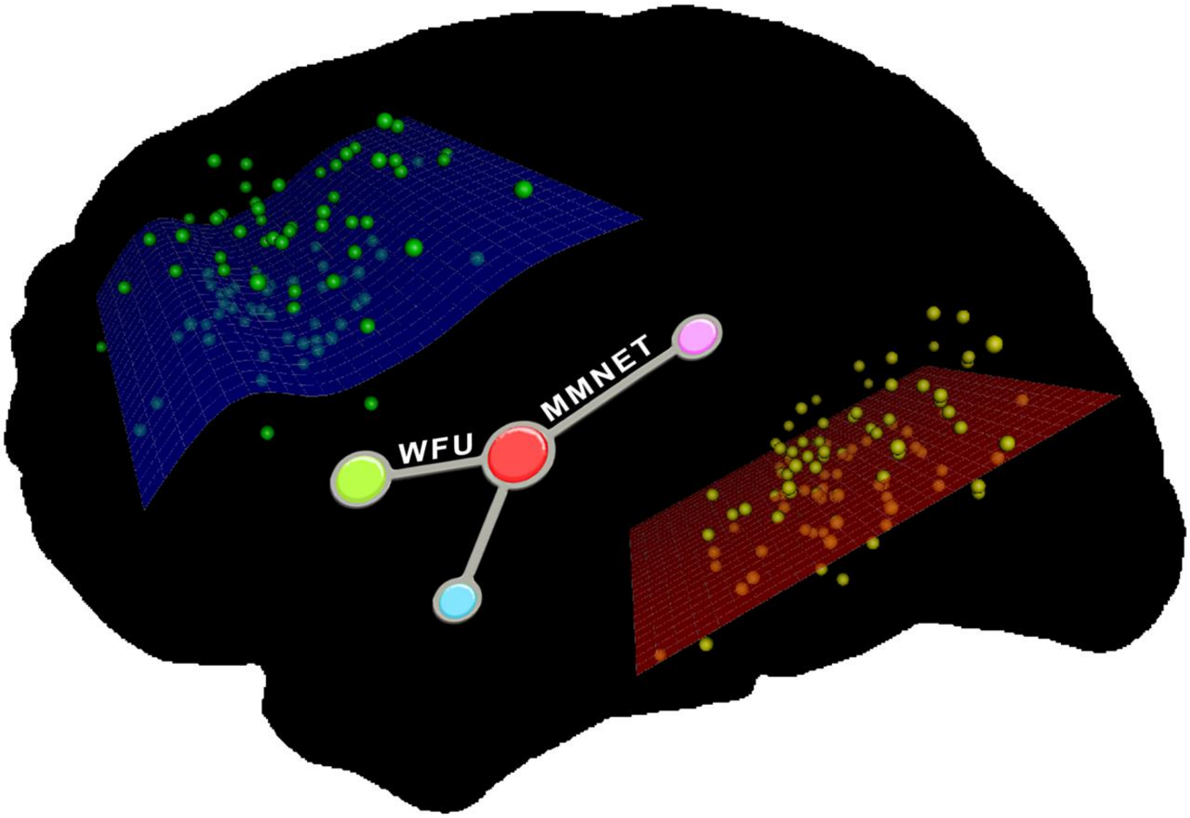
WFU MMNET v1.0 User Manual



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1 Introduction

WFU_MMNET is a freely-available toolbox that provides a multivariate framework to study brain networks. It utilizes a mixed-effects regression framework (Simpson and Laurienti 2015) that allows assessing brain network differences between study populations as well as assessing the effects of covariates of interest such as age and disease phenotypes on brain connections in global (i.e., whole-brain) and local (i.e., subnetworks) brain networks. A variety of neuroimaging data such as fMRI, EEG, MEG, and DTI can be analyzed with this toolbox, which makes it useful for a wide range of studies examining the structure and function of brain networks.

WFU_MMNET is developed in Matlab (The MathWorks Inc., Natick, MA, US) with a user-friendly GUI, under a 64-bit Linux platform. The toolbox uses SAS, R, or Python (depending on software availability) to perform the statistical modeling. It also uses the functions implemented in the brain connectivity toolbox (BCT) (Rubinov and Sporns 2010) to compute the topological network features. This toolbox has been successfully tested under a Linux operating system with Matlab, SAS, R (and the required package – lmerTest), and Python (and the required modules – numpy, scipy, pands, stattsmodels) installed. The user only needs to have one of SAS, R, or Python installed in addition to Matlab. We have also successfully tested the toolbox when the modeling software (SAS or R in this case) is installed in Windows. Any suggestions about the toolbox or the manual would be greatly appreciated.

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The software along with the data and results from a sample case study are provided on NITRC - https://www.nitrc.org/projects/wfu_mmnet

Please post your questions, reports, or comments on the NITRC forum.

2 Installation

2.1 Matlab

A version of R2016b or above is recommended for Matlab as this toolbox was developed in R2016b version. However, it has successfully been tested in R2014b and R2015b versions (Any version above R2014b can be used). At present, the operating system for Matlab should be Linux. We will be releasing an update that can be used with Matlab installed on Windows very soon.

Add BCT path to Matlab search path. You can add the path through either the “addpath” function or “Set Path” option in the Matlab HOME toolstrip:

- Type “addpath(‘/…/path to the BCT folder/..’)” in the Matlab command window.

- Click “Set Path” - > Click “Add with Subfolders…” button- > Select the BCT folder - > Click “OK” button- > Click “Save” button.

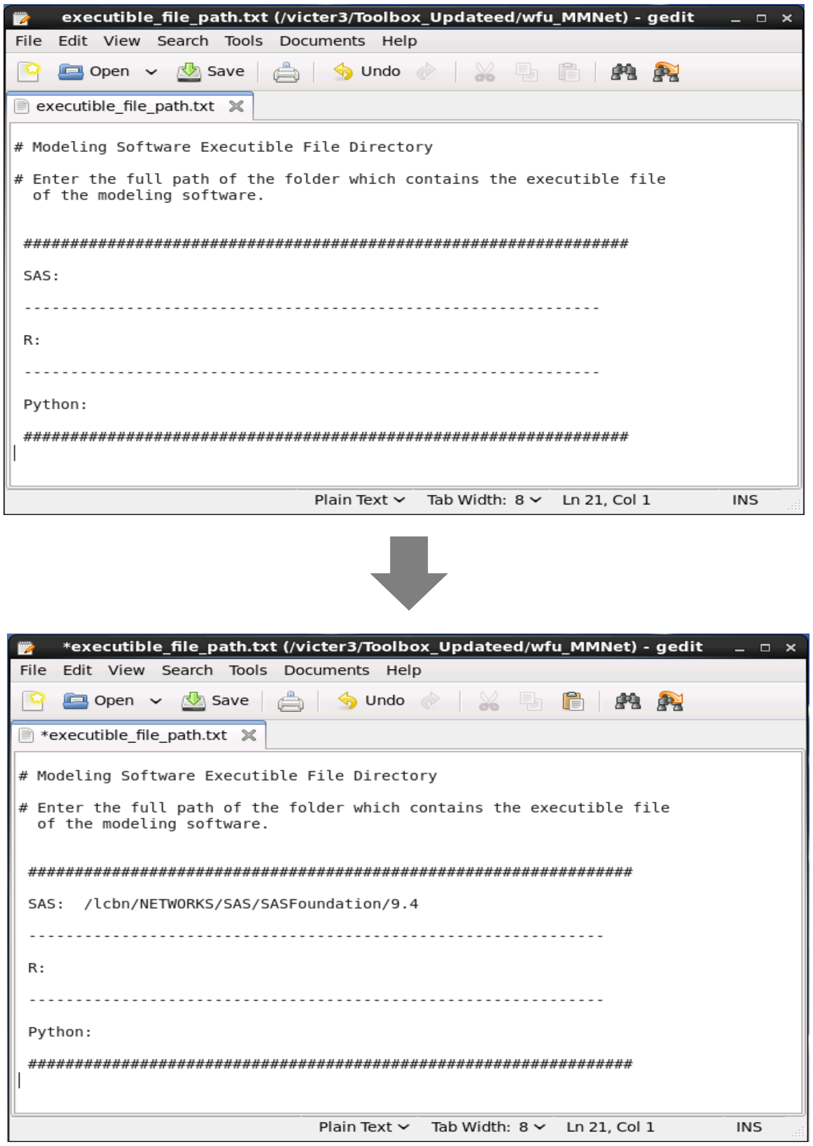
2.2 Modeling software

WFU_MMNET uses SAS, R, or Python for performing the modeling part. Thus, the user needs to have one of SAS, R, or Python (preferably SAS or R) installed on Linux prior to using this toolbox. However, if they are installed on Windows the user can still perform the modeling by making a minor change in the modeling scripts. Python is usually installed on Linux by default. So, we have not provided the Windows option for Python. If you want to use Python, you must have it installed on Linux. Please install the ‘lmerTest’ package if using R, and install ‘numpy’, ‘scipy’, ‘pandas’, and ‘statsmodels’ if using Python.

2.2.1 Adding executable file path

If a modeling software is available in Linux, add the **path of the *folder* that includes its executable file** in the specified location to the “executable_file_path” text file. This text file is in the toolbox folder – i.e., ‘WFU_MMNET’ folder.

- Open the “executable_file_path” text file -> add the path of the folder including executable file in the specified location as shown in fig. 1.



```
# Modeling Software Executible File Directory

# Enter the full path of the folder which contains the executible file
  of the modeling software.


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

 SAS:

 --------------------------------------------------------------

 R:

 --------------------------------------------------------------

 Python:

 #################################################################
```

```
# Modeling Software Executible File Directory

# Enter the full path of the folder which contains the executible file
  of the modeling software.


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

 SAS:  /lcbn/NETWORKS/SAS/SASFoundation/9.4

 --------------------------------------------------------------

 R:

 --------------------------------------------------------------

 Python:

 #################################################################
```

Fig. 1 Adding path of the folder that includes SAS executable file. Add R and Python in the same way. The example shows the location of the SAS folder in the computer environment at Laboratory for Complex Brain Networks.

You can add more than one modeling software (e.g., SAS and Python) if they are available in Linux, and select either one when modeling your datasets.

2.3 Running WFU_MMNET

Add WFU_MMNET path to Matlab search path:

- Click “Set Path” - > Click “Add with Subfolders…” button- > Select the “WFU_MMNET” folder - > Click “OK” button- > Click “Save” button.

Run ‘WFU_MMNET.m’ to start the toolbox - you can type ‘WFU_MMNET’ in the command window of Matlab.

You should see the window shown in fig. 2.

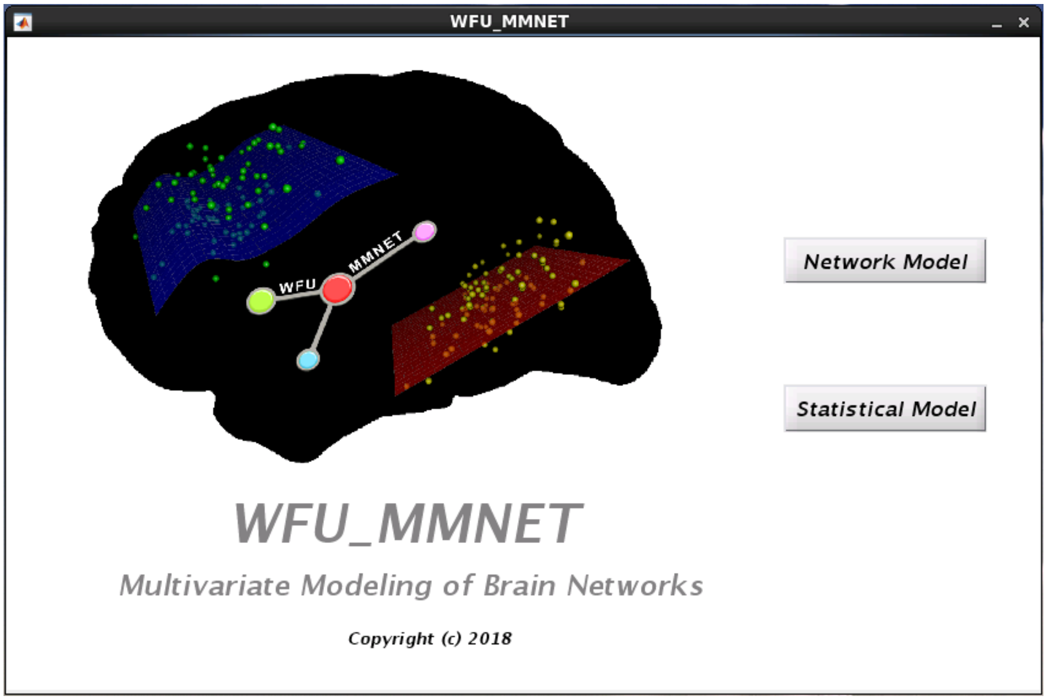


Fig. 2 The main graphical user interface (GUI) of WFU_MMNET.

2.4 Modeling framework

Modeling is done in two main steps using two different GUIs. We have divided it into two steps for an easier, flexible, and more efficient modeling. In the first step, using imaging data files or connectivity matrices, a modeling data frame is constructed through the ‘Network_Model’ GUI. This step is independent of the second step and can be repeated for making different data frames of different datasets or making different data frames for different options of the same dataset. This step is described in section 3.

In the second step, the generated data frame is used by the ‘Statistical_Model’ GUI for constructing the appropriate modeling files and fitting statistical models. This step can also be done independently as long as modeling data frames are available. This step is described in section 4.

2.5 Supported formats

Several data files should be loaded as inputs when using this toolbox. Multiple formats including *mat*, *nii (and nii.gz)*, *csv*, *txt*, *xls*, *xlsx*, and *xlsm* are supported for any loaded data in this toolbox. Loaded 2D numeric files can have row names, column names, or neither. Data files can be loaded directly or via loading a file-list that includes full directory path and file name for the data files.

3 Network model

As mentioned above, modeling is done in two main steps. In the first step, you need to build the modeling data frame through the 'Network_Model' GUI.

Click the 'Network_Model' button in 'WFU_MMNET' to start the 'Network_Model' GUI. You should see the window shown in fig. 3.

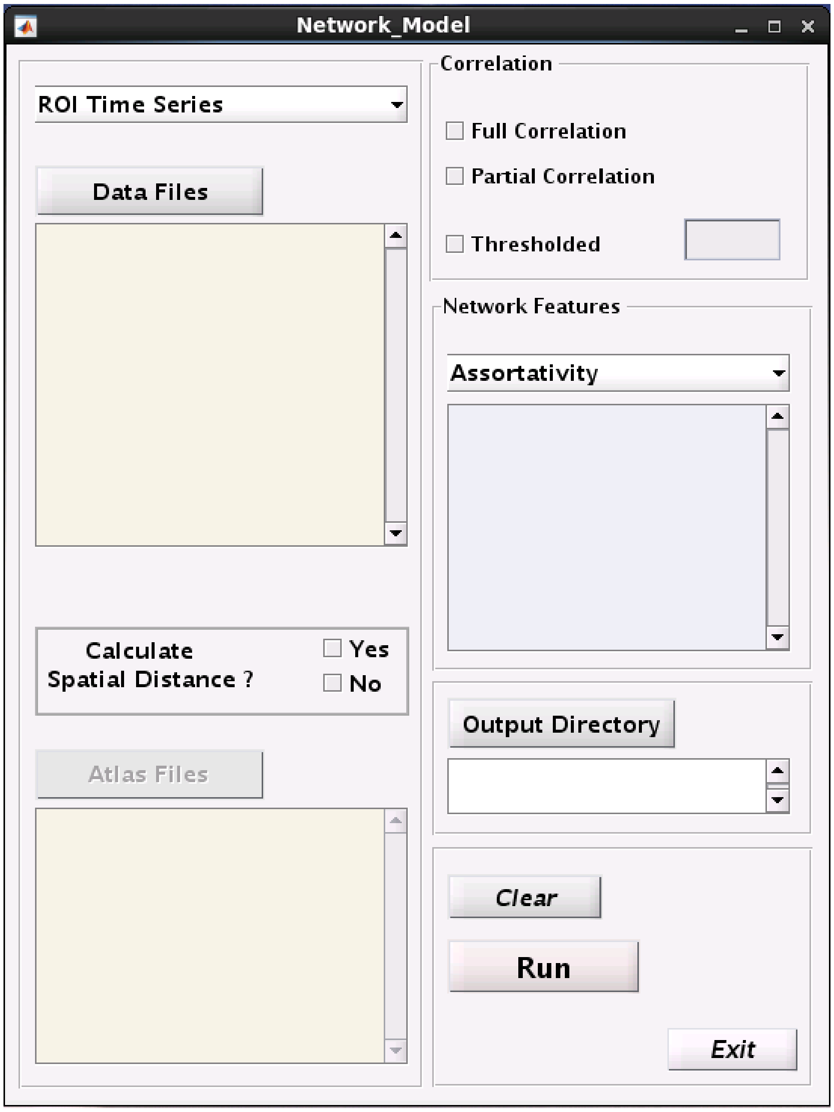
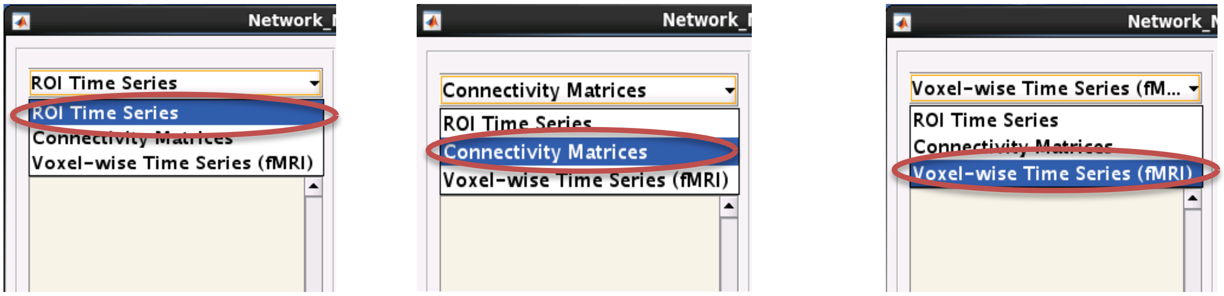


Fig. 3 The network model GUI.

3.1 Imaging data type

Imaging data files can be loaded as both matrices of ROI time series (with rows representing the ROIs and columns representing the time) and connection matrices. FMRI users can also use (preprocessed) 4d voxel-wise time series (and an atlas defining ROIs) instead of ROI time series or connection matrices.

Click the popup dialogue at the top left, and select the appropriate data type for your imaging data (fig. 4). Selecting “Voxel-wise Time Series (fMRI)” enables the “Atlas Files” button for loading the atlas file(s).



A **B** **C**

Fig. 4 Imaging data type. **A.** ROI time series, **B.** Connection matrices, **C.** Voxel-wise time series (only for fMRI users). Selecting “Voxel-wise Time Series (fMRI)” enables the “Atlas Files” button. You should load atlas files prior to loading the data files if using 4d voxel-wise time series.

3.2 Loading data files

Click “Data Files” button to load the data files. Data files can be loaded as matrices of ROI time series (with rows representing the ROIs and columns representing time), connection matrices, or fMRI 4d voxel-wise time series. Load data files directly (fig. 5.A) or via loading a file-list which includes data files’ directories (fig. 5.B). A sample file-list is shown in fig. 6.

Full directories of loaded files will be listed in the list-box, and the number of subjects and ROIs will be displayed (see Fig 5). If the length of loaded time series is different across subjects, a warning message showing the maximum difference will be displayed

Look In: Time_Series

Sub1.mat Sub19.mat Sub27.mat Sub34.mat Sub41.mat Sub4
Sub10.mat Sub2.mat Sub28.mat Sub35.mat Sub42.mat Sub5
Sub11.mat Sub20.mat Sub29.mat Sub36.mat Sub43.mat Sub5
Sub12.mat Sub21.mat Sub3.mat Sub37.mat Sub44.mat Sub5
Sub15.mat Sub22.mat Sub30.mat Sub38.mat Sub45.mat Sub5
Sub16.mat Sub23.mat Sub31.mat Sub39.mat Sub46.mat Sub5
Sub17.mat Sub25.mat Sub32.mat Sub4.mat Sub47.mat Sub5
Sub18.mat Sub26.mat Sub33.mat Sub40.mat Sub48.mat Sub5

File Name: mat" "Sub76.mat" "Sub77.mat" "Sub8.mat" "Sub80.mat" "Sub9.mat"

Files of Type: All Files

Data Files:
/victer3/aa/Time_Series/Sub1.ma
/victer3/aa/Time_Series/Sub2.ma
/victer3/aa/Time_Series/Sub3.ma
/victer3/aa/Time_Series/Sub4.ma
/victer3/aa/Time_Series/Sub5.ma
/victer3/aa/Time_Series/Sub7.ma
/victer3/aa/Time_Series/Sub8.ma
/victer3/aa/Time_Series/Sub9.ma
/victer3/aa/Time_Series/Sub10.m
/victer3/aa/Time_Series/Sub11.m
/victer3/aa/Time_Series/Sub12.m
/victer3/aa/Time_Series/Sub15.m
/victer3/aa/Time_Series/Sub16.m

Subjects: 74 ROIs: 116

Look In: aa

4d
Time_Series
time_series2
.RData
.Rhistory
Covariates_Data.xlsx
Covariates_Data2.xlsx
data_list_file.txt
pace_conn_list.txt

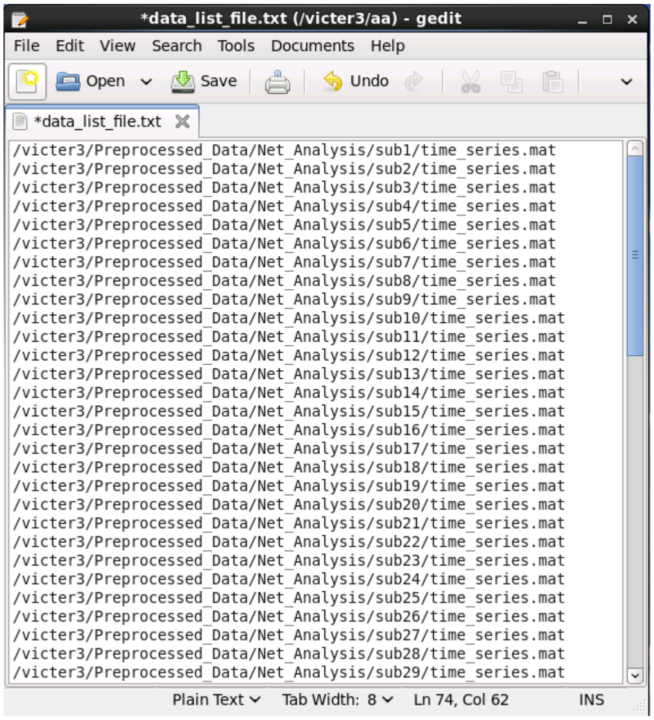
File Name: data_list_file.txt

Files of Type: All Files

Data Files:
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_
/victer3/Preprocessed_Data/Net_

Subjects: 74 ROIs: 116

Fig. 5 Imaging data files. **A.** Loading files directly (files will be sorted). **B.** Loading files via loading the file-list including data files' directories.



```
/victer3/Preprocessed_Data/Net_Analysis/sub1/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub2/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub3/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub4/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub5/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub6/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub7/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub8/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub9/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub10/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub11/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub12/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub13/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub14/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub15/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub16/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub17/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub18/time_series.mat
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/victer3/Preprocessed_Data/Net_Analysis/sub22/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub23/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub24/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub25/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub26/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub27/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub28/time_series.mat
/victer3/Preprocessed_Data/Net_Analysis/sub29/time_series.mat
```

Fig. 6 Sample file-list including data files' directories. You can use file-lists with backslash (\) separated directories as well (i.e., Windows format).

in the command window of Matlab. If data files are selected directly (not via a file-list), the toolbox sorts them and uses the sorted ones in the subsequent analyses.

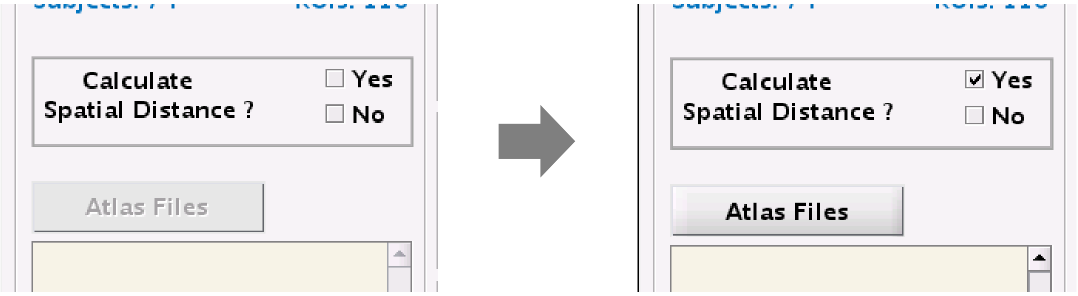
3.3 Spatial distance

As pointed out in (Simpson and Laurienti 2015), spatial distance (anatomical distance) and square of spatial distance between brain regions are important geometric features in predicting the connectivity between brain regions. Thus, we have made it possible to control for their likely confounding effects.

3.3.1 Adding spatial distance via atlas files

Spatial distance can be computed by loading the atlas file(s) defining the ROIs. The toolbox computes Euclidean distances between the centers of mass of the ROIs. To use this option, choose ‘Yes’ next to ‘Calculate Spatial Distance?’ (fig. 7); then, load your atlas file(s) (fig. 8). You can either load a single atlas (i.e., a common atlas for all subjects) or multiple atlas files (i.e., a separate atlas for each subject). The latter case is useful for situations where data are analyzed in the individual subjects’ native space and different atlases are used for each study participant. If loading multiple atlas files, again, you can either load them directly or through a file-list that includes their directories. Loaded imaging files and atlas file(s) must have the same number of ROIs.

A computed spatial distance file for each subject will be saved as a symmetric numeric matrix.



Calculate Spatial Distance ? ☐ Yes ☐ No

Calculate Spatial Distance ? ☑ Yes ☐ No

Fig. 7 Select ‘Yes’ if you want to add the spatial distance via the toolbox. This will enable ‘Atlas Files’ button for loading atlas file(s).

3.3.2 Adding spatial distance manually

If you have already computed spatial distance or have access to it, choose ‘no’ next to ‘Calculate Spatial Distance?’ and skip loading atlas files.

Distance file should be a symmetric numeric matrix with element a_{ij} (and a_{ji}) representing the spatial distance between regions (nodes) i and j. You can add your distance files at the end (after running the model), as detailed in 3.10.

Look In: Atlas_file

AAL_116node_444.nii

File Name: AAL_116node_444.nii

Files of Type: All Files

/victer3/aa/4d/Atlases/Atlas_file

Look In: atlas_files_116

Atlas_116_node_Sub1.mat
Atlas_116_node_Sub10.mat
Atlas_116_node_Sub11.mat
Atlas_116_node_Sub12.mat
Atlas_116_node_Sub13.mat
Atlas_116_node_Sub14.mat
Atlas_116_node_Sub15.mat
Atlas_116_node_Sub16.mat
Atlas_116_node_Sub17.mat
Atlas_116_node_Sub18.mat
Atlas_116_node_Sub19.mat
Atlas_116_node_Sub2.mat
Atlas_116_node_Sub20.mat
Atlas_116_node_Sub21.mat
Atlas_116_node_Sub22.mat
Atlas_116_node_Sub23.mat

File Name: .16_node_Sub9.mat" "Network_Model_Summary.mat" "outdir1.mat"

Files of Type: All Files

/victer3/aa/4d/Atlases/atlas_files

Look In: Atlas_list

Atlasfiles_list.txt

File Name: Atlasfiles_list.txt

Files of Type: All Files

/victer3/aa/4d/Atlases/atlas_files

Fig. 8 Loading atlas files. You can either select a single atlas file or multiple atlas files. In the latter case, the number of loaded atlas files must be the same as the number of loaded imaging data files, and the number of ROIs must be the same across subjects.

3.4 Correlation

If you use connection matrices as your data files, you can skip this section. If you use (ROI or voxel-wise) time series, the connection matrices will be computed through either Pearson full or partial correlation. You can select either one (fig. 9.A). However, if you wish to use methods other than full or partial correlation, you should compute the connection matrices using your preferred method and then load the connection matrices instead of time series. Note that negative connections will be set to zero for the subsequent analyses. A density thresholding option is provided as well to remove weak connections (however there may be benefits to using fully, weighted matrices). If you do decide to use this option, enter the percentage of the strongest connections that you wish to preserve for each subject (fig. 9.B).

Correlation

☐ Full Correlation

☐ Partial Correlation

☐ Thresholded

Network Features

A

Correlation

☑ Full Correlation

☐ Partial Correlation

☑ Thresholded 30

Network Features

B

Fig. 9 Correlation method. **A.** Select full or partial correlation by filling their corresponding checkboxes (negative correlations will be set to zero). **B.** Enter the percentage of the strongest connections that you wish to maintain. For example, here, 70 percent of correlations in each subject's connection matrix will be set to zero and the strongest 30 percent of positive correlations will be maintained**.**

3.5 Network features

Click the popup dialogue and select all the network features that you would like to consider using in your models (fig. 10). Selected network features here will be computed and available (but not required) for use in your statistical models.

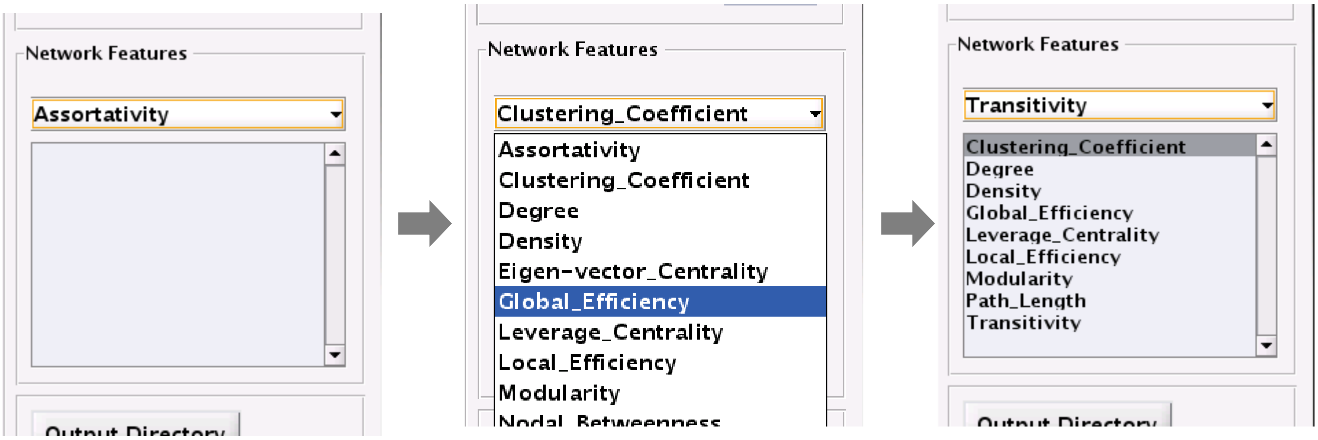


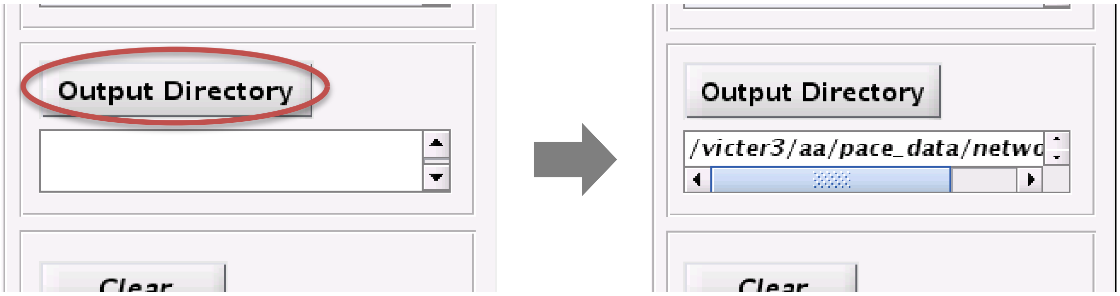
Fig. 10 Topological network features. Click the popup dialogue and select network features that you might want use in your models. You can remove the selected features by clicking on them in the list-box.

Final network features will be selected in the ‘Statistical_Model’ GUI from those you select here. This approach is efficient since network features are computed once (here), while different sets of them can be used in your models later.

Selected features are displayed in the list-box. You can remove the selected features by clicking on them in the list-box. Network features are computed using BCT (Rubinov and Sporns 2010).

3.6 Output directory

Click ‘Output Directory’ and select an output directory (fig. 11). Several files, including *data frame, correlation matrices* (if starting with time series), *network features*, *spatial distance* (if you want to add the spatial distance though the toolbox), *extracted ROI time series* (if starting with 4d voxel-wise time series), and *network model’s summary*, will be stored in this folder. Generated files will be saved in appropriate auto-generated sub-folders in the selected output directory.



/victer3/aa/pace_data/netwo

Fig. 11 Output directory. Generated files will be saved in appropriate sub-folders under this directory.

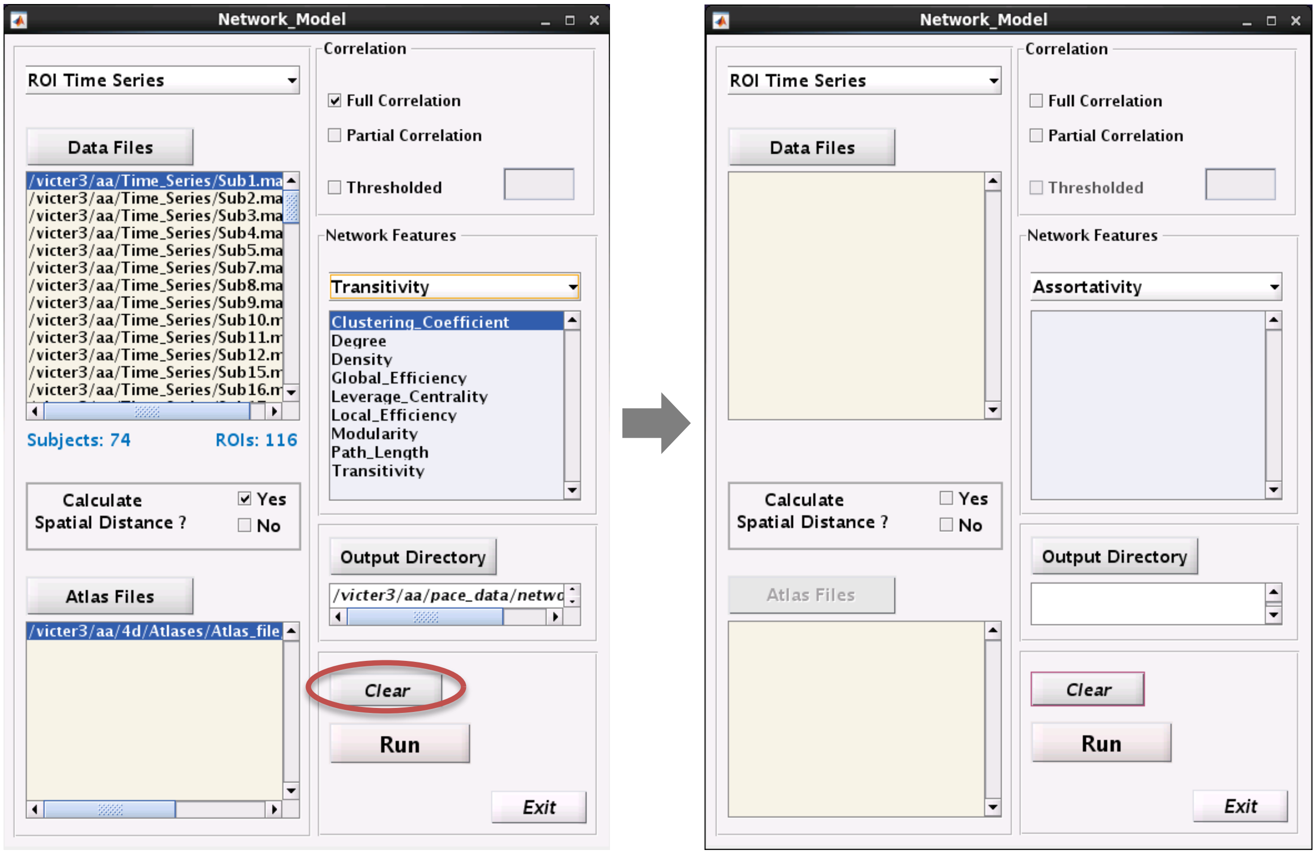
If you use the same directory in different runs, older files will be overwritten by new generated files. So, if you want to keep the generated files of each run, you should use different directories to avoid this. A warning message will be displayed reminding you about this. (Note that the output directory of the 'Network_Model' GUI will be the 'Input Directory' of the 'Statistical_Model' GUI. However, you can run several network models and save them in different directories and start from either one in the statistical model (see 4.10)).

3.7 Clear

Click 'Clear' button to reset the network model (fig. 12).

3.8 Run

Run the network model by clicking 'Run'. Multiple sets of files will be generated during this step, including: extracted ROI time series (if starting with 4d voxel-wise time series), correlation matrices (if starting with time series), network features, spatial distance (if choosing 'Yes' for calculating spatial distance), data frame, network model summary, and a cell file which includes selected network features' names.



Network_Model (before clearing):

ROI Time Series

Data Files:
/victer3/aa/Time_Series/Sub1.ma
/victer3/aa/Time_Series/Sub2.ma
/victer3/aa/Time_Series/Sub3.ma
/victer3/aa/Time_Series/Sub4.ma
/victer3/aa/Time_Series/Sub5.ma
/victer3/aa/Time_Series/Sub7.ma
/victer3/aa/Time_Series/Sub8.ma
/victer3/aa/Time_Series/Sub9.ma
/victer3/aa/Time_Series/Sub10.m
/victer3/aa/Time_Series/Sub11.m
/victer3/aa/Time_Series/Sub12.m
/victer3/aa/Time_Series/Sub15.m
/victer3/aa/Time_Series/Sub16.m

Subjects: 74 ROIs: 116

Calculate Spatial Distance ? ☑ Yes ☐ No

Atlas Files: /victer3/aa/4d/Atlases/Atlas_file

Correlation: ☑ Full Correlation ☐ Partial Correlation ☐ Thresholded

Network Features: Transitivity
Clustering_Coefficient
Degree
Density
Global_Efficiency
Leverage_Centrality
Local_Efficiency
Modularity
Path_Length
Transitivity

Output Directory: /victer3/aa/pace_data/netwo

Network_Model (after clearing):

ROI Time Series

Calculate Spatial Distance ? ☐ Yes ☐ No

Correlation: ☐ Full Correlation ☐ Partial Correlation ☐ Thresholded

Network Features: Assortativity

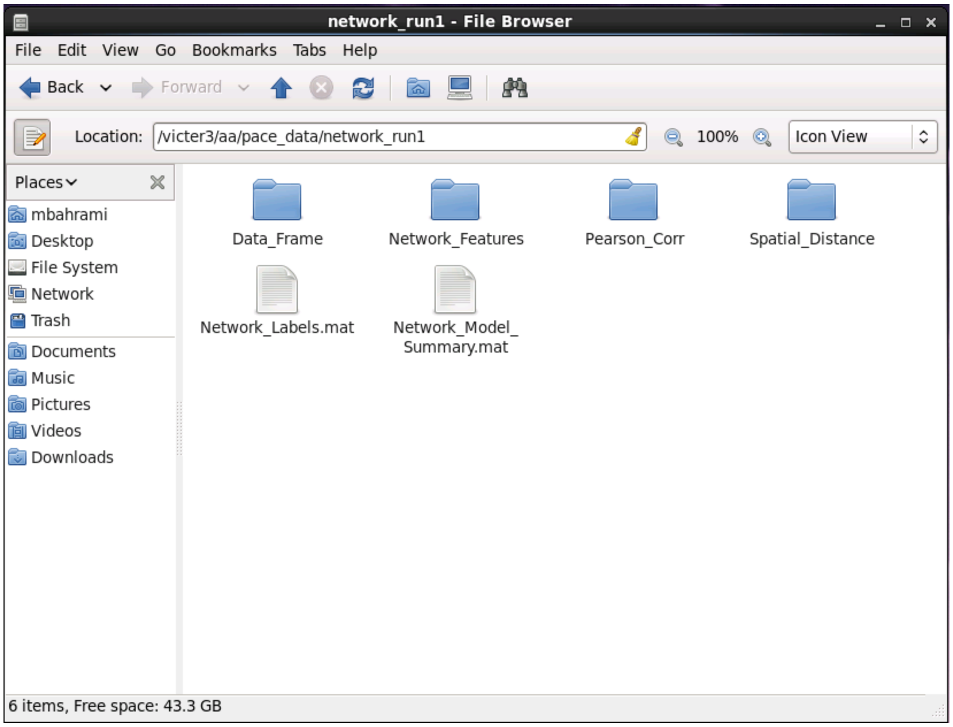
Fig. 12 Resetting network model. Everything will be set to default after clicking ‘Clear’.

All generated files will be saved in appropriate sub-folders in the output directory (fig. 13). If you use a previously used output directory, a question dialogue pops up asking you whether you want to continue to run or not, because, as mentioned earlier, the older files will be overwritten if you opt to continue (fig. 14).

‘Network_Model_Summary.mat’ is a matlab file containing a summary of loaded files and selected options of the network model. To see this file, you can type the following code in the command window of Matlab:

- Load(‘/… your selected output directory …/Network_Model_Summary.mat’);

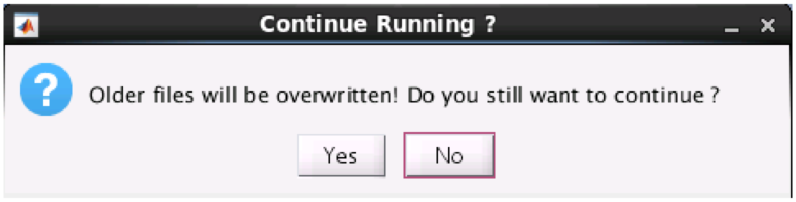
The loaded file will appear in the Matlab’s Workspace at the top right. Double click on this file to see the network summary (fig. 15).



Location: /victer3/aa/pace_data/network_run1

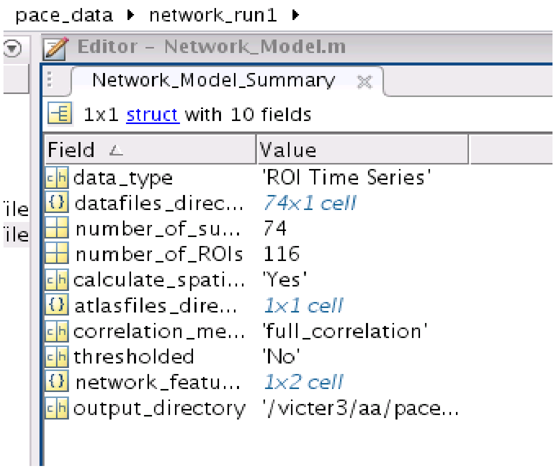
6 items, Free space: 43.3 GB

Fig. 13 Generated files if running a network model with the options shown in fig 12.A. ‘Network_Labels.mat’ is a cell file that includes the names of the selected network features. This file will be used by the ‘Statistical_Model’ GUI in the second step.



Older files will be overwritten! Do you still want to continue ?

Fig. 14 Question dialogue if using the same output directory in different runs.



1x1 struct with 10 fields

Field	Value
data_type	'ROI Time Series'
datafiles_direc...	74x1 cell
number_of_su...	74
number_of_ROIs	116
calculate_spati...	'Yes'
atlasfiles_dire...	1x1 cell
correlation_me...	'full_correlation'
thresholded	'No'
network_featu...	1x2 cell
output_directory	'/victer3/aa/pace...

Fig 15. Network Model Summary. This file shows a summary of loaded files and selected options in the 'Network_Model' GUI. This is useful for future reviews of the model set up.

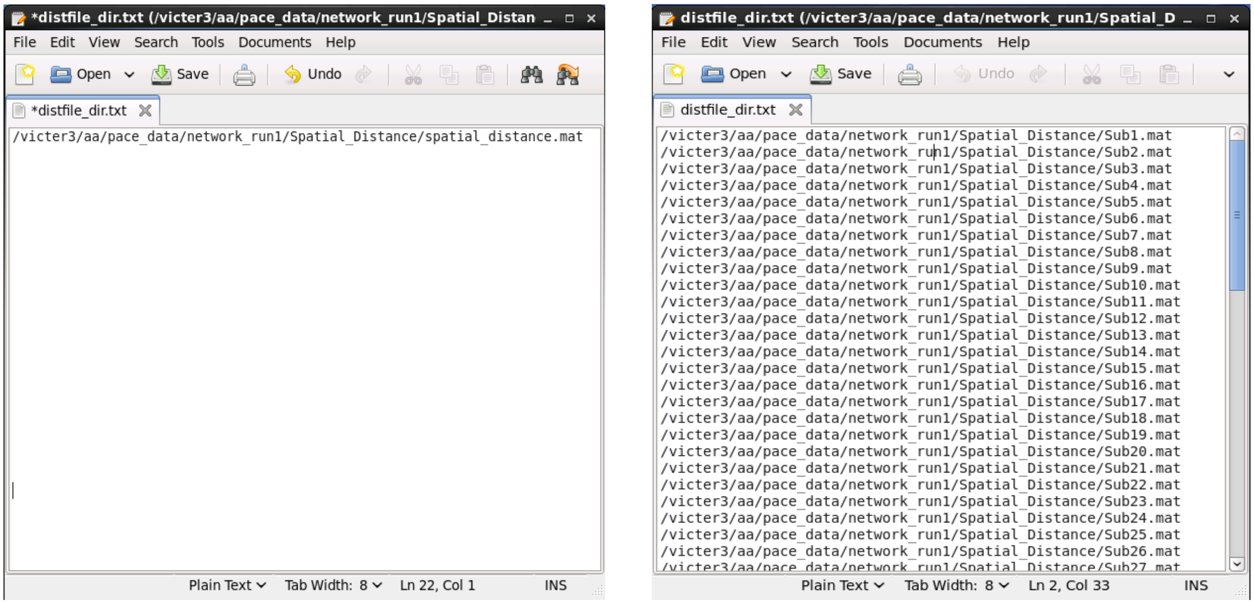
3.9 Running multiple network models

As pointed out before, the 'Network_Model' and 'Statistical_Model' GUIs work independently of each other. So, if you wish to model different datasets or model the same dataset with different options (e.g., using full correlation and partial correlation), you can first run your multiple network models (and choose different output directories for each one); then, start with either one in the statistical modeling GUI.

3.10 Adding spatial distance files manually

If you have already computed spatial distance or have access to it, add your distance file(s) after you finish running the model as detailed below:

- Create a folder and name it 'Spatial_Distance' in the output directory (The directory you have selected for your network model).
- Create a text file in this folder (i.e., 'Spatial_Distance' folder), and name it 'distfile_dir'; Then, add the directory of your spatial distance file(s) to this file (fig. 16).



```
/victer3/aa/pace_data/network_run1/Spatial_Distance/spatial_distance.mat
```

```
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub1.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub2.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub3.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub4.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub5.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub6.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub7.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub8.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub9.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub10.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub11.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub12.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub13.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub14.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub15.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub16.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub17.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub18.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub19.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub20.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub21.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub22.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub23.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub24.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub25.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub26.mat
/victer3/aa/pace_data/network_run1/Spatial_Distance/Sub27.mat
```

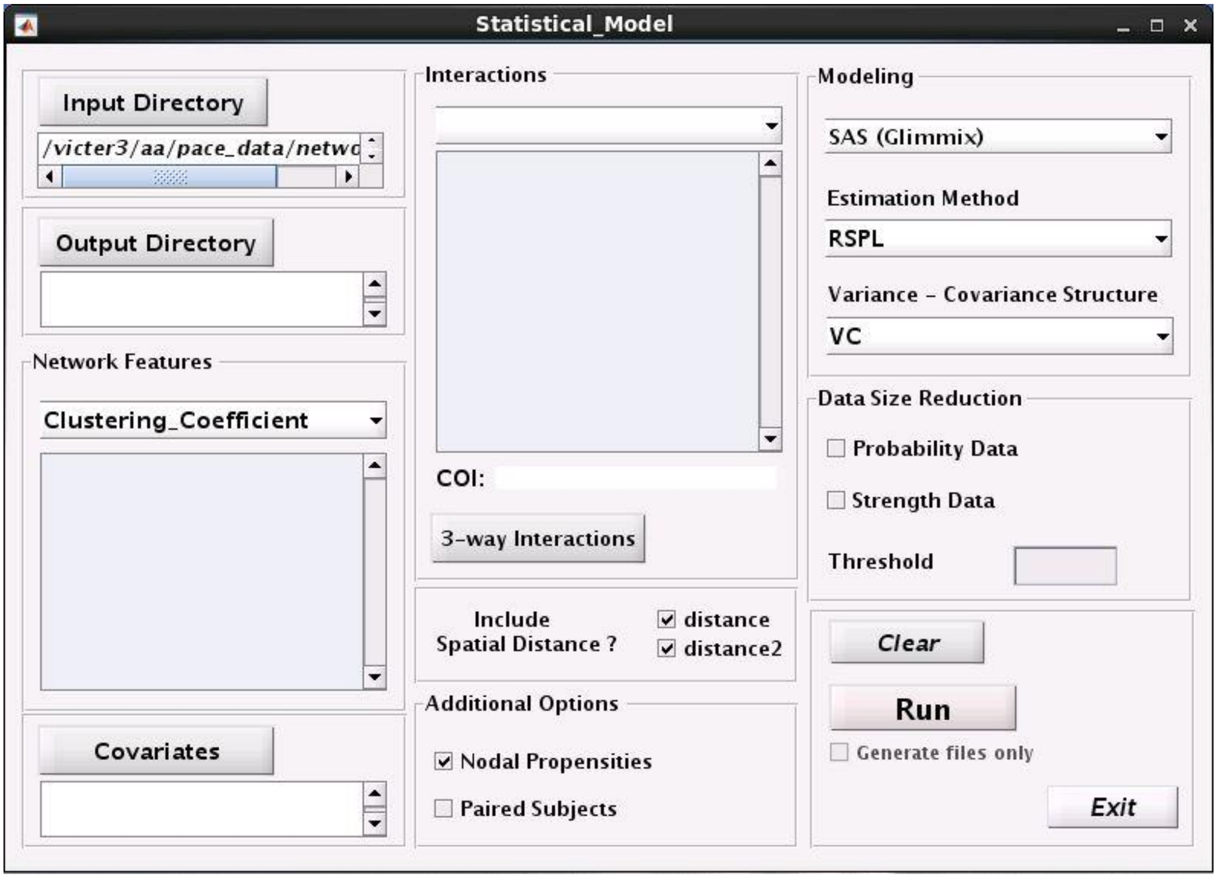
A **B**

Fig. 16 Adding spatial distance manually. First, create a folder and name it ‘Spatial_Distance’ in the output directory. Next, create a text file and name it ‘distfile_dir’ in the ‘Spatial_Distance’ folder. Then, add the directory of your spatial distance file if it is a single file (A), or add the directories if you want to use a separate distance file for each subject (B).

Note that the distance file should be a symmetric numeric matrix with element a_{ij} (and a_{ji}) representing the spatial distance between regions (nodes) i and j.

4 Statistical Model

As pointed out earlier, modeling is done in two main steps. The first step was described in the last section. In the second step, using the ‘Statistical_Model’ GUI and generated files from the first step, appropriate modeling files will be generated and results will be produced. Click the ‘Statistical_Model’ button in ‘WFU_MMNET’ to start the ‘Statistical_Model’ GUI. You should see one of the windows shown in fig. 17 or fig. 18 depending on your current directory in Matlab (i.e., your Matlab’s ‘Current Folder’). If you start the ‘Statistical_Model’ GUI from a directory that you ran a network model, you should see the window shown in fig. 17, otherwise, you should see the window shown in fig. 18.



Input Directory: /victer3/aa/pace_data/netwo

Network Features: Clustering_Coefficient

☑ distance

☑ distance2

☑ Nodal Propensities

☐ Paired Subjects

Modeling: SAS (Glimmix)

Estimation Method: RSPL

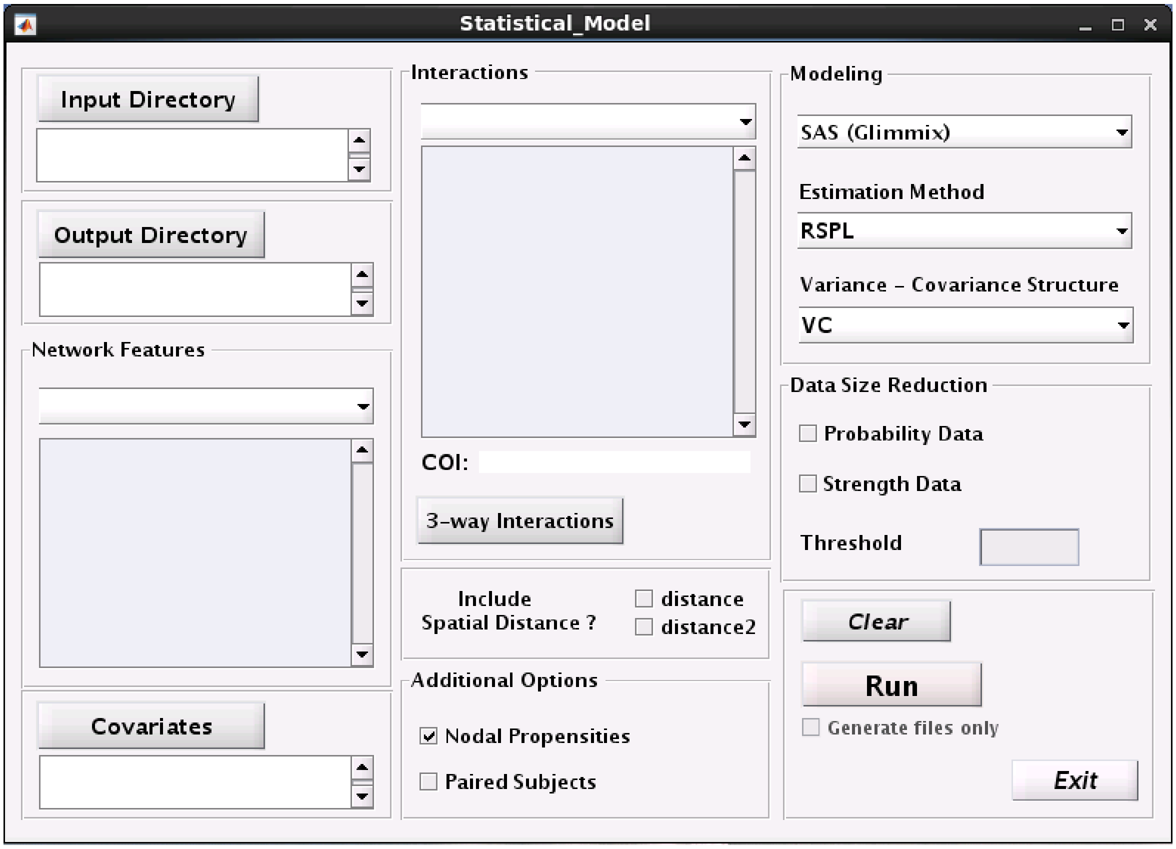
Variance - Covariance Structure: VC

☐ Probability Data

☐ Strength Data

☐ Generate files only

Fig. 17 The statistical model GUI. If you start from a directory that you ran a network model, you will see this window. The ‘Input Directory’ of the statistical model will be set to the ‘Output Directory’ of the network model by default. However, you can change the ‘Input Directory’ if you have run several network models.



Modeling: SAS (Glimmix)

Estimation Method: RSPL

Variance – Covariance Structure: VC

☐ Probability Data

☐ Strength Data

Include Spatial Distance ? ☐ distance ☐ distance2

☑ Nodal Propensities

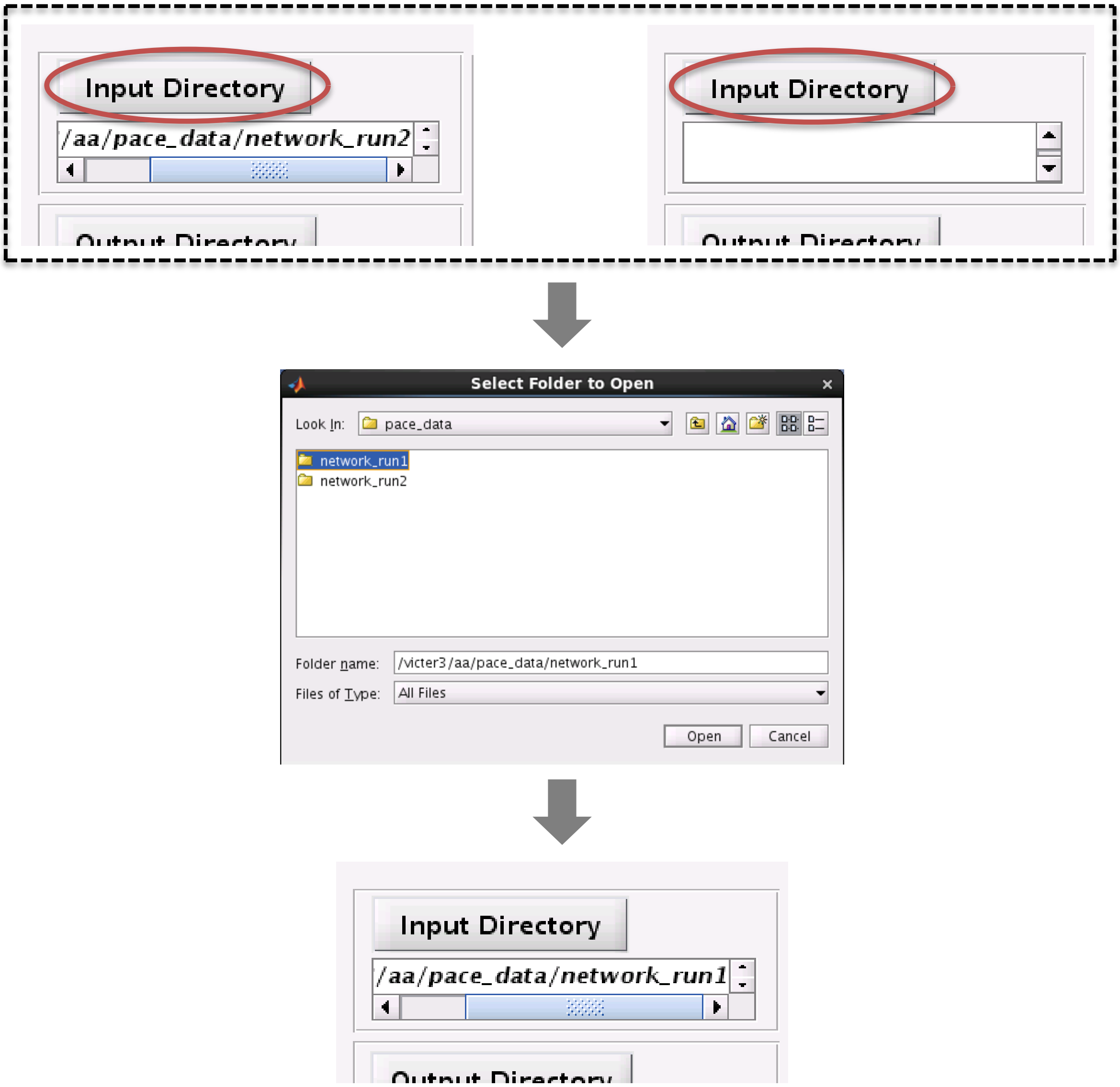
☐ Paired Subjects

☐ Generate files only

Fig. 18 The statistical model GUI. If you start from a directory that you have not run any network model before, you will see this window. Note that the input directory is not specified.

4.1 Input directory

Click 'Input Directory' button and select the input directory (fig. 19). If you start from a directory that you have run a network model, the input directory will be set to the output directory of the 'Network_Model' GUI by default. If you ran multiple network models before starting the 'Statistical_Model' GUI, the input directory will be set to the output directory of the last network model. If the input directory was empty (i.e., if you started from a different directory), or if you ran several network models, you can simply select your desired input directory (fig. 19). Note that the input directory must be the output directory of a previously run network model.



/aa/pace_data/network_run2

Look In: pace_data

Folder name: /victer3/aa/pace_data/network_run1

Files of Type: All Files

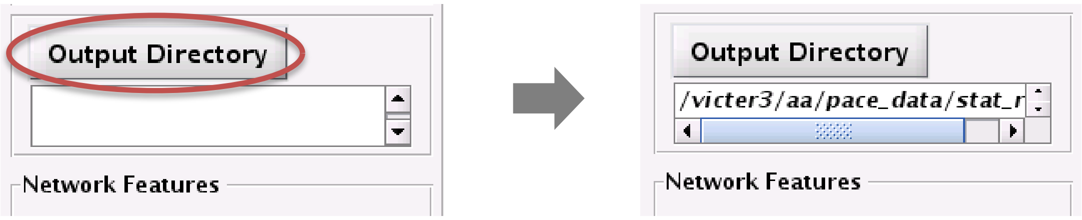
/aa/pace_data/network_run1

Fig. 19 Input directory. Select the output directory of your desired network model as the input directory.

After selecting the input directory, the selected network features in the network model will appear in the popup dialogue of the ‘Network Feature’ panel (see 4.3). Also, checkboxes for ‘distance’ and ‘distance2’ would be filled if you added spatial distance in your network model, otherwise, they would be grayed out.

4.2 Output directory

Click the ‘Output Directory’ button and select an output directory (fig. 20). Generated files, including modeling datasets (used in modeling the probability and strength of brain connections), modeling files (modeling options and equations) used by the modeling software to fit the statistical models, modeling results, and a summary file of the statistical model will be stored in this directory. Again, use different output directories for different runs if you wish to keep the results of your runs, because the older files will be overwritten if you use the same output directory. A warning message will be displayed if using a previously used output directory. After selecting the output directory, the ‘Network_Model_Summary’, which is generated when running the network model, will be copied to the output directory. Although you can see the ‘Network_Model_Summary’ in the network model output as well, having this file in the statistical model output directory helps to know which network model was used in cases of running several network models. The toolbox doesn’t allow using the same directory for the input and output.



/victer3/aa/pace_data/stat_r

Fig. 20 Selecting output directory.

4.3 Network features

Select the network features from the popup dialogue (fig. 21). Network features shown in the popup dialogue are those that you have selected in setting your network model (see 3.5). Note that by changing the input directory, your network feature choices (i.e., features appeared on the popup dialogue) can differ based on the network features that you selected in your network models.

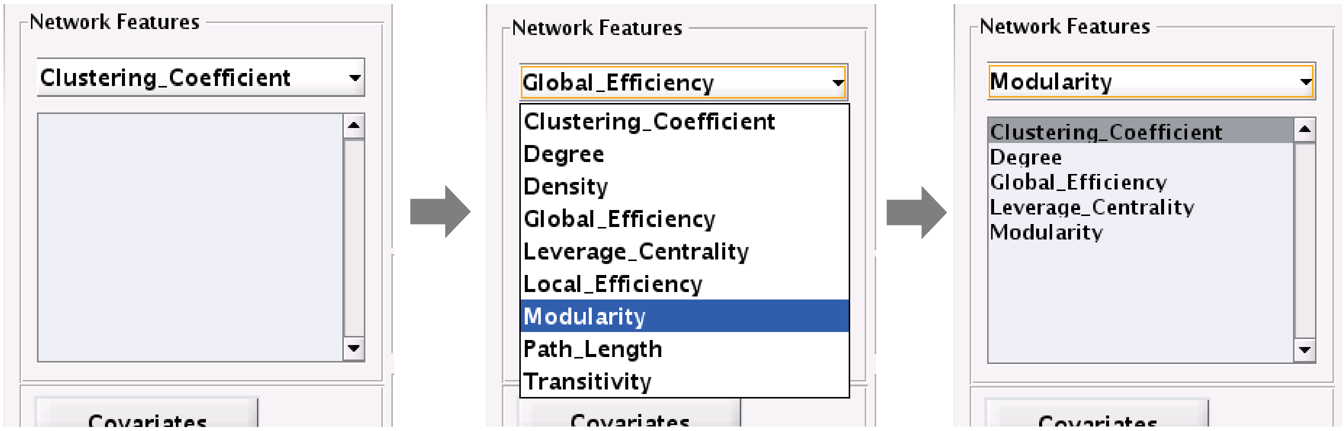


Fig. 21 Topological network features. Click the popup dialogue and select the network features. You can delete the selected features by clicking on them in the list-box.

You can remove the selected features by clicking on them in the list-box.

4.4 Covariates

Covariates data is a 2d single matrix with rows representing the subjects and columns representing the exogenous variables (i.e., all covariates that **are not** network features) (fig. 22). This matrix **must** have row names and column names. The first Column must represent the row names (e.g., subject identifiers), and the second column must be assigned to the main covariate of interest (COI). The COI can be a binary, categorical or continuous variable. In a typical study, the COI is the variable defining study population groups. Continuous or categorical exogenous variables such as age, gender, education, disease phenotypes, or risk factors can make up the other columns of this matrix. **The paired analysis is being finalized and will be provided in a future update.** For paired subject's analysis, the last column of the covariates matrix must be a numeric column in which the same number is used to specify the paired subjects (fig. 23).

Click "Covariates" button and load your covariates data (fig. 24).

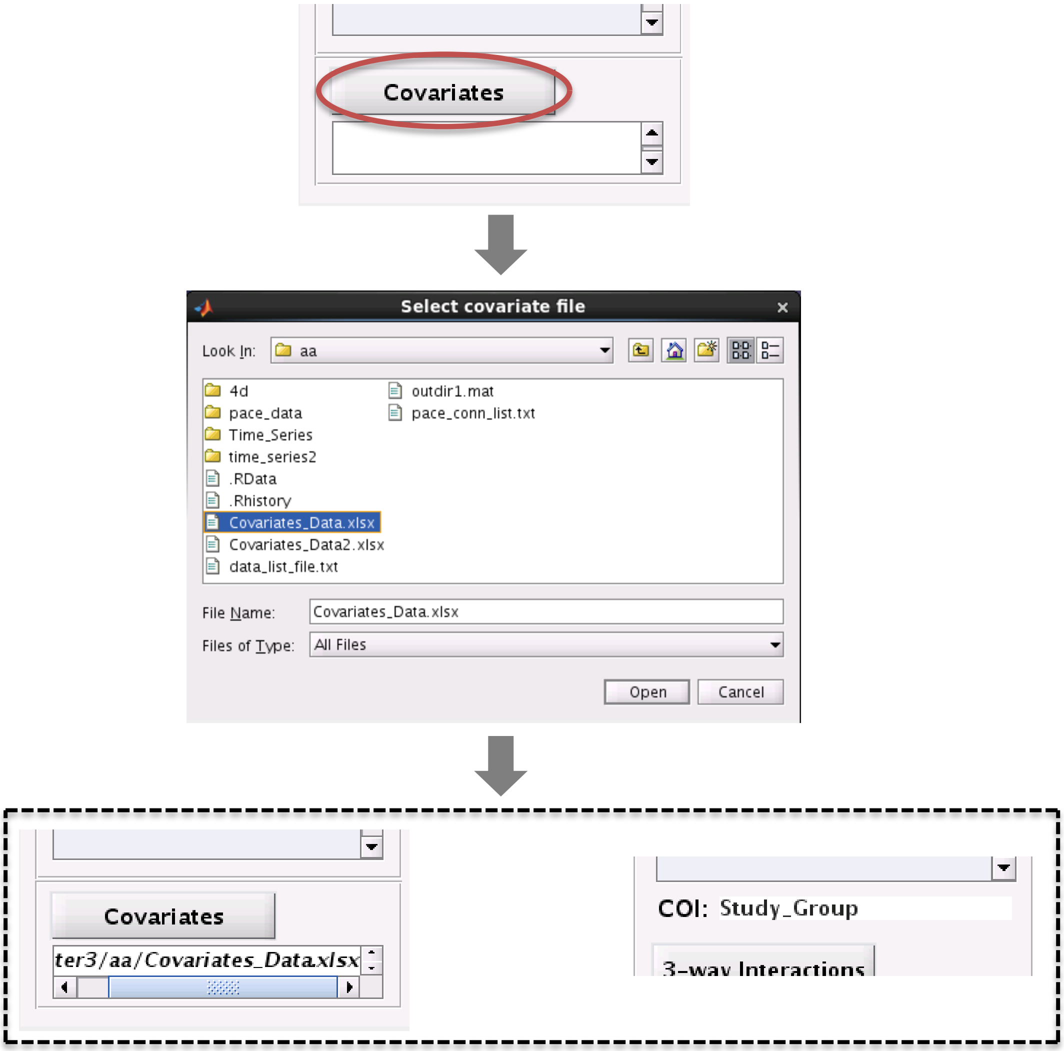
	Study_Population	*BP*	*Age*	*Smoking*	*…*
Subj1	**0**	**95**	**67**	**No**	**--**
Subj2	**0**	**105**	**71**	**Yes**	**--**
….	**…**	**…**	**…**	**…**	**…**
Subj (N-1)	**1**	**140**	**69**	**Yes**	**--**
Subj N	**1**	**120**	**76**	**No**	**--**

Fig. 22 Covariates data format. Sample covariate data with COI as a binary variable defining two study populations.

	Study_Group	*BP*	*Age*	*Smoking*	*…*	*Paired_Subjs*
Subj1	**Pre**	**95**	**67**	**No**	**--**	**1**
…	**…**	**…**	**…**	**…**	**…**	**..**
SubjN	**Pre**	**105**	**76**	**Yes**	**--**	**N**
Subj1	**Post**	**85**	**67**	**No**	**--**	**1**
…	**…**	**…**	**…**	**…**	**…**	**…**
SubjN	**Post**	**100**	**76**	**Yes**	**--**	**N**

Fig. 23 Covariates data format when paired subjects are analyzed. The last column in this case must specify the paired subjects by using the same number for them. Here, the COI is a categorical variable with two categories (i.e., pre vs post). **The paired analysis is being finalized and will be provided in a future update.**

Subjects in this matrix should be arranged in the same order as the loaded imaging files. The toolbox always changes the name of the second column to 'COI' and shows the actual variable name next to the 'COI' in the Interactions panel (fig. 24).



Select covariate file

Look In: aa

File Name: Covariates_Data.xlsx

Files of Type: All Files

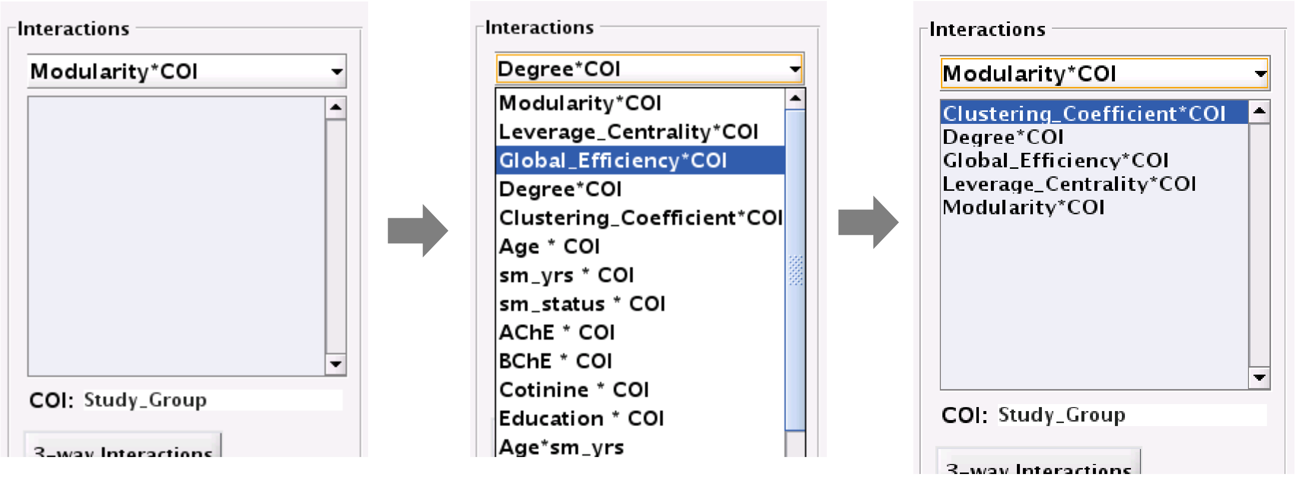
ter3/aa/Covariates_Data.xlsx

COI: Study_Group

Fig. 24 Covariates data file. Click “Covariates” button and load the covariates data matrix. The name of the second column, which must be assigned to the main covariate of interest, will always be changed to ‘COI’ for subsequent analyses.

4.5 Interactions

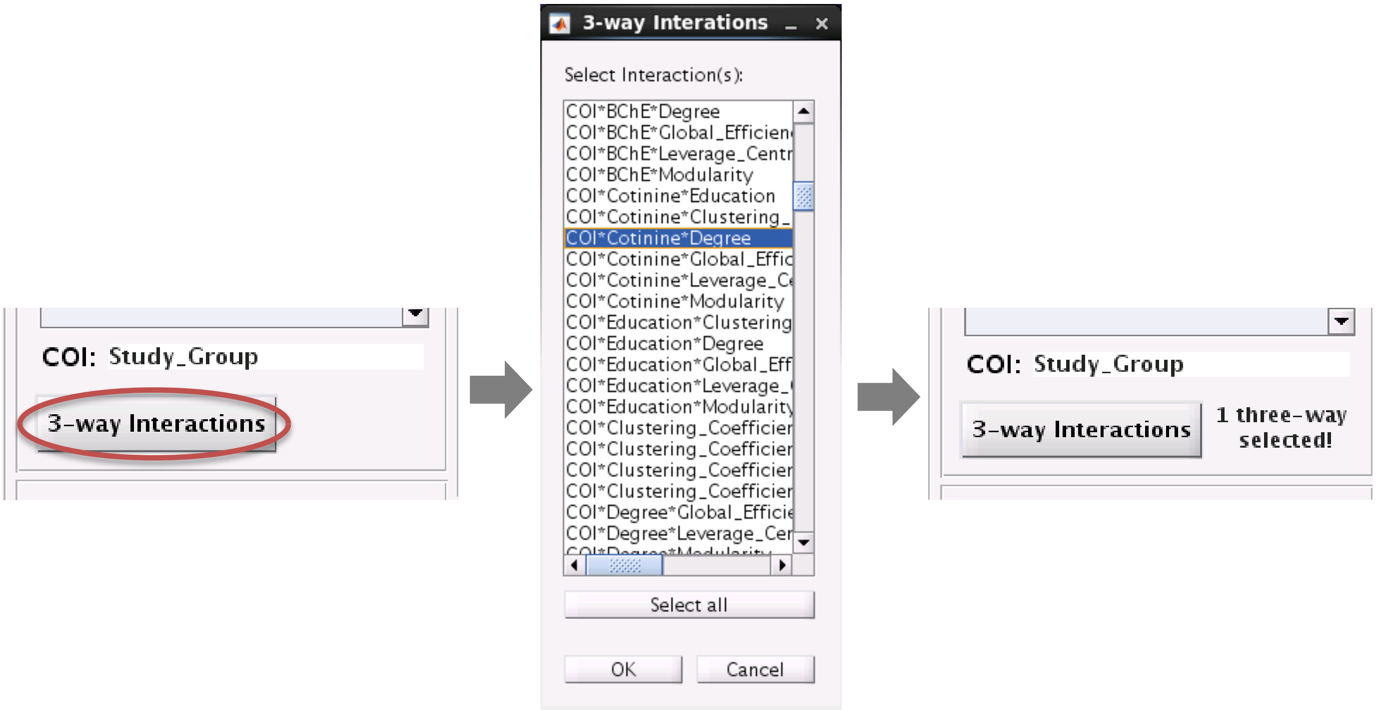
Interactions of the selected network features with COI, as well as other two-way interactions will be added to the popup dialogue in the “Interactions” panel after selecting the network features and loading the covariates data. Click the popup dialogue and choose your desired two-way interactions (fig. 25). We suggest using interactions of the network features with COI.



COI: Study_Group

Fig. 25 Selecting interaction variables.

You can also choose three-way interactions by clicking ‘3-way Interactions’ button (fig. 26). However, the use of three-way interactions should be carefully considered as interpreting them can get very difficult, and using them might also result in convergence issues in fitting models.



1 three-way selected!

Fig. 26 Selecting three-way interactions.

4.6 Spatial Distance

If you skipped calculating spatial distance when setting up the network model, and didn't add it manually either, the 'distance' and 'distance2' checkboxes will be grayed out by default (fig 27. A). However, if spatial distance is available, the checkboxes will be filled by default (fig 27. B). But, you can remove them if you would like to exclude spatial distance from your analysis.

Include Spatial Distance ? ☐ distance ☐ distance2

A

Include Spatial Distance ? ☑ distance ☑ distance2

B

Fig. 27 Spatial distance. **A.** Spatial distance file is not available (i.e., not computed nor manually added when setting up the network model). **B.** Spatial distance is available.

4.7 Nodal propensities and Paired subjects

Nodal propensities are modeled as random effects by default. However, if you are modeling a dataset with a large number of ROIs (e.g., > 100), including the propensities may result in convergence problems, especially in modeling the probability of brain connections. If this occurs, we suggest removing them.

<u>**The paired analysis is being finalized and will be provided in a future update.**</u> Fill the 'Paired Subjects' checkbox if you are using paired subjects in your analysis. The last column of your loaded covariates data file must specify the paired subjects.

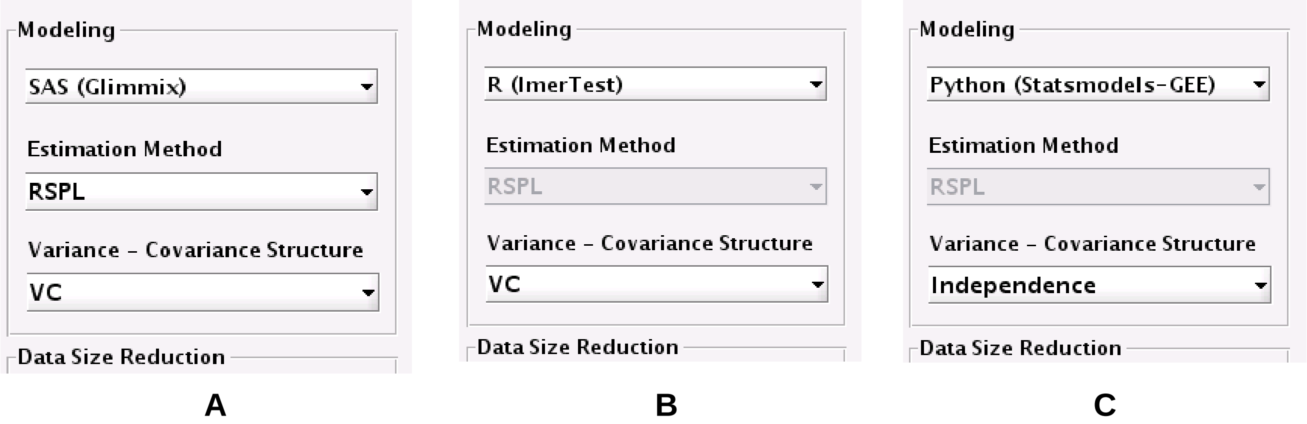
4.8 Modeling

This toolbox uses SAS, R, or Python (depending on software availability) to perform the statistical modeling. Thus, you should have one of them (preferably SAS or R) and required packages installed on Linux before using this toolbox. If the modeling software is installed on Windows, you can still perform the modeling as detailed in the following.

4.8.1 Selecting modeling software

Click the popup dialogue and select the modeling software (fig. 28) even if the modeling software is in Windows.

As described in 2.2.4, if a modeling software was available in Linux, you should add the path of the folder including its executible file to ‘executible_file_path’ as a part of the installation process (before starting the toolbox). The added modeling software will appear with a black color in the popup dialogue in the ‘Modeling’ panel (fig. 29). You can also add more than one modeling software (fig. 30.A). However, you only need one. Also, if no modeling software is available in Linux, leave the ‘executible_file_path’ blank (fig. 30.B). You can perform the modeling in Windows as explained in 4.11.2 .

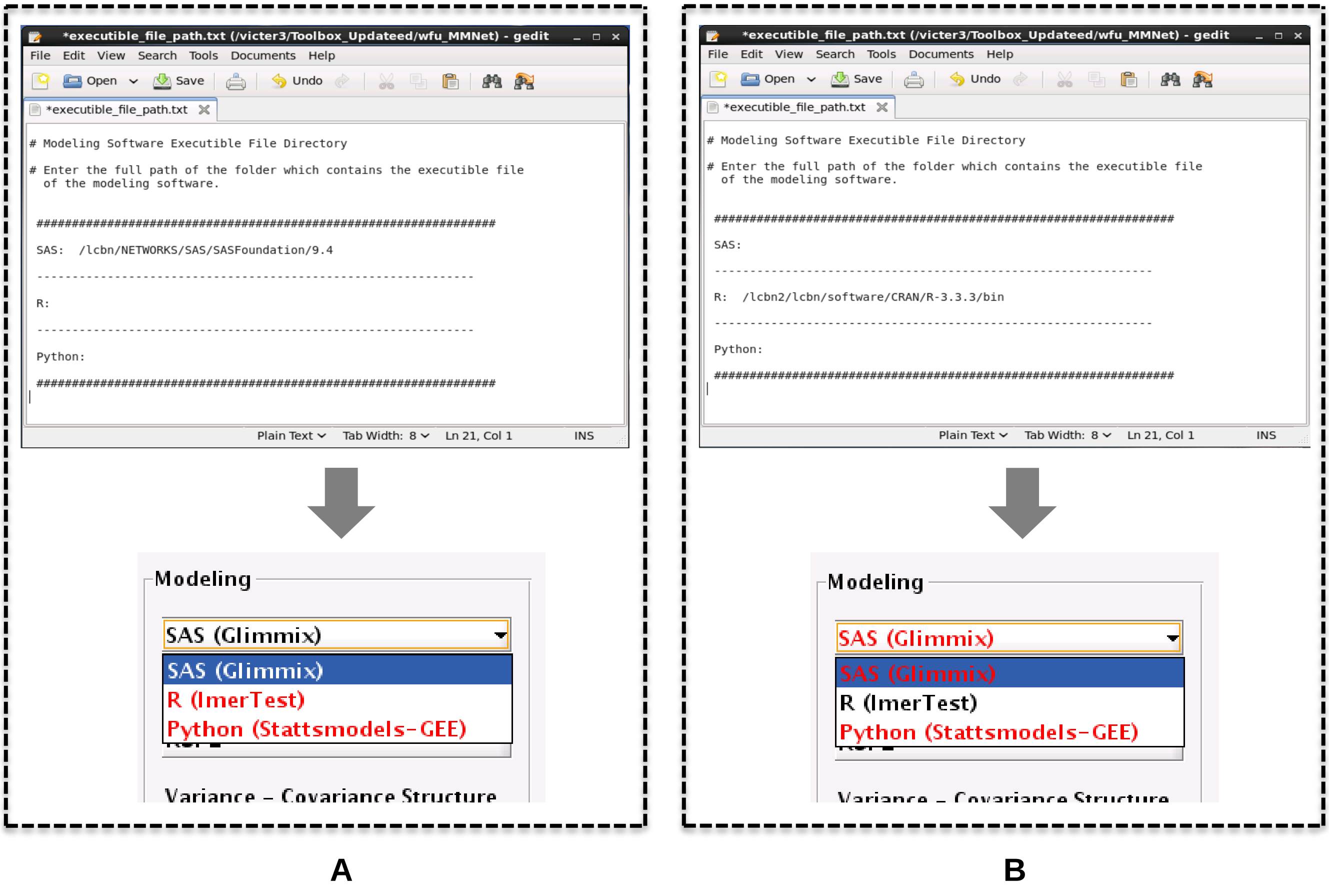


A: Modeling: SAS (Glimmix); Estimation Method: RSPL; Variance - Covariance Structure: VC

B: Modeling: R (lmerTest); Estimation Method: RSPL; Variance - Covariance Structure: VC

C: Modeling: Python (Statsmodels-GEE); Estimation Method: RSPL; Variance - Covariance Structure: Independence

Fig. 28 Selecting modeling software. **A.** SAS, **B.** R, **C.** Python



A:

```
# Modeling Software Executible File Directory

# Enter the full path of the folder which contains the executible file
  of the modeling software.


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

 SAS:  /lcbn/NETWORKS/SAS/SASFoundation/9.4

 --------------------------------------------------------------

 R:

 --------------------------------------------------------------

 Python:

 #################################################################
```

B:

```
# Modeling Software Executible File Directory

# Enter the full path of the folder which contains the executible file
  of the modeling software.


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

 SAS:

 --------------------------------------------------------------

 R:  /lcbn2/lcbn/software/CRAN/R-3.3.3/bin

 --------------------------------------------------------------

 Python:

 #################################################################
```

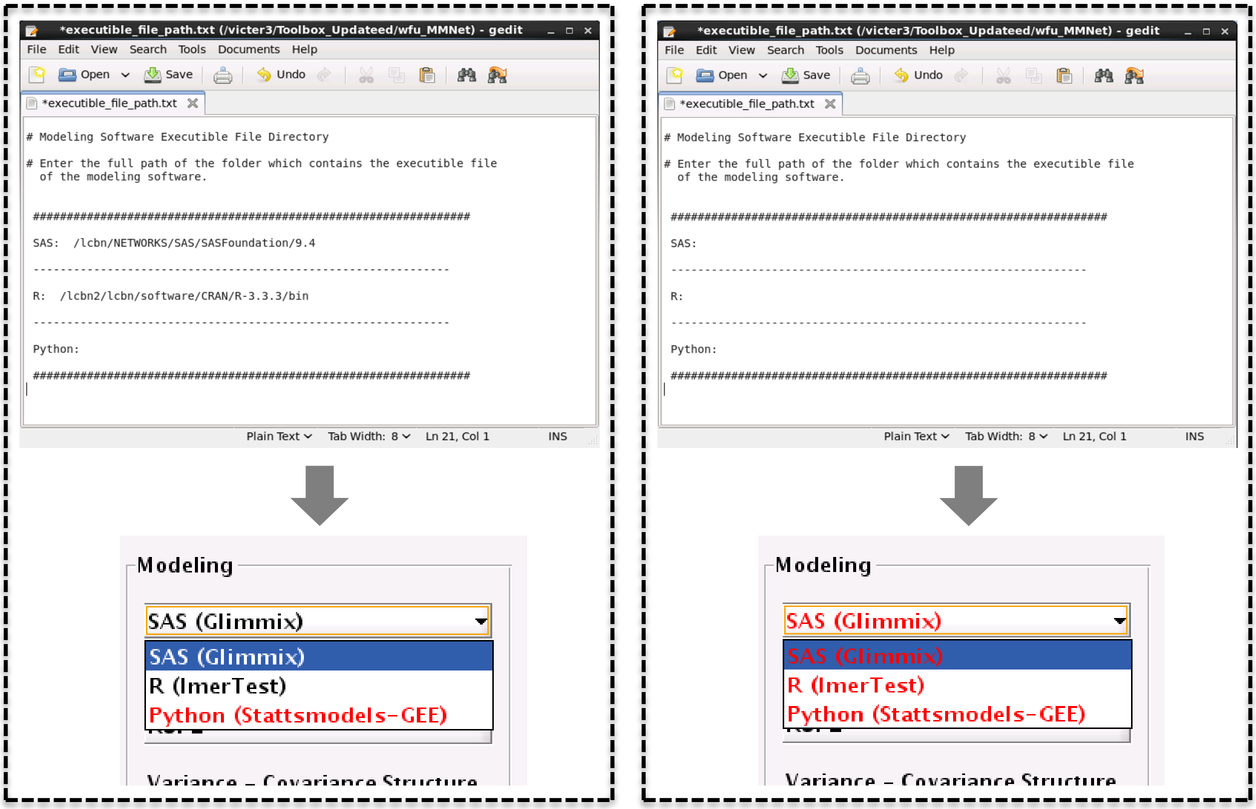
Fig. 29 Available modeling software in Linux. **A.** SAS is available, **B.** R is available.

4.8.2 SAS (Glimmix)

SAS (Glimmix) uses general linear mixed models (GLMMs) to fit statistical models to datasets with correlated samples. We suggest using SAS due to its flexibility and fast computations.

Click the popup dialogue and select ‘SAS (Glimmix)’ (fig. 28.A). The default is also set to ‘SAS (Glimmix)’.

Glimmix allows changing many modeling parameters which make it efficient and flexible for different situations. However, for simplicity and user-friendliness we have only provided two main options as the most important ones in our case: 1) Estimation method, and 2) variance-covariance structure for random effects.



```
# Modeling Software Executible File Directory

# Enter the full path of the folder which contains the executible file
  of the modeling software.


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

SAS:  /lcbn/NETWORKS/SAS/SASFoundation/9.4

-----------------------------------------------------------------

R:  /lcbn2/lcbn/software/CRAN/R-3.3.3/bin

-----------------------------------------------------------------

Python:

####################################################################
```

A

```
# Modeling Software Executible File Directory

# Enter the full path of the folder which contains the executible file
  of the modeling software.


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

SAS:

-----------------------------------------------------------------

R:

-----------------------------------------------------------------

Python:

####################################################################
```

B

Fig. 30 Available modeling software **A.** Both SAS and R are available in Linux. **B.** None of modeling software is available in Linux (If the modeling software is in Windows you should leave the 'executible_file_path' blank as shown here).

Additional modeling options may be provided in the future versions.

Click the 'Estimation Method' popup dialogue and select the estimation method. We suggest using the default estimation method (RSPL). RSPL is a pesudo-likelihood technique in which the estimation is based on a residual likelihood approach. Other available estimation methods are detailed in (Schabenberger 2005). Click the 'Variance – Covariance Structure' popup dialogue and select the variance-covariance structure for the random effects. Most applications use either variance-components (VC) or unstrcutured (UN) structures for the random effects. VC is a simple diagonal matrix which models a different variance component for each random effect. We strongly suggest using this default option as using more complex structures can result in convergence issues. In special cases, such as when nodal propensities are not included (see 4.7), you may use an unstructured matrix that is parameterized in terms of its Cholesky parameterization (i.e., using ‘CHOL’). Other variance-covariance structures have been detailed in (Schabenberger 2005).

4.8.3 R (lmerTest)

Click the popup dialogue and select ‘R (lmerTest)’ (fig. 28.B). If you use R, you need to install ’lmerTest’ package (Kuznetsova, Brockhoff et al. 2015) before using this toolbox. lmerTest uses general linear mixed models as well. It fits a linear mixed model to the strength dataset via a restricted maximum likelihood approach, and fits a generalzied linear mixed model to the probability dataset via a maximum likelihood approach. Two variance-covariance strcutures can be used for modeling the random effects: variance components (VC) and unstructred (UN). We strongly suggest using the ‘VC’ (it is the default option). In certain cases where nodal propensities are not included (see 4.7), you may use the ‘UN’ structure.

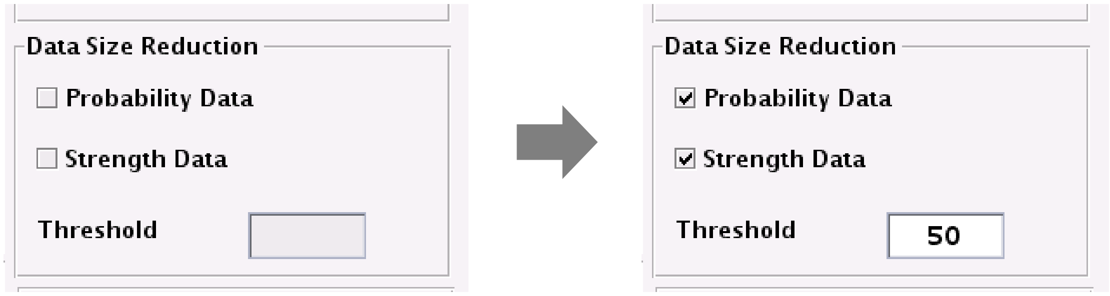
4.8.4 Python (Statsmodels – GEE)

Click the popup dialogue and select ‘Python (Statsmodels - GEE)’ (fig. 28.C). If using Python, you need to install several modules, including: “numpy”, “scipy”, “pandas”, and “statsmodels” before using this toolbox (we suggest not using Python, especially for datasets with a small number of subjects or ROIs.) Unlike SAS (Glimmix) and R (lmerTest) which use GLMMs to fit the models, Python uses generalized estimating equations (GEE). Click on the ‘Variance – Covariance Structure’ popup dialogue and select the covariance structure. Here, only the correlation structure of a random error term is modeled. Three working correlation structures are provided: 1) Independence, 2) Exchangeable, 3) Autoregressive. We suggest using the Independence structure. This structure assumes equal correlation between observations.

4.9 Data Size Reduction

Although we do not suggest reducing the data size by default, modeling large datasets may result in convergence issues or increase the modeling time, especially when using R. Thus, we have provided a k-means clustering data size reduction approach in this toolbox to deal with this problem.

To use this approach, select the data (i.e., probability or strength) by filling its checkbox, and <u>enter the percentage of the data that you wish to **remove**</u> (fig. 31).



Data Size Reduction

☐ Probability Data

☐ Strength Data

Threshold

Data Size Reduction

☑ Probability Data

☑ Strength Data

Threshold 50

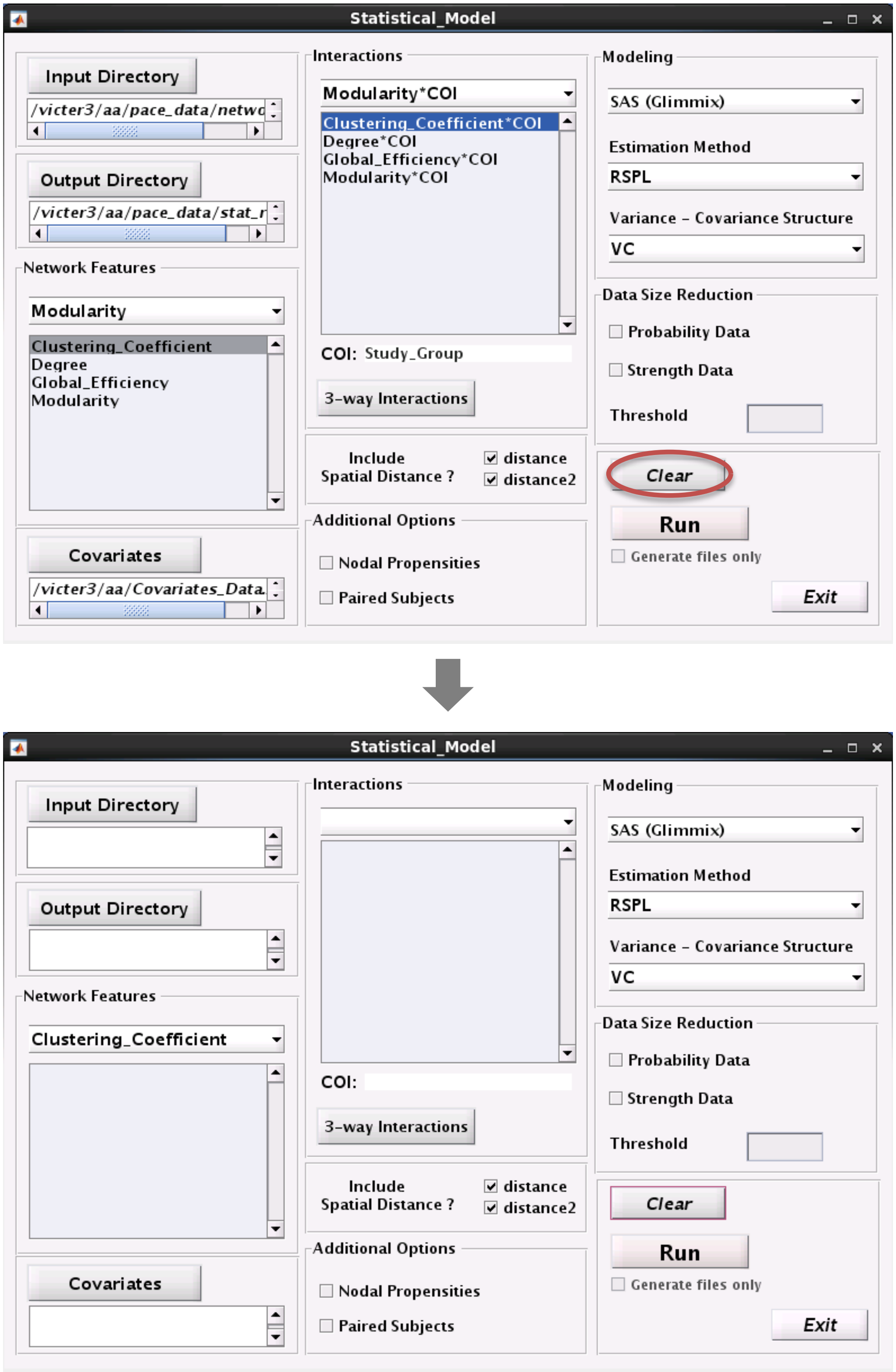
Fig. 31 Data size reduction. Select the data and enter the percentage that you want to <u>remove.</u>

4.10 Clear

Click ‘Clear’ button to reset your statistical model (fig. 32).

4.11 Run

If you click the ‘Run’ button, **first**, using the loaded files and selected options, modeling equations, datasets, and options will be generated; **second**, generated datasets, files and options will be employed by the selected modeling software to fit the statistical models.



Statistical_Model

Input Directory: /victer3/aa/pace_data/netwo

Output Directory: /victer3/aa/pace_data/stat_r

Network Features: Modularity

Clustering_Coefficient
Degree
Global_Efficiency
Modularity

Covariates: /victer3/aa/Covariates_Data

Interactions: Modularity*COI

Clustering_Coefficient*COI
Degree*COI
Global_Efficiency*COI
Modularity*COI

COI: Study_Group

3-way Interactions

Include Spatial Distance ? ☑ distance ☑ distance2

Additional Options
☐ Nodal Propensities
☐ Paired Subjects

Modeling: SAS (Glimmix)

Estimation Method: RSPL

Variance - Covariance Structure: VC

Data Size Reduction
☐ Probability Data
☐ Strength Data
Threshold

Clear

Run

☐ Generate files only

Exit

Statistical_Model

Input Directory

Output Directory

Network Features: Clustering_Coefficient

Covariates

Interactions

COI:

3-way Interactions

Include Spatial Distance ? ☑ distance ☑ distance2

Additional Options
☐ Nodal Propensities
☐ Paired Subjects

Modeling: SAS (Glimmix)

Estimation Method: RSPL

Variance - Covariance Structure: VC

Data Size Reduction
☐ Probability Data
☐ Strength Data
Threshold

Clear

Run

☐ Generate files only

Exit

Fig. 32 Resetting the statistical model. Statistical model will be set to default after clicking 'Clear'.

We have deliberately broken this into two steps to allow modeling in Windows as well. In this case, the modeling can be performed in Windows using the generated files and modifying the modeling scripts.

4.11.1 Modeling in Linux

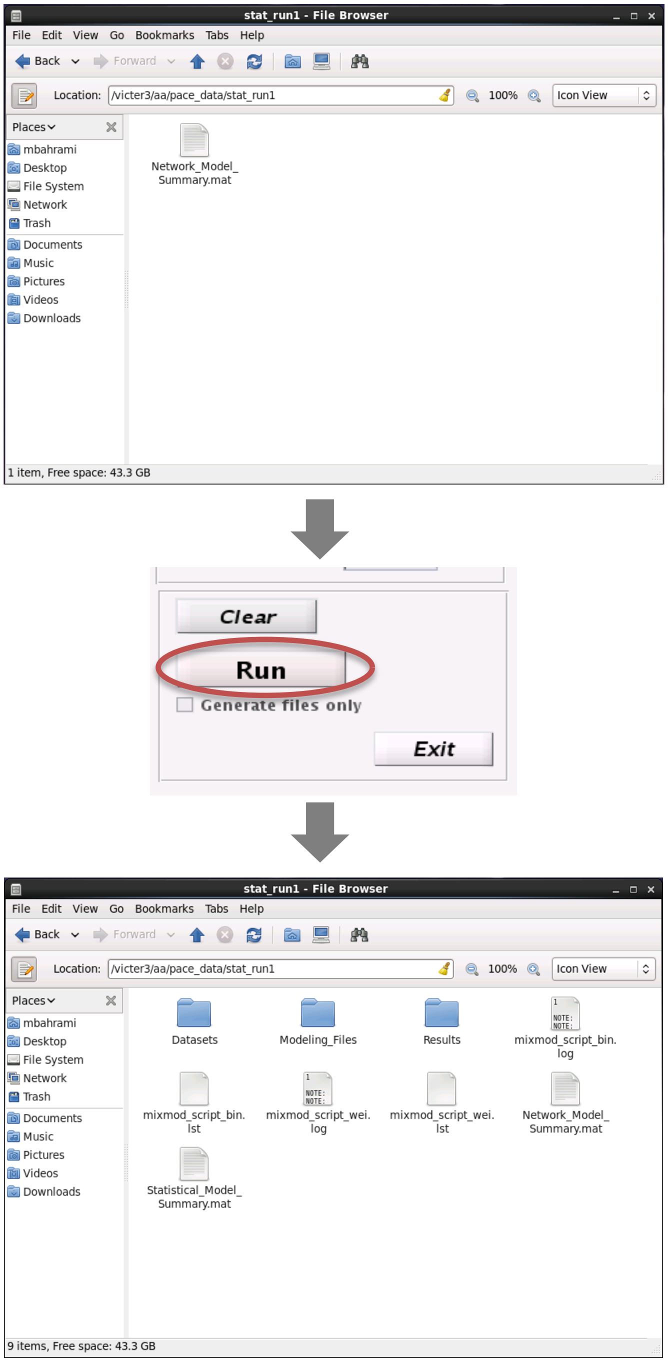
Click the ‘Run’ button to fit the models. First, modeling datasets, equations, and options are generted and saved under appropriate folders in your selected output directory; then, using these files, the modeling software fits the statistical models, and saves the results in the output directory in the ‘Results’ folders (fig. 33).

Results for probability and strength of brain connections are saved under the ‘Results’ folder. The output directory’s name will be appended to the names of the results (fig. 34).

4.11.2 Modeling in Windows

As mentioned earlier, the model fits will be done in two steps: I) Generating modeling datasets, equations, and options, II) Fitting the statistical models using the generated files and the modeling software. If the modeling software is not available in Linux, you still need to generate the files (i.e., doing the first step). Then, you can use these files in Windows to fit the statistical models. Use the following steps for each software in Windows to fit the statistical models:

- **SAS**
  1) Select ‘SAS (Glimmix)’ from the popup dialogue in the modeling panel. This will enable the ‘Generate files only’ checkbox (fig. 35) if it is not already enabled. A warning message will be displayed as well.



Location: /victer3/aa/pace_data/stat_run1

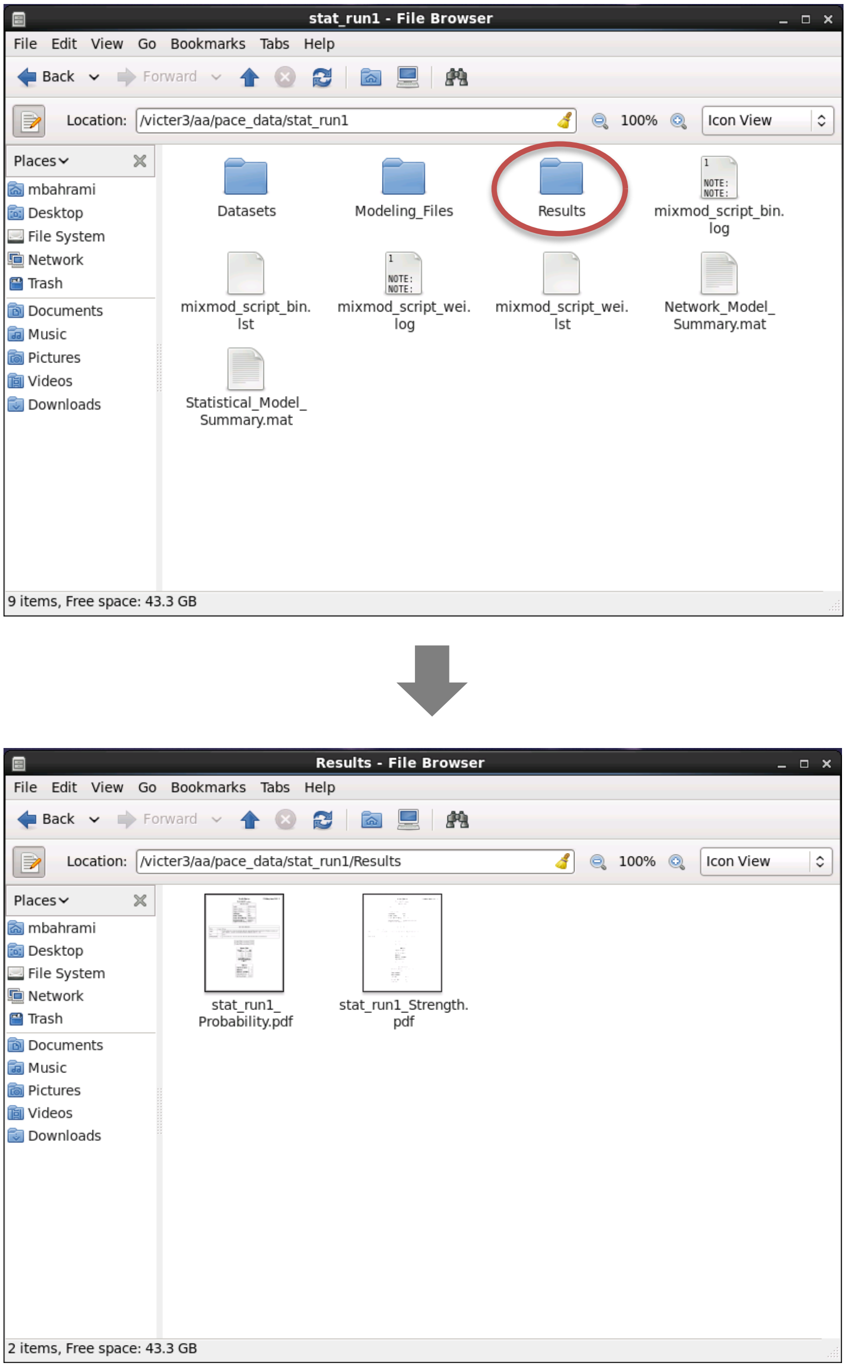
1 item, Free space: 43.3 GB

☐ Generate files only

Location: /victer3/aa/pace_data/stat_run1

9 items, Free space: 43.3 GB

Fig. 33 Running in Linux. Top window shows the output directory before running the model. The only existing file is ‘Network_Model_Summary’ which is the summary of the network model and would be copied here once you select the output directory. The bottom window shows the output directory after running the statistical model. Several files will be generated and saved here. If SAS is selected as the modeling software, the report generated by SAS will be saved in the output directory as well. But, this is not the case for R and Python.



stat_run1 - File Browser

Location: /victer3/aa/pace_data/stat_run1

Datasets
Modeling_Files
Results
mixmod_script_bin.log
mixmod_script_bin.lst
mixmod_script_wei.log
mixmod_script_wei.lst
Network_Model_Summary.mat
Statistical_Model_Summary.mat

9 items, Free space: 43.3 GB

Results - File Browser

Location: /victer3/aa/pace_data/stat_run1/Results

stat_run1_Probability.pdf
stat_run1_Strength.pdf

2 items, Free space: 43.3 GB

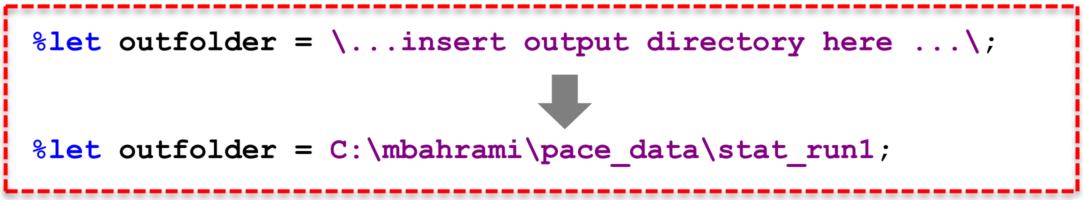
Fig. 34 Results for modeling the probability and strength of brain connections when using SAS. Results obtained from R and Python will be saved in the exact same directory with the exact same name as SAS.

2) Fill the ‘Generate files only’ checkbox, and click ‘Gen files only’ to generate modeling equations, options, and datasets. Generated files will be saved in the output directory (fig. 35).

3) Create a folder and name it ‘Results’ in the output directory.

4) Open ‘mixmod_script_bin’ (or ‘mixmod_script_bin_paired’ if you are doing a paired analysis) in SAS (fig. 36). This script is on ‘SAS_files/SAS_files_Windows’ in ‘WFU_MMNET’ folder. (Run SAS - > Click “File” - > Click “Open Program” - > Open ‘mixmod_script_bin’.)

5) Add the path of the output directory (the directory that you selected in the ‘Statistical_Model’ GUI) to the specified location. An example is shown below:



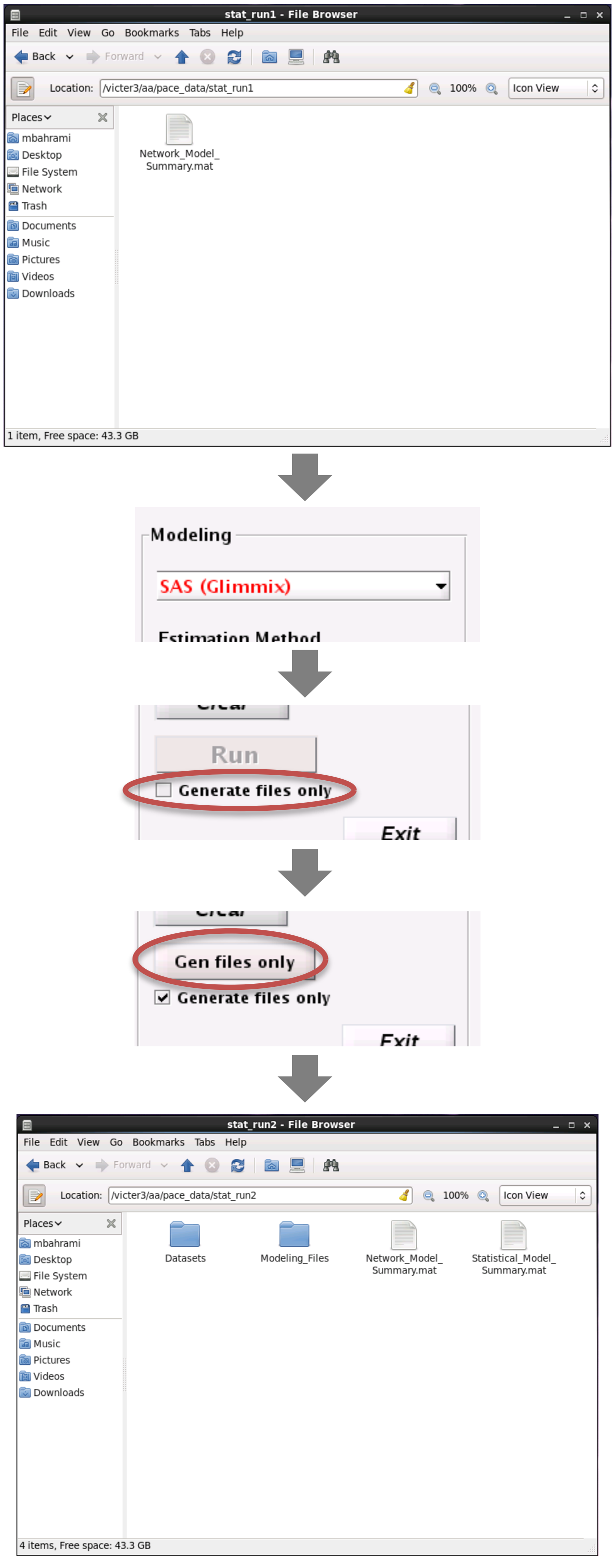
```
%let outfolder = \...insert output directory here ...\;

%let outfolder = C:\mbahrami\pace_data\stat_run1;
```

6) Save this change and run it after closing your Matlab window. You can save and run this by pressing ‘F8’ or using the submit icon (fig. 37).

The results for modeling the probability of brain connections will be saved in the ‘Results’ folder.

Now, you need to repeat steps 4-6 for the ‘mixmod_script_wei’ (or ‘mixmod_script_wei_paired’ if doing a paired analysis): Open ‘mixmod_script_wei’ in SAS in the same way that you opened ‘mixmod_script_bin’; Add the output directory in the exact same way, save it, and run it. The results for brain connection strength will be saved in the ‘Results’ folder.



stat_run1 - File Browser

Location: /victer3/aa/pace_data/stat_run1

Network_Model_Summary.mat

1 item, Free space: 43.3 GB

Modeling: SAS (Glimmix)

☐ Generate files only

☑ Generate files only

stat_run2 - File Browser

Location: /victer3/aa/pace_data/stat_run2

Datasets

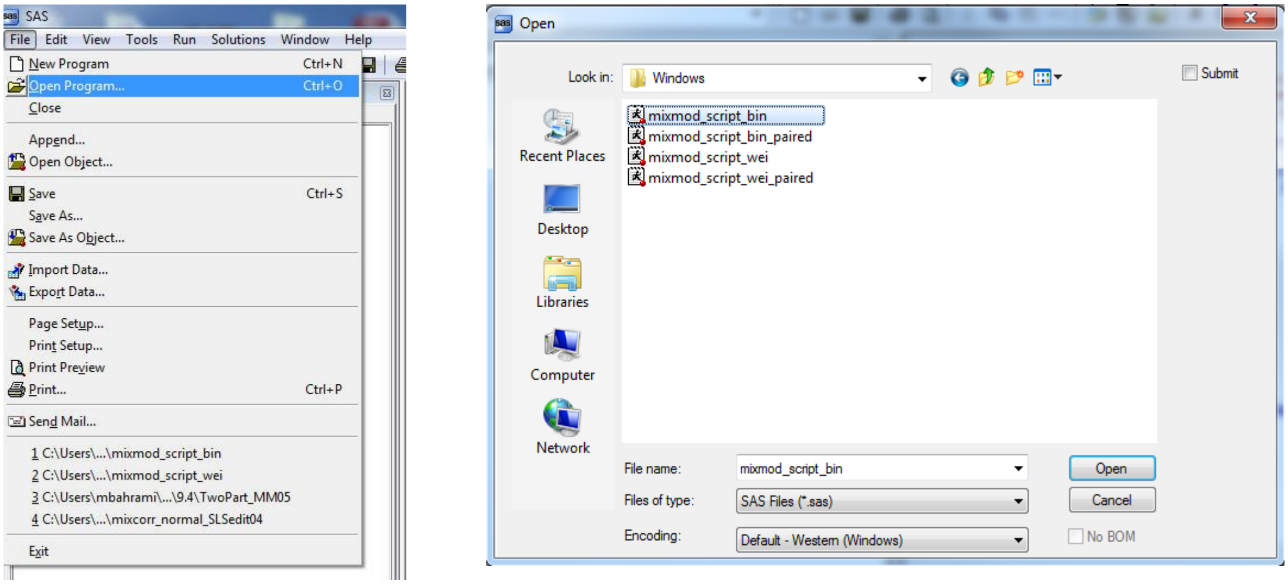
Modeling_Files

Network_Model_Summary.mat

Statistical_Model_Summary.mat

4 items, Free space: 43.3 GB

Fig. 35 Generating modeling files. Top and bottom windows show the output directory before and after generating files, respectively. These files will be used by SAS in Windows to fit the statistical models.



Look in: Windows

File name: mixmod_script_bin

Files of type: SAS Files (*.sas)

Encoding: Default - Western (Windows)

Fig. 36 Openinig 'mixmod_script_bin' in SAS.

Fig. 37 Running the 'mixmod_script_bin' script in SAS

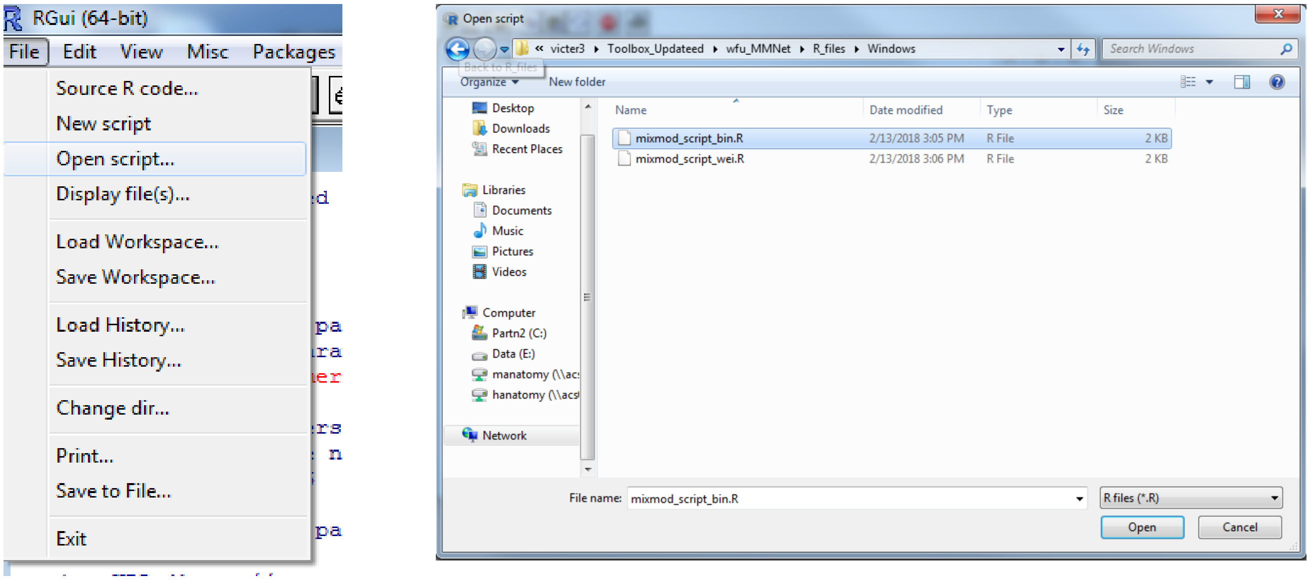
- **R**

1) Open R, and install 'lmerTest' package. You can install this package by typing "install.packages('lmerTest')" in the R console and selecting a CRAN mirror. (> install.packages('lmerTest'); You can also directly define the mirror. (e.g., > install.packages('lmerTest', repos='http://cran.us.r-project.org'))).

2) Open ‘mixmod_script_bin.R’ in R (fig. 38). This script is on ‘R_files\Windows’ in ‘WFU_MMNET’ folder (Run R - > Click on “File” - > Click on “Open script…” - > Open ‘mixmod_script_bin.R’).

3) Add the output directory (The output directory which you selected in ‘Statistical_Model’ GUI) in the specified location. An example is shown below. Note that R ignores the first backslash (\); so, you need to define your path with two backslashes for a single backslash. You can add your path with slashes as well.

```
out_fold_dir <- c(' ... \\... insert output directory here ...\\ ...');
⬇
out_fold_dir <- c(' C:\\mbahrami\\pace_data\\stat_run1');
```



Name	Date modified	Type	Size
mixmod_script_bin.R	2/13/2018 3:05 PM	R File	2 KB
mixmod_script_wei.R	2/13/2018 3:06 PM	R File	2 KB

File name: mixmod_script_bin.R

Fig. 38 Opening ‘mixmod_script_bin.R’ in R.

4) Save the change and run the script after closing the Matlab window (you should select all lines) :

Press ‘Ctrl+A’ -> press ‘Ctrl_R’ or ‘F5’

The result for the probability dataset will be saved in the ‘Results’ folder in the output directory.

Repeat steps 2-4 for the ‘mixmod_script_wei.R’ to model the strength dataset:

1) Open ‘mixmod_script_wei.R’ in R. This script is on ‘R_files\Windows’ folder (Run R - > Click “File” - > Click “Open script…” - > Open ‘mixmod_script_wei.R’.)

2) Add the output directory in the exact same way as you did for the probability dataset.

3) Save the change and run the script (after closing the Matlab window).

The result for the probability dataset will be saved in the ‘Results’ folder in the output directory.

- **Python**

  Python is usually installed on Linux by default. We suggest not using Python for the reasons mentioned in the paper. But, if you wish to use Python you should use the Python installed in Linux as the one for Windows is not provided here.

5 Acknowledgement

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