Research Interests in Human Stroke Evaluation and Monitoring  
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Background

Stroke is a major health problem, affecting approximately 700,000 persons annually in the US alone, with more expected as the average age and life span increase. When a patient enters an emergency room and stroke is suspected, standard procedure is to first use x-ray CT to rule out brain hemorrhage. If the CT is negative, but stroke is concluded based upon behavioral and cognitive measures, then the stroke is assumed to be ischemic, and thrombolytic drugs, e.g., t-PA, may be used to restore blood flow within the ischemic penumbra. The development of t-PA gives new hope for many stroke patients, but since it carries a 6% risk of causing brain hemorrhage, it must is used conservatively. Current guidelines suggest that t-PA be used only within three to six hours of stroke onset. Since many victims arrive for treatment beyond this window and diagnosis takes some time, it is likely that many patients are excluded from treatment unnecessarily. Others may be exposed to risk unnecessarily if the stroke is small or has already reached completion.

Stroke treatment could be much better directed if quantitative measures of the physiological state of ischemic tissue were available. X-ray CT and conventional MRI do not show ischemic tissue which is still viable for rescue, but only dead tissue in the infarcted core. Diffusion tensor-weighted magnetic resonance imaging (MRI) is now being developed to detect ischemic tissue, but MRI machines are expensive, not portable, and not practical for continuous monitoring. Thus MRI technology would be well complemented by a practical, affordable imaging methodology quantifying the physiological state of ischemic tissue. Commercial EEG/EIT acquisition systems which meet these criteria are now being developed by Electrical Geodesics, for example, but much work remain to be done to understand how to analyze these data effectively. The following three topics address the spatial, temporal and theoretical aspects of this problem.

Combined EEG/EIT for stroke detection and monitoring

Ischemic tissue generates pathological oscillations which can be seen in the scalp EEG. In particular, the Fourier power spectrum exhibits increased power in the delta band (1–4 Hz). While this has been known for some time, only recently have EEG sensor systems made acquisition and monitoring practical in clinical settings. Much work remains to use these data effectively to detect and monitor acute ischemic stroke. For example, as is well known, EEG analysis is challenged by the fact that the data are collected on the scalp, and inverse methods must be applied to determine the three-dimensional location of brain current generators. In cognitive applications, these inverse problems typically have no unique solution because the number of generators is not knowable beforehand. In contrast, stroke is usually confined to a single contiguous region, making EEG inverse solutions much more tractable, especially when combined with EIT analysis.

The conduction of electrical fields through the head depends upon the geometry and conductivity of the head tissues for each subject. While it is now common to use structural MRI and x-ray CT to determine head and skull geometry, most researchers continue to use nominal conductivity parameters which are not subject specific. Subject-specific conductivity values may be obtained using electrical impedance tomography (EIT), in which low-level (= 10 µA) electrical currents are injected into the scalp, and the induced potentials are measured at the
remaining electrodes of a dense-array EEG net. Inverse methods are then applied to estimate conductivity parameters. EIT used this way could improve the accuracy with which EEG may detect and localize ischemic tissue. Using EIT rather than diffusion tensor-weighted MRI to determine bulk tissue conductivity may in fact be optimal, since current injected through the scalp at low frequencies (below 100 kHz) is confined the extracellular space, while MRI probes the diffusion tensor in both the intracellular and extracellular space. Only the conductivity through the extracellular space is relevant to EEG and MEG analysis.

EIT itself also provides direct measures of tissue ischemia. Oxygen-deprived cells in the ischemic penumbra undergo a series of physiological changes which include cell swelling. Since this swelling decreases the extracellular space, bulk tissue conductivity decreases by as much as 50%. EIT could therefore provide information about ischemia which is complementary to that of EEG. Ultimately, a combined EEG/EIT methodology based on a Bayesian formalism may be optimal for detecting and localizing acute ischemic stroke. In addition, stroke patients treated with t-PA are usually placed in the ICU, where their heart is monitored but usually not their brain. Modern EEG/EIT systems are practical for continuous monitoring, and could be used to track improvement. Last but not least, since the conductivity of blood is approximately 3 times that of brain tissue, impedance monitoring could also detect cerebral hemorrhage which may be caused by treatment.

**Temporal measures of stroke pathophysiology**

The Fourier power spectrum of EEG time series often exhibits increased power in the delta band (1–4 Hz) over ischemic tissue. Thus a Fourier transform of the scalp EEG, combined with linear and nonlinear inverse methods, could detect and localize ischemic tissue. This particular range of frequencies is arbitrary, however, and more research needs to be done to determine the optimal use of Fourier analysis for detecting and monitoring ischemic stroke. Moreover, Fourier analysis is limited in that it completely characterizes the dynamics of linear systems only. Cortical tissue is comprised of many neurons with nonlinear dynamics and interactions abound. Such complex systems often have dynamical characteristics which can not be captured by Fourier analysis alone. Other established methods of time series analysis which have been useful for characterizing dynamical brain states and other pathologies include the correlation dimension, which quantifies the effective dimensionality of a quasi-oscillatory system, and the largest Lyapunov exponent, which quantifies the degree of predictability of a time series, for example. These measures and others have been demonstrated to be sensitive to cardiac fibrillation, epileptic seizure, and even more subtle disorders such as dementia and Alzheimer's disease. In all cases, the pathological state is characterized by a reduction in signal complexity, and on these grounds we hypothesize that the same can be expected for stroke.

Beyond this general argument, there are also specific facts supporting the hypothesis that complexity measures will be sensitive to cortical ischemia. First, ischemic tissue exhibits large-amplitude coherent oscillations in the delta band (1–4 Hz). Large amplitudes appear in the EEG only when a significant number of nearby neurons are oscillating synchronously, because only then can their electric fields superimpose to be measurable at the scalp. This suggests a higher degree of synchrony in the signal during ischemia, which should be discernible as a reduction in signal complexity. Second, it has been suggested that the increase in delta power is due to deafferentation of connections from the nearby infarcted core. It is consistent to expect that this would allow the cortex in the ischemic penumbra to oscillate in its fundamental modes. This occurs in sleep, for example, when sensory inputs are prevented by the thalamus from reaching
the cortex. Despite these motivations, nonlinear time series analysis has not yet been applied to stroke. Linear (Fourier) and nonlinear time series analysis, combined perhaps with artificial neural networks designed for pattern detection, could improve the detection and quantification of ischemic pathophysiology.

**Neuronal population models of stroke pathophysiology**

In order to better understand how EEG (and MEG) may be used to quantify the pathophysiology of stroke, it is necessary to have theories of cortical dynamics which place the data in a consistent conceptual framework. One approach would be to use NEURON or GENESIS to simulate the effects of metabolic reduction on neuronal oscillations. The failure of the Na-K pump, for example, initiates a chain of physiological events in compromised cells which are reasonably well understood from animal experiments, at least during the acute phase. If a model of cortical tissue were capable of describing healthy tissue oscillations accurately, then tuning the appropriate parameters could allow us to understand changes in the EEG in terms of cellular parameters. This approach has already been successful at explaining changes in alpha (8-13 Hz) power associated with depth of anesthesia. This would be of great interest because most stroke treatments are conceptualized at the cellular level, while EEG data are collected at the scalp. Such an approach based explicitly on discrete neural elements, however, may not be optimal for the description of population phenomena, especially those related to stroke. This is because single EEG detectors are sensitive to the population activity of approximately ten million to a billion neurons, and modeling this many neurons remains computationally prohibitive even with the most modern techniques.

An alternative formulation, termed neural field theory, assumes that the cortex can be meaningfully represented as a spatially continuous system. One first defines a local neural field variable which characterizes the dynamical state of a population of neurons within a small voxel. Popular choices include the mean firing rate or the mean soma membrane potential, where the mean is taken over an ensemble of neurons in each voxel. Interactions between voxels are introduced using a Green's function formalism, which may in principle include arbitrary degrees of inhomogeneity and anisotropy. This approach has several advantages: First, the formulation is initiated at the population level, but is based upon cellular level degrees of freedom. This facilitates understanding brain dynamics on spatial scales corresponding to the EEG, without requiring prohibitively large simulations based upon individual neurons. Second, in some approximations the resulting field equations are amenable to analytical analyses already developed in theoretical physics. This promotes intuition toward the possible classes of solutions, which may in turn drive new hypotheses and experiments. Third, a spatially continuous formulation is not only favorable but arguably necessary for understanding stroke progression, because an important component of stroke is involves changes in extracellular ion concentrations and extracellular diffusion of glutamate and other neurotransmitters. Only in spatially continuous models are diffusion equations naturally integrated with neuronal dynamics.

**Summary**

Together these three approaches to stroke research will help us better characterize and localize ischemic pathophysiology, and improve our understanding of how to relate noninvasive measurements such as EEG and MEG to cellular events during stroke progression and recovery.