behavior have become more and more complex. While some parameters within models can be constrained based on direct observation, there are often many others whose values cannot be directly measured. In these cases, parameters need to be optimized through fitting of simulated data to experimental recordings. Unfortunately there is currently a dearth of efficient optimization procedures for complex models. We have made a series of modifications to the curvilinear gradient method for parameter estimation to automate and accelerate this process. The procedure is able to fit any number of parameters to a model in a reasonable amount of time by utilizing the steepest descent trajectory. By way of example we have used this method to fit and compare several Markov state models describing gating of the hERG potassium channel. The information was used in a myocyte model to simulate a cardiac action potential. We have then extended the simulation from the cell to the tissue level to produce simulations of propagated action potentials. These simulations are run with a view to simulating wild-type, diseased, and drug bound tissue.

1. Hodgkin, A., and Huxley, A. (1952): A quantitative description of membrane current and its application to conduction and excitation in nerve. J. Physiol. 117:500-544.

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Neuroanalysis.Org: Information-Theoretic and Extended Analyses of Neural Coding

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Analyses of neural coding-the representation and processing of spike train information-require multiple methods, because neural systems use many kinds of representations, and many analytic methods require specific types or amounts of data. Complementing widely-available conventional methods, we developed and released open source the following via neuroanalysis.org (Goldberg et al. *Neuroinformatics* 7, 165-178, 2009):

• the downloadable STAToolkit suite of information-theoretic algorithms,
• guidance for algorithmic development, use, and applicability to neural systems, and
• an in-development AnalysisServer.

Toward aiding formulation and tests of hypotheses about neural coding, sensory discrimination, firing pattern variability, synchrony and other relations characterizing multineuronal recordings, we now report expanding capabilities of neuroanalysis.org. Utilizing algorithms, code, and/or insight from twelve collaborators, we expand our set of complementary analytic methods, including additional information measures, dimensional reduction, distinguishing information from purely biophysical variation, and generation of surrogate multineuronal data sets. These include a new entropy estimator (our eighth) the 'NSB' method, aiding analyses of highly undersampled data. Examples and demonstrations serve to inform and guide neurophysiologists to select STAToolkit methods.

Recent publications and presentations describe STAToolkit methodologies, report a new index characterizing how population activity deviates from maximum-entropy models, and discuss applicability of metrics to synaptic processing and large numbers of neurons.

To assist computationally-intensive explorations of databased spike trains, we also offer an in-development AnalysisServer, an open-access dedicated large-scale computational array. 'Analyze' links will enable dataset grouping, parsing, concatenation, and entropy and information determination from data at neurodatabase.org.

Parallel enhancements to neurodatabase.org are intended to aid understanding of neural function in both normal and disease states. We continue to accommodate and solicit an expanding set of data types including recordings from multiple preparations.

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Physical Changes in Macromolecules of Active Zone Material that Regulate the Docking and Fusion of Synaptic Vesicles on the Presynaptic Membrane

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The active zones of axon terminals are where the initial events in synaptic transmission occur. They are characterized by dense aggregates of macromolecules attached to the cytoplasmic surface of the presynaptic plasma membrane, called active zone material (AZM); synaptic vesicles docked on the presynaptic membrane, which contain neurotransmitter; and aggregates of cation channels in the presynaptic membrane that help regulate the fusion of the docked vesicles with the membrane leading to the exocytosis of their neurotransmitter during synaptic transmission. Previous electron tomography (ET) studies on resting frog neuromuscular junctions (NMJs) showed that the AZM is composed of an organized network of elongate macromolecules that fall into several classes, some of which connect to each docked vesicle.

We used ET to study active zone components at frog neuromuscular junctions fixed either at rest or during electrical stimulation of the axon terminals. We found that as vesicle docking proceeds a shortening of certain AZM macromolecules leads both to a several fold increase in the size of the area of close apposition between the vesicle membrane and the presynaptic membrane and to a movement of certain of the cation channels toward the vesicles. Vesicle membranes having large areas of close apposition with the presynaptic membrane preferentially fuse with the presynaptic membrane during synaptic activity. After vesicle membranes fuse with the presynaptic membrane and begin to flatten into it prior to recycling, they dissociate from the AZM in an orderly way. Altogether the findings support the conclusion that AZM helps regulate the docking of synaptic vesicles on the presynaptic membrane, the fusion of docked vesicles with the presynaptic membrane, and the recycling of vesicle membrane after fusion.

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Connections of Synaptic Vesicles to Active Zone Material Before and after Docking on the Presynaptic

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The active zones of axon terminals, which are where the initial events in synaptic transmission occur, are characterized in part by dense aggregates of macromolecules, called active zone material (AZM), attached to the cytoplasmic surface of the presynaptic plasma membrane and by synaptic vesicles docked on the presynaptic membrane, which contain neurotransmitter and fuse with the presynaptic membrane to release their neurotransmitter during synaptic transmission. Previous electron tomography (ET) studies on the 15nm of AZM next to the presynaptic membrane of axon terminals at resting frog and mouse neuromuscular junctions (NMJs) showed that it is composed of an organized network of elongate macromolecules that fall into several classes, one of which, *ribs*, connects to each docked vesicle.

We used ET to study in axon terminals at resting frog NMJs the remaining 45nm of the AZM network deep to the presynaptic membrane. Like that in the initial 15nm, it is a highly organized network containing several classes of elongate macromolecules. Some of these, *spars and booms*, also connect to docked vesicles. Thus, each docked vesicle is connected to 3-4 ribs, 2-3 spars and 4-8 booms. For NMJs that had been fixed during electrical stimulation, we found that at those active zones where the docked vesicles had fused with and flattened into the presynaptic membrane, the vesicles moving from the reserve pool to replace them at the docking sites on the presynaptic membrane are connected to the ribs, spars and booms when 20-30 nm from the membrane. Altogether the findings support the hypothesis (Harlow et al., Nature 409: 479-484, 2001; Nagwaney et al., J. Comp. Neurol. 513: 457-468, 2009) that AZM helps regulate the docking of synaptic vesicles on the presynaptic membrane.

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Endogenous GABA Regulates $GABA_BR$ Conformation and Release Probability at Single Hippocampal Synapses

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Presynaptic $GABA_B$ receptors, consisting of GB_{1a}/GB_2 subunits (GB_{1a}Rs), critically influence synaptic and cognitive functions. However, whether GB_{1a}Rs are activated during basal synaptic activity remains controversial. Here we explored local GB_{1a}R activation at single presynaptic boutons by integrating optical tools for simultaneous monitoring of inter-molecular associations and vesicle release in pyramidal hippocampal neurons. Utilizing fluorescence resonance energy transfer spectroscopy, we found that formation of presynaptic $GB_{1a}R/G_o$-protein complexes does not require synaptic activity. Under quantal transmission, GABA induced conformational rearrangements and increased inter-synapse variability of the GB_{1a}/GB_2 associations. These molecular changes lead to a non-uniform tonic block of vesicle release along dendritic tree of CA1 hippocampal pyramidal neurons. Our findings provide direct evidence for conformational changes within the GB_{1a}/GB_2 heterodimer by endogenous GABA and propose a critical role for the heterodimer conformational dynamics in local regulation of release probabilities at single hippocampal synapses.