------------------------------------------------
     circumf | Coefficient  Std. err.      z    P>|z|     [95% conf. interval]
-------------+----------------------------------------------------------------
phi1         |
       _cons |    191.049   16.15403    11.83   0.000     159.3877    222.7103
-------------+----------------------------------------------------------------
       /phi2 |    722.556   35.15082    20.56   0.000     653.6616    791.4503
       /phi3 |   344.1624   27.14739    12.68   0.000     290.9545    397.3703
------------------------------------------------------------------------------

------------------------------------------------------------------------------
  Random-effects parameters  |   Estimate   Std. err.     [95% conf. interval]
-----------------------------+------------------------------------------------
tree: Identity               |
                     var(U1) |   991.1514   639.4637      279.8776    3510.038
-----------------------------+------------------------------------------------
               var(Residual) |   61.56371   15.89568      37.11466    102.1184
------------------------------------------------------------------------------
```

The results are identical except for the iteration log.

Smart regressions approach to finding initial values

Consider the following NLME model,

$$\mathrm{y}_{ij} = \phi_{1j} + (\phi_{2j} - \phi_{1j}) \exp\{-\exp(\phi_{3j})\,\mathrm{x}_{ij}\} + \epsilon_{ij}$$

where

$$\boldsymbol{\phi}_j = \begin{bmatrix} \phi_{1j} \\ \phi_{2j} \\ \phi_{3j} \end{bmatrix} = \begin{bmatrix} \beta_1 \\ \beta_2 + u_{1j} \\ \beta_3 \end{bmatrix}$$

Here ϕ_{1j} is the asymptote as $\mathrm{x}_{ij} \to \infty$ and ϕ_{2j} is the value of y_{ij} at $\mathrm{x}_{ij} = 0$. Thus initial estimates, $\beta_1^{(0)}$ and $\beta_2^{(0)}$, may be obtained by using the graphical approach as described in *Graphical approach to finding initial values*. To obtain an initial estimate for β_3, notice that, ignoring the error term ϵ_{ij} and setting $u_{1j} = 0$,

$$\log(|\mathrm{y}_{ij} - \beta_1|) = \log(\beta_2 - \beta_1) + \{-\exp(\beta_3)\}\,\mathrm{x}_{ij}$$

Therefore, we can regress $\log(|\mathrm{y} - \beta_1^{(0)}|)$ on x and use the estimated slope, $\widehat{\beta}_x = -\exp(\beta_3^{(0)})$, to obtain the initial value for $\beta_3^{(0)} = \log(-\widehat{\beta}_x)$.

Examples of specifying initial values

When you want to assign initial values for a subset of the model parameters, for example, fixed effects or random-effects covariance parameters, you will often need to know their estimation names or, in other words, how `menl` labels them in `e(b)`. To learn the names, you can fit the model with the `iterate(0)` and `coeflegend` options first.

```
. menl ... , ... iterate(0) coeflegend
```

The `iterate(0)` option specifies to bypass maximization and only report the initial values and the likelihood evaluated at those values. The `coeflegend` option specifies that the legend of the parameters and how to specify them in an expression be displayed rather than displaying the statistics for the parameters.

Keep in mind, however, that `menl` does not perform estimation in the original parameter metric. For computational stability, the estimation is performed, loosely speaking, in a metric that transforms all parameters to be defined on a real line. For example, a log transformation is used for standard deviations, and an inverse hyperbolic tangent transformation is used for correlations. When you specify initial values, you must specify them for parameters in the estimation metric and not the original metric.

`coeflegend` displays parameter names as they are stored in `e(b)`, which, for `menl`, are the names of estimation parameters. If you also want to see parameters in the original metric, you can specify `coeflegend` on replay.

```
. menl ... , ... iterate(0)
. menl, coeflegend
```

For example, recall the NLME model for the soybean data from example 9. Suppose that we want to supply our own initial values.

We fit the model with `iterate(0)` and `coeflegend`:

```
. menl weight = {phi1:}/(1+exp(-(time-{phi2:})/{phi3:})),
> define(phi1: U1[plot], xb)
> define(phi2: U2[plot], xb)
> define(phi3: U3[plot], xb)
> covariance(U*, unstructured) iterate(0) coeflegend
Obtaining starting values by EM:
Computing standard errors:
Mixed-effects ML nonlinear regression           Number of obs     =        412
Group variable: plot                            Number of groups  =         48
                                                Obs per group:
                                                              min =          8
                                                              avg =        8.6
                                                              max =         10

Linearization log likelihood = -740.06177

        phi1: U1[plot], xb
        phi2: U2[plot], xb
        phi3: U3[plot], xb

------------------------------------------------------------------------------
      weight | Coefficient  Legend
-------------+----------------------------------------------------------------
phi1         |
       _cons |   19.26527  _b[phi1:_cons]
-------------+----------------------------------------------------------------
phi2         |
       _cons |   55.05299  _b[phi2:_cons]
-------------+----------------------------------------------------------------
phi3         |
       _cons |   8.385531  _b[phi3:_cons]
-------------+----------------------------------------------------------------
/plot        |
    lnsd(U1) |   1.650846  _b[/plot:lnsd(U1)]
    lnsd(U2) |   1.436634  _b[/plot:lnsd(U2)]
    lnsd(U3) |   .4081525  _b[/plot:lnsd(U3)]
  athcorr(U2,|
         U1) |   .9055785  _b[/plot:athcorr(U2,U1)]
  athcorr(U3,|
         U1) |   .8482105  _b[/plot:athcorr(U3,U1)]
  athcorr(U3,|
         U2) |   1.537798  _b[/plot:athcorr(U3,U2)]
-------------+----------------------------------------------------------------
/Residual    |
     lnsigma |   .1069986  _b[/Residual:lnsigma]
------------------------------------------------------------------------------
Warning: Convergence not achieved.
```

Parameter names are listed within the `_b[]` specifier.

In what follows, we will outline only the syntax of the specifications. If you actually want to run all the examples to see the initialization in action, we suggest that you specify `iterate(0)` for speed.

Let's first specify initial values for fixed effects only. The fixed-effects parameters are `phi1:_cons`, `phi2:_cons`, and `phi3:_cons`. Suppose that we want to initialize them with 19, 55, and 8.

We can type

```
. menl ..., ... initial(phi1:_cons 19 phi2:_cons 55 phi3:_cons 8)
```

Or, more compactly, we can type

```
. local fe phi1:_cons 19 phi2:_cons 55 phi3:_cons 8
. menl ..., ... initial(‘fe’)
```

When you specify the `initial()` option, `menl` does not perform the EM algorithm to initialize the parameters but instead uses the values you supplied. If you specify values for only a subset of parameters, the remaining parameters will be initialized with naïve initial values such as zeros for fixed effects and correlations and ones for variances. Often, you may have good initial values for fixed effects but not for variance components. In this situation, `menl` provides `initial()`'s `fixed` suboption. This option specifies that the supplied values be used for fixed effects but that the EM algorithm still be used to obtain initial values for variance components. If you specify only a subset of values for fixed effects, the remaining fixed effects will still be initialized with zeros even if `fixed` is specified. We recommend that you specify `fixed` when you intend to supply initial values only for the fixed effects.

```
    . local fe phi1:_cons 19 phi2:_cons 55 phi3:_cons 8
    . menl ..., ... initial(‘fe’, fixed)
```

Now suppose that we also want to assign initial values for random-effects parameters. As we mentioned earlier, remember that we assign initial values for standard deviations in the log metric and for correlation in the inverse hyperbolic tangent or atanh metric. For example, if you want to assign an initial value of 2 to σ_ϵ, then you should supply $\log(2)$ to the `initial()` option. Similarly, if you want to assign a value of 0.7 to the correlation of two random effects, then you should provide `atanh`(0.7) to the `initial()` option.

Continuing with example 9, suppose that we want to specify the following initial values for the random-effects covariance parameters:

$$\begin{array}{ccc} \texttt{U1[plot]} & \texttt{U2[plot]} & \texttt{U3[plot]} \\ \left(\begin{array}{l} \sigma_1 \;\;= 5 \\ \rho_{21} = 0.72 \\ \rho_{31} = 0.71 \end{array}\right. & \begin{array}{l} \\ \sigma_2 \;\;= 4 \\ \rho_{32} = 0.94 \end{array} & \left.\begin{array}{l} \\ \\ \sigma_3 = 1.4 \end{array}\right) \end{array}$$

The names of the parameters in the estimation metric that correspond to σ_1, σ_2, and σ_3 are `/plot:lnsd(U1)`, `/plot:lnsd(U2)`, and `/plot:lnsd(U3)` and that correspond to ρ_{21}, ρ_{31}, and ρ_{32} are `/plot:athcorr(U2,U1)`, `/plot:athcorr(U3,U1)`, and `/plot:athcorr(U3,U2)`.

When specifying initial values for free parameters such as random-effects covariance parameters, you can omit the forward slash (/) at the beginning of their names. Keeping in mind that initial values for covariance parameters are supplied in the log and atanh metrics, we can type

```
    . local re_cov          plot:lnsd(U1) log(5)            // log(5)
    . local re_cov ‘re_cov’ plot:lnsd(U2) 1.4               // log(4)
    . local re_cov ‘re_cov’ plot:lnsd(U3) 0.34              // log(1.4)
    . local re_cov ‘re_cov’ plot:athcorr(U2,U1) atanh(0.72) // atanh(0.72)
    . local re_cov ‘re_cov’ plot:athcorr(U3,U1) 0.89        // atanh(0.71)
    . local re_cov ‘re_cov’ plot:athcorr(U3,U2) 1.7         // atanh(0.94)
    . menl ... , ... initial(‘fe’ ‘re_cov’ Residual:lnsigma 0.5)
```

In the above, we also specified an initial value of 0.5 for the log of the error standard deviation. For parameters `/plot:lnsd(U1)` and `/plot:athcorr(U2,U1)`, instead of specifying the values, we specified the corresponding expression. This is allowed, as long as your expression is simple and does not contain spaces.

Instead of using parameter names, we can specify a list of values directly in the `initial()` option, in which case we must also specify `initial()`'s `copy` suboption.

```
    . menl ... , ... initial(19 55 8 1.6 1.4 0.34 0.9 0.89 1.7 0.5, copy)
```

Or we can provide these values as a matrix:

```
. matrix initvals = (19, 55, 8, 1.6, 1.4, 0.34, 0.9, 0.89, 1.7, 0.5)
. matrix list initvals
initvals[1,10]
     c1   c2   c3   c4   c5   c6   c7   c8   c9  c10
r1   19   55    8  1.6  1.4  .34   .9  .89  1.7   .5

. menl ... , ... initial(initvals, copy)
```

If we label the columns of the `initvals` matrix properly, we do not need to specify `copy`:

```
. local fullcolnames : colfullnames e(b)
. matrix colnames initvals = `fullcolnames'
. matrix list initvals
initvals[1,10]
            phi1:         phi2:         phi3:        /plot:        /plot:
           _cons         _cons         _cons      lnsd(U1)      lnsd(U2)
r1            19            55             8           1.6           1.4

           /plot:        /plot:        /plot:        /plot:   /Residual:
                  athcorr(U2,   athcorr(U3,   athcorr(U3,
        lnsd(U3)           U1)           U1)           U2)      lnsigma
r1           .34            .9           .89           1.7           .5

. menl ... , ... initial(initvals)
```

Using a properly labeled initial-value matrix, we can also specify initial values for a subset of parameters. For example, we can specify initial values for fixed effects only as follows:

```
. matrix initvals = initvals[1,1..3]
. matrix list initvals
initvals[1,3]
     phi1:  phi2:  phi3:
    _cons  _cons  _cons
r1     19     55      8

. menl ... , ... initial(initvals)
```

Stored results

`menl` stores the following in `e()`:

Scalars

`e(N)`	number of observations
`e(N_nonmiss)`	number of nonmissing *depvar* observations, if `tsmissing` is specified
`e(N_miss)`	number of missing *depvar* observations, if `tsmissing` is specified
`e(N_ic)`	number of nonmissing *depvar* observations to be used for BIC computation when `tsmissing` is specified
`e(k)`	number of parameters
`e(k_f)`	number of fixed-effects parameters
`e(k_r)`	number of random-effects parameters
`e(k_rs)`	number of variances
`e(k_rc)`	number of covariances
`e(k_res)`	number of within-group error parameters
`e(k_eq)`	number of equations
`e(k_feq)`	number of fixed-effects equations
`e(k_req)`	number of random-effects equations
`e(k_reseq)`	number of within-group error equations
`e(df_m)`	model degrees of freedom
`e(df_c)`	degrees of freedom for comparison test
`e(ll)`	linearization log (restricted) likelihood

`e(ll_c)`	log likelihood, comparison model
`e(chi2)`	χ^2
`e(chi2_c)`	χ^2 for comparison test
`e(p)`	p-value for model test
`e(p_c)`	p-value for comparison test
`e(rank)`	rank of `e(V)`
`e(rc)`	return code
`e(converged)`	`1` if converged, `0` otherwise
Macros	
`e(cmd)`	`menl`
`e(cmdline)`	command as typed
`e(depvar)`	name of dependent variable
`e(ivars)`	grouping variables
`e(title)`	title in estimation output
`e(varlist)`	variables used in the specified equation
`e(key_N_ic)`	`nonmissing obs`, if `tsmissing` is specified
`e(tsmissing)`	`tsmissing`, if specified
`e(tsorder)`	`tsorder()` specification
`e(eq_`*depvar*`)`	user-specified equation
`e(tsinit_`*depvar*`)`	`tsinit()` specification for `L.{`*depvar*`:}`
`e(expressions)`	names of defined expressions, *expr_1*, *expr_2*,..., *expr_k*
`e(expr_`*expr_i*`)`	defined expression *expr_i*, i=1,...,k
`e(tsinit_`*expr*`)`	`tsinit()` specification for `L.{`*expr*`:}`
`e(hierarchy)`	random-effects hierarchy structure, `(`*path*`:`*covtype*`:`*REs*`) (`...`)`
`e(revars)`	names of random effects
`e(rstructlab)`	within-group error covariance output label
`e(timevar)`	within-group error covariance `t()` variable, if specified
`e(indexvar)`	within-group error covariance `index()` variable, if specified
`e(covbyvar)`	within-group error covariance `by()` variable, if specified
`e(stratavar)`	within-group error variance `strata()` variable, if specified
`e(corrbyvar)`	within-group error correlation `by()` variable, if specified
`e(rescovopt)`	within-group error covariance option, if `rescovariance()` specified
`e(resvaropt)`	within-group error variance option, if `resvariance()` specified
`e(rescorropt)`	within-group error correlation option, if `rescorrelation()` specified
`e(groupvar)`	lowest-level `group()` variable, if specified
`e(chi2type)`	`Wald`; type of model χ^2 test
`e(vce)`	`conventional`
`e(method)`	`MLE` or `REML`
`e(opt)`	type of optimization, `lbates`
`e(crittype)`	optimization criterion
`e(properties)`	`b V`
`e(estat_cmd)`	program used to implement `estat`
`e(predict)`	program used to implement `predict`
`e(marginsok)`	predictions allowed by `margins`
`e(marginsnotok)`	predictions disallowed by `margins`
`e(marginsdefault)`	default `predict()` specification for `margins`
`e(asbalanced)`	factor variables `fvset` as `asbalanced`
`e(asobserved)`	factor variables `fvset` as `asobserved`
Matrices	
`e(b)`	coefficient vector
`e(Cns)`	factor-variable constraint matrix
`e(V)`	variance–covariance matrix of the estimators
`e(V_modelbased)`	model-based variance
`e(b_sd)`	random-effects and within-group error estimates in the standard deviation metric
`e(V_sd)`	VCE for parameters in the standard deviation metric
`e(b_var)`	random-effects and within-group error estimates in the variance metric
`e(V_var)`	VCE for parameters in the variance metric
`e(cov_#)`	random-effects covariance structure at the hierarchical level $k-\#+1$ in a k-level model
`e(hierstats)`	group-size statistics for each hierarchy
Functions	
`e(sample)`	marks estimation sample

In addition to the above, the following is stored in `r()`:

Matrices	
`r(table)`	matrix containing the coefficients with their standard errors, test statistics, p-values, and confidence intervals

Note that results stored in `r()` are updated when the command is replayed and will be replaced when any r-class command is run after the estimation command.

Methods and formulas

Methods and formulas are presented under the following headings:

Introduction
Variance-components parameters
Inference based on linearization
Initial values

Introduction

Recall (1), a two-level NLME model, from the *Introduction*,

$$y_{ij} = \mu\left(\mathbf{x}'_{ij},\, \boldsymbol{\beta},\, \mathbf{u}_j\right) + \epsilon_{ij} \quad i = 1, \dots, n_j;\; j = 1, \dots, M$$

where M is the number of clusters and, for each cluster j, n_j is the number of observations in that cluster; $\mathbf{y}_j = (y_{1j}, y_{2j}, \dots, y_{n_j j})'$ is the $n_j \times 1$ response vector; $\mathbf{X}_j = (\mathbf{x}_{1j}, \mathbf{x}_{2j}, \dots, \mathbf{x}_{n_j j})'$ is the $n_j \times l$ matrix of covariates, including within-subject and between-subjects covariates; $\boldsymbol{\beta}$ is the $p \times 1$ vector of unknown parameters; $\mathbf{u}_j$ is the $q \times 1$ vector of random effects; and $\boldsymbol{\epsilon}_j = (\epsilon_{1j}, \epsilon_{2j}, \dots, \epsilon_{n_j j})'$ is the $n_j \times 1$ vector of within-group or within-cluster errors. $\mathbf{u}_j$'s follow a multivariate normal distribution with mean 0 and $q \times q$ variance–covariance matrix $\boldsymbol{\Sigma}$, and $\boldsymbol{\epsilon}_j$'s follow a multivariate normal distribution with mean 0 and $n_j \times n_j$ variance–covariance matrix $\sigma^2 \boldsymbol{\Lambda}_j$; $\mathbf{u}_j$'s are assumed to be independent of $\boldsymbol{\epsilon}_j$'s. Depending on the form of $\boldsymbol{\Lambda}_j$, σ^2 is either a within-group error variance σ^2_ϵ or a squared scale parameter σ^2. For example, when errors are i.i.d., that is, when $\boldsymbol{\Lambda}_j$ is the identity matrix, $\sigma^2 = \sigma^2_\epsilon$ is the within-group error variance. When $\boldsymbol{\Lambda}_j$ corresponds to the heteroskedastic power structure, σ^2 is a multiplier or a scale parameter.

Positive-definite matrices $\boldsymbol{\Sigma}/\sigma^2$ and $\boldsymbol{\Lambda}_j$ are expressed as functions of unconstrained parameter vectors $\boldsymbol{\alpha}_u$ and $\boldsymbol{\alpha}_w$, respectively, to recast a constrained optimization problem into an unconstrained one. Thus $\boldsymbol{\alpha}_u$ contains unconstrained random-effects covariance parameters and $\boldsymbol{\alpha}_w$ contains unconstrained within-group error covariance parameters. $\boldsymbol{\Lambda}_j$ may also depend on the random effects $\mathbf{u}_j$ and the fixed effects $\boldsymbol{\beta}$. For more details about $\boldsymbol{\Sigma}$ and $\boldsymbol{\Lambda}_j$ and about functional forms of parameter vectors $\boldsymbol{\alpha}_u$ and $\boldsymbol{\alpha}_w$ given different covariance structures, see *Variance-components parameters*.

Based on (1), the marginal, with respect to $\mathbf{u}_j$'s, log likelihood for $\left(\boldsymbol{\beta}, \boldsymbol{\alpha}, \sigma^2\right)$ is

$$L(\boldsymbol{\beta}, \boldsymbol{\alpha}, \sigma^2) = \log\left\{\prod_{j=1}^{M} \int f\left(\mathbf{y}_j | \mathbf{X}_j, \mathbf{u}_j; \boldsymbol{\beta}, \boldsymbol{\alpha}_w, \sigma^2\right) f\left(\mathbf{u}_j; \boldsymbol{\alpha}_u\right) d\mathbf{u}_j\right\} \tag{25}$$

where $\boldsymbol{\alpha} = (\boldsymbol{\alpha}'_u, \boldsymbol{\alpha}'_w)'$, $f\left(\mathbf{y}_j | \mathbf{X}_j, \mathbf{u}_j; \boldsymbol{\beta}, \boldsymbol{\alpha}_w, \sigma^2\right)$ is the conditional density of $\mathbf{y}_j$ given $\mathbf{X}_j$ and $\mathbf{u}_j$, and $f\left(\mathbf{u}_j; \boldsymbol{\alpha}_u\right)$ is the density of $\mathbf{u}_j$.

In general, there are no closed-form expressions for (25) or the marginal moments of an NLME model. This is because the random effects $\mathbf{u}_j$ enter the model nonlinearly, making the q-dimensional integral in (25) analytically intractable in all but simpler cases. Several estimation techniques have been proposed for estimating parameters $\boldsymbol{\beta}$, $\boldsymbol{\alpha}$, and σ^2, including numerical integration of the integral in (25) by using an adaptive Gaussian quadrature and a linearization of the mean function in (1) by using a Taylor-series expansion.

`menl` implements the linearization method of Lindstrom and Bates (1990), with extensions from Pinheiro and Bates (1995), which is described in *Inference based on linearization*.

Variance-components parameters

For numerical stability, maximization of (25) is performed with respect to the unique elements of the matrix $\boldsymbol{G} = \boldsymbol{\Sigma}/\sigma^2$ expressed as logarithms of standard deviations for the diagonal elements and hyperbolic arctangents of the correlations for off-diagonal elements. Let $\boldsymbol{\alpha}_u$ be the vector containing these elements. For example, if we assume that the elements of the random-effects vector $\mathbf{u}_j$ are independent, then $\boldsymbol{\Sigma}$ is diagonal and $\boldsymbol{\alpha}_u$ will contain q distinct parameters—q logarithms of standard deviations. Table 1 lists the vectors of parameters $\boldsymbol{\alpha}_u$ for all random-effects covariance structures supported by `menl` in the `covariance(`*vartype*`)` option.

Table 1. Variance-components parameters

vartype	$\boldsymbol{\alpha}'_u$
`independent`	$(g_1, g_2, \ldots, g_q)$
`exchangeable`	(g_1, g_{12})
`identity`	g_1
`unstructured`	$(g_1, g_2, \ldots, g_q, g_{12}, g_{13}, \ldots, g_{q-1q})$

Notes: $g_u = \log(\sqrt{[\mathbf{G}]_{uu}})$, $g_{uv} =$ `atanh`$([\mathbf{G}]_{uv})$.
`unstructured` has $q(q+1)/2$ parameters.

The within-group error covariance matrix is parameterized as follows,

$$\mathrm{Var}\left(\boldsymbol{\epsilon}_j|\mathbf{u}_j\right) = \sigma^2\boldsymbol{\Lambda}_j\left(\mathbf{X}_j, \boldsymbol{\beta}, \mathbf{u}_j, \boldsymbol{\alpha}_w\right) = \sigma^2\mathbf{S}_j\left(\boldsymbol{\delta}, \boldsymbol{\upsilon}_j\right)\mathbf{C}_j(\boldsymbol{\rho})\mathbf{S}_j\left(\boldsymbol{\delta}, \boldsymbol{\upsilon}_j\right)$$

where $\boldsymbol{\alpha}_w = \left(\boldsymbol{\delta}^{*\prime}, \boldsymbol{\rho}^{*\prime}\right)'$ and $\boldsymbol{\delta}^*$ and $\boldsymbol{\rho}^*$ are unconstrained versions of $\boldsymbol{\delta}$ and $\boldsymbol{\rho}$ defined in table 2 and table 3, respectively. For example, for a positive δ_1, $\delta_1^* = \log\left(\delta_1\right)$. $\mathbf{S}_j = \mathbf{S}_j\left(\boldsymbol{\delta}, \boldsymbol{\upsilon}_j\right)$ is an $n_j \times n_j$ diagonal matrix with nonnegative diagonal elements $g\left(\boldsymbol{\delta}, \upsilon_{1j}\right), g\left(\boldsymbol{\delta}, \upsilon_{2j}\right), \ldots, g\left(\boldsymbol{\delta}, \upsilon_{n_j j}\right)$ such that $\mathrm{Var}\left(\epsilon_{ij}\right) = \sigma^2[\mathbf{S}_j]^2_{ii} = \sigma^2 g^2\left(\boldsymbol{\delta}, \upsilon_{ij}\right)$, where υ_{ij}'s are the values of a variance covariate or the values of a mean function $\mu\left(\mathbf{x}'_{ij}, \boldsymbol{\beta}, \mathbf{u}_j\right)$, in which case $\boldsymbol{\Lambda}_j$ will depend on $\mathbf{X}_j$, $\boldsymbol{\beta}$, and $\mathbf{u}_j$. $\mathbf{C}_j = \mathbf{C}_j(\boldsymbol{\rho})$ is a correlation matrix such that $\mathrm{corr}\left(\epsilon_{ij}, \epsilon_{kj}\right) = \left[\mathbf{C}_j\right]_{ik} = h\left(|t_{ij} - t_{lj}|, \boldsymbol{\rho}\right)$, where t_{ij} is a value of a time variable for time-dependent correlation structures such as AR, MA, and Toeplitz structures or an index variable for `banded` and `unstructured` correlation structures. A list of the supported $g(\cdot)$ and $h(\cdot)$ functions is given in table 2 and table 3, respectively.

Carroll and Ruppert (1988) introduced various variance functions $g\left(\boldsymbol{\delta}, \upsilon_{ij}\right)$ to model heteroskedasticity, which were further studied in the context of NLME models by Davidian and Giltinan (1995). Table 2 lists variance functions supported by the `resvariance(`*resvarfunc* ...`)` option.

Table 2. Supported variance functions $g(\cdot)$

resvarfunc	$g(\boldsymbol{\delta}, \upsilon_{ij})$	$\boldsymbol{\delta}'$
`identity`	1	–
`linear`	$\sqrt{\upsilon_{ij}}$	–
`power`	$c + \lvert\upsilon_{ij}\rvert^{\delta}$	(c, δ), $c \geq 0$
`power, noconstant`	$\lvert\upsilon_{ij}\rvert^{\delta}$	δ
`exponential`	$\exp(\delta\upsilon_{ij})$	δ
`distinct`	$\sum_{l=1}^{L} \delta_l I(\upsilon_{ij} = l)$	$(\delta_1 = 1, \delta_2, \ldots, \delta_L)$

In table 2, the variance function `distinct` models a distinct parameter δ_l for each level l ($l = 1, 2, \ldots, L$) of the index variable $\upsilon_{ij} \in \{1, 2, \ldots, L\}$ such that for $\upsilon_{ij} = l$, $\text{Var}(\epsilon_{ij}) = \sigma_l^2 = \sigma^2\delta_l^2$, where $\delta_1 = 1$ for identifiability purposes and $\delta_l = \sigma_l/\sigma$. `menl` estimates and stores results as δ's but displays results as variances σ_l^2, $l = 1, \ldots, L$.

The variance function $g(\cdot)$ and thus the within-group error covariance may depend on $\boldsymbol{\beta}$ and $\mathbf{u}_j$ through $\mu(\cdot)$, when $\upsilon_{ij} = \mu_{ij} = \mu\left(\mathbf{x}'_{ij}, \mathbf{u}_j, \boldsymbol{\beta}\right)$ in table 2. This is particularly appealing in PK applications, where there is often considerable intraindividual heterogeneity that is modeled, for example, as a power function of the mean.

The within-group error correlation structure is governed by the $h(\cdot)$ function. Table 3 lists correlation structures that are supported by the `rescorrelation(`*rescorr* ...`)` option and also have a closed-form expression. In addition, the AR and MA correlation structures are defined below.

The `ar` p structure assumes that the errors have an AR structure of order p. That is,

$$\epsilon_{ij} = \phi_1\epsilon_{i-1,j} + \cdots + \phi_p\epsilon_{i-p,j} + z_{ij}$$

where z_{ij} are i.i.d. Gaussian with mean 0 and variance σ_z^2. `menl` reports estimates of $\phi_1, \ldots, \phi_p$ and the overall error variance σ_ϵ^2, which can be derived from the above expression. This structure has a closed-form expression only for $p = 1$, in which case $\phi_1 = \rho$ is the correlation between error terms.

The `ma` q structure assumes that the errors are an MA process of order q. That is,

$$\epsilon_{ij} = Z_i + \theta_1 Z_{i-1} + \cdots + \theta_q Z_{i-q}$$

where Z_l are i.i.d. Gaussian with mean 0 and variance σ_Z^2. `menl` reports estimates of $\theta_1, \ldots, \theta_q$ and the overall error variance σ_ϵ^2, which can be derived from the above expression.

Table 3. Within-group error correlation functions $h(\cdot)$

rescorr	$h(\lvert t_{ij}-t_{lj}\rvert,\boldsymbol{\rho})$	Expression	$\boldsymbol{\rho}$
`identity`	$h(k)$	$I(k=0)$	–
`exchangeable`	$h(k,\rho)$	$\rho,\ k=1,2,\dots$	$\rho,\ \lvert\rho\rvert<1$
`ar 1`	$h(k,\rho)$	$\rho^k,\ k=0,1,\dots$	$\rho,\ \lvert\rho\rvert<1$
`ar` p, $p>1$	$h(k,\boldsymbol{\phi})$	no closed form	$(\phi_1,\phi_2,\dots,\phi_p)$
`ctar1`	$h(s,\rho)$	$\rho^s,\ s\geq 0$	$\rho,\ \lvert\rho\rvert<1$
`ma` q	$h(k,\boldsymbol{\theta})$	$\begin{cases}\dfrac{\sum_{j=0}^{q-\lvert k\rvert}\theta_j\theta_{j+\lvert k\rvert}}{\sum_{j=0}^{q}\theta_j^2} & k\leq q\\ 0 & k>q\end{cases}$	$(\theta_0=1,\theta_1,\dots,\theta_q)$
`toeplitz`	$h(k,\boldsymbol{\rho})$	$\rho_k I(k\leq q),\ k=1,2,\dots,q$	$(\rho_1,\rho_2,\dots,\rho_q)$
`banded`	$h(\lvert i-l\rvert,\boldsymbol{\rho})$	$\rho_{il}I(\lvert i-l\rvert\leq q),\ 1\leq i<l\leq n_j$	$\{\rho_{il}\colon 0<l-i\leq q\}$
`unstructured`	$h(\lvert i-l\rvert,\boldsymbol{\rho})$	$\rho_{il},\ 1\leq i<l\leq n_j$	$\left(\rho_{12},\dots,\rho_{(n_j-1)n_j}\right)$

You can build many flexible within-group error covariance structures by combining different functions $g(\cdot)$ and $h(\cdot)$, that is, by combining the `resvariance()` and `rescorrelation()` options. For example, you can combine an AR(1) correlation structure with a heteroskedastic structure that is expressed as a power function of the mean by specifying `rescorrelation(ar 1, t(timevar))` and `resvariance(power _yhat)`.

Inference based on linearization

Let's write (1), equivalently, in matrix form as

$$\mathbf{y}_j=\boldsymbol{\mu}\left(\mathbf{X}_j,\boldsymbol{\beta},\mathbf{u}_j\right)+\boldsymbol{\Lambda}_j^{\frac{1}{2}}\left(\mathbf{X}_j,\boldsymbol{\beta},\mathbf{u}_j,\boldsymbol{\alpha}_w\right)\boldsymbol{e}_j$$

Here $\boldsymbol{\mu}\left(\mathbf{X}_j,\boldsymbol{\beta},\mathbf{u}_j\right)$ depends on $\boldsymbol{\beta}$ and $\mathbf{u}_j$ through the function $\boldsymbol{d}(\cdot)$ in (2), and $\boldsymbol{e}_j$'s $\sim N\left(\mathbf{0},\sigma^2 I_{n_j}\right)$, where I_{n_j} is the identity matrix of dimension n_j. In what follows, for brevity, we suppress the dependence of $\boldsymbol{\mu}$ and $\boldsymbol{\Lambda}_j$ on $\mathbf{X}_j$.

Following Lindstrom and Bates (1990), we will initially assume that $\boldsymbol{\Lambda}_j$ does not depend on $\mathbf{X}_j$, $\boldsymbol{\beta}$, and $\mathbf{u}_j$ or, equivalently, on $\boldsymbol{\phi}_j$ but rather on j only through its dimension; that is, $\boldsymbol{\Lambda}_j=\boldsymbol{\Lambda}_j(\boldsymbol{\alpha}_w)$. Therefore, heteroskedastic structures that depend on the mean are not yet allowed in this context. Toward the end of this section, we will present a modified version of the algorithm that accounts for the dependence of $\boldsymbol{\Lambda}_j$ on $\boldsymbol{\phi}_j$.

Lindstrom and Bates discuss a natural extension of the methods for the LME models to NLME models. For a known $\boldsymbol{\alpha}$ (and thus known $\boldsymbol{\Sigma}$ and $\boldsymbol{\Lambda}_j$) and σ^2, the estimates of $\boldsymbol{\beta}$ and $\mathbf{u}_j$ jointly minimize

$$\sum_{j=1}^{M}\left[\log\lvert\boldsymbol{\Sigma}\left(\boldsymbol{\alpha}_u\right)\rvert+\mathbf{u}_j'\left\{\boldsymbol{\Sigma}\left(\boldsymbol{\alpha}_u\right)\right\}^{-1}\mathbf{u}_j+\log\left\lvert\sigma^2\boldsymbol{\Lambda}_j\left(\boldsymbol{\alpha}_w\right)\right\rvert\right.$$
$$\left.+\,\sigma^{-2}\left\{\mathbf{y}_j-\boldsymbol{\mu}\left(\boldsymbol{\beta},\mathbf{u}_j\right)\right\}'\boldsymbol{\Lambda}_j^{-1}\left(\boldsymbol{\alpha}_w\right)\left\{\mathbf{y}_j-\boldsymbol{\mu}\left(\boldsymbol{\beta},\mathbf{u}_j\right)\right\}\right]$$

which is twice the negative log likelihood for $\boldsymbol{\beta}$ when $\mathbf{u}_j$ is fixed or twice the negative log of the posterior density of $\mathbf{u}_j$ when $\boldsymbol{\beta}$ is fixed. Consequently, one strategy for estimating $\boldsymbol{\beta}$ and (predicting) $\mathbf{u}_j$ is to minimize the above objective function with respect to $\boldsymbol{\beta}$ and $\mathbf{u}_j$ given suitable estimates of $\boldsymbol{\alpha}$ and σ^2. Estimation of $\boldsymbol{\alpha}$ and σ^2 can be accomplished by using MLE with respect to the marginal density of $\mathbf{y}_j$, in which $\mathbf{u}_j$'s are integrated out. But because no closed-form expression for this density is available, we approximate the conditional distribution of $\mathbf{y}_j$ given $\mathbf{u}_j$ by a multivariate normal distribution with an expectation that is linear in $\mathbf{u}_j$ and $\boldsymbol{\beta}$. This is illustrated in step 2 of the algorithm below.

Lindstrom and Bates (1990) propose the following two-step estimation method or alternating algorithm.

Step 1 (PNLS step). Given current estimates $\widehat{\boldsymbol{\alpha}}$ (and thus $\widehat{\boldsymbol{\alpha}}_u$ and $\widehat{\boldsymbol{\alpha}}_w$) of $\boldsymbol{\alpha}$ and $\widehat{\sigma}^2$ of σ^2, minimize with respect to $\boldsymbol{\beta}$ and $\mathbf{u}_j$

$$\sum_{j=1}^{M}\Big[\log\left|\boldsymbol{\Sigma}\left(\widehat{\boldsymbol{\alpha}}_u\right)\right| + \mathbf{u}_j'\left\{\boldsymbol{\Sigma}\left(\widehat{\boldsymbol{\alpha}}_u\right)\right\}^{-1}\mathbf{u}_j + \log\left|\widehat{\sigma}^2\boldsymbol{\Lambda}_j\left(\widehat{\boldsymbol{\alpha}}_w\right)\right| \\ + \widehat{\sigma}^{-2}\left\{\mathbf{y}_j - \boldsymbol{\mu}\left(\boldsymbol{\beta},\mathbf{u}_j\right)\right\}'\boldsymbol{\Lambda}_j^{-1}\left(\widehat{\boldsymbol{\alpha}}_w\right)\left\{\mathbf{y}_j - \boldsymbol{\mu}\left(\boldsymbol{\beta},\mathbf{u}_j\right)\right\}\Big] \tag{26}$$

Define $\boldsymbol{\Delta}$ such that $\sigma^2\boldsymbol{\Sigma}^{-1} = \boldsymbol{\Delta}'\boldsymbol{\Delta}$. Note that $\boldsymbol{\Delta} = \boldsymbol{\Delta}(\boldsymbol{\alpha}_u)$, but for notational convenience, this dependency is suppressed throughout the rest of this section. Equation (26) is equivalent to minimizing the penalized least-squares objective function

$$\text{PNLS step:} \qquad \sum_{j=1}^{M}\left[\left|\left|\left\{\boldsymbol{\Lambda}_j'(\boldsymbol{\alpha}_w)\right\}^{-1/2}\left\{\mathbf{y}_j - \boldsymbol{\mu}\left(\boldsymbol{\beta},\mathbf{u}_j\right)\right\}\right|\right|^2 + ||\boldsymbol{\Delta}\mathbf{u}_j||^2\right]$$

with respect to $\boldsymbol{\beta}$ and $\mathbf{u}_j$ while holding the current estimates of $\boldsymbol{\alpha}$ (and, consequently, of $\boldsymbol{\Delta}$ and of $\boldsymbol{\Lambda}_j$) fixed. `pnlsopts(iterate(#))` iterations are performed at this step, unless the convergence criterion (CC) is met. The CC for PNLS optimization is controlled by `pnlsopts(nrtolerance(#))` and one of `pnlsopts(ltolerance(#))` or `pnlsopts(tolerance(#))`; see *menlmaxopts* for details.

Denote the resulting estimates as $\widehat{\mathbf{u}}_j$ and $\widehat{\boldsymbol{\beta}}$.

In the absence of random effects in the model (see example 19), the previous formulas no longer include the random effects and related components. In particular, $\mathbf{u}_j$ and $\boldsymbol{\Delta}$ are set to $\mathbf{0}$, and $\boldsymbol{\alpha} = \boldsymbol{\alpha}_w$. In this case, the PNLS step reduces to what we call a GNLS estimation step. Furthermore, if no within-group error covariance structure is specified, that is, when all observations are assumed i.i.d., $\boldsymbol{\Lambda}_j\left(\boldsymbol{\alpha}_w\right)$ is set to the identity matrix I, and the PNLS step reduces to the classical NLS estimation.

Step 2 (LME step). Perform a first-order Taylor-series expansion of the model mean function around the current estimates of $\boldsymbol{\beta}$ and of the conditional modes of the random effects $\mathbf{u}_j$, yielding

$$\mathbf{y}_j = \boldsymbol{\mu}\left(\widehat{\boldsymbol{\beta}},\widehat{\mathbf{u}}_j\right) + \widehat{\mathbf{X}}_j\left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}}\right) + \widehat{\mathbf{Z}}_j\left(\mathbf{u}_j - \widehat{\mathbf{u}}_j\right) + \boldsymbol{\Lambda}_j^{\frac{1}{2}}\left(\boldsymbol{\alpha}_w\right)\boldsymbol{e}_j \tag{27}$$

where

$$\widehat{\mathbf{X}}_j = \left.\frac{\partial \boldsymbol{\mu}\left(\boldsymbol{\beta}, \mathbf{u}_j\right)}{\partial \boldsymbol{\beta}'}\right|_{\boldsymbol{\beta}=\widehat{\boldsymbol{\beta}}, \mathbf{u}_j=\widehat{\mathbf{u}}_j}$$
$$\widehat{\mathbf{Z}}_j = \left.\frac{\partial \boldsymbol{\mu}\left(\boldsymbol{\beta}, \mathbf{u}_j\right)}{\partial \mathbf{u}_j'}\right|_{\boldsymbol{\beta}=\widehat{\boldsymbol{\beta}}, \mathbf{u}_j=\widehat{\mathbf{u}}_j}$$

Model (27) is essentially an LME model, and we use notations $\widehat{\mathbf{X}}_j$ and $\widehat{\mathbf{Z}}_j$ for the derivatives to emphasize this. That is, $\widehat{\mathbf{X}}_j$ and $\widehat{\mathbf{Z}}_j$ represent the corresponding fixed-effects and random-effects design matrices of an LME model.

Thus the approximate conditional distribution of $\mathbf{y}_j$ is

$$\mathbf{y}_j|\mathbf{u}_j \sim N\left\{\boldsymbol{\mu}\left(\widehat{\boldsymbol{\beta}}, \widehat{\mathbf{u}}_j\right) + \widehat{\mathbf{X}}_j\left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}}\right) + \widehat{\mathbf{Z}}_j(\mathbf{u}_j - \widehat{\mathbf{u}}_j),\, \sigma^2\boldsymbol{\Lambda}_j\right\}$$

Because the expectation is now linear in random effects $\mathbf{u}_j$, the approximate conditional distribution of $\mathbf{y}_j$, along with distribution of $\mathbf{u}_j$, allows us to approximate the marginal distribution of $\mathbf{y}_j$ as

$$\mathbf{y}_j \sim N\left\{\boldsymbol{\mu}\left(\widehat{\boldsymbol{\beta}}, \widehat{\mathbf{u}}_j\right) + \widehat{\mathbf{X}}_j\left(\boldsymbol{\beta} - \widehat{\boldsymbol{\beta}}\right) - \widehat{\mathbf{Z}}_j\widehat{\mathbf{u}}_j,\, \sigma^2\mathbf{V}_j(\boldsymbol{\alpha})\right\} \tag{28}$$

where $\mathbf{V}_j(\boldsymbol{\alpha}) = \widehat{\mathbf{Z}}_j\boldsymbol{\Delta}^{-1}\left(\boldsymbol{\Delta}^{-1}\right)'\widehat{\mathbf{Z}}_j{}' + \boldsymbol{\Lambda}_j\left(\boldsymbol{\alpha}_w\right)$.

Let $\widehat{\mathbf{w}}_j = \mathbf{y}_j - \boldsymbol{\mu}\left(\widehat{\boldsymbol{\beta}}, \widehat{\mathbf{u}}_j\right) + \widehat{\mathbf{X}}_j\widehat{\boldsymbol{\beta}} + \widehat{\mathbf{Z}}_j\widehat{\mathbf{u}}_j$. Estimation of $\boldsymbol{\alpha}$ and σ^2 can now be accomplished by maximizing the log likelihood corresponding to the approximate marginal distribution in (28),

$$\text{LME step:}\quad \begin{aligned} l_{\mathrm{LB}}(\boldsymbol{\alpha}, \boldsymbol{\beta}, \sigma^2) = -\frac{n}{2}\log\left(2\pi\sigma^2\right) - \frac{1}{2}\sum_{j=1}^{M}\Big\{ &\log|\mathbf{V}_j(\boldsymbol{\alpha})| \\ &+ \sigma^{-2}\left(\widehat{\mathbf{w}}_j - \widehat{\mathbf{X}}_j\boldsymbol{\beta}\right)'\mathbf{V}_j{}^{-1}(\boldsymbol{\alpha})\left(\widehat{\mathbf{w}}_j - \widehat{\mathbf{X}}_j\boldsymbol{\beta}\right)\Big\}\end{aligned} \tag{29}$$

where $n = \sum_{j=1}^{M} n_j$.

Alternatively, when the `reml` option is specified, we take an REML approach and maximize

$$l_{\mathrm{LB},R}(\boldsymbol{\alpha}, \sigma^2) = l_{\mathrm{LB}}(\boldsymbol{\alpha}, \widehat{\boldsymbol{\beta}}(\boldsymbol{\alpha}), \sigma^2) - \frac{1}{2}\sum_{j=1}^{M}\log\left|\sigma^{-2}\widehat{\mathbf{X}}_j{}'\mathbf{V}_j{}^{-1}(\boldsymbol{\alpha})\widehat{\mathbf{X}}_j\right| \tag{30}$$

The LME step (step 2) of the alternating algorithm consists of optimizing an LME log likelihood, in which the response vector is given by $\widehat{\mathbf{w}}_j$ and the fixed- and random-effects design matrices are given by $\widehat{\mathbf{X}}_j$ and $\widehat{\mathbf{Z}}_j$, respectively. `lmeopts(iterate(#))` iterations are performed at this step, unless the CC is met. The CC for LME optimization is controlled by `lmeopts(nrtolerance(#))` and one of `lmeopts(ltolerance(#))` or `lmeopts(tolerance(#))`; see *menlmaxopts* for details.

The LME step produces estimates $\widehat{\boldsymbol{\alpha}}$ and $\widehat{\sigma}^2$. (The estimates $\widehat{\boldsymbol{\beta}}$ can also be obtained at this step, but it is generally more computationally efficient to compute them at the PNLS step.) These estimates will now be used in step 1, the PNLS step.

In the absence of random effects in the model (see example 19), $\mathbf{u}_j$, $\widehat{\mathbf{u}}_j$, $\boldsymbol{\Delta}$, and $\widehat{\mathbf{Z}}_j$ are all set to $\mathbf{0}$, and $\boldsymbol{\alpha} = \boldsymbol{\alpha}_w$. In this case, the LME step is referred to as the ML step or, if the `reml` option is specified, the REML step in the `menl` output. Furthermore, if all observations are assumed i.i.d., then step 2 of the alternating algorithm is not needed, and only step 1 (NLS) is performed.

Stopping rules. One PNLS step and one LME step correspond to one iteration of the alternating algorithm. The log likelihood reported by `menl` at each iteration is the log likelihood (29) or, if the `reml` option is specified, (30) from the last iteration of the LME step. `menl` refers to this log likelihood as "linearization log likelihood" because it corresponds to the log likelihood of the LME model, which was the result of the linearization of the NLME model. The algorithm stops when the linearization likelihoods from successive iterations satisfy `ltolerance(#)`, when the parameter estimates from successive iterations satisfy `tolerance(#)`, or if the model does not converge, when the maximum number of iterations in `iterate()` is reached; see *menlmaxopts* for details about maximization options. Because the alternating algorithm does not provide a joint Hessian matrix for all parameters, there is no check for the tolerance of the scaled gradient; thus the convergence cannot be established in its strict sense. The convergence is declared based on the stopping rules described above.

When $\boldsymbol{\Lambda}_j = \boldsymbol{\Lambda}_j\left(\boldsymbol{\beta}, \mathbf{u}_j, \boldsymbol{\alpha}_w\right)$ depends on $\mathbf{u}_j$ and $\boldsymbol{\beta}$, which is the case, for example, with `resvariance(power _yhat)` and `resvariance(exponential _yhat)`), an intermediate step between the PNLS and the LME step is performed to replace the fixed effects and random effects in $\boldsymbol{\Lambda}_j$, or more precisely in the variance function $g(\cdot)$, by their current estimates from the PNLS step. After that, $\boldsymbol{\Lambda}_j\left(\boldsymbol{\alpha}_w; \widehat{\boldsymbol{\beta}}, \widehat{\mathbf{u}}_j\right) = \boldsymbol{\Lambda}_j(\boldsymbol{\alpha}_w)$ depends only on $\boldsymbol{\alpha}_w$ because both $\mathbf{u}_j$ and $\boldsymbol{\beta}$ are held fixed at their current estimates throughout the LME step.

Efficient methods for computing (29) or (30) are given in chapters 2 and 5 of Pinheiro and Bates (2000). Namely, to simplify the optimization problem, one can express the optimal values of $\boldsymbol{\beta}$ and σ^2 as functions of $\boldsymbol{\alpha}$ (and thus of $\boldsymbol{\Delta}$ and $\boldsymbol{\alpha}_w$) and work with the profiled log likelihood of $\boldsymbol{\alpha}$.

For the PNLS step, the objective function to be minimized is the penalized sum of squares

$$\sum_{j=1}^{M}\left[||(\boldsymbol{\Lambda}_j')^{-1/2}\left\{\mathbf{y}_j - \boldsymbol{\mu}\left(\boldsymbol{\beta}, \mathbf{u}_j\right)\right\}||^2 + ||\boldsymbol{\Delta}\mathbf{u}_j||^2\right]$$

By adding "pseudo"-observations to the data, the PNLS problem can be reexpressed as a standard nonlinear least-squares problem. Thus step 1 of the alternating algorithm is sometimes called the "pseudodata step". Define pseudo-observations $\widetilde{\mathbf{y}}_j$ as follows:

$$\widetilde{\mathbf{y}}_j = \begin{bmatrix} (\boldsymbol{\Lambda}_j')^{-1/2}\mathbf{y}_j \\ \mathbf{0} \end{bmatrix} \qquad \widetilde{\boldsymbol{\mu}}\left(\boldsymbol{\beta}, \mathbf{u}_j\right) = \begin{bmatrix} (\boldsymbol{\Lambda}_j')^{-1/2}\boldsymbol{\mu}\left(\boldsymbol{\beta}, \mathbf{u}_j\right) \\ \boldsymbol{\Delta}\mathbf{u}_j \end{bmatrix}$$

Then, the PNLS step can be rewritten as

$$\sum_{j=1}^{M}||\widetilde{\mathbf{y}}_j - \widetilde{\boldsymbol{\mu}}\left(\boldsymbol{\beta}, \mathbf{u}_j\right)||^2$$

Hence, for values of $\boldsymbol{\alpha}$ and σ^2 fixed at the current estimates, the estimation of $\boldsymbol{\beta}$ and $\mathbf{u}_j$ in the PNLS step can be regarded as a standard nonlinear least-squares problem. A popular iterative estimation technique for standard nonlinear least-squares is the Gauss–Newton method (see Pinheiro and Bates [2000, chap. 7] for more details).

After the completion of the alternating algorithm, an extra LME iteration is performed, with fixed effects profiled-out of the likelihood, to reparameterize $[\boldsymbol{\alpha}, \log(\sigma)]$ to their natural metric and to compute their standard errors with the delta method. This step is labeled `Computing standard errors:` in the output of `menl`. If you are interested only in standard errors for fixed effects, you can skip this step by specifying the `nostderr` option, in which case standard errors for the random-effects and within-group error covariance parameters will not be computed and will be shown as missing in the output table. The standard errors for the fixed effects are obtained from the PNLS step, and the standard errors for random-effects parameters are obtained from the LME step.

Inference on the parameters of the NLME model is based on the approximating LME model with log likelihood and restricted log likelihood functions defined in (29) and (30). Therefore, all the inferential machinery available within the context of LME models can be used. For example, under the LME approximation, the distribution of the (restricted) MLE $\widehat{\boldsymbol{\beta}}$ of the fixed effects is

$$\widehat{\boldsymbol{\beta}} \sim N\left\{\boldsymbol{\beta},\, \sigma^2\left(\sum_{j=1}^{M}\widehat{\mathbf{X}}_j{}'\mathbf{V}_j{}^{-1}(\boldsymbol{\alpha})\widehat{\mathbf{X}}_j\right)^{-1}\right\}$$

and for random-effects and within-group error parameters is

$$\begin{bmatrix} \widehat{\boldsymbol{\alpha}} \\ \log\widehat{\sigma} \end{bmatrix} \sim N\left\{\begin{bmatrix} \boldsymbol{\alpha} \\ \log\sigma \end{bmatrix}, I^{-1}(\boldsymbol{\alpha},\sigma)\right\}$$

where

$$I(\boldsymbol{\alpha},\sigma) = -\begin{bmatrix} \partial^2 l_{\mathrm{LB}_p}/\partial\boldsymbol{\alpha}\partial\boldsymbol{\alpha}' & \partial^2 l_{\mathrm{LB}_p}/\partial\log\sigma\partial\boldsymbol{\alpha}' \\ \partial^2 l_{\mathrm{LB}_p}/\partial\boldsymbol{\alpha}\partial\log\sigma & \partial^2 l_{\mathrm{LB}_p}/\partial^2\log\sigma \end{bmatrix}$$

and $l_{\mathrm{LB}_p} = l_{\mathrm{LB}_p}(\boldsymbol{\alpha},\sigma)$ is the approximated log likelihood from the LME step with fixed effects profiled out. Because inference is based on the LME approximation of the original NLME model, asymptotic results are technically "approximately asymptotic" and are thus less accurate than the asymptotic inferential results for LME models as described in [ME] **mixed**.

Initial values

The PNLS step requires starting values for $\boldsymbol{\beta}$ and $\mathbf{u}_j$. These are obtained from the EM algorithm; see, for example, Bates and Pinheiro (1998) for details. You can control optimization within the EM algorithm by specifying the `emtolerance()` and `emiterate()` options. You can also supply your own initial values; see *Examples of specifying initial values*. NLME models are often sensitive to initial values, so it is good practice to try different sets of initial values to verify that your results are robust to them.

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Also see

[ME] **menl postestimation** — Postestimation tools for menl

[ME] **meglm** — Multilevel mixed-effects generalized linear models

[ME] **mixed** — Multilevel mixed-effects linear regression

[ME] **me** — Introduction to multilevel mixed-effects models

[R] **nl** — Nonlinear least-squares estimation

[U] **20 Estimation and postestimation commands**