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Summary

This repository contains MATLAB and NEURON code and data (**Optimization** folder) as well as experimental measurement data (**Implementation** folder) for the following article:

- Wang B, Zhang J, Li Z, Grill WM, Peterchev AV, Goetz SM. Optimized Monophasic Pulses with Equivalent Electric Field for Rapid-Rate Transcranial Magnetic Stimulation. Journal of Neural Engineering 2023; 20: 036027. https://doi.org/10.1088/1741-2552/acd081.

The code performs waveform optimization for transcranial magnetic stimulation (TMS) and simulates neural activation using several models to obtain thresholds of the optimized waveforms. The experimental data include measured coil current, coil voltage, and the induced electric field of the optimized waveforms implemented with a modular pulse synthesizer TMS device. The code also performs visualization and generates most of the figures in the article, where detailed descriptions of the results are given.

The code for performing simulations using the single- and two- compartment models is implemented in MATLAB according to the following articles:

1. McIntyre CC, Richardson AG, Grill WM. Modeling the Excitability of Mammalian Nerve Fibers: Influence of Afterpotentials on the Recovery Cycle. Journal of Neurophysiology 2002; 87: 995–1006. https://doi.org/10.1152/jn.00353.2001
2. Mainen ZF, Sejnowski TJ. Influence of dendritic structure on firing pattern in model neocortical neurons. Nature 1996; 382: 363–6. https://doi.org/10.1038/382363a0

The code for performing simulations using Blue Brain neuron models is adapted from the following articles:

3. Aberra AS, Wang B, Grill WM, Peterchev AV. Simulation of transcranial magnetic stimulation in head model with morphologically-realistic cortical neurons. Brain Stimulation 2020; 13: 175–89. https://doi.org/10.1016/j.brs.2019.10.002.
4. Aberra AS, Peterchev AV, Grill WM. Biophysically Realistic Neuron Models for Simulation of Cortical Stimulation. Journal of Neural Engineering 2018; 15: 066023. https://doi.org/10.1088/1741-2552/aadbb1.
5. Wang B, Aberra AS, Grill WM, Peterchev AV. Responses of Model Cortical Neurons to Temporal Interference Stimulation and Other Transcranial Alternating Current Stimulation Modalities. Journal of Neural Engineering 2023; 19: 066047. https://doi.org/10.1088/1741-2552/acab30.

Triangular optimal waveforms from previous work are recreated under the Creative Commons Attribution License Waveform from the following article:

6. Goetz SM, Truong CN, Gerhofer MG et al. Analysis and Optimization of Pulse Dynamics for Magnetic Stimulation. PLOS ONE 2013; 8: e55771. https://doi.org/10.1371/journal.pone.0055771

File and data organization

Color code: **folders**; key code and data; auxiliary code and data; visualization code; parameters.

- **Optimization** folder: contains the MATLAB optimization and NEURON simulation code and relevant results in binary and text formats (.txt files) and compiled MATLAB format (.mat files).
  - step1_opt_Ivec_RMSE_E.m: first/optimization step. Generates optimized waveforms without amplitude adjustment saved to **Optimization**/opt_RMSE_E_%s_dt_%d_us.mat, where the string is mp, hs, or bp for monophasic, half-sine, or bipolar waveforms, respectively, and the integer is the time step (in microseconds) used for the optimization (5, 10, or 20 for mp, and 10 for hs and bp).
  - coil_loss_I.m: cost function of waveform optimization. Calculates coil loss for an input of coil current waveform. Used by step1_opt_Ivec_RMSE_E.m.
  - RMSE_abs_I.m: constraint of waveform optimization. Root-mean-square error of corresponding electric field for an input of coil current. Used by step1_opt_Ivec_RMSE_E.m.
  - TMS_wave.m: reads TMS waveforms from MagproX100_TMS_waves.mat. Used by step1_opt_Ivec_RMSE_E.m.
  - MagproX100_TMS_waves.mat: recorded electric field waveforms of monophasic, half-sine, or bipolar TMS pulses.
  - step2_simple_models.m: performs simulations of simple neuron models [1-2] for conventional pulses and optimized waveforms generated by first step. Appends simulation data to **Optimization**/opt_RMSE_E_%s_dt_%d_us.mat.
  - step2_BlueBrain_models.m: performs simulation of Blue Brain neuron models [3-5] for conventional pulses and optimized waveforms generated by first step. Results stored in **Optimization**/opt_RMSE_E_%s_dt_10_us_BB_%d.mat, where the string is mp, hs, or bp, and the integer is the cell ID number of the models. Layer 2 pyramidal cells: 1–5; Layer 4 interneurons: 11–15; Layer 5 pyramidal cells: 16–20.
  - step2_BB_MP_10us.slurm: sample script for running Blue Brain neuron simulations with conventional monophasic and optimized monophasic-equivalent pulses on a compute cluster. Adjust MATLAB path as needed.
  - Goetz13_opt_simple_models.m: performs simulation of simple neuron models [1-2] for optimized waveforms from previous work [6]. Waveforms are stored in **Optimization**/Goetz2013_prev_opt.mat and simulations results are appended to the same file.
  - Goetz13_opt_BlueBrain_models.m: performs simulation of Blue Brain neuron models [3-5] for optimized waveforms from previous work [6]. Results stored in **Optimization**/Goetz2013_prev_opt_%d.mat.
  - add_rm_paths.m: setting up paths for simulations of Blue Brain neuron models. Used by step2_BlueBrain_models.m and Goetz13_opt_BlueBrain_models.m.
  - find_threshold_BB.m: threshold search function for Blue Brain neuron models. Used by step2_BlueBrain_models.m and Goetz13_opt_BlueBrain_models.m.
  - plot_step2_results.m: performs scaling of the optimized waveforms and generates panels B of Figures S2, S12, and S13. Appends scaled waveforms and additional data to **Optimization**/opt_RMSE_E_%s_dt_10_us.mat. All three types of waveforms.
  - plot_opt_Ivec_RMSE_E.m: generates panel A of Figures S2, S12, and S13. After running plot_step2_results.m, running this function also generates corresponding panel C and entire figure. All three types of waveforms.
  - plot_opt_Ivec_RMSE_E_dt.m: generates Figure S1. Monophasic waveforms only.

- plot_opt_Ivec_RMSE_E_subset.m: generates panel A of Figure 2. Monophasic waveforms only.
- plot_step2_results_subset.m: generates panel B of Figure 2. After running plot_opt_Ivec_RMSE_E_subset.m, running this function also generates the entire Figure 2. Monophasic waveforms only.
- plot_step2_MP_vs_BP.m: generates Figure S5. Combines data from all waveforms.
- plot_step2_MP_vs_BP_subset.m: generates Figure 4. Combines data from all waveforms.
- plot_AP_delay.m: generates Figures S3. Monophasic waveforms only.
- plot_final_RMSE.m: generates panel A of Figure S4. Monophasic waveforms only.
- plot_runtime.m: generates Figures S6. Monophasic waveforms only.

- **Results** folder: contains optimization and simulation results. Total of 66 files.
  - opt_RMSE_E_%s_dt_%d_us.mat: results of waveform optimization (generated by step1_opt_Ivec_RMSE_E.m), simple neuron model simulations (appended by step2_simple_models.m), and waveform amplitude adjustment (appended by plot_step2_results.m). The string is mp, hs, or bp for monophasic, half-sine, or bipolar waveforms, respectively, and the integer is the time step (in microseconds) used for the optimized (5, 10, or 20 for mp, and 10 for hs and bp). Total of 5 files.
  - opt_RMSE_E_%s_dt_10_us_BB_%d.mat: compiled simulation results of the Blue Brain neuron models (generated by step2_BlueBrain_models.m). The string is mp, hs, or bp, and the integer is the ID number of the cell models. Layer 2 pyramidal cells: 1–5; Layer 4 interneurons: 11–15; Layer 5 pyramidal cells: 16–20. Total of 45 (3×15) files.
  - Goetz2013_prev_opt.mat: triangular optimal waveforms from previous work [6] and results of simple neuron model simulation results (appended by Goetz13_opt_simple_models.m).
  - Goetz2013_prev_opt_%d.mat: compiled simulation results of the Blue Brain neuron models using triangular optimal waveforms from previous work [6] (generated by Goetz13_opt_BlueBrain_models.m).The integer is the ID number of the cell models. Total of 15 files.
- **Simple_Neuron_Models** folder: simulation code for single- and two-compartment models.
  - find_threshold.m: threshold search function for simple models.
  - tridiag.m: solves tri-diagonal system of cable equation.
  - stim_RMG.m: simulation routine for single compartment axonal node.
  - RMG_model.m: parameters of single compartment axonal node.
  - RMG.m: ion channel mechanisms of single compartment axonal node.
  - stim_Mainen.m: simulation routine for two-compartment cortical neuron model.
  - Mainen_model.m: parameters of two-compartment cortical neuron model.
  - Mainen_%s.m: ion channel mechanisms of two-compartment cortical neuron model. The string is Na, Kv, Km, KCa, and Ca for sodium, fast potassium, slow voltage-dependent potassium, slow calcium-dependent potassium, and calcium ion channels.
  - **Logs** folder: simulation logs. For optimized waveforms, the filename is in the form of log_%s_%s_%d_%d%s.txt, with the first string indicating model type (RMG or Mainen), second string describing waveform type (mp, hs, or bp), the numbers indicating the optimization parameters (1–5, for the five pulse duration and five RMSE constraints), and for bp waveforms an optional _rev suffix for reversed pulse direction. For conventional pulse shapes and optimized waveforms from previous work, the filename is in the form of log_%s_%s_%d.txt, with the first string indicating model type (RMG or Mainen), second string describing waveform type (TMS_mp, TMS_hs, TMS_bp, or prev_opt), and the number indicating the duration for conventional pulses (1–5, for the five pulse

duration used for the optimization) or ID of the previous optimized waveforms (1–3, for the three coil voltage constraints of 990 V, 1960 V, and 4800 V used in the previous work [6]).

- **BB_Utility_functions** folder: functions for running simulations using Blue Brain neuron models
  - cellmodelnames.m: cell name for a given cell ID.
  - default_v_inits.m: default transmembrane potential for a given cell.
  - output_morph_params.m: settings for morphological adjustment in the NEURON code.
  - MATLAB_NRN_interface.m: prepare and run NEURON simulations for activation threshold search and process data.
  - create_mat_data_folder.m: create folder for storing MATLAB data.
  - create_nrn_folder.m: create temporary folder for storing NEURON data.
  - save_data.m: save data obtained from activation threshold search.
  - nrn_vread.m: read binary file written by NEURON.
  - write_vector_bin.m: write binary file for NEURON.
- **BB_Neuron_Files** folder:
  - **cells** folder: contains the Blue Brain neuron models.
  - **Mod_files** folder: contains the membrane mechanisms .mod files.
  - **coords** folder: folder for writing the coordinates files of the neuron models.
  - init_MPSTMShoc: loading all hoc files to prepare the simulation.
  - defvars.hoc: definition of variables and objects.
  - O2d.hoc: 2d object array.
  - getParams.hoc: load parameters from files written by MATLAB code.
  - ssprocinit.hoc: steady state initialization of neuron transmembrane potential.
  - interp_coordinates.hoc: set coordinates and topology of neuron model.
  - cell_chooser.hoc: choose neuron model from library of cells.
  - edit_morphology.hoc: functions for modification of neural morphology.
  - myelin_biophysics.hoc: functions for adjusting the properties of myelin.
  - get_es.hoc: calculate extracellular potentials.
  - stim_wave_import.hoc: import stimulation waveforms of electric field and current injection.
  - saveDatavector.hoc: functions for saving vector(s).
  - threshold_finder.hoc: function for finding neural activation threshold.
  - init_save_record.hoc: functions for initializing objects for recording action potentials and transmembrane potential and for saving the results.
  - run_stim.hoc: function for running threshold searches.
- **BB_Data** folder: simulation results for Blue Brain neuron models
  - **L%d_%s_%d** folder: results for individual cell model, with the first number indicating the cortical layer, the string providing the specific model name (see **BB_Utility_functions/**cellmodelnames.m), and the last number specifying the clone number (1–5). The folders contain:
    - Threshold_orientation_map_%s_t_vecID_%d_per%d.mat: intermediate results of the simulations, compiling all threshold for a given combination of waveform (string: mp, hs, bp, or old_opt), pulse duration (ID 1–5, corresponding to the five pulse durations), and RMSE constraint (0.25,

0.5, 1, 2, and 4, as well as 0 for conventional pulses and optimized waveforms from previous work [6]). Total of 93 (3×5×6+3) files.

- The intermediate results (threshold orientation maps) consist of simulation results of 200 electric field orientations. The simulation logs (log.txt files) and results (data.mat files) of each orientation are saved in a separate subfolders which are generated during the simulation. These subfolders and their contents are not included in the repository due to the sheer number (18,600 subfolders per cell model) and redundancy of the data (contained in **Results**/opt_RMSE_E_%s_dt_10_us_BB_%d.mat and **L%d_%s_%d**/Threshold_orientation_map_%s_t_vecID_%d_per%d.mat).

  - **Figures** folder: figures and panels in .fig and .tif format.

- **Implementation** folder: contains the experimental recordings, and MATLAB code for data analysis and visualization.
  - **cvs** folder: contains recorded coil voltage, coil current, and electric field. Total of 26 (5×5+1) .csv files.
  - process_data_all.m: function to compile all recordings into Recording_processed.mat.
  - import_tek_4col.m: function importing individual .csv files.
  - process_CVS.m: function processing imported .csv data.
  - Recording_processed.mat: compiled and processed recording.
  - process_meta_data.m: process metadata about recording from Recordings_0628.xlsx and save to metadata.mat.
  - Recordings_0628.xlsx: metadata of recording files, and voltage of DC capacitors.
  - metadata.mat: processed metadata.
  - plot_recorded_waveforms.m: generates Figure S7 and S8.
  - plot_recorded_waveforms_subset.m: generates Figure 3.
  - plot_RMSE_recorded.m: generates panel B of Figure S4. After running **optimization**/plot_final_RMSE.m, running this function generates entire Figure S4.
  - plot_pulse_loss_energy.m: generates Figure S11.
  - plot_pulse_loss_energy_subset.m: generates Figure 5.
  - plot_FFT.m: generates Figures S9 and S10.
  - **Figures** folder: figures and panels in and .tif format.