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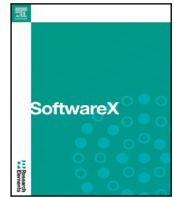
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Original software publication

eCOALIA: Neocortical neural mass model for simulating electroencephalographic signals

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ABSTRACT

This paper introduces eCOALIA, a Python-based environment for simulating intracranial local field potentials and scalp electroencephalography (EEG) signals with neural mass models. The source activity is modeled by a novel neural mass model respecting the layered structure of the neocortex. The whole-brain model is composed of coupled neural masses, each representing a brain region at the mesoscale and connected through the human connectome matrix. The forward solution on the electrode contracts is computed using biophysical modeling. eCOALIA allows parameter evolution during a simulation time course and visualizes the local field potential at the level of cortex and EEG electrodes. Advantaged with the neurophysiological modeling, eCOALIA advances the *in silico* modeling of physiological and pathological brain activity.

Code metadata

Current code version
Permanent link to code/repository used for this code version
Permanent link to Reproducible Capsule
Legal Code License
Code versioning system used
Software code languages, tools, and services used
Compilation requirements, operating environments & dependencies
Link to developer documentation/manual
Support email for questions

V1
<https://github.com/yymm2/eCOALIA>
GNU GENERAL PUBLIC LICENSE Version 3, 29 June 2007
git
python3.10 or 3.11
PyQt6>=6.6.1, Numpy>=1.23.5, Scipy>=1.10.1, matplotlib>=3.8.3, vtk>=9.2.6
<https://github.com/yymm2/eCOALIA/blob/main/README.md>
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1. Motivation and significance

Electroencephalography (EEG) recordings are invaluable tools in clinical and research settings, offering insights into the complexities of brain function. From clinical diagnosis of neurological conditions to monitoring brain activity during surgeries, EEG plays a crucial role in healthcare. Beyond medical applications, EEG is utilized in cognitive research to study attention, memory, and language while also serving as a cornerstone in the development of brain-computer interfaces and neurofeedback therapy. With its ability to map brain function and detect abnormalities, EEG stands at the forefront of understanding the human brain and advancing medical treatments. However, deciphering

the neurophysiological factors leading to electroencephalographic observations remains limited in humans due to the unavailability of simultaneous multiscale (from single cells to populations of cells) recordings. Computational modeling can fill this gap.

Whole-brain modeling has now become a standard method for *in silico* exploration of the healthy and pathological brain dynamics [1], and interpretation of the electrophysiological recordings. Whole-brain modeling tools have made predictions between the electrophysiological recordings and simulations based on the relation between excitation/inhibition [2], noise level, variations on whole-brain connectivity matrices [3], or give insights on functional activity and controllability [4–7]. However, they are limited in detailing neurophysiological factors leading to a typical type of transient activity.

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The most common whole-brain modeling and multimodel imaging platform is The Virtual Brain (TVB) [8,9]. More recently, a Python package was released for whole-brain modeling for simulating BOLD (blood-oxygen-level-dependent) signals [10]. These tools face two main issues. First, they assume that measured signals are either a direct reflection of the firing rate or membrane perturbations, while the layered structure of the neocortex imposes a more complex picture for the generation of electrophysiological signals. Second, they focus on simulating oscillatory activity without accounting for the physiology of transient signals, such as interictal epileptic discharges or event-related potentials. eCOALIA addresses these issues with a neurophysiologically plausible approach.

The groundbreaking nature of eCOALIA comes from the fact that it follows the layered structure of the neocortex and includes different inhibitory and excitatory neuronal populations. In addition to simulating cortical oscillations, the model simulates signal morphology of transient events (interictal epileptic discharges and event-related potentials) observed at the level of EEG electrodes [11]. The implementation of the neocortical layered structure allows distinguishing the layer-wise impact of the intra- and inter-regional (cortico-cortical and subcortico-cortical) interactions on the signal morphology. Therefore, eCOALIA can help to uncover the population-level physiological mechanism leading to observed events. This generic model can be developed further for patient-specific modeling and source localization of EEG signals [12], for generating a large amount of data for training artificial intelligence algorithms, and for optimization of brain stimulation technologies.

2. Software description

2.1. Model description

eCOALIA is based on a generic model of a neocortical region [11, 12], which accounts for excitatory and inhibitory neuronal subpopulations found in the neocortex. Each brain region is represented by the NMM given in (1) which is connected to other brain regions according to the structural network of the human brain; which combines axonal connections and propagation delays between regions. These connectivity matrices were generated using the Human Connectome Project database [13] with Diffusion Tensor Imaging and Tractography techniques. In particular, the connectivity matrices were created using data from 487 adult subjects. Fractional anisotropy values were extracted from each subject and then averaged. These connectivity matrices represent the strength of the connections between neural masses. The delay matrix, which represents the time it takes for signals to travel between regions, was calculated using a distance matrix multiplied by an average signal propagation velocity of 7.5 m/s [14].

The generic NMM accounts for the firing rate, synaptic kinetics and connectivity between the subpopulations. The post-synaptic potential (PSP) emitted by a single neuronal subpopulation i in a particular brain region K reads:

$$\ddot{y}_{K,i} = \frac{W_{K,i}}{\tau_{w_{K,i}}} \left(S \left(\sum_{K,j} C_{\{K,j\} \rightarrow \{K,i\}} y_{K,j} + \sum_{M,j} C_{\{M,j\} \rightarrow \{K,i\}} y_{M,j} \right) \right) \quad (1)$$

$$- \frac{2}{\tau_{w_{K,i}}} \dot{y}_{K,i} - \frac{1}{\tau_{w_{K,i}}^2} y_{K,i} + \frac{W_{K,i}}{\tau_{w_{K,i}}},$$

where $W_{K,i}, \tau_{w_{K,i}}$ are PSP amplitude and time constant, $C_{\{K,j\} \rightarrow \{K,i\}}$ is the coupling coefficient calibrating the afferent PSP from a subpopulation $\{K, j\}$ within the region K and $C_{\{M,j\} \rightarrow \{K,i\}}$ from a subpopulation $\{M, j\}$ within the region M . The sigmoidal transfer function $S(\cdot)$ relates the membrane perturbations of the subpopulation $\{K, i\}$ due to incoming signals to its firing rate. The NMM representing a neocortical column integrates two excitatory subpopulations (P (P) and P' ($P1$)), and four types of inhibitory interneurons (i.e., neuroglia form cells (NGFC), vasoactive intestinal peptide (VIP), parvalbumin (PV) and somatostatin (SST) positive interneurons), represented by six subpopulations (PV

(I1), PV' (I1b), SST (I2), VIP (I3), NGFC (I4) and NGFC' (I4)). The NMM representing the thalamus integrates one excitatory subpopulations (thalamic nucleus cells (TC)) and two types (slow and fast) of inhibitory neuronal subpopulations (reticular neurons ($RT1, RT2$)). All the subpopulations within the region K can receive inputs from the excitatory subpopulation of the region M (subpopulation P for the neocortical regions and subpopulation TC for the thalamus). The model is schematized in Fig. 1 and the model equations are given in Supplementary Material. The model equations are integrated using the Euler-Maruyama integration scheme [15] which is suitable when model incorporates statistical phenomenon.

2.2. Forward problem

The source activity (model output) is computed from the synaptic inputs targeting the layer V excitatory neurons. The macroscopic EEG signal is computed using the current dipole approximation [16,17]:

$$\phi(r) = \frac{1}{4\sigma\pi} \frac{\sum_{n=1}^M I_n^{axial}(t) \bar{d}_n \cos(\theta)}{|r - r_{source}|^2}, \quad (2)$$

where $I_n^{axial}(t) = \eta y(t)$ is an axial current along the vector \bar{d}_n at r_{source} and $\cos(\theta)$ is the angle between \bar{d}_n and the distance vector from the source and the electrode E. The parameter σ is the conductivity of the extracellular milieu and $\eta = 10^{-3} S$ is a conversion factor relating the PSP to postsynaptic current [18].

The simulated source activity defines a time series, S of $N_R \times T$ matrix, N_R being the number of brain regions and T the size of the time vector of the simulated activity. eCOALIA uses the Colin head model [19] and Desikan Atlas [20] with $N_R = 66$ neocortical regions, which are available on Brainstorm [21]. A lead field matrix A ($66 \times N_E$), generated from 3-layer Boundary Element Method (BEM) model [22, 23], was used to compute the projection of the source activity onto the N_E number of EEG contacts. The X ($N_E \times T$) matrix of simulated EEG signals is obtained by $X = AS$.

2.3. Software architecture

The software was designed to be used via a Python script that instantiate a Cortex model which represents the brain with its interacting regions each modeled by a NMM. The user can load a simulation file or can modify the cortex model directly. It is possible to integrate parameter variations along the simulation as well as stimulation signals that account for electrical stimulation therapies (deep brain stimulation or transcranial electrical stimulation). Some visualization tool can be used to display the source LFP and EEG time series and their spectrograms. A 3D view allows also to display the LFP onto a 3D mesh of the cortex. Parameter evolution and stimulation can be displayed as well. The use of scripts gives the flexibility for employing user-specific routines and fine tuning of the simulation.

The provided documentation for the software package offers comprehensive explanations and illustrative examples for using classes and functions. This includes instantiating of a model, tuning parameters, conducting simulations, and visualizing results.

The software package includes two scripts for performing single node ($N_{NMM} = 1$) and whole brain ($N_{NMM} = 67 - 1$ thalamic and 66 neocortical regions) simulations, and one script for creating a network from scratch:

- Single node simulation: a Python script is available on the repository to simulate a single node simulation starting from a previously saved simulation file. The node's parameters can be changed and an external stimulation can be applied. Displayed results of the source signal can be firing rates of the subpopulations, PSPs, LFP, or the mean membrane potential of the layer V excitatory neurons using the EEG_view module. Additionally, the time courses of parameter evolution and stimulation signals are

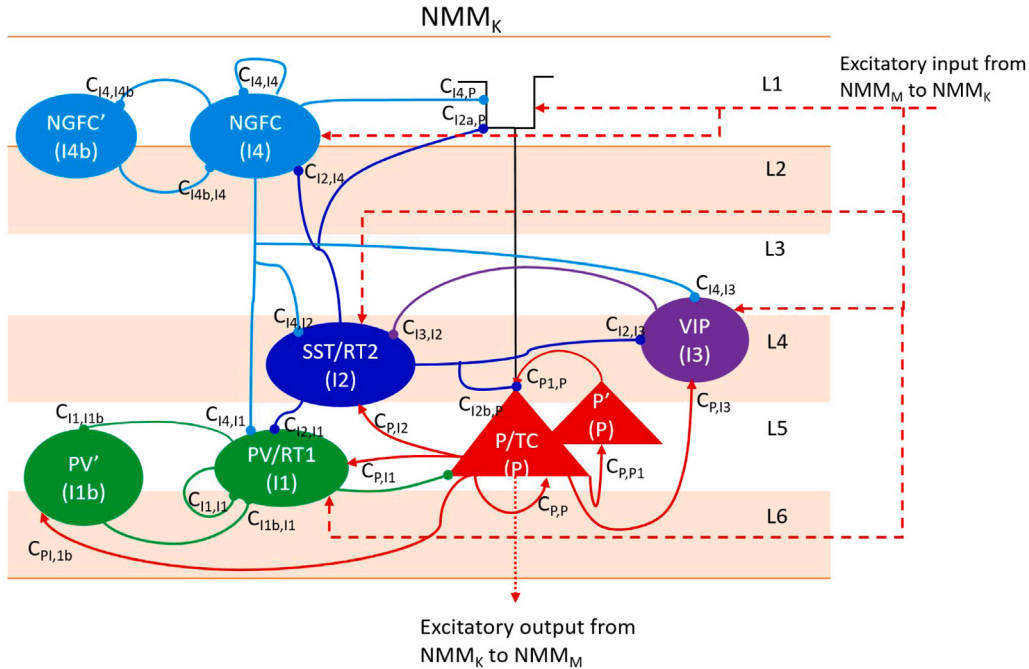


Fig. 1. Single NMM with the labels of the subpopulations and connectivity coefficients as coded in eCOALIA.

displayed in separate windows. The number of NMMs and their parameters, parameter evolution, and the parameters of the stimulation signal are saved in a user-named txt file, which can be loaded for a new simulation.

- Whole-brain simulation: a Python script is available on the repository to simulate 67 nodes starting from a previously saved simulation file including parameter sets and evolutions, coupling matrices, and stimulation. After loading the saved simulation files, the script can be modified to include parameter variations and stimulation signals on desired nodes. Simulated network activity is projected to scalp electrodes. In this projection the first node represented the thalamus was excluded, since it is not considered in the lead field matrix.

After solving the system of differential equations, six different displays appear: time courses and spectrogram of LFP signals, parameter evolution, stimulation, and the time courses of EEG signal, as well as a spatial projection of the source (LFP) signals onto the cortex 3D mesh.

As it is for the single node simulation, the whole-brain simulation can be saved in a txt file, which can be loaded for a new simulation later on.

- Network from scratch: a network of NMMs can be created and saved for further simulations by defining the number of NMMs, the connectivity and delay matrices, their parameter values and evaluations, and stimulation signals. Similar to single node simulation, results of the numerical integration, parameter evaluation, and stimulation signals can be displayed. While eCOALIA uses by default the Colin head model, the Desikan atlas, and lead field matrices for 66 cortical regions, the user can replace them with other head models, brain atlases, and lead field matrices.

2.4. Software functionalities

In this section we introduce briefly the functionalities of eCOALIA. Implementation details are given in the developer documentation (see “Code metadata”).

2.4.1. Parameter exploration

The parameter evolution module enables the analysis of the model’s dynamics in response to parameter variations. Users have the flexibility to define a series of temporal points corresponding to specific parameter values in a numpy list and choose the interpolation technique to infer parameter values throughout the specified time span.

2.4.2. Stimulation

In order to mimic the impact of a certain type of brain stimulation (e.g. transcranial electrical stimulation), eCOALIA includes a stimulation module. The stimulation module enables applying an external stimulation to a single NMM or concurrently to multiple ones. A stimulation signal perturbs the membrane of the subpopulations of the NMMs if it is applied before the sigmoid functions or the synapses if it is applied after the sigmoid functions. The impact of the stimulation signal is scaled to differentiate the stimulation impact on the subpopulation. The stimulation signal can take a diverse range of forms (including sinusoidal, square, sawtooth, triangular, ramp, chirp, or mono/biphasic pulses). Each form has different parameters, such as amplitude, frequency, start time, and end time, that can be adjusted (Table 1) Furthermore, different types of stimulation signals can be combined if applied on the same NMM to investigate potential synergistic effects.

2.4.3. Selection of the scalp EEG

The scalp EEG signal is computed by solving the forward problem, which corresponds to the projection of the source activity of size $N_R = 66$ onto the N_E number of scalp EEG contacts (Section 2.2). Since the real EEG caps that are available to clinicians and researchers have different numbers of contacts, the eCOALIA user may want to develop pipelines including direct comparison between the simulation results and real recordings. For this, eCOALIA provides 8 different lead field matrices that correspond to artificial EEG caps containing different number of electrodes ($N_E = \{21, 32, 65, 110, 131, 200, 256, 257\}$).

Table 1
Stimulation forms and required parameters.

Type of the stimulation	Required parameters
For all types	Starting time, end time
Constant	Amplitude
Sinus, Square, Sawtooth, Triangle	Amplitude, frequency, phase
Ramp	Starting amplitude, end amplitude
Sinus Ramp	Starting amplitude, end amplitude, frequency, phase
Square Pulse Biphasic	Amplitude, frequency, phase, pulse width
Chirp	Amplitude, starting frequency, end frequency, phase
Chirp Pulse	Amplitude, starting frequency, end frequency, phase, pulse width
Chirp Pulse Biphasic	Amplitude, starting frequency, end frequency, phase, pulse width
Square Pulse Rand	Amplitude, frequency, phase, pulse width
Square Pulse Biphasic Rand	Amplitude, frequency, phase, pulse width

2.4.4. Displaying source signal on neocortex

The Source View window projects the source activity on the cortex model and displays the EEG contacts with their names around the cortex model. The source activity is highlighted with a color code computed from the energy in the frequency domain (delta, theta, alpha, beta, and gamma bands) or amplitude domain (maximum, mean, and root mean square (RMS)). Time evaluation of the source activity within a sliding window defined by the user can be visualized by pressing the play button. This evaluation is performed within a sliding window defined by the user, with the default being 1 s. The Source View window contains sliding bars that allow the user to adjust transparency and brightness. Additionally, the user can select from a variety of color maps.

3. Illustrative examples

Usage of the software package is illustrated with two examples of whole-brain simulation. The simulation files of these examples are available on the GITHUB repository. The parameter sets are given in Supplementary Material.

Fig. 2 demonstrates a whole-brain simulation of a typical epileptic discharge recorded during interictal periods (outside of seizures). In this example, epileptic activity is associated with the right-precentral (r-PREC) region, as shown on LFP and Source View windows. The source signal is projected on 32 scalp-EEG channels as represented by markers positioned around the cortex. We can appreciate the large amplitude signals on the contacts closer to the r-PREC region, namely Cz, F4, FC6, FC2 C4, and CP2, as it can be verified.

The second example is a whole-brain simulation of a resting state and eyes-closed alpha band activity under healthy conditions (Fig. 3). In this example, parameters of the left and right occipital lobes are changed in $t = [2, 7]$ seconds to mimic the transition from resting state to eyes-closed alpha-band activity. The parameter evolution is visualized in the Parameter Evolution window. Notice that in this example we used an alpha-band filter and the coolwarm color code while demonstrating the alpha-band activity on the head model. The source signal is projected on 32-EEG channels.

4. Impact

Whole-brain modeling plays a key role in the discovery and analysis of electrophysiological signals [8–10,22]. Despite this importance, modeling the morphology of electrophysiological signals has been less of a concern of the whole-brain modeling tools.

To address this challenge, we present eCOALIA, a Python-based modular software. eCOALIA integrates a neurophysiologically plausible model of a neocortical column that interacts via human connectome at the macroscale. Parameter variation functionality allows the user

to explore the parameter space of eCOALIA. Stimulation signals can be used to test how electrical stimulation can interact with cortical activity. 2-dimensional time and 3-dimensional spatial representations of simulated activity simplify the interpretation of simulations. Projection on EEG electrodes with different numbers of contacts can facilitate the comparison between the simulations and available recorded signals. The modular structure of the software facilitates further implementations and explorations.

Quantifying the similarity between simulated and real EEG signals is challenging due to asynchronous event timing, limiting the accuracy of classical methods like cross-correlation. Although, the current version of the software lacks direct tools for comparing real and simulated EEG signals, visual inspection can still be useful. Additionally, the built-in spectrogram tool allows frequency-based comparisons, helping assess whether both signals exhibit similar rhythms and patterns. Further analytical methods, such as coherence analysis or phase locking value, could improve this comparison which would be implemented in future.

Different than the earlier version of the software [22], which simulates healthy brain activity [14], eCOALIA can simulate both healthy and pathological brain dynamics [12]. Therefore, it enables studying the impact of perturbations caused by pathological activity on healthy ones, which is an asset for brain research. By providing an *in silico* ground truth, eCOALIA can be used to develop inverse solution methods for estimating cortical-level sources [14,24] or as a data-generator for training machine learning algorithms [25].

5. Conclusions

We introduced the eCOALIA software for neurophysiologically plausible modeling of whole-brain dynamics. Thanks to the biophysical solution of the forward problem, eCOALIA can simulate EEG signals by respecting the observed morphology of pathophysiological events. eCOALIA advances the realism of simulated EEG signals, interpretation of recordings, and patient-specific whole-brain modeling.

CRedit authorship contribution statement

Elif Köksal-Ersöz: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Maxime Yochum:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Data curation, Conceptualization. **Pascal Benquet:** Writing – review & editing, Project administration, Conceptualization. **Fabrice Wendling:** Writing – review & editing, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Fabrice Wendling reports financial support was provided by European Research Council. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

<https://github.com/yymm2/eCOALIA>.

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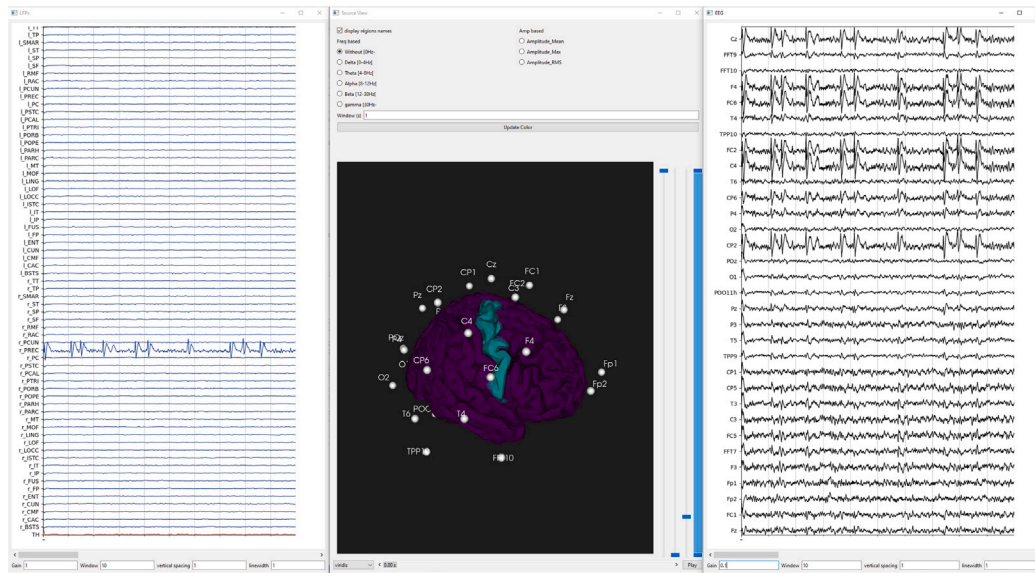


Fig. 2. Whole-brain simulation of epileptic discharges. Left: Source activity given by local field potential. The right-precentral (r-PREC) region undergoes spike-and-wave discharges. Middle: Project of the source activity on the head model. The green region undergoes spike-and-wave discharges. Right: EEG signals measured by the scalp electrodes shown on the left panel. Corresponding simulation files is available on the code repository (“Code metadata table”) [src/SaveFiles/67NMM_spikewave_2.txt](https://doi.org/10.1016/j.softx.2024.101924). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

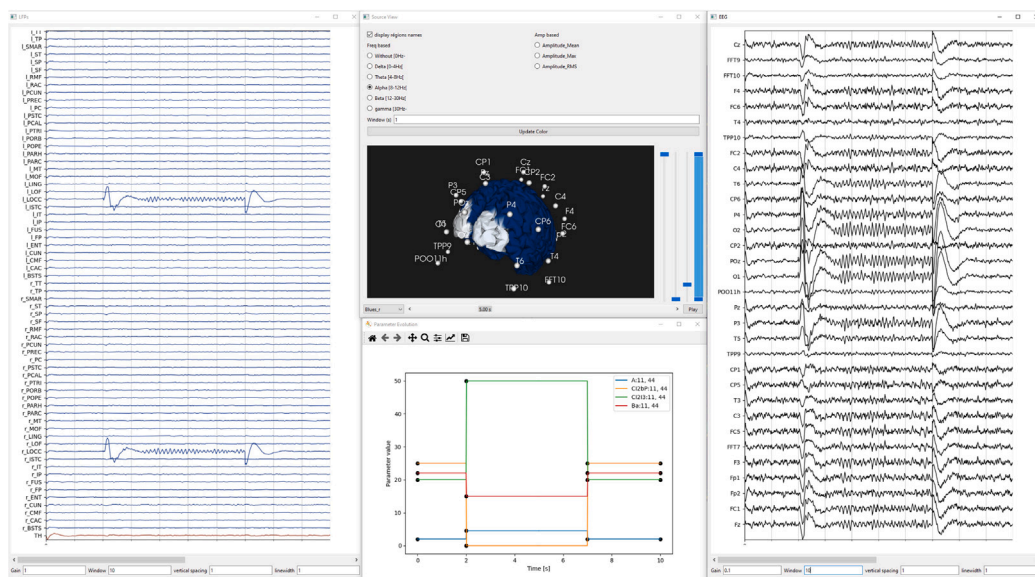


Fig. 3. Whole-brain simulation of alpha-band oscillations. Left: Source activity given by local field potential. The left occipital lobe (l-LOCC) and the right occipital lobe (r-LOCC) undergo alpha-band oscillations in $t = [2, 7]$ seconds. Top middle: Project of the source activity on the head model with the occipital lobes in light blue. Bottom middle: The corresponding parameter evolution yielding these alpha-band activities. The legend indicates the indexes of the NMMs of which parameters were varied. In this example, the parameters $A_{12b,p}$, $C_{12,13}$, and B_a of the 11th and 44th NMMs were modified. Right: EEG signals measured by the scalp electrodes shown on the left panel. Corresponding simulation files is available on the code repository (“Code metadata table”) [src/SaveFiles/67NMM_resting_alpha_4.txt](https://doi.org/10.1016/j.softx.2024.101924). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Appendix A. Supplementary data

Supplementary material related to this article can be found online at <https://doi.org/10.1016/j.softx.2024.101924>.

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