Software Tutorial

'Neuropathological Function Estimations': A User-Friendly Module for Analyzing Neural Activity in Neurological Disorders

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Instructions for installation and use System requirements:

☐ The software has been tested on MATLAB (versions: R2021b, R2023b, R2024a) and as a standalone application on Windows, Linux, and macOS.

☐ MATLAB Runtime is required to run the GUI (see **Installation guide**).

Installation guide:

Instructions to install:

☐ **For Windows**:

1) Navigate to the folder where the App Installer is located.

2) Double-click on MyAppInstaller_web.exe.

3) Choose the locations where to install the software and MATLAB Runtime and follow the on-screen instructions.

☐ **For macOS**:

1) Navigate to the folder where the App Installer is located.

2) Run the App Installer:

- Open the terminal and execute the following command:

open /path/to/your/appinstaller/folder/MyAppInstaller_mcr.app

3) Choose the locations where to install the software and MATLAB Runtime. Note: some mac systems may deny external applications to run. In that case, please follow these steps:

1) Open the Terminal or navigate to the folder where the App Installer is located.

2) Execute the following command:

chmod –R 755 /path/to/your/appinstaller

- In your path, if there are any spaces in the folder names, replace the spaces with (\ ).

3) Double-click on MyAppInstaller_mcr:

- A prompt will appear saying the app cannot be opened because the developer is not verified.

- Go to Settings > Privacy & Security. Find the message about the app and click Open Anyway to allow it to launch.

- A prompt will appear asking if you are sure you want to open the app despite the developer not being verified.
- Select Open Anyway to launch the app.

4) Choose the locations and download MATLAB Runtime and the software.

 For Linux:

1) Navigate to the folder where the App Installer is located.
2) Double-click on MyAppInstaller_web.install.
3) Choose the locations where to install the software and MATLAB Runtime and follow the on-screen instructions.

Typical install time:

 The typical installation time on a "normal" desktop computer ranges from **5 to 15 minutes**, depending on system performance and available resources.

Demo:

Instructions to run on data:

 For Windows:

1) Navigate to the directory where the software is located.
2) Run the application:
   - Double-click   neuropathological_function_estimations.exe   to launch the software.

 For macOS:

1) Navigate to the folder where the software is located.
2) Run the application:
   - Open a terminal and execute the following command to launch the software.

   open /path/to/your/app/folder/neuropathological_function_estimations.app

For Linux:

1) Navigate to the folder where the software is located.
2) Run the application:

- Open a terminal and execute the following command to launch the software.

./run_neuropathological_function_estimations.sh

/path/to/your/runtime/folder

For illustrative examples, please refer to **A comprehensive step-by-step guide to utilizing the toolbox** along with the example data provided with the software.

How to run the software on new data:

☐ When you open the software, you will be prompted to upload four files: connectivity, pathological factors, functional indicators, and surrogate optimization intervals (please check that the format of files aligns with the provided examples). Then, you will be asked to enter the cohort and the subject, as well as the required values. Note that you can always modify the parameters and values by choosing to enter a custom value. Lastly, you will be invited to choose the location where you would like to save your results, (optionally) check for errors and press RUN to start the calculations. For more information, please see **A comprehensive step-by-step guide to utilizing the toolbox.**
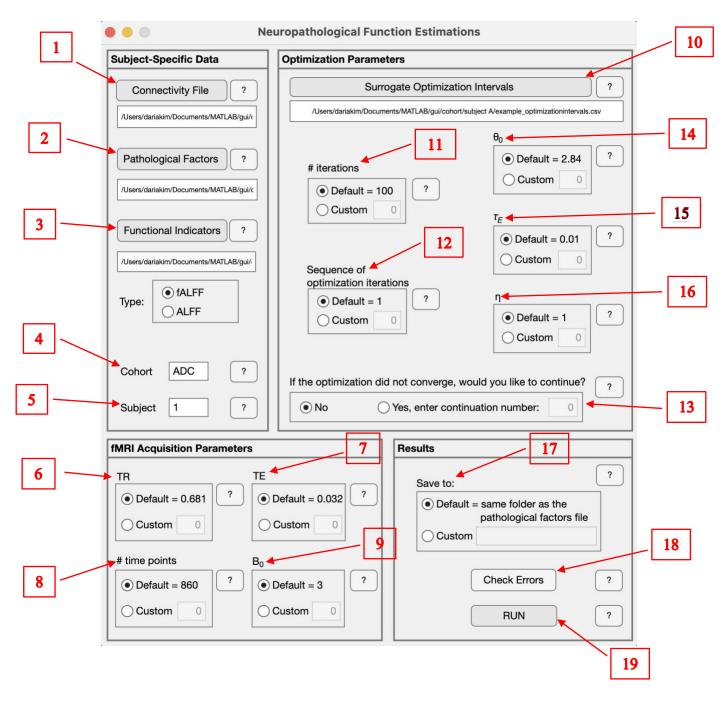
Expected output:

☐ The software opens a window with a summary of results, containing estimated pathological influences, objective function value at the solution, and the reason why the optimization algorithm stopped. It also creates two files: a .mat file and .csv file that contain all the information about your parameter estimations results. For more information, please see **A comprehensive step-by-step guide to utilizing the toolbox.**

Expected run time for demo on a "normal" desktop computer:

☐ Here is the expected run time based on trials with example data and default parameters:

- **Windows**: On Intel64 Family 6 Model 186 Stepping 2 GenuineIntel @ 2.2 GHz, 16 GB Total Physical Memory: ~1h/100 iterations
- **macOS**: On Apple M2, @ 3.5 GHz, 8 GB Total Physical Memory: ~1h20min/100 iterations
- **Linux**: On Intel(R) Core(TM) i7-9700K CPU @ 3.6 GHz, 32 GB Total Physical Memory: ~ 30min/100 iterations

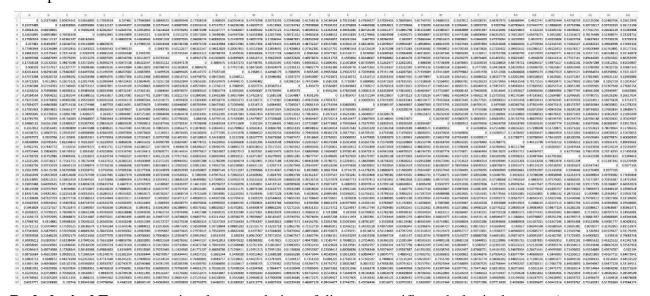# A comprehensive step-by-step guide to utilizing the toolbox

Legend:

Subject-Specific Data:

1) **Connectivity File**: table/matrix representing the connections between different brain regions. Each value in the matrix corresponds to the strength of a connection between two regions and is typically in the [0,1] range. Please ensure the file you select is a .csv file.

   This input is required. Press on the button to enter the address to the file.

   Example:

2) **Pathological Factors**: regional accumulation of disease-specific pathological agents (e.g., in Alzheimer's disease: Aβ, tau, and Aβ·tau imaged through PET). Please ensure that the file you select is a .csv file and that the columns refer to the number of factors and that the rows refer to the number of regions in your brain parcellation. Typically, each pathological factor is normalized to the [0,1] interval (by dividing by the maximum value across subjects and regions). This input is required. Press on the button to enter the address to the file.

   Example:

3) **Functional Indicators**: measurements of brain activity. You can currently choose between two resting-state fMRI indicators: ALFF (Amplitude of Low-Frequency Fluctuations) or fALFF (fractional ALFF). Please ensure that the file you select is a .csv file with one column – each row containing a regional value – and then choose whether it refers to ALFF or fALFF. This input is required. Press on the button to enter the address to the file.

Example:

4) **Cohort**: tag for organizing the results on your group of subjects. This input is required.

5) **Subject**: participant's identifier for organizing the results. This input is required.

fMRI Acquisition Parameters:

6) **TR (Repetition Time)**: time interval between two consecutive volume acquisitions in your rs-fMRI protocol. Please make sure that the value you enter is in seconds (e.g., 0.681 s) and is a positive value.

7) **TE (Time Echo)**: time interval between the RF pulse and the signal measurement. Please make sure that the value you enter is in seconds (e.g., 0.032 s) and is a positive value.

8) **# time points**: number of individual images (volumes) taken over time during a scan. Note that the entered value must be a positive number.

9) **B_0**: strength of the fMRI scanner's main magnetic field, measured in Tesla (T). Note that the entered value must be a positive number (e.g., 3 T or 1.5 T).

Optimization Parameters:

10) **Surrogate Optimization Intervals**: a .csv file containing surrogate optimization options such as the bounds and constraints. This input is required. Press on the button to enter the address to the file. The file should be organized as follows:

First column: lower bounds (lb), i.e., a lower constraint for the interval in which each factor's neuronal activity influences are searched for.

Second column: upper bounds (ub), i.e., an upper constraint for the interval in which each factor's neuronal activity influences are searched for.

Next N-factor columns [optional]: linear inequality matrix for establishing the relationships between the neuronal activity influences.

Last column [optional]: linear inequality constraints for the neuronal activity influences.

The program will search for a global minimum of the objective function in the region lb $<=$ x $<=$ ub, that satisfies the inequalities $A*x <= b$. For more details, see https://www.mathworks.com/help/gads/surrogateopt.html   Example:

	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P
1	-0.02	0.02	1	1	1	0.02										
2	-0.02	0.02	-1	-1	-1	0.02										
3	-0.02	0.02	1	1	-1	0.02										
4	NaN	NaN	1	-1	-1	0.02										
5	NaN	NaN	1	-1	1	0.02										
6	NaN	NaN	-1	1	1	0.02										
7	NaN	NaN	-1	1	-1	0.02										
8	NaN	NaN	-1	-1	1	0.02										
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11) **# iterations**: determines how many times the optimization algorithm will update the variables to improve the solution. A higher number of iterations makes it more likely for the optimization to converge, however it may take longer to complete. A lower number may produce results faster but could stop before finding an optimal solution. Note that the entered value must be a positive number.

12) **Sequence of optimization iterations**: creates an initial seed for the optimization, for reproducibility, and a tag for saving the results. We recommend exploring multiple sequences of random sample points to retain the best solution in terms of the objective function value as the optimization algorithm, surrogateopt, will perform different evaluations based on the seed value. Note that the entered value must be a positive number.

13) **Continuation number**: the trial from which you would like to resume the calculations. For example, if you ran the calculations once and the optimization did not converge, you would enter "1" in the textbox to pick up from the initial ("0") trial. The "Continuation" section is used if the optimization fails to converge at the initially entered number of iterations. The algorithm will start from the previously evaluated points Note that the entered value must be a positive integer.

15) $\square_0$: baseline neuronal firing parameter. Neuropathological alterations are modeled as linear deviations from this value by each pathological factor. Note that the entered value must be a positive number.

16) $\square_E$: time-constant controlling the decay of excitatory activity after stimulation (i.e., frequency of the neuronal oscillators). The inhibitory analogous parameter is twice the

selected value for $\square_E$. Please make sure that the value you enter is in seconds (e.g., 0.01 s) and is a positive value.

17) $\square$: global coupling strength scaling the anatomical connectivity matrix. Note that the entered value must be a positive number.

Results:

18) **Save to**: allows you to select the location where the results files will be saved. If you click on "Default", the results will be saved in the same location as your "Pathological Factors" file. If you click on "Custom", a window will open, allowing you to navigate through your folders and choose a specific location.

19) **Check Errors**: verifies that the files and values you have entered do not contain any errors. If an error is found, a window will open with an explanation of the issue, allowing you to correct it before proceeding. It is strongly recommended to click this button and review any errors before starting each trial.

20) **RUN**: The "Run" button starts the calculations once you have entered all required files and values and (optionally) checked for errors. After clicking this button, a progress bar will appear, showing the number of completed iterations. You may cancel the optimization at any point. The program will finish the current iteration and save the evaluations up to that point. The main results are printed on the screen.

Outputs:

The program will create two files for each sequence of optimization iterations:

a) A .mat file (tagged by cohort, subject, sequence of optimization iterations and continuation number) with the following variables:

ExcitabilityEffect: a [1 x number of factors] vector with the estimated pathological factors influences on neuronal activity.

ObjFuncVal: the objective function value at the estimated pathological influences.

exitflag: the reason why the optimization algorithm stopped.

output: a structure describing the optimization procedure *trials*: a structure containing all the evaluated points and the objective function values at those points.

For more information, please see https://www.mathworks.com/help/gads/surrogateopt.html.

b) A .csv file with the summary results at the last run trial of the optimization procedure.

For example:

	A	B	C	D	E	F
1	ExcitabilityEffect_Factor1	ExcitabilityEffect_Factor2	ExcitabilityEffect_Factor3	ObjFuncVal	exitflag	
2	-0.013560923	-0.000534117	-0.002807747	0.687509721	0	
3						