**CoTiMA: A package for R to perform Continuous Time Meta-Analysis**

Christian Dormann & Markus Homberg

**General description**

Continuous time meta-analysis (CoTiMA) performs meta-analyses of correlation matrices of repeatedly measured variables. As always, variables are measured at discrete time points (e.g., today at 4pm, next week on Monday etc.), which imposes a problem for meta-analysis of studies that repeatedly measured the variables because the time lags between measurement could vary across studies. However, so-called continuous time math can be used to ‘extrapolate’ or ‘intrapolate’ the results from all studies to any desired time lag. By this, effects obtained in studies that used different time lags can be meta-analyzed. In a nutshell, CoTiMA fits models to empirical data using the structural equation model (SEM) packages OpenMx and CTSEM, the effects specified in a SEM are related to parameters that are not directly included in the model (i.e., *continuous time parameters;* together, they represent the *continuous time structural equation model,* ctsem) which is done in a fashion similar to other SEM programs (e.g., like *a* = *b* × *c* to test for mediation in MPLUS) using matrix algebra functions (e.g., matrix exponentiation, which is not available in MPLUS), and statistical model comparisons and significance tests are performed on the continuous time parameter estimates.

Of course, extrapolating or intrapolating effects always rests on particular assumptions. A critical assumption is the underlying causal model that describes the process under investigation. For example, a causal system that describes how a single variable that is measured repeatedly (e.g., X1, X2, X2, etc.) could propose that X1 affects X2, X2 affects X3 and so forth. This is called a first order autoregressive structure and the model which is used by default for a CoTiMA of a single variable. In a two-variable model of X and Y, the underlying CoTiMA model is a cross-lagged model with autoregressive effects for X and Y and, in addition, a cross-lagged effect of Xt on Yt+1 and of Yt on Xt+1. More complex models (e.g., including Xt on Yt+1 and Xt on Yt+2) could be meta-analyzed, too, but they require user-specific adaptations. More simple models (e.g., Xt on Yt+1 but not Yt on Xt+1) are easier to implement and several specific models (e.g., Xt on Yt+1 exactly of the same size as Yt on Xt+1) could be optionally requested. Usually, researchers are interested in the sizes of these effects rather than the correlations on which they are based. Thus, correlations of primary studies serve as an input for CoTiMA and synthesized (i.e., meta-analytically aggregated) effect sizes represent the output of CoTiMA.

To prepare a CoTiMA, users have to supply information about the primary studies to be meta-analyzed. Primary study information has to be stored into ‘objects’ (everything in R is an object). These objects have to have particular names (delta\_t*i*, sampleSize*i*, empcov*i*, and optionally pairwiseN*i*, empMean*i*, empVar*i*, studyNumer*i*, moderator*i*, with *i* indicating the study number). This is illustrated with the following examples. In the following, required input by the used is printed in **Courier New 9pt bold face**, output on the screen or in generated files is printed in Courier New 9pt, and references to the user input or output is printed in Courier New 12pt.

**Entering Primary Study Information**

*Case 1: Introducing Study with 2 Time Points, Correlations based on Listwise Deletion, and Moderators*

**empcov1 <- matrix(c(1.00, 0.47, 0.61, 0.34,**

**0.47, 1.00, 0.34, 0.69,**

**0.61, 0.34, 1.00, 0.44,**

**0.34, 0.69, 0.44, 1.00), nrow=4, ncol=4)**

**delta\_t1 <- 18**

**sampleSize1 <- 1378**

**moderator1 <- c(1, 1, 2)**

This example is the first (*i* = 1) of several primary studies to be meta-analyzed. It comprises 2 variables measured at 2 measurement occasions, which results in correlation matrix with 4 rows (nrow) and 4 columns (ncol; i.e., a 4 x 4 correlation matrix), that is stored in the object empcov1. The order of the variables has to be V1 at Time 0, V2 at Time 0, V1 at Time 1, and V2 at Time 1 – note that it is common in the continuous math literature to number time points starting with 0. In the automatically generated output files, these two variables are labeled “V1” and “V2” (in rarely needed optional output “eta1” and “eta2” are used as labels). This matrix has to be symmetric; for example, the correlation in row 2 and column 3 (i.e., the correlation of V2 at Time 0 with V1 at Time 1 should be identical to the correlation in row 3 and column 2. Lack of symmetry is automatically detected by CoTiMA, a warning is issued, and processing is interrupted.

Primary study 1 had a time lag of 18 months, which is stored in the object delta\_t1. One could also use 1.5 to indicate a 1.5 years lag. Any time scale is possible, but it has to be used consistently across primary studies. It is recommended to use a time scale that allows representing the shortest time lag among all primary studies as a short integer value. For example, if the shortest time lag was half a year, it is recommended to use the number of months as time scale and 6 as the value for delta\_t.

Primary study 1 further had a sample size of 1278, which is stored in the object sampelSize1. In cases in which the correlation matrix includes correlations based on pairwise deletion of missing values, sample sizes vary between correlations, too. This could be specified in a different manner as explained later.

Finally, primary study 1 had some characteristics that make it different from some or all of the other primary studies. These characteristics are called moderators and they may affect the effect sizes. For instance, a moderator could be coded 1 for studies conducted in Europe and 2 for North America, or the moderator could vary from -2 to 2 based on rating of the quality of the respective study. In this example, it is intended to analyze 3 moderators and for primary study 1 these were all 1 and stored as a vector (note the “c” before the parentheses, which represents a *c*olumn vector in R) in the object moderator1. Note that in each application of CoTiMA only a single moderator could be analyzed, and we show later how to select the first, second or third one.

After adding the information of two or more primary studies in the same way, a CoTiMA could be performed. Before demonstrating how this is accomplished, we use four further examples to illustrate possible variations in providing primary study information.

**Technical notes on correlations matrices.** (1) Although it would be less laborious to enter only lower triangular correlation matrices, the requirement to have full correlation matrices serves to double check if correlations are entered correctly. Small typographical errors could have large consequences such as time-consuming and poor convergence in fitting the model to the data. (2) Although it is preferred to analyze correlation matrices in meta-analyses rather than covariances, the option to analyze covariances is available; CoTiMA automatically switches to the analysis of covariances if vectors of variances (empVar*i*) are provided, but this is not recommended. (3) CoTiMA depends on OpenMx, which performs all required computations. OpenMx can handle correlation matrices as input, but for a couple of reasons the correlation matrices are internally used to generate “pseudo raw data” using the package MASS. These pseudo raw data exactily (!) replicate the entered correlation matrices. We elaborate later that computing pseudo raw enables (a) dealing with missing correlations, (b) dealing with matrices based on pairwise deletion of missing values, and (c) having a compatible format to simultaneously meta-analyze primary studies that provide correlations and primary studies providing raw data (with or without missing values).

*Case 2: Introducing Three Time Points, Correlations with a Missing Variable*

**delta\_t2 <- c(12, 11)**

**sampleSize2 <- 668**

**empcov2 <- matrix(c(1.00, 0.41, 0.62, NA, 0.58, 0.36,**

**0.41, 1.00, 0.33, NA, 0.32, 0.58,**

**0.62, 0.33, 1.00, NA, 0.58, 0.37,**

**NA, NA, NA, NA, NA, NA,**

**0.58, 0.32, 0.58, NA, 1.00, 0.46,**

**0.36, 0.58, 0.37, NA, 0.46, 1.00), nrow=6, ncol=6)**

**moderator2 <- c(1, 2, 2)**

Compared to primary study 1, three changes are introduced in case 2. First, primary study 2 comprises three measurement occasions, which are separated by 12 and 11 months. Therefore, two time lags instead of one have to be entered and stored as a vector in delta\_t2. Second, the correlation matrix includes NA, which means that this correlation is “not available”. In panel studies, this usually occurs if a variable has been left out at one or more measurement occasions. In CoTiMA, the pattern of NA has to reflect such a case, that is, variables have to be missing completely, for example, the fourth variable (V2 at Time 1) in this example. It is not possible to have actual values for correlation in the cells [4,2], [2,4], and [4,4] of empcov2 – they have to be NA! CoTiMA performs a check whether this condition is met and interrupts if it is not.

**Technical Note on NA correlations.**  Internally, NA entries are first replaced by (very) small random values. Then, using the package MASS, pseudo raw data are generated as explained before. Finally, the missing variables are deleted from the pseudo raw data. When fitting single studies to a continuous time structural equation model, this is only possible if three or more measurement occasions are available because otherwise the model would not be mathematically identified (i.e., less empirical information are available than parameters to be estimated). In CoTiMA, when effects are aggregated across studies, this is possible if at least one single study provides all correlations for all variables analyzed at two measurement occasions.

*Case 3: Introducing N for Correlations based on Pairwise Deletion*

**empcov3 <- matrix(c(1.00, 0.44, 0.74, 0.36, 0.71, 0.32,**

**0.44, 1.00, 0.35, 0.66, 0.38, 0.65,**

**0.74, 0.35, 1.00, 0.43, 0.83, 0.35,**

**0.36, 0.66, 0.43, 1.00, 0.41, 0.71,**

**0.71, 0.38, 0.83, 0.41, 1.00, 0.44,**

**0.32, 0.65, 0.35, 0.71, 0.44, 1.00), nrow=6, ncol=6)**

**delta\_t3 <- c(12, 12)**

**moderator3 <- c(2, 2, 2)**

**pairwiseN3 <- matrix(c(658, 650, 631, 599, 0, 599,**

**650, 644, 630, 588, 0, 578,**

**0, 0, 0, 0, 0, 0,**

**631, 630, 640, 632, 0, 630,**

**579, 588, 632, 633, 0, 599,**

**579, 578, 630, 599, 0, 633), nrow=6, ncol=6)**

Entering primary study 3 shows two further features of CoTiMA. First, there is no object sampleSize3 (it could be, but CoTiMA would ignore it). Reason is that the correlation matrix of primary study 3 is based on pairwise deletion of missing values. Therefore, a matrix with the pairwise sample sizes has to be provided and stored in pairwiseN3. In most instances, there are no entries 0 in the pairwise N-matrix. We did so here to illustrate a second option for telling CoTiMA that a variable was missing in a primary study. This is usually not recommended, but it could have some use as explained in the subsequent technical note. The second feature illustrated with primary study 3 is that the order in which the objects are entered has changed. In fact, one could first enter all delta\_t*i* of the primary studies, then all sampleSizes*i* etc.

**Technical Note on Zero Pairwise *N*.** Usually, correlations for pairwise N that are 0 would not be available in the corresponding empcov object, so why should one specify a correlation to be based on *N* = 0? Sometimes, there is reason to believe that a correlation in a correlation table found in a primary study is incorrect because, for example, it seems to be too large, too low, of questionable sign, makes a matrix non-positive definite etc. Rather than overwriting the corresponding row and column in the empcov object, one could set the pairwise *N* to 0. This is particularly useful the primary study did not apply pairwise deletion and rather used listwise deletion. Then, a pairwise N-matrix is filled with the listwise N in all cells, except those rows and columns representing the variable that should be left out from analysis.

*Case 4: Introducing Start Values*

**delta\_t4 <- 96**

**sampleSize4 <- 556**

**empcov4 <- matrix(c(1.00, 0.39, 0.41, 0.19,**

**0.39, 1.00, 0.23, 0.44,**

**0.41, 0.23, 1.00, 0.26,**

**0.19, 0.44, 0.26, 1.00), nrow=4, ncol=4)**

**moderator4 <- c(2, 1, 1)**

**startValues4 <- c( -0.05, -0.02, 0.01,**

**-0.03, -1.19, 0.13, -1.48,**

**0.00, 0.45, -0.12)**

Entering information of primary study 4 is basically done as in the example of primary study 1 except that – in addition to the time lag, sample size, correlations, and moderator values – a vector of starting values is stored in the object startValues4. Reason is that some models have difficulties in finding the proper solution (i.e., the solution with the lowest possible -2 log likelihood value). Guessing possible starting values is of little value – the start values above make little intuitive sense but work perfectly. However, a reliable option is to use CoTiMA to automatically fit a model may (up to several thousands of) times, select the one with the best fit, and take the estimated parameter values and enter then as startValues. This could be done with little effort as explained shortly, and it usually ensures fast and proper solutions in subsequent CoTiMAs.

**Technical Note on Start Values.** An even faster, more convenient, and even more reliable way to ensure proper model fit is to save the model fit object once a proper solution for a primary study is found and then reload the fit object later. This is also easily accomplished as explained later. However, providing a vector of starting values is a much more practical way to make the published results of a CoTiMA reproducible. Correlation matrices, sample sizes, length of time lags are usually documented in most longitudinal meta-analyses anyway, and adding the starting values of a single or a couple of studies does not make manuscripts considerably longer.

*Case 5: Introducing Raw Data*

**rawData5 <- list(fileName="data5.dat", missingValues=-99,   
standardize=TRUE, header=TRUE, dec=".", sep=" ")**

**moderator5 <- c(2, 1, 1)**

Sometimes, researchers have access to raw data gathered in primary studies, which is usually a better alternative than correlation matrices. The lines above show how enter information of a primary study for which raw data are available. The required information is put together in a list. In R, a list is a list (sic!) that has elements, which have their own labels (like in a shopping list, in which you summarize the planned purchases in subitems like "vegetables", "cheese" etc..). The raw data have to be included in an ordinary text file, and the name of the file should be stored in “fileName”. Possibly missing values should be specified, and only a single value is possible (-99 is assumed by default), and be stored in the list element “missingValues”. Whether or not the raw data should be standardized, which implies the analysis of correlations, or not, which implies the analysis of covariance, could be specified by setting the element “standardized” to either “TRUE” (default and recommended) or to “FALSE”. Whether or not the raw data files include a header with variable names (as for the example data below) could be specified by setting the element “header” to either “TRUE” (default) or to “FALSE”. Finally, a decimal delimited (default = “.”) and the characters separating the values from each another (default = “ “) could be defined using the list elements “dec” and “sep”, respectively. Note that in meta-analysis, moderators are usually study characteristics (e.g., the average age of a sample) rather than characteristics of individual study participants. Therefore, moderator values are not taken from a raw data file, but they are defined directly for a primary study that does provide raw data by assigning values to the moderator object. However, time lags could vary among participants within a primary study (usually they do not). Therefore, they generally have to be included as the last column(s) of the raw data file. Below the example data (read from the file name: data5.dat) used in this chapter are shown.

X\_T0 Y\_T0 X\_T1 Y\_T1 dT1

0.835 2.328 -0.778 2.969 11

1.555 2.634 1.977 1.807 12

3.209 1.849 2.291 2.795 12

0.456 0.235 0.244 0.738 13

-0.832 2.160 0.904 1.595 11

1.821 3.900 0.476 3.358 12

1.692 2.120 1.470 1.406 12

2.225 3.612 3.220 3.728 13

0.644 0.781 1.330 1.193 11

1.118 0.306 1.159 0.167 12

0.249 1.802 0.388 1.658 12

0.416 2.351 0.127 1.705 13

1.046 2.285 0.132 1.843 11

-0.434 1.637 1.060 3.038 12

0.188 2.587 -99.000 -99.000 12

0.612 0.776 -99.000 -99.000 13

2.200 2.638 -99.000 -99.000 11

1.750 -99.000 -99.000 -99.000 12

0.250 -99.000 -99.000 -99.000 12

-99.000 2.750 -99.000 -99.000 13

-99.000 1.250 -99.000 -99.000 11

-99.000 -99.000 0.180 -99.000 12

-99.000 -99.000 2.490 -99.000 12

-99.000 -99.000 0.476 -99.000 13

-99.000 -99.000 0.854 -99.000 11

-99.000 -99.000 -99.000 2.987 12

-99.000 -99.000 -99.000 2.087 12

-99.000 -99.000 -99.000 0.927 13

**Putting Everything Together**

The final requirement before conducting a CoTiMA is to summarize all primary study information in a list. Since could become laborious when many primary studies are analyzed, CoTiMA comes with an additional function “compileListOfPrimaryStudies”, which works properly if the objects were properly labeled, as explained earlier (i.e., using objects named (i.e., delta\_t*i*, sampleSize*i*, empcov*i*, moderator*i*, startValues*i*, pairwiseN*i*, rawData*i*). The first example below shows how to put all 5 primary studies into a list. The second example compiles a list that includes only the first and last of the 5 studies. Lists of primary studies can have any desired name:

**firstStudyList <- compileListOfPrimaryStudies(selectedStudies=1:5)**

**secondStudyList <- compileListOfPrimaryStudies(selectedStudies=c(1, 5))**

**Technical Note on Study Lists.** A study list puts all possible objects that contain information about a single primary study into a list, and then all lists into an overall list (e.g., firstStudyList). When creating the list (of lists), information that were unavailable for a primary study (e.g., raw data in most instances), are treated in a particular fashion. When it is aimed at compiling a study list of *k* primary studies without using the “compileListOfPrimaryStudies” function, it is recommended to first create a template of 2 studies using “compileListOfPrimaryStudies”, and then investigate the structure of the resulting object to adapt it to one’s special needs.

**Conducting CoTiMA: A Commonly Encountered Problem**

After entering the primary study information and putting them together in a list, a CoTiMA could be performed. Recall that our example includes some ‘difficult’ cases such as missing variables and correlations based on pairwise deletion of missing values. Some problems could be expected, and it is recommended to firstly inspect the fit resulting when the single studies are fitted to a continuous time structural equation model. Model fitting is done anyway by CoTiMA; it cannot be circumvented because more complex subsequent models use the resulting estimates as starting values for finding proper solutions. Fitting single study models could be achieved by applying the following CoTiMA:

**CoTiMA1Fit <- CoTiMA(workingDirectory="/Users/…/CoTiMA/DOCUMENTATION/",**

**sourceDirectory="/Users/.../CoTiMA/CURRENT VERSION/",**

**resultsFileName="CoTiMA 1.txt",**

**filePrefix="CoTiMA 1",**

**timeUnit="Months",**

**primaryStudies=firstStudyList,**

**nlatents=2**

**)**

The list element workingDirectory defines where possible raw data can be found and where CoTiMA results are saved. Usually, the current R-Script used to perform the CoTiMA (i.e., all of the things described above) will be located there, too. The list element sourceDirectory defines where the CoTiMA function and all other auxiliary functions (e.g., compileListOfPrimaryStudies) can be found. All numerical summary information as well as the results of all statistical analyses performed are saved in the file name assigned to the element resultsFileName. Note that in subsequently performed CoTiMAs, all new results will be appended at the end of an already existing file if resultsFileName not changed. All figures created are automatically assigned a pre-defined name, which could be augmented by a prefix assigned to filePrefix. Note that if the filePrefix is *not* changed in subsequently performed CoTiMAs, all new results will NOT be appended and already existing files will be overwritten. The time scale used in all created figures is then assigned to the element timeUnit.

The next elements are used to specify what exactly the CoTiMA should do. The list element primaryStudies is used to define the primary study information that should be analyzed, that is, the previously created list. The list element nlatents=2 specifies how many (latent) variables are analyzed. Two things are noteworthy. First, in continuous time modeling, the ‘number of latent variables’ refers to the latent variable per measurement occasion, and this number has to be invariant across measurement occasions. Second, without using more advance user-specified models, the number of latent variables is identical to the number of manifest (observed) measurements (indicators). There are no measurement models involving multiple indicators.

Now, the CoTiMA function can be applied. When this is done for the first time, it may take quite a while to download and attach the required packages on which CoTiMA depends (e.g., ctsem, OpenMx). Then CoTiMA initiates the fitting process and by default will stop after a possible solution is found. At this stage, one would (probably) obtain the following or similar output on the screen as below, at which CoTiMA waits for a user input to continue or quit.

V1toV1 (SE) V1toV2 (SE) V2toV1 (SE) V2toV2 (SE)

Study No 1 -0.0306 0.0023 0.0018 0.0020 0.0061 0.0022 -0.0215 0.0018

Study No 2 -2.6638 0.7135 267.0289 141.8241 5.7986 1.5374 -591.2176 312.8110

Study No 3 -0.0164 0.0020 0.0083 0.0030 0.0042 0.0025 -0.0363 0.0031

Study No 4 -0.0102 0.0012 0.0006 0.0011 0.0021 0.0011 -0.0088 0.0010

Study No 5 -0.0599 0.0394 0.0113 0.0238 0.0037 0.0322 -0.0268 0.0191

Press 'q' to quit or any other key to continue. Press ENTER afterwards.

These are the estimated continuous time auto effects (which should be negative) and cross effects (which could be positive or negative) of the 5 studies analyzed separately. It is quite obvious that some of the estimated parameters for primary study 2 are out of range. In particular cross effects and their associated standard errors (SE) should virtually never be larger than 1.0 in absolute value, whereas this is the case for V1toV2 and V1toV2 of primary study 2. Our experience is out-of-range-estimates occur roughly in 10% of the primary studies even if they used listwise deletion, for example, because of minor typos in the reported correlation matrices. In cases of primary studies that used pairwise deletion or that did not measure all variables at all measurement occasions, problems in fitting the models could be even more frequent. In many (not all) instances the problems could, however, be fixed with dome patience. Patience is required when fitting a single primary study hundreds or thousands of times, relying on the fact that some slight variations in the fitting process, which are introduced automatically be OpenMx, will here and then result in better model fit (i.e., lower -2 log likelihood values; 8369.399 instead of 8695.7260 in the present example) with reasonable parameter estimates. Fortunately, this could be done automatically and only patience is required. The following code could be used:

**listOfPrimaryStudies <- compileListOfPrimaryStudies(selectedStudies=2)**

**CoTiMA2singleFit <- CoTiMA(**

**workingDirectory="/Users/…/CoTiMA/DOCUMENTATION/",**

**sourceDirectory="/Users/…/CoTiMA/CURRENT VERSION/",**

**resultsFileName="tmp.txt"**

**filePrefix="tmp",**

**primaryStudies=listOfPrimaryStudies,**

**nlatents=2**

**timeUnit="Months",**

**refits=200,**

**saveSingleStudyModelFit=c("tmp", 2)**

**)**

The function compileListOfPrimaryStudies compiles a list with a single primary study, that is, the critical primary study 2. This list is then handed over to the CoTiMA function, where a new resultsFileName (tmp.txt) and a new filePrefix (tmp) are used to prevent confusion with previously generated output files. More importantly, a new argument is used, that is, refits=200, to make CoTiMA fitting the model 200 times. Finally, another new argument is used: saveSingleStudyModelFit=c("tmp", 2). The model-fit (a pretty large automatically generated list object with all information of the fitting process and all results) will be saved to a file with the automatically generated name “tmp studyFit2.rds” in a subdirectory of the current working directory named “tmp singleStudyFits”. With a bit of luck, the following output should appear on the screen after some time (could be up to 30 minutes):

V1toV1 (SE) V1toV2 (SE) V2toV1 (SE) V2toV2 (SE)

Study No 1 -0.0543 0.0041 0.0115 0.0037 0.0187 0.0043 -0.0292 0.0031

Press 'q' to quit or any other key to continue. Press ENTER afterwards.

This is the expected outcome and at this stage one should not (!) enter ‘q’ to quit but rather any other key or just ENTER. This will result in a couple of messages like below, which are no of too much importance.

Only a single primary study was handed over to CoTiMA. No further (meta-) analyses can be conducted.

I guess this stop is intended! You could ignore further warning messages such as "sqrt(n-2): NaNs produced"

Error in CoTiMA(workingDirectory = "/Users/.../CoTiMA/DOCUMENTATION/", :

Hopefully the solution is reasonable. Set refits to a higher value if this is not the case.

The really important result of is the file containing the model fit. The function importStartValues can now be applied to directly store the required start values in an object. The content of the object (startValues2 in the present example) could then also be displayed on screen, which is useful for copy and pasting in order to report the used start values in research articles to make results reproducible. This could be achieved by the following code (note that the last subdirectors after the final slash / , i.e., tmp singleStudyFits, was generated by the CoTiMA function applied just before):

**startValues2 <- importStartValues(filePrefix="tmp", modelName="studyFit",**

**modelNumber="1",**

**directory="/Users/.../DOCUMENTATION/tmp singleStudyFits")**

**round(startValues2, 4)**

**Conducting CoTiMA with Main Effects**

Now, a full CoTiMA could be performed. However, the list of studies to be handed over to CoTiMA has to be compiled again to include the just generated starting values for primary study 2. In the example three new arguments are introduced and the saveSingleStudyModelFit argument has changed to save the fit of all 5 primary studies. The argument refits=1 overrides the default value 5, which makes fitting much faster, but which is not recommended before it is obvious that the model does fit well. The argument confidenceIntervals=TRUE enables computation of confidence intervals, which is also not recommended before it is obvious that the model does fit well because computing confidence intervals could be quite time consuming. Confidence intervals are not necessarily symmetric and provide a better means to assess significance of parameter estimates than using their standard errors. Finally, saveDRIFTAllModelFit=c("CoTiMA 2") is used to save the model fit of the CoTiMA, that is, the model in which all 4 drift coefficients are constrained to be invariant across the 5 primary studies. Savin the model fits of the single studies as well as the fit of the CoTiMA model is useful because they can be re-loaded later when other models are fitted. This could save a lot of time in particular if there are many primary studies or several studies which are require long time to be properly fitted.

**listOfPrimaryStudies <- compileListOfPrimaryStudies(selectedStudies=1:5)**

**CoTiMA2Fit <- CoTiMA(workingDirectory="/Users/.../CoTiMA/DOCUMENTATION/",**

**sourceDirectory="/Users/.../CoTiMA/CURRENT VERSION/",**

**resultsFileName="CoTiMA 2.txt",**

**filePrefix="CoTiMA 2",**

**primaryStudies=listOfPrimaryStudies,**

**nlatents=2**

**refits=1,**

**confidenceIntervals=TRUE,**

**saveSingleStudyModelFit=c("CoTiMA 2", 1:5),**

**saveDRIFTAllModelFit=c("CoTiMA 2")**

**)**

As before, computation stops after the 5 primary studies were fitted separately and their drift coefficients and associated standard errors are displayed on screen. Since no further problems seem to be present, one could press ENTER and CoTiMA will continue

V1toV1 (SE) V1toV2 (SE) V2toV1 (SE) V2toV2 (SE)

Study No 1 -0.0306 0.0023 0.0018 0.0020 0.0061 0.0022 -0.0215 0.0018

Study No 2 -0.0543 0.0041 0.0115 0.0037 0.0187 0.0043 -0.0292 0.0031

Study No 3 -0.0164 0.0020 0.0083 0.0030 0.0042 0.0025 -0.0363 0.0031

Study No 4 -0.0102 0.0012 0.0006 0.0011 0.0021 0.0011 -0.0088 0.0010

Study No 5 -0.0599 0.0394 0.0113 0.0238 0.0037 0.0322 -0.0268 0.0191

Press 'q' to quit or any other key to continue. Press ENTER afterwards.

**Results of CoTiMA with Main Effects**

After subsequent computations, the results are stored in the object CoTiMA2Fit and the several files can be found in the working directory. These files belong to one of three categories: *fitted models*, a *results file* which summarizes the statistical tests performed, and a series of *figures*.

*Fitted Models*

The saved files withthefitted models are not of too much interest because their main purpose is to be re-loaded in subsequent CoTiMAs to save computation time. Therefore, they are just briefly described here. Recall that the file prefix was set to CoTiMA 2. Among others, a subdirectory named “CoTiMA 2 singleStudyFits” is generated in which the fitted models are saved, without and with confidence intervals (CI):

* CoTiMA 2 studyFit1.rds
* CoTiMA 2 studyFit2.rds
* etc.
* CoTiMA 2 studyFitCI1.rds
* CoTiMA 2 studyFitCI2.rds
* etc.

For the CoTiMA model with all drift coefficients invariant across primary studies, the fitted models without and with confidence intervals are saved, too. To increase computational speed, the fitted model with confidence intervals is saved in different files, and each saved file contains the confidence interval for one out of four drift coefficients:

* CoTiMA 2 homDRIFTallFit.rds
* CoTiMA 2 homDRIFTallFitCI1.rds
* CoTiMA 2 homDRIFTallFitCI2.rds
* CoTiMA 2 homDRIFTallFitCI3.rds
* CoTiMA 2 homDRIFTallFitCI4.rds

It is possible (but not necessary) to load the fitted models and investigate the results using the summary function. For example, the estimated parameters and their standard errors or the estimated drift parameters and their confidence intervals could be inspected as follows:

**tmpFit <- readRDS("/Users/.../CoTiMA/DOCUMENTATION/CoTiMA 2 singleStudyFits/  
CoTiMA 2 studyFitCI2.rds")**

**summary(tmpFit)$ctparameters**

Value Matrix StdError

V1toV1 -0.054325347 DRIFT 0.004137095

V1toV2 0.011458641 DRIFT 0.003659109

V2toV1 0.018676536 DRIFT 0.004275774

V2toV2 -0.029168688 DRIFT 0.003068419

diffusion\_eta1\_eta1 0.092639531 DIFFUSION 0.007946019

diffusion\_eta2\_eta1 0.007594721 DIFFUSION 0.016679651

diffusion\_eta2\_eta2 0.048234093 DIFFUSION 0.008230945

T0var\_eta1\_eta1 0.998503272 T0VAR 0.027341628

T0var\_eta2\_eta1 0.409386225 T0VAR 0.055750242

T0var\_eta2\_eta2 0.998502546 T0VAR 0.024937900

**summary(tmpFit)$omxsummary$CI**

lbound estimate ubound

V1toV1 -0.06284688 -0.05432535 -0.04655758

V1toV2 0.00449899 0.01145864 0.01896788

V2toV1 0.01045931 0.01867654 0.02729610

V2toV2 -0.03564401 -0.02916869 -0.02350779

Recall that the significance of a parameter estimate is assessed by its T-value, which is the parameter estimate divided by its standard error; it should b *T*-value > 1.96 for *p* < .05, or *T*-value > 2.58 for p < .01. However, virtually all important results are also summarized in the results file CoTiMA 2.txt, and inspecting this result file is usually all what is needed.

*Results File*

The results file has several sections, depending on the specification of the CoTiMA. In the present case, we only requested the single study model fits (no argument exists to avoid fitting these models) and the CoTiMA with all drift effects being invariant across primary studies. To briefly describe the results file, we highlight the major sections and extract some parts to present them as examples here. The first part is a summary of the model specified:

###################################################################################

--------------------------------- CoTiMA Parameters -------------------------------

###################################################################################

Number of latent variables (nlatents): 2

Number of iterations to be used by ctsem (retryattempts): 30

Number of re-fits used by this CoTiMA Function (refits): 1

...

Named in parentheses are the arguments of the CoTiMA function. All available arguments including retryattempts as shown above are explained in detail later. Next, some statistics summarizing the primary study information are displayed:

###################################################################################

------------------------------ Primary Study Statistics----------------------------

###################################################################################

-------------------------------- Sample Sizes -------------------------------------

Sample Sizes (k): 1378 668 806 556 28

Reported sample sizes should be treated with some caution. Primary studies with

correlations matrices with pairwise deleted missing values or raw data with missing

do not have a single number representing the sample size. However, the internal

algorithm used to transform the correlation matrix with pairwise deleted missing values into pseudo raw data estimates how large the sample size had to be at least in order to reproduce the pattern of pairwise N provided for the primary studies.

Overall Sample Size (N): 3436

Primary study No. 3 had a correlation matrix with pairwise deleted cases. N was:

[,1] [,2] [,3] [,4] [,5] [,6]

[1,] 658 650 0 631 599 579

[2,] 650 658 0 630 588 578

[3,] 0 0 0 0 0 0

[4,] 631 630 0 638 623 600

[5,] 599 588 0 623 630 560

[6,] 579 578 0 600 560 610

Some cases were lost during pseudo raw data generation. Lost N was

1 2 3 4 5 6

1 0 -20 0 -16 -11 -1

2 -20 0 0 -15 0 0

3 0 0 0 0 0 0

4 -16 -15 0 0 -30 -12

5 -11 0 0 -30 0 0

6 -1 0 0 -12 0 0

Overall lost N was: -105

Relative lost N was: -0.0114

---------------------------------- Time Lags --------------------------------------All Time Lags (deltas): 11 12 12 12 12 18 96

Mean Time Lag (delta): 24.71429

...

The reported sample sizes should be treated with some caution. Recall that primary study 3 provided a correlation matrix with pairwise deleted missing values. Thus, there is no single number representing the sample size of this study. However, the internal algorithm used to transform the correlation matrix with pairwise deleted missing values into pseudo raw data revealed that the overall sample size of this study had to be at least 806 (even though the largest pairwise N was only 658) to produce the pattern of pairwise *N* provided in pairwiseN3. Still, the empirical correlation matrix is exactly reproduced by the pseudo raw data created and no single pairwise N is larger than empirically available, making any claims of statistical significance conservative.

The next section presents the results of all primary studies analyzed separately (i.e., a summary of the single study model fits):

###################################################################################

--------------- All Studies Analyzed Separately (~ Heterogeneity Model) -----------

###################################################################################

-------------------------------- Coefficients -------------------------------------

All Drift Coefficients and their Standard Errors (SE):

V1toV1 (SE) V1toV2 (SE) V2toV1 (SE) V2toV2 (SE)

Study No 1 -0.0306 0.0023 0.0018 0.0020 0.0061 0.0022 -0.0215 0.0018

Study No 2 -0.0543 0.0041 0.0115 0.0037 0.0187 0.0043 -0.0292 0.0031

Study No 3 -0.0164 0.0020 0.0083 0.0030 0.0042 0.0025 -0.0363 0.0031

Study No 4 -0.0102 0.0012 0.0006 0.0011 0.0021 0.0011 -0.0088 0.0010

Study No 5 -0.0599 0.0394 0.0113 0.0238 0.0037 0.0322 -0.0268 0.0191

All Drift Coefficients and their 95% Confidence Intervals (Not Necessarily Symmetric):

[1] "Study No. 1"

lbound estimate ubound

V1toV1 -0.035 -0.031 -0.026

V1toV2 -0.002 0.002 0.006

V2toV1 0.002 0.006 0.010

V2toV2 -0.025 -0.021 -0.018

[1] "Study No. 2"

lbound estimate ubound

V1toV1 -0.063 -0.054 -0.047

V1toV2 0.004 0.011 0.019

V2toV1 0.010 0.019 0.027

V2toV2 -0.036 -0.029 -0.024

...

------------------------------- Fit Statistics -------------------------------------2 Log Likelihood: 35773.7

Overall Number of Estimated Parameters: 50

Degrees of Freedom (Standard SEM type. NOT OpenMx/CTSEM type): 22

Note that the -2 log likelihood value is identical to the value that would be obtained with a multi-sample model in which all parameters were allowed to vary across primary studies (i.e., a heterogeneity model).

The next section presents the results of the CoTiMA model, that is, a multi-sample model in which all parameters except the four drift parameters were allowed to vary across primary studies. By constraining the four drift parameters to be invariant across primary studies, they are meta-analytically aggregated:

###################################################################################---------- Multi-Sample Homogeneity Model (all Drift Coefficients Invariant) ------###################################################################################-------------------------------- Coefficients -------------------------------------

Synthesized/Aggregated Drift Coefficients and their Standard Errors (SE):

V1toV1 (SE) Tvalue V1toV2 (SE) Tvalue

Fixed Effects -0.0280 0.0017 -16.7834 0.0068 0.0014 4.7055

upper bound -0.0262 NA NA 0.0084 NA NA

lower bound -0.0314 NA NA 0.0040 NA NA

V2toV1 (SE) Tvalue V2toV2 (SE) Tvalue

Fixed Effects 0.0091 0.0015 5.9991 -0.0241 0.0014 -16.7603

upper bound 0.0112 NA NA -0.0228 NA NA

lower bound 0.0061 NA NA -0.0270 NA NA

------------------------------- Fit Statistics -------------------------------------2 Log Likelihood: 36011.17

Overall Number of Estimated Parameters: 34

Degrees of Freedom (Standard SEM type. NOT OpenMx/CTSEM type): 38

Comparison with Unconstrained Modell (All Samples Analyzed Separately (~Heterogeneity Model)):

Delta(df): 16

Delta(-2LL) (= Delta(Chi-square)): 237.4681

p-value (with double number of digits): 0

...

The -2 log likelihood difference test shows that, as virtually always in meta-analysis, the assumption of invariance across primary study does not apply. In many (cross-sectional) meta-analyses of effects sizes, the amount of effect size heterogeneity among primary studies is frequently assessed using I2-values. Together with a typical fixed effects and random effects analysis, they are presented in the next section of the results file. Since the computation of these values is extremely fast, they are always contained in the results file:

###################################################################################---- Fixed Effects Analysis of Drift Coefficients (Taken From Heterogeneity Model) ###################################################################################-------------------------- Analysis of Fixed And Random Effects -------------------

-------- i.e., All Drift Effects in All Studies Analyzed Separately (not a CoTiMA)

Fixed Effects Analysis (Borenstein et al., 2007)

V1toV1 V1toV2 V2toV1 V2toV2

Mean -0.0343 0.0067 0.0069 -0.0245

Fixed Effect -0.0166 0.0021 0.0038 -0.0150

Variance of Fixed Effect 0.0000 0.0000 0.0000 0.0000

Standard Error of Fixed Effect 0.0009 0.0009 0.0009 0.0008

Upper Limit of Fixed Effect -0.0149 0.0038 0.0056 -0.0134

Lower Limit of Fixed Effect -0.0184 0.0004 0.0021 -0.0167

Z-Value -18.5075 2.4020 4.2271 -17.9513

p(Z) 0.0000 0.0082 0.0000 0.0000

tau square 0.0001 0.0000 0.0000 0.0001

Q 151.5836 13.0462 15.4041 117.5721

H square (H2) 37.8959 3.2615 3.8510 29.3930

Upper Limit of H2 48.2349 5.2211 6.0693 38.1631

Lower Limit of H2 29.7730 2.0374 2.4435 22.6384

I square (I2) 97.3612 69.3396 74.0328 96.5978

Upper Limit of I2 98.3712 88.0355 89.5455 97.9818

Lower Limit of I2 95.7249 21.4292 35.5022 94.2647

Random Effects Analysis (Borenstein et al., 2007)

V1toV1 V1toV2 V2toV1 V2toV2

Random Effect -0.0277 0.0041 0.0059 -0.0237

Variance of Random Effect 0.0000 0.0000 0.0000 0.0000

Standard Error of Random Effect 0.0056 0.0017 0.0019 0.0045

Upper Limit of Random Effect -0.0168 0.0075 0.0097 -0.0148

Lower Limit of Random Effect -0.0386 0.0007 0.0021 -0.0325

Z-Value -4.9856 2.3338 3.0569 -5.2446

p(Z) 0.0000 0.0098 0.0011 0.0000

Upper Limit of Prediction Interval -0.0063 0.0092 0.0119 -0.0062

Lower Limit of Prediction Interval -0.0492 -0.0011 -0.0001 -0.0412

*Figures*

Further, a series of graphic files is generated that show the plots, in which the continuous time drift effects are transformed into their discrete time counterpart across a range of possible time lags:

* CoTiMA 2\_CoTiMA results for auto-regressive effects of V1.png
* CoTiMA 2\_CoTiMA results for auto-regressive effects of V2.png
* CoTiMA 2\_CoTiMA results for cross-lagged effects of V1toV2.png
* CoTiMA 2\_CoTiMA results for cross-lagged effects of V2toV1.png

An example for a plot showing the discrete time cross-lagged effects of V1toV2 is shown in Figure 1. The grey slopes show the expected cross-lagged effects of the 5 primary studies that could be expected across time lags ranging from 1 to 144 months. The dots represent the effects actually found for the respective time lag(s) of the primary studies. The dashed black line represents the expected meta-analytically aggregated cross-lagged effect, and the grey and dashed vertical line represents the average time lag found in primary studies.

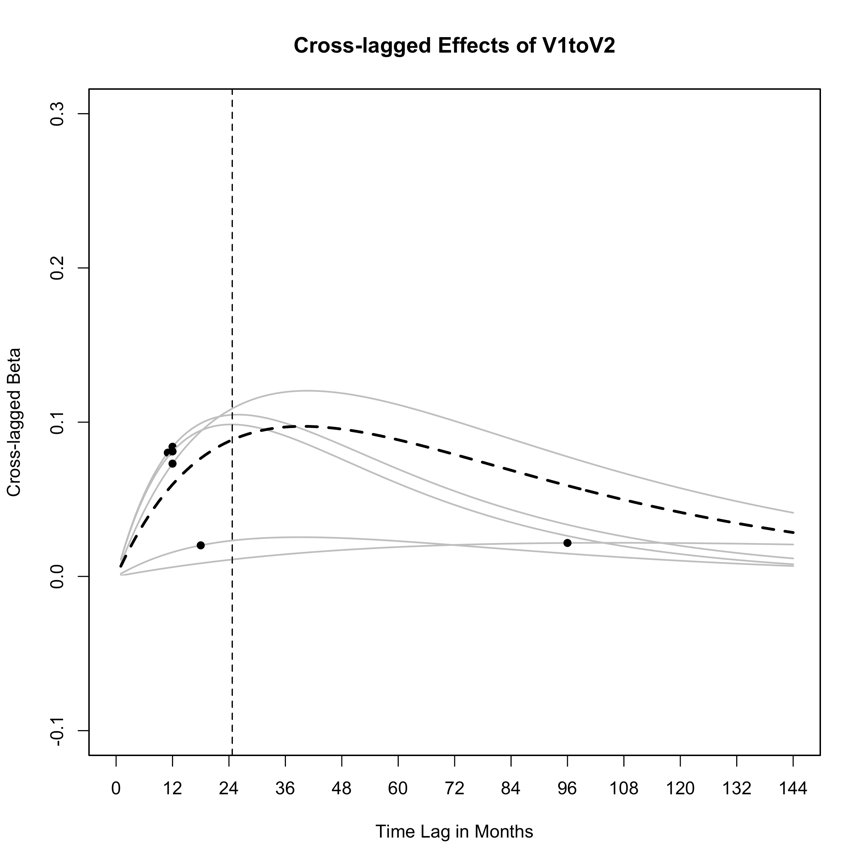


Figure 1. Cross-lagged effects of V1toV2 across a range of possible discrete time lags.

**Conducting CoTiMA with Moderated Effects**

CoTiMA could also be used to analyze if parameters vary across categories of a moderator, for example, 1 (for Europe) and 2 (for US). Note that currently all moderator values are treated as categories rather than continuous variables. For example, if the quality ratings vary from -2 to 2, CoTiMA analyzes if the aggregated effects vary among the 5 categories (i.e., -2., -1, 0, 1, 2). CoTiMA does not yet perform meta-regression.

Conducting a CoTiMA with moderators is straightforward. When entering the primary study information earlier, we already entered 3 possible moderator values per primary study. Only two arguments need to be specified: We have to set testModeratorModel=TRUE and specify which of the 3 moderators (i.e., the first, second, or third) should be analyzed by specifying the appropriate number (e.g., moderatorNumber = 1). Although not necessary, the following specification requests that single model fits and the previously fitted CoTiMA ("CoTiMA 2") are loaded and the results of the moderator model is saved ("CoTiMA 3") after execution:

**CoTiMA3Fit <- CoTiMA(workingDirectory="/Users/.../CoTiMA/DOCUMENTATION/",**

**sourceDirectory="/Users/.../CoTiMA/CURRENT VERSION/",**

**resultsFileName="CoTiMA 3.txt",**

**filePrefix="CoTiMA 3",**

**primaryStudies=listOfPrimaryStudies,**

**nlatents=2,**

**checkSingleStudyResults=FALSE,**

**timeUnit="Months",**

**testModeratorModel=TRUE,**

**moderatorNumber=1,**

**refits=1,**

**confidenceIntervals=TRUE,**

**loadSingleStudyModelFit=c("CoTiMA 2", 1:5),**

**loadDRIFTAllModelFit=c("CoTiMA 2"),**

**saveModeratorModelFit=c("CoTiMA 3")**

**)**

**Results of CoTiMA with Moderated Effects**

Again, the results are stored (in the object CoTiMA3Fit), and the several files have been created in the working directory. Again, these files belong to one of three categories: *fitted models*, a *results file* which summarizes the statistical tests performed, and a series of *figures*. We deal with the results file and the figures here.

*Results File*

The results file has only two interesting section in addition to the previous output file. The first interesting section presents the results of a model, in which all 4 drift parameters varied conditional on the moderator categories (groups). For instance, in Moderator Group 1 (Mod. Grp. 1) the cross effect V1toV2 was .0034 whereas in Mod. Grp. 2 it was .0160. In both Mod. Grp. 1 (Tvalue = 2.0946) and Mod. Grp. 1 (Tvalue = 4.3720) T-values were larger than the critical value for alpha = 5% (i.e., 1.96) and, thus, statistically significant.

In addition, the model fit of this moderator model was compared with the CoTiMA model, in which the 4 drift parameters did not vary across moderator categories but were rather invariant. Note that a 𝜒2-difference test and a -2 log likelihodd difference test are equivalent and they show that with 𝛥*df* = 4 and 𝛥𝜒2 = 48.6007 the model with the moderator included fitted significantly better.

###################################################################################------ Full Drift Moderator Model (all Drift Coefficients Vary Among Moderators) --###################################################################################

V1toV1 V1toV2 V2toV1 V2toV2

Mod. Grp. 1 -0.0248 0.0034 0.0079 -0.0157

(SE) 0.0023 0.0016 0.0018 0.0015

Tvalue -10.5595 2.0946 4.4113 -10.1866

Mod. Grp. 2 -0.0313 0.0106 0.0105 -0.0332

(SE) 0.0025 0.0024 0.0026 0.0022

Tvalue -12.6001 4.3720 4.0830 -14.8656

-2 Log Likelihood: 35962.57

Overall Number of Estimated Parameters: 38

Comparison with Multi-Sample Homogeneity Model (all Drift Coefficients Invariant):

Delta(df): 4

Delta(-2LL) (= Delta(Chi-square)): 48.6007

p-value (with double number of digits): 0

A sign. value (p < .05) indicates that entire process (i.e., the full Drift Matrix) varies conditional on moderator values.

The second interesting section presents the results of a model, in which all each of the 4 drift parameters in a one-by-one fashion varied conditional on the moderator groups. Inspecting the effect V1toV2 again as before shows some slight differences. For Moderator Group 1 (the parameters in the rows below have the suffix \_M1) the cross effect V1toV2 was 0.0079 (instead of .0034 as before), whereas in the Moderator Group 2 (suffix \_M2) it was 0.0052 (instead of .0160 as before). In both Group 1 (Tvalue = 4.5457) and Group 2 (Tvalue = 2.6767) T-values were larger than the critical value for alpha = 5% (i.e., 1.96) and, thus, statistically significant. Further note that the -2 log likelihood difference test yielded that with 𝛥*df* = 1 and 𝛥𝜒2 = 1.3515 the model with the moderator included did not fit significantly better than the CoTiMA model, in which all drift parameters were invariant across moderator groups. Thus, Group 1 does not significantly vary across moderator groups.

###################################################################################-- Single Drift Moderator Models –

-- (only one Coefficient Varies within a Model Column) --

###################################################################################-------------------------------- Coefficients -------------------------------------

Synthesized/Aggregated Drift Coefficients and their Standard Errors (SE):

V1toV1 V1toV2 V2toV1 V2toV2

V1toV1\_M1 -0.0253 NA NA NA

(SE) 0.0022 NA NA NA

Tvalue -11.5721 NA NA NA

V1toV2\_M1 NA 0.0079 NA NA

(SE) NA 0.0017 NA NA

Tvalue NA 4.5457 NA NA

V2toV1\_M1 NA NA 0.0089 NA

(SE) NA NA 0.0019 NA

Tvalue NA NA 4.6189 NA

V2toV2\_M1 NA NA NA -0.0171

(SE) NA NA NA 0.0015

Tvalue NA NA NA -11.2554

V1toV1\_M2 -0.0301 NA NA NA

(SE) 0.0021 NA NA NA

Tvalue -14.2870 NA NA NA

V1toV2\_M2 NA 0.0052 NA NA

(SE) NA 0.0020 NA NA

Tvalue NA 2.6767 NA NA

V2toV1\_M2 NA NA 0.0093 NA

(SE) NA NA 0.0019 NA

Tvalue NA NA 4.7839 NA

V2toV2\_M2 NA NA NA -0.0305

(SE) NA NA NA 0.0019

Tvalue NA NA NA -16.0633

------------------------------- Fit Statistics ------------------------------------

V1toV1 V1toV2 V2toV1 V2toV2

-2 Log Likelihoods: 36007.99 36009.82 36011.14 35974.33

V1toV1 V1toV2 V2toV1 V2toV2

Overall Number of Estimated Parameters: 35 35 35 35

V1toV1 V1toV2 V2toV1 V2toV2

Delta(df): 1 1 1 1

V1toV1 V1toV2 V2toV1 V2toV2

Delta(-2LL) (= Delta(Chi-square)): 3.1813 1.3515 0.0305 36.8406

V1toV1 V1toV2 V2toV1 V2toV2

p-value (with double number of digits): 0.07448362 0.2450126 0.8613108 0

A sign. value (p < .05) indicates that the Drift Coefficients vary among moderator groups):

*Figures*

Further, a series of graphic files is generated that show the plots, in which the *moderated* continuous time drift effects are transformed into their discrete time counterpart across a range of possible time lags. These plots are created for the model in which all 4 drift effects were moderated simultaneously, and the 4 models in which the 4 drift effects were moderated separately. As an example, the plot with all four effects moderated simultaneously is shown here:

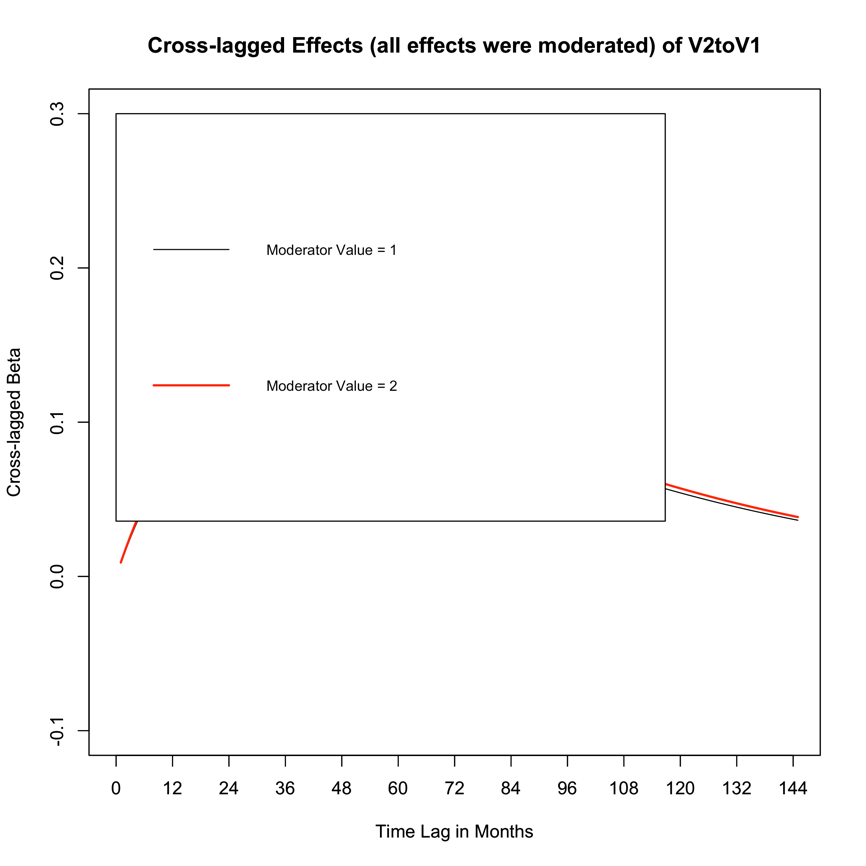


Figure 2. Cross-lagged effects of V1toV2 for both moderator categories across a range of possible discrete time lags.

**Conducting CoTiMA with Pre-Defined or User-Specified Effects**

There are further model tests that can be requested by setting their arguments to TRUE. We provide an overview of all predefined models in the next subsection. Their advantage is that possible statistical model comparisons among these models are performed automatically and figures are created on demands. However, it is also possible fit user-specified models, which is at the cost that model comparison have to be performed by the used.

Outlining how a user-specified model could be fitted is straightforward, but we should note that many possible models probably do not make much sense. However, to demonstrate the capability of CoTiMA to handle user-specific effects, we use a model that applies different features. We set up a model with 4 assumptions, which go above and beyond assuming that all effects vary among primary studies:

1. The correlations between V1 and V2 at Time 0 are invariant across primary studies.
2. The autoregressive effect of V1 (i.e., V1toV1) is invariant across primary studies.
3. The cross effect V2toV1 is fixed at .070 for all primary studies.
4. The cross effects V1toV2 varies across moderator groups.

Note that an effect that is moderated can neither be invariant across primary studies nor can it vary freely. In fact, effects are hierarchically nested in the sense that invariant effect models are nested in moderated effects models, which are nested in freely varying effect models.

Setting up a user-specified model starts with (1) specifying which primary studies should be included (including possible loading the file with the fits of previously fitted single study models are saved). The (saved) fit objects contain most information required (e.g., sample sizes, time points, the OpenMx model specification etc.), which minimizes user-required specifications. (2) Define the vector with the moderator values to be used for analysis. (3) Specification of the effects that are moderated or invariant (all others vary freely) and put them in lists. (4) fit the model and inspect results. The following code shows how to specify a model based on the 4 assumptions enumerated above.

Firstly, a possible moderator could be selected. In the example, the first [1] out of 3 values provided earlier of all 5 primary studies studies is selected and the vector with the alltogether 5 values is stored in the object moderatorValues1.

Secondly, it is specified that the Time 0 variance covariance matrix is invariant across group. This is achieved by specifiying a 2 × 2 matrix with all entries labeled “groupfixed”, which is a pre-defined label making the effect invariant. Note that entries above the diagonal are all set “0” because of the way variance-covariance matrices are internally represented in CoTiMA. Further note that by using the argument byrow=TRUE the matrix is filled row-wise rather than the default in R to fill them column-wise because row-wise filling allows the display to mirror the shape of the matrix. This matrix is stored in the object fixedUserModel1T0VAR, but any other legitimate object name is possible, too.

Thirdly, the constraints are imposed on the drift matrix. Recall that the diagonal of the drift matrix contains the auto effects, and in the case of 2 variables the value below the diagonal represents the effect of V1toV2 and the value above the diagonal the effect V2toV1. The label “groupfixed” is used again and in this case makes the auto effect of V1 (i.e., V1toV1) invariant across groups. Further, the effect of V2toV1, which is located above the diagonal, ist set to .070. The difference between using groupfixed and particular values as parameter labels is that the former estimates the parameter whereas the later fixes it to the value provided; in both cases the parameter is nevertheless assumed to be invariant across primary studies. This option also offers the opportunity to eliminate effects completely from the model, for example, by fixing the value of 0.0 instead of .070. This matrix is stored in the object fixedUserModel1DRIFT.

Fourthly, it is specified which effects are moderated. In the present case, the pre-defined term “moderated” is used to specify the effects “V1toV2” and “V2toV1” to vary across moderator groups. Note, however, that it is impossible that the effect “V2toV1” is moderated and at the same time, as specified in the previously defined fixedUserModel1DRIFT matrix, fixed across primary studies. CoTiMA will detect this inconsistency and assume the effect is fixed (at .070).

Fifth, the objects with the matrices defining which parameters are invariant across groups are put together in a list named listOfFixedModelMatrices1. Similarly, the objects with the matrices defining which parameters are moderated across groups are put together in a list named listOfModeratorModelMatrices1.

Sixth, finally, the CoTiMA model is defined with few changes compared to the previous models. Whereas pre-defined models are requested by setting their argument to TRUE or FALSE (see the table of arguments provided in the next section), in order to test a user-specified model the model specification has to be provide. This is done by assigning the chosen model specification to the list testUserSpecifiedModel. The testUserSpecifiedModel argument has elements with particular names, of which some could be left out. One list element is moderatorValues, to which the just previously created object moderatorValues1 is assigned. In a similar vein, the elements listOfFixedModelMatrices and listOfModeratorModelMatrices are populated by the just previously created objects listOfFixedModelMatrices1 and listOfModeratorModelMatrices1, respectively. Further, we request the fitted model to be saved by using saveUserSpecifiedModel=c("CoTiMA 4"). Finally, fitting of the regular CoTiMA model was de-selected by setting testDRIFTallModel=FALSE to save some time.

**moderatorValues1 <- c(moderator1[1], moderator2[1], moderator3[1], moderator4[1],   
 moderator5[1])**

**fixedUserModel1T0VAR <- matrix(c("groupfixed", "0",**

**"groupfixed", "groupfixed"), 2, 2, byrow=TRUE)**

**fixedUserModel1DRIFT <- matrix(c("groupfixed", .070,**

**"V1toV2", "V2toV2"), 2, 2, byrow=TRUE)**

**moderatedUserModel1DRIFT <- matrix(c("V1toV1", "moderated", # see text**

**"moderated", "V2toV2"), 2, 2, byrow=TRUE)**

**listOfFixedModelMatrices1 <- list(DRIFT=fixedUserModel1DRIFT,   
 T0VAR=fixedUserModel1T0VAR)**

**listOfModeratorModelMatrices1 <- list(DRIFT=moderatedUserModel1DRIFT)**

**CoTiMA4Fit <- CoTiMA(workingDirectory="/Users/.../CoTiMA/DOCUMENTATION/",**

**sourceDirectory="/Users/.../CoTiMA/CURRENT VERSION/",**

**resultsFileName="CoTiMA 4.txt",**

**filePrefix="CoTiMA 4",**

**primaryStudies=listOfPrimaryStudies,**

**nlatents=2,**

**checkSingleStudyResults=FALSE,**

**timeUnit="Months",**

**refits=1,**

**confidenceIntervals=TRUE,**

**testUserSpecifiedModel=list(singleStudyModelFits=1:5,**

**moderatorValues=moderatorValues1,**

**listOfFixedModelMatrices=listOfFixedModelMatrices1,**

**listOfModeratorModelMatrices=**

**listOfModeratorModelMatrices1),**

**testDRIFTallModel=FALSE,**

**saveUserSpecifiedModel=c("CoTiMA 4"),**

**loadSingleStudyModelFit=c("CoTiMA 2", 1:5)**

**)**

**Results of CoTiMA with Pre-Defined or User-Specified Effects**

The default summary of results of fitting user-specified models is rather short. There are not plots or automatically generated model comparisons as there are too many possibilities. In cases in which the user wants to have more information about the fitted model, it is recommended to load the generated file with the fitted object into the R environment and inspect the content in detail. Here, we focus on the generated results file and the part which summarizes the user-specified model fit.

###################################################################################-------------------------- Summary of user-specified Model. -----------------------###################################################################################$estimatedParameters

Est. SE T-value lbound ubound

V1toV1 -0.0898 0.0027 -33.4928 -0.0923 -0.0872

V1toV2\_M1 0.0177 0.0038 4.6430 0.0164 0.0207

V2toV2\_G1 -0.0358 0.0038 -9.4297 -0.0437 -0.0342

V1toV2\_M2 0.0407 0.0041 9.9470 0.0379 0.0429

V2toV2\_G2 -0.0579 0.0048 -12.0307 -0.0679 -0.0553

V2toV2\_G3 -0.0598 0.0039 -15.2969 -0.0620 -0.0575

V2toV2\_G4 -0.0240 0.0033 -7.2541 -0.0309 -0.0228

V2toV2\_G5 -0.0578 0.0227 -2.5409 -0.1290 -0.0204

diffusion\_eta1\_eta1\_G1 -1.0282 0.0238 -43.1172 NA NA

diffusion\_eta2\_eta1\_G1 -0.0436 0.0111 -3.9154 NA NA

diffusion\_eta2\_eta2\_G1 -1.5170 0.0296 -51.2147 NA NA

diffusion\_eta1\_eta1\_G2 -1.0157 0.0228 -44.6371 NA NA

diffusion\_eta2\_eta1\_G2 -0.1142 0.0152 -7.4978 NA NA

diffusion\_eta2\_eta2\_G2 -1.3727 0.0431 -31.8637 NA NA

diffusion\_eta1\_eta1\_G3 -1.0392 0.0337 -30.8622 NA NA

diffusion\_eta2\_eta1\_G3 -0.1487 0.0156 -9.5453 NA NA

diffusion\_eta2\_eta2\_G3 -1.3743 0.0302 -45.4610 NA NA

diffusion\_eta1\_eta1\_G4 -0.9544 0.0379 -25.1955 NA NA

diffusion\_eta2\_eta1\_G4 -0.1447 0.0152 -9.5152 NA NA

diffusion\_eta2\_eta2\_G4 -2.0696 0.0748 -27.6732 NA NA

diffusion\_eta1\_eta1\_G5 -0.8967 0.1788 -5.0162 NA NA

diffusion\_eta2\_eta1\_G5 -0.1139 0.0691 -1.6485 NA NA

diffusion\_eta2\_eta2\_G5 -1.4753 0.2280 -6.4694 NA NA

T0var\_eta1\_eta1 -0.0013 0.0123 -0.1031 NA NA

T0var\_eta2\_eta1 0.4360 0.0166 26.2853 NA NA

T0var\_eta2\_eta2 -0.1072 0.0124 -8.6742 NA NA

$fixedParameters

Est. SE Note

V2toV1 "0.07" "-" "fixed value"

$Minus2LogLikelihood

Minus2LogLikelihood

36528.48

$numberOfEstimatedParameters

Number of estimated parameters

26

This section of the results file has 4 subsections. First, the estimated parameters (Est.) are shown, together with their standard errors (SE) and T-values (T-value). In addition, confidence intervals were computed for all drift parameters. Note that the suffixes \_G are used to label parameters varying across primary studies (groups) and \_M are used to label parameters varying across moderator groups. Thus, V1toV1 is invariant across all primary studies, V1toV2 is different for moderator group 1 (V1toV2\_M1) and moderator group 2 (V1toV2\_M2). The auto effect of V2 (V2toV2) varies across all 5 primary studies (V2toV2\_G1, V2toV2\_G2, V2toV2\_G3, V2toV2\_G4, & V2toV2\_G5). The diffusion parameters are unconstrained and all vary across all primary studies. Finally, the Time 0 variances and covariances (correlation) are invariant across all primary studies.

The second subsection ($fixedParameters) is just a remineder that the effect of V2toV1 was fixed to 0.07 by the user.

The third subsection ($Minus2LogLikelihood) displays the -2 log likelihood value, which is 36528.48. This could become useful in combination with the number of estimated parameters displayed in the final subsection ($numberOfEstimatedParameters), which is 26. It becomes useful to compare the model with a more or with a less constrained model. For example, the heterogeneity model (i.e., all primary studies analyzed separately) is less restrictive. It had a -2log likelihood value of 35773.7 and estimated overall 50 parameters (see p. xx above). A -2log likelihood difference test, which is equivalent to a Chi-square difference test, yield 𝛥𝜒2 = (36528.48-35773.7) = 754.78, with 𝛥df = (50-26) = 24, and the significance (*p* < .001) is easily evaluated in R by using:

1-pchisq(36528.48-35773.7, 50-26).

Thus, the constraints imposed in the user-specified model led to a significant reduction in model fit. The user-specified model has to be rejected.

**CoTiMA Arguments**

*Overview over arguments*

|  |  |  |  |
| --- | --- | --- | --- |
| Argument | Default | Possible Values & Example | Explanation |
| *Basic Settings* | | | |
| workingDirectory | NULL | A path with ‘/’ instead of ‘\’. Ex: {/Users/temp/} | CoTiMA stops if workingDirectory is not defined. |
| sourceDirectory | NULL | path with ‘/’ instead of ‘\’-  Ex: {/Users/temp/} | NOT NECESSARY IN A PACKAGE |
| resultsFileName | CoTiMA.txt | Any name, usually with suffix. Ex: {CoTiMA2.txt} | File is appended if the name is not changed during repeated applications of CoTiMA. |
| filePrefix | CoTiMA | Any name Ex: {CoTiMA2} | Prefix for the figure files and the model fit files that are created. |
| primaryStudies | NULL | A list with primary study information.  Ex: Would be too long to be displayed here | List elements include vectors of time lags (deltas), vectors of sample Sizes (sampleSizes), empirical correlation matrices (empcovs), vectors of moderator values (moderators), vectors of start values (startValues), vectors of study numbers (studyNumbers), matrix with pairwise sample sizes (pairwiseNs), raw data file name (rawData), vectors of empirical means (empMeans), vector of empirical variances (empVars).  Proper list structure could be ensured by using the function compileListOfPrimaryStudies. |
| *Workflow* | | | |
| activateRPB | FALSE | TRUE/FALSE | Enables sending automated messages to mobile phones and computers on which the ‘push bullet’ app is installed. Useful when models are tested that might take hours or days. |
| checkSingleStudyResults | TRUE | TRUE/FALSE | Interrupts computations after single primary studies are fitted and their drift coefficients are displayed on screen. Useful for checking it proper solutions were achieved. |
| *General Model Setup* | | | |
| Nlatents | NULL | Any number larger than 0.  Ex: {2} | The number of latent variables. Should correspond to the number per time point (do not sum up across time points). |
| *Fitting Parameters* | | | |
| retryattempts | 30 | Any number larger than 0.  Ex: {20} | Number of iterations to be used by OpenMx. |
| refits | 5 | Any number larger than 0.  Ex: {1000} | Number of re-fits used by CoTiMA. Usually, 1 is sufficient, but large number could be useful if fitting single primary studies until proper fit is achieved and starting values are available. |
| extraRefits | c() | Any (vector of) numbers representing primary studies to be analyzed  Ex: {c(1, 3:4)} | Defines a subset of primary studies for which more refits than specified by refits should be performed. |
| factorExtraRefits | 1 | Any number larger than 0.  Ex: {200} | The number by which refits is multiplied for those primary studies provided in the vector of extraRefits |
| NPSOL | FALSE | TRUE/FALSE | Uses NPSOL optimizer instead of default optimizer CSOLNP. NPSOL sometimes better estimates, e.g., for confidence intervals). If it is not yet installed, this will be done including with the newest version of OpenMx. |
| coresToUse | c(1) | Either 1 or 0 or a negative number.  Ex: {-1} | Specifies the number of available computer cores to be used and can speed up processing considerably. Usually problems occur on Windows machines if other values than 1 are used. Typically, one would chose -1, which indicates that all cores/threats except 1 will be used. |
| useCTMultigroupFitAlt | FALSE | TRUE/FALSE | Instead of using the ctMultigroup function provided with CTSEM, CTMultigroupFitAlt represents an alternative is available which could be much faster if large models (large sample, many time points) are analyzed. |
| *Figure Parameters* | | | |
| plotCrossEffects | TRUE | TRUE/FALSE | Plot discrete time cross-lagged effects. |
| plotAutoEffects | TRUE | TRUE/FALSE | Plot discrete time autoregressive effects. |
| TimeUnit | ‘timeUnit’ | Any unit/scale with quotation marks.  Ex: {‘Months’} | The unit used to label the x-axis of generated figures. |
| timeRange | From 0 to 1.5 × largest time lag found in primary studies | A list with smallest value, largest value, and step width.  Ex:  list(1,100,.10) | Range of the x-axis across which plots are generated. Changing the limits of the y-axis could be useful to have identical axes across a range of analyses.  Also the range of the x-axis across which the a-prior statistical power for subsequent primary studies is computed. |
| yLimitsForEffects | min(effects)-.05 & max(effects) + .05 | Vector with limits of the effect sizes (y-axis).  Ex: {c(-.20, 1.0)} | Changing the limits of the y-axis could be useful to have identical axes across a range of analyses. |
| Digits | 4 | Any positive number including 0.  Ex: {4} | The rounding used in the display of the output. In many journals 2 is common, but continuous time effects could be rather small and 3 or 4 is recommended. The rounding does not affect the computational accuracy. |
| *Specific Model Tests* | | | |
| testHeterogeneityModel | FALSE | TRUE/FALSE | The heterogeneity model is a multi-sample CTSEM model with all parameters varying freely across primary samples. It takes a lot of time to fit the heterogeneity model, and TRUE It is usually not recommended because the parameter estimates and the model fit value (-2 log likelihood) is identical to the estimates and (sum of) -2 log likelihood values resulting from fitting the primary studies separately (which is always done anyway). |
| testDRIFTallModel | TRUE | TRUE/FALSE | The CoTiMA model! Drift effects are invariant across all primary studies, whereas T0-(co-)variances and diffusion parameters vary freely. A -2 log likelihood-difference test automatically compares the model fit with the fit of the heterogeneity model. |
| testDRIFTallWOdtModel | FALSE | TRUE/FALSE | Tests a model in which all(!) time lags in all studies are made equal (i.e., change to the mean value of all time lags). Although the model is not a statistically nested version of the CoTiMA model (testDRIFTallModel), a descriptive comparison of their -2 log likelihood values could reveal if consideration of time lags improves model fit compared to a discrete time SEM. |
| testDRIFTSingleModel | FALSE | TRUE/FALSE | Similar to the CoTiMA model (testDRIFTallModel), but multiple models are fittest in each of which only 1 (instead of all) drift parameters varies freely across primary studies. |
| testDRIFTCrossModel | FALSE | TRUE/FALSE | Fits a series of 2 models and compares their -2 log likelihood values to determine, if the (at least 2) aggregated cross effects are identical or whether there is some evidence of ‘causal priority’. |
| testDRIFTAutoModel | FALSE | TRUE/FALSE | Fits a series of 2 models and compares their -2 log likelihood values to determine, if the (at least 2) aggregated auto effects are identical. |
| testAllInvariantModel | FALSE | TRUE/FALSE | In addition to the CoTiMA model (testDRIFTallModel), invariance of T0-(co-)variances and diffusion parameters is assumed, too. This model is automatically estimated (i.e., FALSE is overruled) if statisticalPower is requested. |
| testModeratorModel | FALSE | TRUE/FALSE | Moderator analyses are conducted if set to TRUE. |
| moderatorNumber | c() | Any value within the length of the moderator*i*-object provided when entering primary study information.  Ex: {1} | CoTiMA can only perform a single moderator analysis each time it is used. It is recommended to load the fit of primary studies, set testModeratorModel=TRUE and all other model tests to FALSE for rapid performance of moderator analyses. |
| testUserSpecifiedModel | list() | List with predefined elements.  Ex. provided in a separate table below | CoTiMA can only perform a single user-sepcified analysis each time it is used. It is recommended to load the fit of primary studies, set saveUserSpecifiedModel=TRUE and all other model tests to FALSE for rapid performance of moderator analyses. |
| *Further Analyses* | | | |
| confidenceIntervals | FALSE | TRUE/FALSE | Confidence intervals for all requested models are performed. Could be time consuming. |
| statisticalPower | c() | Vector with values between 0 and 1.  Ex: {c(.80,.90} | Computes a-priori required sample sizes for future primary studies for the statistical power values enumerated in the vector. Computations are based on the (restrictive) model in which all parameters are set invariant across primary studies (testAllInvariantModel)  Also, post-hoc statistical power is computed for the primary studies included. |
| yLimitsForPower=c() | c(0, 3×max(N)) | Vector with limits of the required sample sizes (y-axis).  Ex: {c(0, 1000)} | Changing the limits of the y-axis could be useful to have identical axes across a range of analyses. |
| fixedAndRandomEffects | TRUE | TRUE/FALSE | Performs fixed and random effects analysis (Borenstein et al., 2009) and computes a variety indices and estimates. Computations are based on the drift effects in the single study model fits (not the CoTiMA model).  Fixed effect estimates include: mean values; fixed effect estimates; variance of fixed effect estimates; standard error of fixed effect estimates as well as their upper and lower limits, their z-values and probabilities; tau square, Q, H square as well their upper and lower limits; and  I square and their upper and lower limits.  Random effect estimates include: random effect estimates; variance of random effect estimates; standard error of random effect estimates as well as their upper and lower limits, their zvalues, and probabilities; and the upper and lower limits of prediction intervals. |
| publicationBias | FALSE | TRUE/FALSE | Perform Egger's tests, draw funnel plots, and compute PET-PEESE estimates. |
| *Save & Load Fitted Models* | | | |
| saveSingleStudyModelFit | c() | Vector with a name as first element followed by the number of primary studies to be saved.  Ex: c(‘Mod1’, c(1, 3:4, 6) | Saving model fits of single primary studies and re-loading them later ensure fast and reliable fitting of more complex models. Save model fits of primary studies have to be provided if user-specified CoTiMA-models are supplied for testing. |
| loadSingleStudyModelFit | c() | Vector with a name as first element followed by the number of primary studies to be re-loaded.  Ex: c(‘Mod1’, c(1, 3:4, 6) | see above. Note that the ‘name’-part of the vector could be used to load models saved with a different name compared to the possible filePrefix in a currently tested model. |
| saveHeterogeneityModelFit | c() | Vector with a name.  Ex. {‘Model1’} |  |
| loadHeterogeneityModelFit | c() | Vector with a name.  Ex. {‘Model1’} |  |
| saveDRIFTAllModelFit | c() |  |  |
| loadDRIFTAllModelFit | c() |  |  |
| saveDRIFTSingleModelFit | c() |  |  |
| loadDRIFTSingleModelFit | c() |  |  |
| saveDRIFTCrossModelFit | c() |  |  |
| loadDRIFTCrossModelFit | c() |  |  |
| saveDRIFTAutoModelFit | c() |  |  |
| loadDRIFTAutoModelFit | c() |  |  |
| saveDRIFTallWOdtModelFit | c() |  |  |
| loadDRIFTallWOdtModelFit | c() |  |  |
| saveAllInvariantModelFit | c() |  |  |
| loadAllInvariantModelFit | c() |  |  |
| saveHomAllWOSingleDriftModelFit | c() |  |  |
| loadHomAllWOSingleDriftModelFit | c() |  |  |
| saveModeratorModelFit | c() |  |  |
| loadModeratorModelFit | c() |  |  |
| saveUserSpecifiedModel | c() |  |  |
| loadUserSpecifiedModel | c() |  |  |

*Arguments for User-Specified Models (testUserSpecifiedModel)*

|  |  |  |  |
| --- | --- | --- | --- |
| Argument | Default | Possible Values & Example | Explanation |
| *Basic Settings* | | | |
| singleStudyModelFits | All single model fits previously fitted or loaded | Selection of subsets of studies is possible.  Ex. {singleStudyModelFits = 1:3} | Nothing will happen if single study model fits are not provided. |
| moderatorValues | NULL | Vector containing the moderator values representing the (selected) primary studies. Ex. {c(1,1,2,2,2)} | If moderatorValues are not provided, moderation analysis is impossible even if a listOfModeratorModelMatrices is provided. |
| listOfFixedModelMatrices | NULL | List with 3 pre-defined elements, i.e., list((T0VAR=NULL, DIFFUSION=NULL, DRIFT=NULL) | The 3 matrices in the list could make use of the label “groupfixed” to make parameters invariant across primary studies, or use a numerical value instead of “groupfixed”to fix the parameter across primary studies to this value. For example, assigning the value 0.0 to an element of the DRIFT matrix eliminates the drift parameter from the model. |
| listOfModeratorModelMatrices | NULL | List with 3 pre-defined elements, i.e., list((T0VAR=NULL, DIFFUSION=NULL, DRIFT=NULL) | The 3 matrices in the list could make use of the label “moderated” to let the parameter vary across the moderator groups (i.e., the values assigned to moderatorValues). |