PI(s) of MSM U01: Gianluca Lazzi, Theodore W. Berger
Institution(s): University of Utah, Salt Lake City, University of Southern California
MSM U01 Grant Number: GM104604
Title of Grant: Predictive Modeling of Bioelectric Activity on Mammalian Multilayered Neuronal Structures in the Presence of Supraphysiological Electric Fields

Model Credibility Plan – 2018 Update

Summary of project topic

The end goal of this multiscale modeling research is to bridge the gap existing between three-dimensional, full-wave, macro-modeling of electrical and magnetic biointeractions (global modeling) and cellular-level modeling strategies. This research effort aims to predict spatio-temporal distributions of active neurons based on current densities created by multi-electrode electrical stimulation, and dependent upon a set of "core models" of molecular (receptor-channel kinetics), synaptic, neuron, and multi-neuron activity. These models and their inputs and outputs must be integrated into a global model of the extracellular media/matrix including relevant multi-electrode arrays. Successful modeling at these levels will allow hypotheses about space-time patterns of electrical stimulation to produce predictions about the number and distribution of activated inputs (based on known spatial distributions of afferent axons). The linked molecular, synaptic, neuron, multi-neuron, and global model will provide the basis for emerging predictions of the spatio-temporal distribution of active neurons and thus, the spatio-temporal distributions of spike train activity that encode all information in the nervous system.

A. and B. List of planned actions outlined in Model Credibility plan and corresponding information gained

List of planned actions outlined in Model Credibility plan	Brief description of information gained by each credibility action
Systematic calibration and evaluation	**Development of scale-linking methodologies** The credibility of the methodology inherently relies upon (i) the accuracy obtained during the training phase of the model and the subsequent validation phase, and (ii) the resulting reduction in computational complexity. Our results show virtually identical results when comparing parametric (complex) models and their input-output equivalents. Model and methodology evaluations are performed on a daily and weekly basis. Quantitative evaluation of the effects of structural changes in the IO modeling methodology are ongoing. The measurable outcomes consist of (i) prediction accuracy in training and validation phases with respect to mechanistic model, and (ii) memory and CPU-bound computational loads. **Admittance Model (AM)-NEURON: Hippocampus Model** Without exception, all AM-NEURON analysis reported in recent publications, abstracts, or presentations is either supported with a thorough sensitivity analysis or validated with clear measures of error using experimental or analytically determined ground-truths [1-20]. Data were sourced from the literature or through complimentary experiments performed on rodents by members of the Berger lab. As a rule, these comparative data sources were declared alongside the analysis at the time and place of first presentation. **Large-Scale Model: Hippocampus** The large-scale model is calibrated at multiple scales (i.e. at synaptic, dendritic, neuronal and population levels) to ensure that the model can appropriately represent hippocampal function.
Parameters optimization	**Development of scale-linking methodologies** The optimization algorithm we use is gradient descent; the objective function aims at reducing the mean square error between the output of the complex mechanistic model and the one given by the reduced IO model in response to the same input data. Parameters calibration for every IO model consists of a training phase that inherently comprises the aforementioned optimization procedure. **Admittance Model (AM)-NEURON: Hippocampus Model** When calibrating the AM-NEURON model for predicting Dentate evoked potentials, a sophisticated multi-objective function was used to optimize stimulating parameters to find more ideal conditions for tissue-prosthesis interfaces [1-3,11-17]. **Large-Scale Model: Hippocampus** For model elements with few parameters, the bisection method is applied to determine the optimal parameter. This has been applied to optimize synaptic weights and time constants. The neuron model parameters are optimized using an evolutionary multi-objective optimization (EMOO) approach in which the various electrophysiological properties (e.g., threshold, resting membrane potential, fast afterhyperpolarization amplitude, etc.) are used as objectives by which the channel conductances are optimized. The parameters for the density distributions for axon arbors are obtained using a least-squares approach. At the network level, a grid-search is applied to search for the appropriate synaptic weight parameters to achieve the appropriate oscillation frequencies.

List of planned actions outlined in Model Credibility plan	Brief description of information gained by each credibility action
Documentation	**Development of scale-linking methodologies** Extensive description of the IO models structure and parameters is made available in the publications [21] and [22]. Notably, further generalization of the methodology will result in the release of code (and associated API/documentation) that may be applicable to a larger number of input-output pairs, which will result in broader appeal to a wider community. **Admittance Model (AM)-NEURON: Hippocampus Model** At present, models are primarily documented through papers, posters, and presentations that were mentioned previously. We plan on releasing more complete AM-NEURON models for public consumption and are anticipating to make this possible through (i) generalization away from strict dependencies on hardware resources that are likely prohibitive to other community members (e.g. large computing clusters) and (ii) generalization of models to make software valuable beyond simple recapitulation of our work but to facilitate development of novel models in support of a user's own work. Relating to the AM-NEURON model of extracellular electrical stimulation and recording of the hippocampus, https://www.bitbucket.org/ .git repositories have been established along with extensive instructions for proper installation of dependencies and effective use of the code. This tool allows for collaboration, version control, and simple open source distribution, which include various versions of the AM-NEURON software [1-17]. These repositories are being used jointly between the Lazzi and Berger labs, where each of these is either under active development, receiving finishing documentation, or undergoing testing. **Large-Scale Model: Hippocampus** Previous versions of the model have been documented in journal and conference publications. Due to the extensive amounts of code that is necessary to instantiate, test, and simulate the large-scale model, efforts are underway to format, streamline, and comment the code to facilitate the further development of the large-scale model internally but also be more accessible for use by the public.
Independent evaluation	**Development of scale-linking methodologies** For all projects, following generalization procedure mentioned above, code (with corresponding documentation and test data) will be sent out to third-party evaluators in accordance with NIH guidelines/instructions.
Model sharing and reuse	**Development of scale-linking methodologies** We believe all projects and associated methodologies may have a significant impact on the way multiscale modeling is currently performed; we consequently place a high importance on disseminating this technology and making sure it will be readily applicable to a broad community.

C. Actions and activities classified within the CPMS TSR framework

RULE	UPDATE FOR ACTIVITIES
Rule 1 – Define context clearly.	Aims to predict spatio-temporal distributions of active neurons based on current densities created by multi-electrode electrical stimulation, and dependent upon a set of "core models" of molecular (receptor-channel kinetics), synaptic, neuron, and multi-neuron activity
Rule 2 – Use appropriate data.	All data were generated using validated (and using detailed parametric models which structure and parameters values are published and shared)
Rule 3 – Evaluate within context.	All models are evaluated within their respective contexts and corresponding levels of granularity. Abstract models are data-driven models, i.e. parameters of the models are estimated while minimizing error between parametric (detailed and computationally complex) model and output of the abstract model.
Rule 4 – List limitations explicitly.	Mechanistic models drive their predictive powers from the test protocols with which they were initially calibrated and tested; significant variations in the simulation protocols may consequently affect model predicivity levels. Our input-output (data-driven) models perform best within training bounds, which are explicitly cited in the publications.
Rule 5 – Use version control.	Our group uses subversion versioning system. All changes to model structure and parameters values are recorded and kept track of.
Rule 6 – Document adequately.	Within the versioning system, all changes are documented in human-readable text.
Rule 7 – Disseminate broadly.	Detailed models out of prototyping phase and used for development of input-output models were published and their code shared on open-source database (ModelDB). IO model structure was also described in multiple publications. Other IO models will be similarly shared as they become available.
Rule 8 – Get independent reviews.	As part of the BioMedical Simulation Resource (BMSR), our research directions and efforts undergo third-party evaluation. More granular models evaluation will take place for the renewal of this research effort according to requirements of the grant and the proposed timeline.
Rule 9 – Test competing implementations.	We compared our IO models to multiple IO and mechanistic implementations, which helped us quantitatively determine our model's capabilities and limitations (details in publications).
Rule 10 – Conform to standards.	Our models are developed using best coding practices and operating procedures.

D. Description of how the planned activities will lead to a credible model

The activities described above are in line with the ten simple rules defined by the Committee on Credible Practice in Modeling and Simulation in Healthcare, and provide significant added value in terms of credibility to the models our groups develop.

E. Progress to-date and plans for the next reporting cycle (6 months).
We anticipate following the same iterative process (based on the ten simple rules) used so far.
More specifically for the large-scale hippocampal model, we anticipate additional neurons to be added within the dentate gyrus and CA3 by mid-2019, and neurons in the CA1 by the beginning of 2020. Individual neuron model evaluations and subsequent network level evaluations will be performed as the neuron models become ready.
Notably, a stronger effort will be placed on generating further documentation describing models features, parameters and limitations to a more general audience, thereby opening the models for the community.

Relevant Publications:

[1] Bingham, C. S., Loizos, K., Gene, J. Y., Gilbert, A., Bouteiller, J. M. C., Song, D., ... & Berger, T. W. (2018). Model-Based Analysis of Electrode Placement and Pulse Amplitude for Hippocampal Stimulation. IEEE Transactions on Biomedical Engineering.

[2] Bingham, C.S., Bouteiller, J-M.C., Song, D., Berger, T.W. (2018). Graph-Based Models of Cortical Axons for the Prediction of Neuronal Response to Extracellular Electrical Stimulation. IEEE Engineering in Medicine and Biology Society (EMBC). In print.

[3] Bingham, C. S., Loizos, K., Yu, G., Gilbert, A., Bouteiller, J.-M., Song, D., … Berger, T. W. (2016). A large-scale detailed neuronal model of electrical stimulation of the dentate gyrus and perforant path as a platform for electrode design and optimization. In 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (pp. 2794–2797). IEEE. http://doi.org/10.1109/EMBC.2016.7591310

[4] Bingham, C.S., Nathan, Romil, Bouteiller, J.-M., Song, D., Lazzi, G., Berger, T.W. (2016). A model of axonal branching for medium and long-range fibers in a multi-scale model of hippocampal tissue. Neuroscience 2016 Abstracts. San Diego, CA: Society for Neuroscience, 2016. Online.

[5] Hendrickson, P. J., Bingham, C., Song, D., & Berger, T. W. (2016). A bi-directional communication paradigm between parallel NEURON and an external non-neuron process. In Engineering in Medicine and Biology Society (EMBC), 2016 IEEE 38th Annual International Conference of the (pp. 1413-1416). IEEE.

[6] Gilbert, A., Loizos, K., Yu, G., Hendrickson, P., Berger, T.W., Lazzi, G. (2016). An analysis of ephaptic effects within a multi-scale model of the hippocampus. IEEE International Symposium on Antennas and Propagation and URSI National Radio Science Meeting, Fajardo, Puerto Rico. Accepted March 2016.

[7] Gilbert, A., Loizos, K., Lazzi, G. (2016). A 3D computational model for analyzing the effect of ephaptic coupling on neural stimulation." URSI National Radio Science Meeting, Boulder, CO, Jan. 2016.

[8] Hendrickson, P., Loizos, K., Gilbert, A., Song, D., Lazzi, G., Berger, T.W. (2016). A closed-loop multi-scale simulation paradigm for accurate modeling of electrical stimulation in hippocampus. Society for Neuroscience Annual Meeting, San Diego, CA, Nov. 2016.

[9] Loizos, K., Gilbert, A., Lazzi, G. (2016). Towards a closed-loop multi-scale simulation strategy for accurate modeling of hippocampal electrical stimulation. 39th Annual Int'l Conference of the IEEE Engineering in Medicine and Biology Society, Orlando, Fl, Submitted April 2016.

[10] Xu, H., Weltman, A., Hsiao, M.-C., Scholten, K., Meng, E., Berger, T. W., & Song, D. (2016). A flexible parylene probe for in vivo recordings from multiple subregions of the rat hippocampus. In 2016 38th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (pp. 2806–2809). IEEE. http://doi.org/10.1109/EMBC.2016.7591313

[11] Cline, J., Bingham, C.S., Loizos, K., Yu, G., Hendrickson, P., Bouteiller, J.M., Berger, T., Lazzi, G. (2015). Estimation of initiated local field potential by neurons in heterogeneous tissue environment using admittance method. IEEE USNC-URSI, (1), 7817. http://doi.org/10.1109/USNC-URSI.2015.7303594

[12] Bingham, C.S., Loizos, K., Guo, Y., Yu, G., Hendrickson, P.J., Bouteiller, J.-M., Lazzi, G., Berger, T.W. (2015). Multi-scale simulation of extracellular electrode stimulation in the dentate gyrus. Program No. 372.12. Neuroscience 2015 Abstracts. Chicago, IL: Society for Neuroscience, 2015. Online.

[13] Loizos, K., Cline, J., Yu, G., Bingham, C.S., Hendrickson, P., Lazzi, G., Berger, T.W. (2015). Computational study of local field potential in a heterogeneous 3D model of rat hippocampus. Society for Neuroscience Annual Meeting, Chicago, Il, Oct. 2015.

[14] Gilbert, A., Loizos, K., Yu, G., Hendrickson, P., Lazzi, G., Berger, T.W. (2015). Optimizing electrode placement using a multiscale model of the hippocampus. IEEE International Symposium on Antennas and Propagation and URSI National Radio Science Meeting, Vancouver, Canada, July 2015.

[15] Gilbert, A., Loizos, K., RamRakhyani, A., Hendrickson, P., Berger, T.W., Lazzi, G. (2015). A 3D admittance-Level computational model of a rat hippocampus for improving prosthetic design. 37th Annual Int'l Conference of the IEEE Engineering in Medicine and Biology Society, Milan, Italy, Aug. 2015.

[16] Loizos, K., RamRakhyani, G., Lazzi, G. (2015). Simulation study for estimating effective resistivity in heterogeneous neural tissues. IEEE International Symposium on Antennas and Propagation and URSI National Radio Science Meeting, Vancouver, Canada, July 2015.

[17] Xu, H., Weltman, A., Hsiao, M.-C., Scholten, K., Meng, E., Berger, T. W., & Song, D. (2015). Design of a flexible parylene-based multi-electrode array for multi-region recording from the rat hippocampus. In 2015 37th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) (pp. 7139–7142). IEEE. http://doi.org/10.1109/EMBC.2015.7320038

[18] Xu, H., Hsiao, M.-C., Song, D., & Berger, T. W. (2014). Recording place cells from multiple sub-regions of the rat hippocampus with a customized micro-electrode array. In 2014 36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (pp. 4876–4879). IEEE. http://doi.org/10.1109/EMBC.2014.6944716

[19] Soussou, W., Gholmieh, G., Han, M., Ahuja, A., Song, D., Hsiao, M., … Berger, T. W. (2006). Mapping spatio-temporal electrophysiological activity in hippocampal slices with conformal planar multi-electrode arrays. Advances in Network Electrophysiology - Using Multi-Electrode Arrays, (4), 127–152. http://doi.org/10.1007/0-387-25858-2_6

[20] Gholmieh, G., Soussou, W., Han, M., Ahuja, A., Hsiao, M. C., Song, D., … Berger, T. W. (2006). Custom-designed high-density conformal planar multielectrode arrays for brain slice electrophysiology. Journal of Neuroscience Methods, 152(1–2), 116–129. http://doi.org/10.1016/j.jneumeth.2005.08.021

[21] Hu, E. Y., Bouteiller J-M. C., Song D., Baudry M., Berger T. W., Volterra representation enables modeling of complex synaptic nonlinear dynamics in large-scale simulations, Frontiers in Computational Neuroscience, vol. 9, 2015; DOI: 10.3389/fncom.2015.00112

[22] Hu, E. Y., Mergenthal A., Bingham C. S., Song, D. Bouteiller J-M. C., Berger T. W., A Glutamatergic Spine Model to Enable Multi-Scale Modeling of Nonlinear Calcium Dynamics , Frontiers in Computational Neuroscience, vol. 12, 2018, DOI: 10.3389/fncom.2018.00058