722-Pos
Study of BDNF-TrKB Trafficking Regulated by Neuronal Activity in Hippocampal Neurons by Live Cell Imaging
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Brain-derived neurotrophic factor (BDNF) is a protein that regulates neuronal survival and synaptic plasticity in brain. BDNF binds and activates receptor tyrosine kinase TrkB and the trafficking of phosphorylated TrkB triggers multiple intracellular pathways involved in neuronal development. It is not clear, however, whether BDNF is transported with TrkB in a signaling complex.
It has been reported that the number of surface TrkB and the phosporylation of TrkB is enhanced by high frequency neuronal activity, but whether the trafficking of TrkB is also modulated by neuronal activity has not been addressed. To investigate this problem, we transfect hippocampal neurons with BDNF-eGFP or TrkB-mCherry and separately plate them on two sides of a PDMS chamber. We look at 1) whether BDNF and TrkB are co-transported; 2) whether the transportation flux, speed and other features are affected by high frequency field stimulation. The results may help us to understand the mechanism under synaptic plasticity and memory formation.

723-Pos
Increasing the Potassium Channel Density in Regularly Spiking Pyramidal Cells can Turn them into Fast Spiking
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The threshold dynamic of neurons can be classified into two main types: regular spiking neurons, showing a continuous frequency-stimulation current relationship and thus an arbitrarily low frequency at threshold current, and fast spiking neurons, showing a discontinuous relationship and a minimum frequency for repetitive firing. In a previous investigation of a hippocampal neuron model, we showed that the membrane density of critical ion channels is important for the bifurcation type and consequently for the threshold dynamics; it can cause the model to switch between fast and regular spiking. In the present study we extend our previous analysis with experimental tests, using the dynamic clamp technique. We injected currents, calculated from voltage clamp descriptions of potassium currents, into regularly spiking pyramidal cells, thereby altering their threshold dynamics to fast spiking. The results confirm the conclusion from the previous study that the type of threshold dynamics of neurons can critically depend on the channel density. Moreover, we show by analysing other well-described membrane models with techniques from nonlinear dynamical system theory how the channel density as bifurcation parameter is influenced by other parameters such as channel kinetics, in some cases reducing the threshold dynamics exclusively to fast spiking. In conclusion, the overall structure of the phase space around the stationary potentials must be taken into account when trying to understand the threshold dynamics of neurons, and, consequently, the global oscillatory activity of networks of neurons.

724-Pos
A Computer Model Study of Tonic Spiking and Bursting in Thalamic Relay Neurons
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Thalamic relay neurons process visual signals from retina on the way to cortex, and seem to encode the information in dual modes: tonic spiking and bursting. The mode of firing depends critically on the history of membrane potential. For example, when the membrane rests at levels close to the firing threshold, relay neurons generate tonic spikes, but when the membrane is sufficiently hyperpolarized by IPSCs, they produce bursts. Therefore, it seems that the visual signal from retina to cortex is not only transferred but also transformed by thalamus. Studies have shown that the bursting mode can be attributed to the low-threshold T-type Ca^{2+} ion channels that are highly expressed in these neurons. We have developed a detailed model neuron, based on anatomically realistic models of Thalamic relay neurons, to examine the ionic mechanisms that are responsible for the dual mode firings both at the ion channel level and cellular level. Consistent with experimental data, we show that (1) when the membrane potential is close to the resting membrane potential, the model neuron fires tonic spikes; (2) when sufficiently hyperpolarized for about 100ms, the model neuron is able to fire bursts due to the deinactivation of T-type calcium channels that contribute the majority of the inter-burst current via slow deactivation. In addition, we investigate the effects of epilepsy-linked mutations in the neuronal Na^{+} channel and T-type Ca^{2+} channel on the dual mode of firing using experimentally based gating models. Our results demonstrate that sodium and T-type calcium channel mutations promote and accelerate tonic and burst firing.

725-Pos
Models Of Paraventricular Nucleus (PVN) Sympathetic Neurone Modulation by Glucose and Hypoglycaemia
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Hypoglycaemia activates much of the sympathetic nervous system (Fagius 2003. Acta Physiol. Scand. 177:337-343) and this is likely to be important to glucose counter-regulation. The PVN is ideally suited to mediate this response since it contains a high density of spinally-projecting sympathetic control neurones. Furthermore, inactivation of the PVN with lignocaine blunts counter-regulation (Evans *et al.* 2003 Am. J. Physiol. 284:R57-65).
Our *in vitro* data show paradoxical responses of PVN sympathetic control neurones (SPNs) to hypoglycaemia: They express K_{ATP} channels and most are inhibited or unaffected by hypoglycaemia, whereas *in vivo* they appear to be activated by hypoglycaemia. There could be several possible explanations, however, in this study we explored the possibility that the paradox is accounted for by network properties in the PVN, and differential expression of K_{ATP} channels.
We constructed very simple Neuron (Hines & Carnevale 1997. Neural Comput. 9:1179-1209) models of SPNs with inputs from both excitatory ''Netstim'' neurones and inhibitory interneurones. The interneurones are also driven by excitatory ''Netstim'' neurones. Both interneurones and SPNs incorporate identical K_{ATP} channels, but the latter with a lower density. We modelled the situation where this network is intact (*in vivo*) and where the inhibitory interneurones were lost (*in vitro*).
In the *in vitro* model, SPN K_{ATP} conductance was sufficient for the expected (dose-related) decrease in action potential frequency with hypoglycaemia. Interestingly, however, with no changes to the set-up of the SPN neurones, but re-introduction of input from the inhibitory interneurones, the effect of hypoglycaemia was reversed. Hypoglycaemia now activated SPNs. This model also reproduced the common observation that whilst SPNs in brain slice experiments tend to be ''spontaneously'' active, they tend to be silent *in vivo*, but activated by $GABA_A$ inhibition.

726-Pos
Effects of Cellular Adaptations to Partial Demyelination on Spike Patterns in a Model Axon
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In a computational model, axons undergoing demyelination can produce a wide variety of spike patterns ranging from conduction failure to high-frequency bursting. We have simulated cellular adaptations to partial demyelination to understand what an axon might gain from adaptations to changes in excitability. Observed clinical phenomena in multiple sclerosis include an increase in axon diameter and the aggregation of mitochondria during demyelination. We, therefore, examined the effect of axon diameter swelling and increased activity of Na-K pumps on axonal excitability. Increasing the diameter of a partially demyelinated axon by 2-fold (as has been observed in human cases) had the effect of increasing the ''safety factor'' for successfully conducting a single spike across a demyelinated patch by 37% uniformly across a wide range of ion channel densities. At the other end of pathological spike behavior range, the un-evoked burst-pattern threshold was unaffected by the girth doubling at physiologically relevant densities of ion channels. Only at unusually high densities was a lower burst-threshold observed (−43%). But another measure of burst activity was altered by cable swelling. In the control demyelinated axon the frequency of bursting followed an oscillating pattern that was dependent on membrane current density. This sinusoidal frequency-density relationship was nearly flattened, or damped, by axon swelling. We addressed mitochondrial accumulation by assuming this cellular adaptation would impact Na-K pump activity. We discovered that increasing the Na-K pump activity only in the demyelinated areas caused early termination of the un-evoked bursting behavior. Our results suggest new interpretations of previous clinical and electrophysiological observations related to axonal intrinsic excitability in demyelination diseases. NIMH R01MH079076 and HHMI.

727-Pos
An Improved Curvilinear Gradient Method for Parameter Estimation in Complex Model Systems: Application to Gating of A Cardiac Ion Channel
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Since the seminal work of Hodgkin and Huxley1 describing a model of the neuronal action potential, there has been tremendous interest in the power of mathematical modeling in the field of ion channel research. However, as we learn more about the physiology of these molecules the models describing their

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.

728-Pos

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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729-Pos

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.

730-Pos

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.

731-Pos

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.