crystallography, single-molecule FRET and MD simulation. Allosteric is in play for 3 very different systems: an enzyme, a phoshorylation-mediated signaling protein and the inhibition of rhodopsin kinase via protein/protein interactions. For the latter example, binding by conformational selection and not via an induced fit is directly demonstrated by flux measurements, the only rigorous test for the two opposing mechanisms.
The presented data stress the point that highly choreographed chemical integrity AND optimized conformational sampling is a prerequisite for efficient enzyme catalysis. The power of an intimate marriage between NMR and other biophysical methods and MD simulations including a variety of novel pathway algorithms will be illustrated.

1924-Symp
Structures of Biomolecular Complexes from Heterogeneous Data and Bayesian Data Analysis
Michael Nilges[1,2], Guillaume Bouvier[1], Paulo R. Batista[1], Yannick Spill[1,3].
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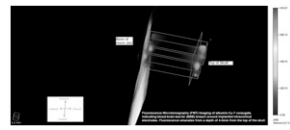
To characterize 3D structures of large and often flexible macromolecular complexes, multiple sources of structural data at multiple resolutions need to be combined. Integrating these data into one consistent picture poses particular difficulties: data are much more sparse than in high resolution methods; data sets from heterogeneous sources are of highly different and unknown quality and information content and may be mutually inconsistent; data are in general averaged over large ensembles and long measurement times. Also pre-existing structural knowledge is of different quality, ranging from high-resolution structures over homology models to low resolution models.
We will outline a general framework, principally based on Bayesian probability theory. Appropriate models for the major data types used in hybrid approaches (electron microscopy, cross-linking/ mass spectrometry, various spectroscopy techniques, SAXS, ..) need to be developed, as well as representations to include structural knowledge for individual components of the complexes. We are working towards a multi-scale and multi-technique version of the approach we introduced for NMR (Rieping et al., Science 309, 303-305, 2005), implemented in the program ISD. We present examples with data from SAXS and from chemical cross-linking / mass spectrometry.

1925-Symp
Multiscale Simulation of Multiprotein Assemblies: The Challenges of Ultra-Coarse-Graining
Gregory A. Voth, Ph.D.
University of Chicago, Chicago, IL, USA.
A multiscale theoretical and computational methodology will be described for studying biomolecular systems across multiple length and time scales, providing a systematic connection between molecular-scale interactions, coarse-grained models, and mesoscopic phenomena. At the heart of the approach is a methodology for deriving ''ultra'' coarse-grained models that embody the underlying molecular-scale interactions because the approach is based on systematic principles from statistical mechanics. However, a critical component of the methodology is also its connection to experimental structural data, such as cryo-EM or x-ray, when developing the ultra-coarse-grained models, thus making it ''hybrid'' in its character. Important results from our multiscale simulations will be presented that describe key features of large multiprotein complexes, such as the HIV-1 virus capsid, actin filaments, and (if time allows) protein-mediated remodelling of membranes.

Symposium: Interface of Brain and Machines

1926-Symp
Is the Extent of Blood-Brain-Barrier Breach Predictive of Intracortical Electrode Performance?
Ravi Bellamkonda, Lohitash Karumbaiah, Tarun Saxena, Qi Wang, Garrett Stanley.
Georgia Institute of Technology, Atlanta, GA, USA.
The feasibility of intracortical electrode based long-term recordings has been demonstrated. However, long-term stable recordings remain unpredictable and elusive. Several factors including electrode impedance, astroglial scar, and chronic inflammation have been proposed as potential determinants of electrode failure. In an extensive study comparing intracortical electrode shape, size and implantation condition, we have identified that the single most important predictor of electrode performance is the extent of blood-brain-barrier breach around electrodes. using a combination of non-invasive imaging of the blood-brain-barrier using fluorescence microtomography (FMT), immunohistochemistry and cytokine analysis, we correlate electrode performance to the inflammatory tissue reaction and the underlying molecular mechanisms that ultimately result in neuronal apoptosis and recording failure. We suggest that establishing a molecular link between electrode parameters quantitatively via blood-brain-barrier imaging and cytokine analysis, along with the ultimate functional performance of electrodes enables us to not only predict electrode performance but also design strategies to improve performance.



1927-Symp
Control Theoretic Inverse Models in Bird Song Learning: Theory and Experiment
Surya Ganguli.
Stanford University, Stanford, CA, USA.
Learning to imitate any motor act imposes a challenge for any neural system; it must be able to convert the sensory perception of a motor act into the appropriate motor commands required to reproduce that act. We propose a novel mechanism for achieving this conversion through a simple Hebbian learning mechanism, operating within a sensorimotor feedback loop, that gives rise to control theoretic inverse models. Our framework predicts the existence of mirror neurons whose sensory and motor responses display a temporal mirroring offset equal to the sensorimotor loop delay. In collaboration with the Hahnloser laboratory, we test this prediction by chronically recording from the cortical output area of a basal-ganglia pathway involved in song learning in a songbird vocal learner. Sensory responses mirror motor-related activity with an offset of about 40 ms, in accordance with loop delays estimated using electrical and auditory stimulation. Thus, cortico-basal ganglia pathways could potentially support motor learning through circuit mechanisms more powerful than simple reinforcement strategies.

1928-Symp
Intracortical Brain-Computer Interfaces for the Restoration of Communication and Mobility
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For people with stroke, spinal cord injury, neuromuscular diseases, or other neurologic illnesses, currently available assistive and rehabilitation technologies are inadequate. In severe brainstem stroke and advanced ALS, patients may suddenly or progressively enter a locked-in state of being awake and alert but unable to move or communicate. Through clinical translation based on decades of basic neuroscience research, intracortically-based ''brain-computer interfaces'' are poised to revolutionize our ability to restore lost function. Over the past decade, neurotechnologies which record the individual and simultaneous activities of dozens to hundreds of cortical neurons have yielded new understandings of cortical function. This preclinical research, generally performed with healthy, neurologically intact non-human primates, has demonstrated that direct neural control of virtual and physical devices can be achieved. Recently, this exciting research has been translated into pilot clinical trials (IDE) of an intracortically-based neural interface system (BrainGate, www.braingate2.org), seeking to determine the feasibility of persons with tetraplegia controlling a computer cursor or other devices simply by imagining movement of their own hand. A variety of methods for decoding brain signals are being tested with the hope of not only restoring communication, but also providing a control signal for the reanimation of paralyzed limbs. A recent paper in Nature described a woman with brainstem stroke who used the BrainGate system to control a robotic arm to serve herself her morning coffee, demonstrating not only the critical ability to reach-and-grasp in her immediate, multidimensional environment, but also to perform a key activity of daily living using an intracortical BCI. In BrainGate-related research, early glimpses into the activities of dozens of individual cortical neurons in humans are also providing new insights and might provide new diagnostic and therapeutic modalities for people with epilepsy.

1929-Symp
Recent Work Toward a High-Performance Neural Interface
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A better understanding neural population function would be an important advance in systems neuroscience. The change in emphasis from the single neuron to the neural ensemble has made it possible to extract high-fidelity information about movements that will occur in the near future. This ability is due to the distributed nature of information processing in the brain. Neurons