



## Two-level model with autocorrelated errors

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### 3.2.6 Models based on the Reisby data

#### The data

The data set is from a study described in Reisby *et. al.* (1977) that focused on the longitudinal relationship between imipramine (IMI) and desipramine (DMI) plasma levels and clinical response in 66 depressed inpatients (37 endogenous and 29 non-endogenous). Following a placebo period of 1 week, patients received 225 mg/day doses of imipramine for four weeks. In this study, subjects were rated with the Hamilton depression rating scale (HDRS) twice during the baseline placebo week (at the start and end of this week) as well as at the end of each of the four treatment weeks of the study. Plasma level measurements of both IMI and its metabolite DMI were made at the end of each week. The sex and age of each patient were recorded and a diagnosis of endogenous or non-endogenous depression was made for each patient.

Although the total number of subjects in this study was 66, the number of subjects with all measures at each of the weeks fluctuated: 61 at week 0 (start of placebo week), 63 at week 1 (end of placebo week), 65 at week 2 (end of first drug treatment week), 65 at week 3 (end of second drug treatment week), 63 at week 4 (end of third drug treatment week), and 58 at week 5 (end of fourth drug treatment week). The sample size is 375. Data for the first 10 observations of all the variables used in this section are shown below in the form of a SuperMix spreadsheet file, named **reisby.ss3**.

	(A) PATIEN	(B) HDRS	(C) WEEK	(D) WEEKSQ	(E) ENDOG	(F) WxEND
1	101.00	26.00	0.00	0.00	0.00	0.00
2	101.00	22.00	1.00	1.00	0.00	0.00
3	101.00	18.00	2.00	4.00	0.00	0.00
4	101.00	7.00	3.00	9.00	0.00	0.00
5	101.00	4.00	4.00	16.00	0.00	0.00
6	101.00	3.00	5.00	25.00	0.00	0.00
7	103.00	33.00	0.00	0.00	0.00	0.00
8	103.00	24.00	1.00	1.00	0.00	0.00
9	103.00	15.00	2.00	4.00	0.00	0.00
10	103.00	24.00	3.00	9.00	0.00	0.00

The variables of interest are:

- Patient is the patient ID (66 patients in total).
- HDRS is the Hamilton depression rating scale.
- WEEK represents the week (0, 1, 2, 3, 4 or 5) at which a measurement was made.
- WEEKSQ represents the squared values of WEEK.
- ENDOG is a dummy variable for the type of depression a patient was diagnosed with (1 for endogenous depression and 0 for non-endogenous depression).
- WxENDOG represents the interaction between WEEK and ENDOG, and is the product of WEEK and ENDOG.

## A 2-level random intercept-and-slope model with autocorrelated errors

In the mixed models discussed so far, it was assumed that the level-1 errors are conditionally independent from each other. However, the errors could be correlated over time. Different types of correlated error structures are available in SuperMix: the first-order stationary autoregressive process, stationary AR(1), the first-order non-stationary autoregressive process, non-stationary AR(1), the first-order stationary moving average process, MA(1), the first-order stationary autoregressive moving average process, ARMA(1), and a general Toeplitz autocorrelation structure.

The stationary AR(1) and ARMA(1) use the stationary assumption, that is that the variance of errors is constant over time and that the covariance of errors from differing times depends only on the time interval between these time points and not on the starting time point. The assumption of stationarity is relaxed in the other two types of models. In SuperMix, the maximum marginal likelihood (MML) solution at convergence is obtained by first using the EM algorithm and then Fisher scoring iterations.

## The non-stationary AR(1) model

Level-1 model:

$$\text{HDRS}_{ij} = b_{0i} + b_{1i} \times \text{WEEK}_{ij} + b_{2i} \times \text{WxENDOG}_{ij} + e_{ij},$$

where

$$e_{ij} = \rho e_{i,j-1} + \varepsilon_{ij}$$

with  $\rho$  denoting the AR coefficient.

Level-2 model:

$$b_{0i} = \beta_0 + \beta_3 \times \text{ENDOG}_i + v_{0i}$$

$$b_{1i} = \beta_1 + v_{1i}$$

$$b_{2i} = \beta_2$$

We can rewrite the model as follows:

$$\begin{aligned} \text{HDRS}_{ij} &= \beta_0 + \beta_1 \times \text{WEEK}_{ij} + \beta_2 \times \text{ENDOG}_{ij} + \beta_3 \times \text{WEEK} \times \text{ENDOG}_{ij} \\ &\quad + u_{0i} + u_{1i} \times \text{WEEK}_{ij} + e_{ij} \\ &= \beta_0 + (\beta_1 + u_{1i}) \times \text{WEEK}_{ij} + \beta_2 \times \text{ENDOG}_{ij} + \beta_3 \times \text{WEEK} \times \text{ENDOG}_{ij} \\ &\quad + e_{ij} + u_{0i} \end{aligned}$$

The difference between the present and previous models lies in the assumption concerning the error term. Previously, we assumed that  $\mathbf{e}_i = (e_{i1}, e_{i2}, \dots, e_{in_i})' : N(\mathbf{0}, \sigma^2 \mathbf{I}_i)$ , where  $\mathbf{I}_i$  is an identity matrix of order  $n_i \times n_i$ . Now we assume that the errors are autocorrelated, and that  $\mathbf{e}_i : N(\mathbf{0}, \sigma^2 \mathbf{\Omega}_i)$ , where  $\mathbf{\Omega}_i$  is the autocorrelation matrix.

## The analysis – step 1: starting values from a non-AR model

Two types of iteration algorithms, EM and Fisher scoring, are used for fitting an autoregressive model:

- The EM solution proceeds by assigning starting values for the structural and population parameters.

- The Fisher scoring procedure utilizes the first derivatives and expected values of the second derivatives to obtain improved parameter estimates.

Although the Fisher scoring solution is a significant improvement in terms of speed of convergence over the EM solution, it can fail in the estimation of the covariance matrix of the random effects when these terms become very small. The most reliable way to minimize the chance of encountering convergence problems is first obtaining the starting values by running the model without autocorrelated errors, then substituting the starting values obtained prior to fitting the AR model.

Recall that in Section 3.2.4 we fitted the model

Level-1 model:

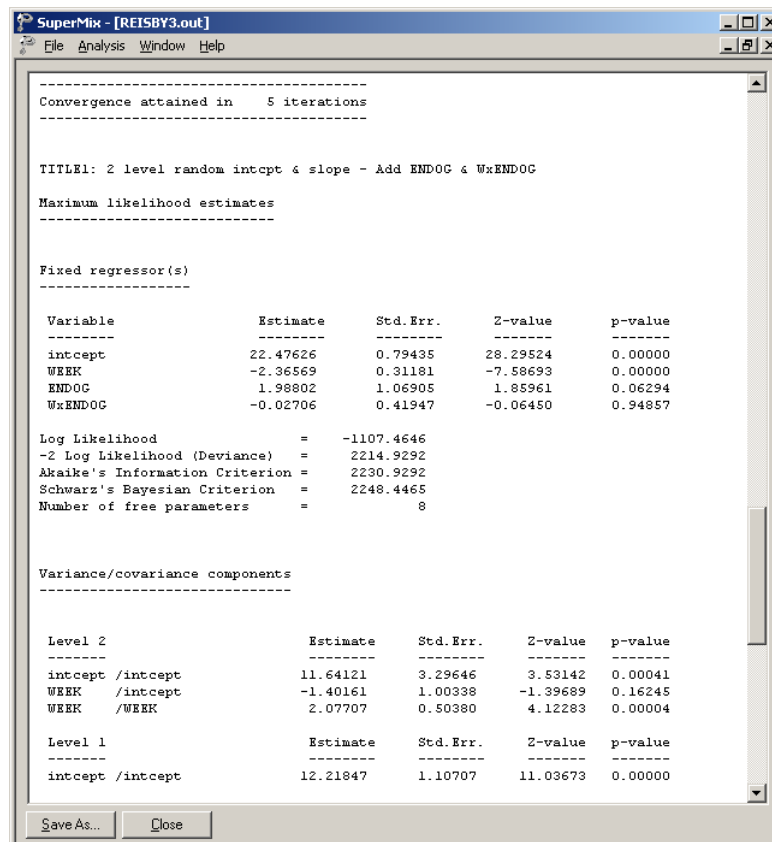
$$\text{HDRS}_{ij} = b_{0i} + b_{1i} \times \text{WEEK}_{ij} + b_{2i} \times \text{WxENDOG}_{ij} + e_{ij}$$

Level-2 model:

$$b_{0i} = \beta_0 + \beta_3 \times \text{ENDOG}_i + v_{0i}$$

$$b_{1i} = \beta_1 + v_{1i}$$

$$b_{2i} = \beta_2$$



The estimates obtained for that model are repeated above. The level-2 estimated variance of intercept and WEEK are 11.64121 and 2.07707 respectively. The estimated level-2 covariance is  $-1.40161$ . The estimated level-1 variance is 12.21847. These numbers will be used as the starting values in the non-stationary AR model to be fitted next.

## The analysis – step 2: non-stationary AR model

We modify the model setup file, **reisby3.mum**, by first saving the file as **reisby\_ar2.mum**. Change the title on the **Configuration** screen. Keep the settings of the **Variables** tab the same as before.

Click on the **Starting Values** tab. Select the **user-defined** option from the **Starting Values** drop down list to activate the grid fields for the starting values. Input the starting values we obtained from **reisby.out** to generate the following screen.

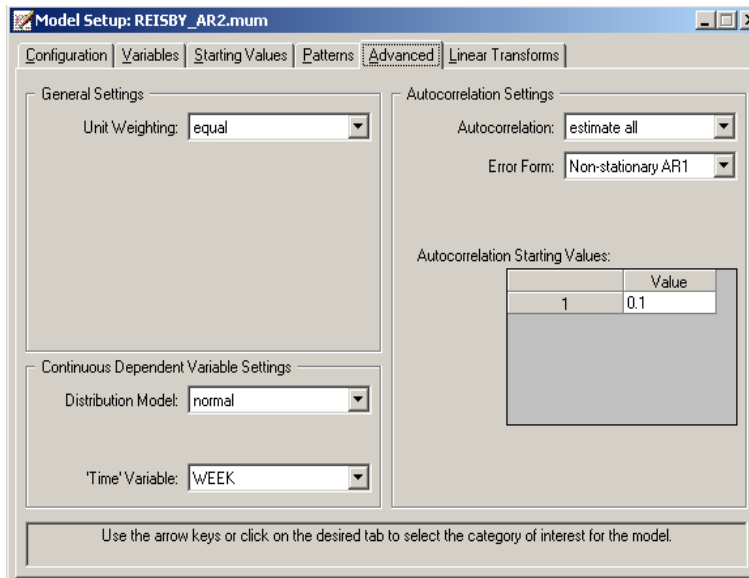
The screenshot shows the 'Model Setup: REISBY\_AR2.mum' dialog box with the 'Starting Values' tab selected. The 'Starting Values' dropdown is set to 'user-defined' and the 'Starting Error Variance' is 12.218. Below this, there are two tables for starting values.

Explanatory Variables:		Level-2 (Co)variance Starting Values:	
	Value		Value
intercept	22.47626	intercept variance	11.641
WEEK	-2.36569	intercept, WEEK	-1.402
ENDOG	1.99802	WEEK variance	2.077
WxENDOG	-0.02706		

Use the arrow keys or click on the desired tab to select the category of interest for the model.

Click on the **Advanced** tab to proceed to the **Advanced** screen. First, select the **estimate all** option from the **Autocorrelation** drop down list; then select **Non-stationary AR1** as the **Error Form** and specify **WEEK** as the **'Time' Variable**. Input 0.1 in the **Autocorrelation Starting Values** grid field to get the **Advanced** screen as shown below.

Save the changes to **reisby\_ar2.mum** and run the model to produce the output file **reisby\_ar2.out**.

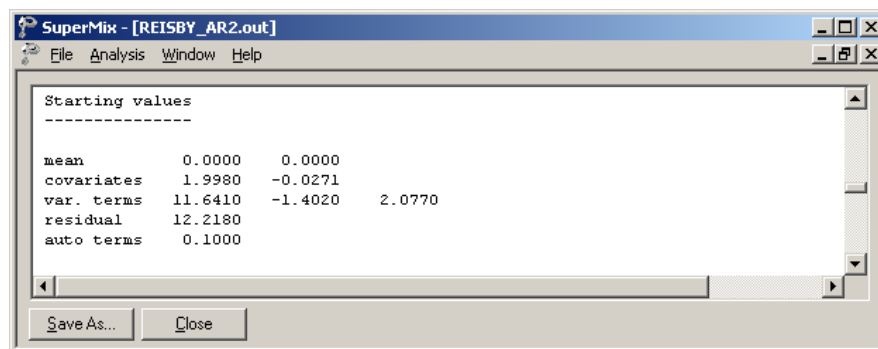


### 3.1.1.1 Interpreting the output

The output for the AR model first shows the syntax information of the model setup. The number of observations, hierarchical structure of the 2-level model and descriptive statistics follow next.

#### The starting values

The starting values could either be user-defined or program generated. In our case the user-defined starting values are listed below.

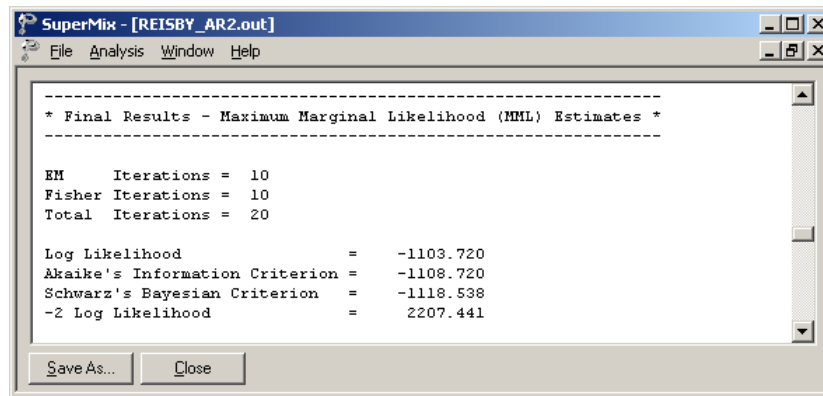


The **Starting values** section in the output file corresponds with the starting values we specified in the **Starting Values** and **Advanced** screens. The **mean** row refers to the starting values for the fixed regressors, which are intercept and WEEK in this example. The **covariates** row contains the starting values for ENDOG and WxENDOG. The elements of the **var. terms** row are the starting values for the level-2 variance/covariance matrix. The

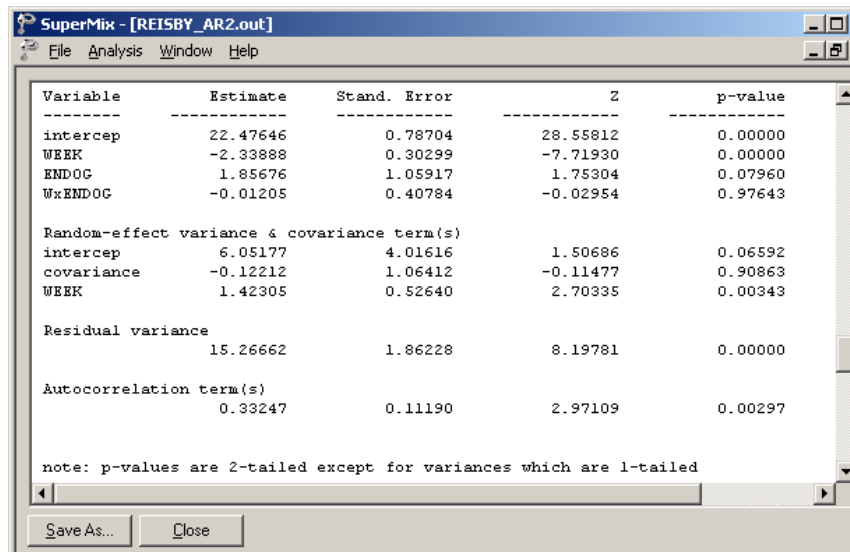
**residual** value is the starting error variance. The **auto term(s)** is the autocorrelation starting value(s).

### The maximum marginal likelihood (MML) estimates

The starting values section is followed by the **Final Results**. The maximum marginal likelihood (MML) solution at convergence is obtained by first using the EM algorithm and then Fisher scoring iterations. The AIC, SBC and  $-2$  log likelihood (deviance) are given right below the iteration information.



As shown above, the convergence is obtained after 10 EM and 10 Fisher iterations. The log likelihood value can be used to perform likelihood ratio tests.



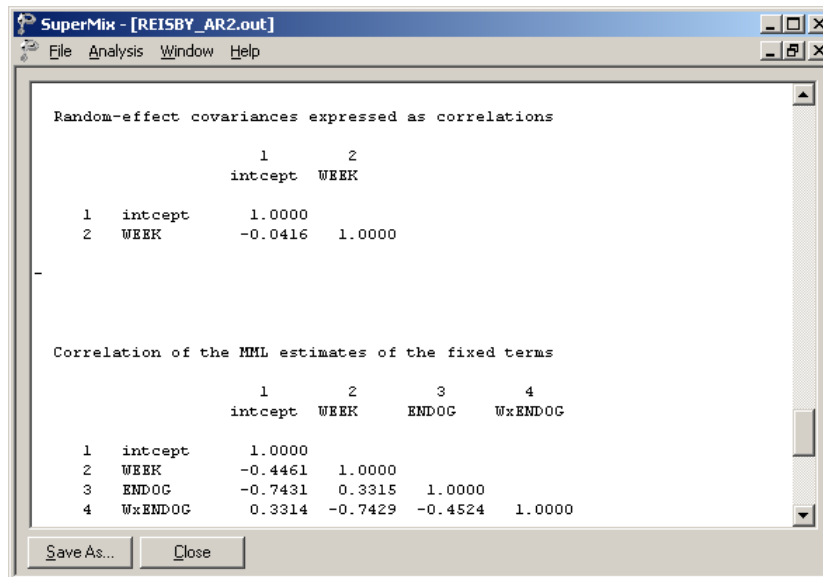
For each model parameter, maximum marginal likelihood estimates, standard errors,  $z$ -values, and  $p$ -values are provided. These  $p$ -values are two-tailed, except for the variance parameters where one-tailed  $p$ -values are given.

Considering the estimated fixed effects, the initial level of severity for non-endogenous patients is approximately 22.5 on the HDRS, while the endogenous patients start about 1.9 units higher. The difference in initial severity is almost significant ( $p < 0.0790$ ). The reason that the intercept and endogenous effect reflect HDRS levels at week 0 is due to the coding of WEEK that was used, namely, 0 to 6. Using other codings of WEEK would change the meaning of these regression coefficients.

Both groups exhibit an overall weekly rate of improvement of roughly 2.3 units which is highly significant. In terms of the random-effect variance and covariance terms, there is a significant rate of improvement ( $p < 0.00343$ ). The variation in patients' initial severity is marginally significant at 0.066. However, the overall covariation between those two terms are significant at a 10% level ( $p > 0.90864$ ).

### Correlation of the MML estimates

Finally, correlation matrices are also provided for the estimates of all model parameters. It is important to realize that these correlation matrices are not correlations of the variables themselves, but correlations of the estimated model parameters. These matrices may be helpful in determining the degree to which collinearity is present in terms of the model parameters.



It is interesting to note that, when the correlations are rounded to two decimal places, equalities exist between the correlations:



$$\begin{aligned}
r(\text{INTCEPT}, \text{ENDOG}) &= r(\text{WEEK}, \text{WxENDOG}) = -0.74 \\
r(\text{INTCEPT}, \text{WEEK}) &= r(\text{ENDOG}, \text{WxENDOG}) = -0.45 \\
r(\text{ENDOG}, \text{WEEK}) &= r(\text{INTCEPT}, \text{WxENDOG}) = 0.33
\end{aligned}$$

From the fixed effect results we see that the WxENDOG effect was not significant ( $p = 0.976$ ). It is reasonable to assume that, with the interaction term omitted from the model, the correlations between the intercept, ENDOG and WEEK coefficients will be close to those reported above.

## Level-2 Bayes results

The residual file **reisby\_ar2.ba2** offers the opportunity to take a closer look at the results by individual patient. Select the **Analysis, View L-2 Bayes Results** option to open the Bayes results as shown below. The contents of this file are displayed for the first 7 patients. Two lines of information are given for each patient, containing, in order of appearance,

- the number of the patient in the data set,
- the number of the empirical Bayes coefficient,
- the empirical Bayes estimate,
- the estimated variance of the Bayes coefficient, and
- the name of the associated coefficient as used in the model.

Patient ID	Coefficient #	Empirical Bayes Estimate	Estimated Variance	Coefficient Name
101	6	22.77116	3.59726	intercept
101	6	-3.72001	0.48751	WEEK
103	6	25.13207	3.59726	intercept
103	6	-2.40102	0.48751	WEEK
104	6	23.27913	3.59726	intercept
104	6	-3.61190	0.48751	WEEK
105	6	21.60314	3.59726	intercept
105	6	-2.43564	0.48751	WEEK
106	5	22.43105	3.59802	intercept
106	5	-1.58380	0.65884	WEEK
107	5	21.54122	3.60701	intercept
107	5	-2.88802	0.48829	WEEK
108	6	20.75564	3.59726	intercept
108	6	-3.16081	0.48751	WEEK
112	5	22.05407	3.59802	intercept

The user can obtain patient-specific predicted HDRS scores using the empirical Bayes estimates for each patient.

## Model comparison

In Table 3.5, the estimates of the regular model without an autoregressive term and the non-stationary AR(1) are summarized. Note that the AIC and BIC values obtained from the AR(1) model were multiplied by  $-2.0$  in order to facilitate comparison over the models.

**TABLE 3.5: Comparison of models with and without AR(1) term**

	<b>no AR term</b>	<b>Non-stationary AR(1)</b>
intcept	22.47626 (0.79435)	22.47646 (0.78704)
WEEK	-2.36569 (0.31181)	-2.33888 (0.30299)
ENDO	1.98802 (1.06905)	1.85677 (1.05917)
WxENDO	-0.02706 (0.41947)	-0.01205 (0.40784)
Log Likelihood	-1107.4646	-1103.72
Akaike's Information Criterion	2214.9292	2217.44
Schwarz's Bayesian Criterion	2230.9292	2237.076
-2 Log Likelihood	2248.4465	2207.441
Number of free parameters	8	9

We notice that the estimates of both models are close to each other. The estimated variances of the non-stationary AR(1) model are smaller for all the parameters. The deviance is  $2248.4465 - 2207.441 = 41.0055$  with 1 degree of freedom, which is highly significant. Thus, we conclude that in this example, the non-stationary AR(1) model fits the data better.