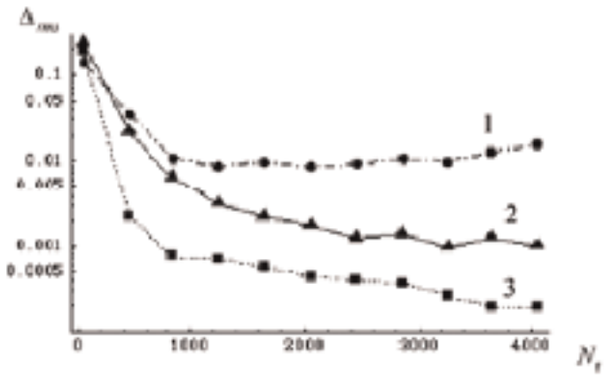
applications of the method of numerical differentiation based on the polynomial approximation include the possibility of the robust error analyses of rate constants value determined by application of NMM. This error analyses will be used for error analysis of rate constants determined using NMM from experimental Fluorescence Correlation Spectroscopy data.



3277-Pos Radical Pair-Based Magnetoreception

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Board B580

Every season many species of birds migrate due to an endogenous program that is designed to propagate the species through breeding and provision of larger food sources. The mystery of this biological phenomenon is how the birds are able to navigate to their new environment. One source of directional information that is always present is the Earth's dipolar magnetic field, which magnetic field experiments have shown that birds can use to determine migratory directions. However, the lack of an obvious site for a magnetic sensor, combined with the ability of magnetic fields to pass through all tissue has prevented the discovery of the mechanism responsible for the detection of Earth-strength fields. Two primary models have risen to the forefront of magnetoreception research: magnetite and radical pairs. In the radical pair model, the magnetic field affects a photochemical reaction step that involves light-induced creation of an intermediate pair of radicals. Recent experiments suggest that the blue-light receptor cryptochrome, which has been discovered in birds, plants, and other animals, is a promising candidate for a photomagnetoreceptor. Its presence in plants allows one to apply molecular biological and genetic approaches in order to determine the molecular basis of photochemical magnetoreception. Here, we report experimental measurements of magnetic field effects on hypocotyl growth in *Arabidopsis thaliana.* We determine the detection threshold of static magnetic field effects via dose-response curve measurements. We also investigate the effects of combined oscillating and static magnetic fields to obtain information about the chemical nature of the magnetosensitive reaction step through resonance effects. The results, combined with collaborative studies at the protein level, are compared to a conceptual model of the photochemical magnetic detection mechanism in cryptochromes with the goal of explaining how small magnetic effects in one reaction step can lead to stable physiological responses.

3278-Pos Systems Biology Of Compartmentalized cAMP Signaling In Cardiac Myocytes

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Board B581

The diffusible second messenger cAMP plays a critical role in regulating cardiac myocyte function. While it is often assumed that receptor activation produces a uniform change in cAMP levels throughout the entire cell, this does not easily explain many experimental observations. In the present study, a quantitative computational approach was used to further test the hypothesis that cAMP signaling in cardiac myocytes is compartmentalized. The model used incorporates existing kinetic data on the signaling pathways involved in regulating cAMP production and degradation into a theoretical cell consisting of three different compartments:

1. a subsarcolemmal space associated with caveolar membrane domains of the cell that are enriched in type II protein kinase A (PKA-II);
2. a subsarcolemmal space associated with cholesterol-rich lipid rafts that do not include caveolin; and
3. a bulk cytoplasmic compartment that makes up >90% of the cytosolic volume.

The behavior of the model was previously validated using a PKA-II FRET-based biosensor to estimate cAMP levels in the caveolar domain of adult ventricular myocytes (Biophys J *92*:3317–31, 2007). In the present study, we compared the behavior of the model with cAMP responses detected by a freely diffusible Epac2 FRET-based biosensor. By assuming that a small but significant fraction of receptor-dependent signaling occurs in the plasma membrane associated with the bulk cytoplasmic compartment, the new version of the model suggests that responses detected by the Epac2-based probe correlate closely with cAMP levels in that domain. These results demonstrate that the model is able to accurately describe the significant differences in cAMP concentration that exist between the caveolar and bulk cytoplasmic domains both under basal conditions as well as in response to receptor activation.

Bioinformatics

3279-Pos Prevalence of EH1 Motifs in Hox and Fox Domain Containing Transcription Factors from the Sponge *Suberites domuncula*

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Board B582

A transcription factor is a part of the system that controls the transcription of genetic information from DNA to RNA. It typically switches on cascades of genes by binding to specific parts of DNA using protein domains. Hox and Fox protein domain families are thought to play an important role in the regulation of developments of cells, tissues and/or organs of fungi, plants and animals. These domains may include short, frequently highly conserved, protein motifs. There is a considerable research interest in various transcriptional and regulatory roles of these motifs. EH1 motifs, found in some transcription factors, mediate interactions with TLE/Groucho family transcriptional corepressors. A number of EH1 motifs have been found in higher metazoans. However, very few have been reported from basal phyla like Porifera. Our research on conserved novel EH1 motifs from the sponge *Suberites domuncula* provides a framework for an understanding of transcriptional activity of these motifs in higher metazoans, including humans. We systematically searched *S. domuncula* proteome for occurrences of conserved EH1 motifs using motif recognition and database searching techniques. We identified a number of novel EH1 motifs in Hox and Fox domains of the sponge. We discuss the apparently complex regulatory system and the existence of Groucho mediated repression in these primitive metazoans. The origin and prevalence of the EH1 homologs in insects and vertebrates are also discussed. Some of the sponge EH1 motifs are highly conserved in humans. This suggests that the motifs' functions during the development might be similar to that in higher metazoans. Given the importance of the EH1 motifs in transcriptional regulation, our findings of new EH1 motifs in Fox and Hox families should aid further studies on their regulatory and transcriptional roles.

3280-Pos Protein Sequence Homology Parameters Applied to the Prediction of Solvent Accessible Residues

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Board B583

We have shown a strong correlation between sequence variability (as indicated by homologous proteins) scaled as a Shannon entropy (sequence entropy) and query protein hydrophobicity (Liao, H. et al., 2005. Protein Eng. Des. Sel. 18, 59–64). Two major regions are indicated when plotting these parameters versus inverse packing density. Here the second region (associated with less than 12 C-alpha per 9-angstrom radius) is essentially flat and consistent with the most flexible residues, typically showing significant exposure to solvent. However, sequence entropy and other homology-based calculations - including fraction of aligned elements that are strongly hydrophobic, gapped, or small in volume - for individual query residue sequence positions show a fair amount of noise with respect to the corresponding average aggregate values having the same packing density. What is encouraging is our most recent work has shown that simple sets of filters, based on sequence entropy and these other homology-based parameters, successfully predict most surface accessible residues for a variety of protein sequences, including cytochrome c, tryptophan synthase, and alpha-synuclein.

3281-Pos A New Computational Intelligent Approach to Protein Tertiary Structure Prediction

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Board B584

In silico protein structure prediction is one of the most challenging problems in computational biology. Despite the tremendous interest and effort invested in this field, current computational methods are far from being able to consistently and accurately predict protein structures. Here we present a novel computational intelligent approach for protein tertiary structure prediction. Our prediction system consists of two phases:

1. generating good candidate structures, and
2. identifying and selecting the best candidates.

The candidate structure generation is based on a combination of sophisticated procedures including statistical modeling, application of fuzzy logic and neural network methods, structural sequence alignment, multidimensional scaling techniques and efficient refinement methods. For a given protein, the proposed approach leads to a large collection of candidate structures of various qualities. We have developed two classes of selection methods for identifying the best quality structures from the collection of candidates. The first method is specific to our candidate structure generation method and predicts RMSD values based on selected features using linear regression or decision trees. The second method is generic and independent of our candidate generation method. It is based on commonly used energy functions, such as Dfire. When applicable, the predictions of the two classes of methods are combined using neural networks to form a final prediction of RMSD. Our computational intelligent approach can utilize the information in the known protein structure database more effectively and efficiently than existing methods. Tested on a set of 200 protein sequences from the PDB, our method demonstrated very promising results.

3282-Pos A Fast Methodology For High Throughput Comparison Of Tertiary Structure And Physicochemical Properties

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Board B585

Identification and characterization of proteins with similar tertiary structures and physicochemical properties provides critical infor-

mation for investigating function and evolution. As protein structure databases continue to grow, there will be increasing need for fast and efficient strategies for protein structure search and comparison. Most conventional methods do not provide fast comparison of both structural and chemical information of proteins. Hence, we propose a method based on 3D Zernike descriptors for comparing global physicochemical properties of the protein surface. The utilization of protein surfaces as the bases for comparison is most appropriate due to their direct relevance to protein function. 3D Zernike descriptors are series expansions of a given three-dimensional function that compactly represent a protein surface and its corresponding physicochemical properties. Consequently, it takes approximately a minute to compare a query structure against thousands of protein structures in a database. Two criterions were used to evaluate the performance of the descriptors:

1. the ability to distinguish similar protein shapes and
2. the ability to compare proteins of similar physicochemical properties.

The protein shape similarity performance was evaluated on a dataset of 2432 protein structures by the CE algorithm. Despite the difference in shape representation, 3D Zernike descriptor showed 89.6% accuracy in retrieving proteins of the same conformation defined by CE. Further, the protein physicochemical comparison was performed on several protein families including, globins, TIM barrel proteins, and representative group of homologous themophilic and mesophilic proteins. Our results indicate that 3D Zernike descriptors were able to distinguish both magnitude and pattern of chemical quantities on the protein surface. Taken together, we demonstrate the high throughput applicability of 3D Zernike descriptors in recognizing global and local physicochemical of protein surfaces.

3283-Pos Evolution Of Distinct EGF Domains With Specific Functions

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Board B586

EGF domains are extracellular protein modules cross-linked by three intradomain disulfides. Past studies suggest the existence of two types of EGF domain with three-disulfides, human EGF-like (hEGF) domains and complement C1r-like (cEGF) domains, but to date no functional information has been related to the two different types, and they are not differentiated in sequence or structure databases. We have developed new sequence patterns based on the different C-termini to search specifically for the two types of EGF domains in sequence databases. The exhibited sensitivity and specificity of the new pattern-based method represents a significant advancement over the currently available sequence detection techniques. We re-annotated EGF sequences in Swiss-Prot looking for functional relationships that might correlate with EGF type. Based on our structural analysis of EGF domains with three-disulfide bonds and comparison to laminin and integrin-like EGF domains with an additional interdomain disulfide, we propose that these hEGF and cEGF domains may have arisen from a four-disulfide ancestor by selective loss of different cysteine residues. We show that important post-translational modifications of three-disulfide EGFs, including unusual forms of glycosylation, hydroxylation and posttranslational proteolytic processing, are dependent on EGF subtype. For example, EGF domains that are shed from the cell surface and mediate intercellular signaling are all hEGFs, as are all human EGF receptor family ligands. These experimental data suggest that functional specialization has accompanied subtype divergence.

3284-Pos Homology Modeling of Signalling Glycoprotein from Camel (SPU-40) and Its Functional Characterization

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Board B587

Camel signaling protein (SPU-40) belongs to family of recently discovered SPX-40 proteins expressed during mammary gland involution. SPX-40 acts normally as a protective signaling factor that determines which cells are to survive the drastic tissue remodeling that occurs during involution. Certain cancers surreptitiously utilize the proposed normal protective signalling by SPX-40 proteins for their survival and metastasize. Therefore, SPU40-like proteins are an important target for the rational structure-based drug-design against breast cancer.

Crystal structures of signalling glycoproteins from bovine, sheep, goat and buffalo were used as templates for modeling SPU-40 with Modeler *v*8.2 from Discovery Studio1.7 (Accelrys Inc.). The four models obtained were energy minimized using the molecular mechanics force field CharmM. The quality of the modeled structure was reviewed with PROCHECK and Profiles-3D. The final model adopts a conformation with a classical $(\beta/\alpha)_8$ - barrel fold of triosephosphate isomerase and a small $\alpha + \beta$ domain similar to that observed in other SPX-40 proteins. Structure analysis revealed the presence of carbohydrate binding groove and a potential protein-protein binding site having structural homology to FK binding proteins. The binding characteristics of carbohydrates, their docking mode, and possible interactions with SPU-40 were simulated by applying the docking module Ligandfit and CDocker. Molecular dynamics simulation of SPU-40 was performed to observe the trajectory of carbohydrate binding residues in an explicit solvent. Their conformations averaged over 200-psec trajectory were in agreement with available crystallographic structures. This study has further provided insights into the mechanism and energetics of carbohydrate binding including conformational changes in the key residues involved.

3285-Pos Terminology for Neuroscience Data Discovery: Multi-Tree Syntax and Investigator-Derived Semantics

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Board B588

The Neuroscience Information Framework (NIF), being developed for the NIH Blueprint for Neuroscience Research and available in its beta version at http://neurogateway.org, is built upon a set of coordinated terminology components enabling data and web-resource description and selection.

We have selected a straightforward syntax designed for ease of use and for navigation by familiar web interfaces. Datasets, neuroinformatic software tools, web resources, or other entities are characterized by multiple descriptors, each addressing core concepts (e,g, data type, acquisition technique, molecule, cell type, anatomy, ...). Terms for each concept are organized in a tree structure, providing is-a and has-a relations. Broad general terms near each root span the concept and spawn more detailed entries for specificity. Related but distinct concepts (e.g., brain area and depth) are specified by separate trees, for easier navigation than would be required for graph representation.

Sematics enabling NIF data discovery derive in part from multiple expert 2- day workshops at which investigators in particular systems (vision, olfaction), areas (cerebellum, thalamus, hippocampus), preparations (molluscs), disease (neurodegerative disease), or techniques (microscopy, computation and modeling, neurogenetics) derive consensus term lists.

Workshop-derived integrated term lists are available Open Source at http://brainml.org. Other NIF components supply and relate complementary terminologies; one such literature-derived thrust is at http://textpresso.org/neuroscience.

Framework development is supported by NIH Neuroscience Blueprint Contract No. HHSN271200577531C via NIDA; BrainML development by MH57153 from NIMH. In addition to funders, we thank workshop contributors and developers too numerous to cite.

3286-Pos Genome-wide Prediction Of DNA-binding Proteins And Knowledge Mining Of Function Specific Rules

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Board B589

Structural genomics projects aim to boost the number of solved structures for identified proteins. However, structure alone is often insufficient to assign a protein a particular function. We introduce an efficient, accurate method to recognize DNA-binding proteins using only the domain boundaries and the sequence. Our method infers from the sequence a set of weak structural attributes and performs comparably to previous methods over a large, rigorous benchmark. We also compare our method to blast illustrating both the power of our method and the rigor of each dataset. Finally, we elucidate the important feature interactions of a simplified model and analyze how specific rules capture general mechanisms that extend across all the DNA-binding motifs. This analysis indicates that DNA-binding proteins possess characteristics that cross existing categories (transcription factors, nucleases, etc.) and these characteristics capture functional mechanisms that also cross these same categories.

3287-Pos Demographics Of Organisms: A Linguistic Text Comparison Approach To Relational Mapping Of The Sequences Of Whole Chromosomes/ genomes

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Board B590

Despite the rapidly accumulating whole chromosome/genome sequences (WCSs) of many organisms, there are no robust methods at present that compare WGCSs to assess relatedness among compared organisms. Almost all current methods requires (1) multiple sequence alignment of one or more genes common among them with sufficient homologies, (2) assurance that none of the selected genes were acquired by the organisms through lateral gene transfer, and (3) the gene sequences selected have sufficient information to represent respective organisms., because not all genes of one organism are present in other organisms, and gene orders are different among organisms. Thus, WCS cannot be compared by conventional alignment methods. Therefore, current methods use the multiple alignment of sequences of small subunit ribosomal RNA or DNA/RNA or amino acid sequences of collection of selected genes common among compared organisms. The results of such comparison varies depending on the selection of the genes to be aligned. We present a method and preliminary results that addresses these issues by compariange WCSs without sequence alignment, without any alignment, to obtain overall similaritites and differences of WCSs among compared WCSorganisms, which then, can be used to analyze various demographic distributions and to construct the phylogeny of relatedness of present-day organisms or viruses. of DNA/RNA and proteins in WCS spaces, and 3-D protein structures in structure space.

3288-Pos 'Forbidden' Disulfides: Their Role As Redox Switches

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Board B591

The ability to distinguish between structural and redox-active disulfides is important for elucidating protein function. Experimentally, the two types of disulfide can be distinguished by their redox

potentials. Disulfide redox potentials measured in thiol-disulfide oxidoreductases range from -120mV to -270mV. For disulfides serving structural purposes, the redox potential can be as low as -470mV. However individual measurements of this kind are difficult and time consuming. Computational approaches that can identify and characterize redox active disulfides will contribute significantly to our understanding of disulfide redox-activity.

Seminal studies by Richardson and Thornton defined the constraints imposed by protein structure on disulfide formation and flagged forbidden regions of primary or secondary structure seemingly incapable of forming disulfide bonds between resident cysteine pairs. With respect to secondary structure, disulfide bonds were not found between cysteine pairs:

– A. on adjacent β-stands;
– B. in a single helix or strand;
– C. on non-adjacent strands of the same β-sheet.

In primary structure, disulfide bonds were not found between cysteine pairs:

– D. adjacent in the sequence.

Here we identify nine different types of disulfides that occupy these forbidden regions. Most have high torsional energies, a quantity that has been related to the ease with which a disulfide can be reduced. It has been observed that sources of strain in a protein structure, such as residues in forbidden regions of the Ramachandran plot and *cis*-peptide bonds, are found in functionally important regions of the protein and warrant further investigation. Here we show that many of these "forbidden" disulfides act as redox-regulated switches of protein function.

Regulatory Networks & Systems Biology - II

3289-Pos Smooth turning mechanism of crawling *C. elegans*

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Board B592

Caenorhabditis elegans (*C. elegans*) is the model organism with relatively simple anatomy and well characterized genetic information. There has been a great deal of efforts to understand the mechanism of *C. elegans* locomotion. When crawling on a solid surface, *C. elegans* moves forward and backward by propagating dorso-ventral contraction waves toward the opposite direction of its movement, the mechanisms of which have been extensively analyzed through mechanical and neural modeling. In these studies their simple straight motions are mainly considered while the turning mechanism in crawling is mostly neglected.

In this research, we propose a simple mathematical model for the turning of crawling *C. elegans*. It reveals that the worm regulates the bending curvature and interval between ridges of its muscular waves during the turns. These regulations lead to the changes of two major motion parameters, namely the ratio of amplitude to wavelength and body length normalized wavelength. The proposed model indicates that the worm is able to turn by causing the changes in these two parameters, which is consistent with what we observe in experiments.

3290-Pos Nf-kappaB Subunit P65 Antagonizes The Nrf2-are Pathway By Depriving Cbp From Nrf2 And Facilitating Recruitment Of Hdac3 To Mafk

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Board B593

Constitutively activated NF-κB occurs in many inflammatory and tumor tissues. Does it interfere with anti-inflammatory or anti-tumor signaling pathway? Here, we report that NF-κB p65 subunit repressed the Nrf2-antioxidant response element (ARE) pathway at transcriptional level. In the cells where NF-κB and Nrf2 were simultaneously activated, p65 unidirectionally antagonized the transcriptional activity of Nrf2. In p65-overexpressed cells, the ARE-dependent expression of heme oxygenase-1 was strongly suppressed. Experiments with luciferase reporters containing AREs of various anti-inflammatory genes showed that overexpression of p65 significantly inhibited the Nrf2-mediated ARE-driven gene expression, while knockdown of the endogenous NF-κB obviously enhanced the Nrf2-mediated gene expression. However, it was found that p65 inhibited the ARE-driven gene transcription in a way that was independent on its own transcriptional activity. Immunoprecipitation analysis showed that overexpression of p65 inhibited, but knockdown of p65 enhanced the association of CREB binding protein (CBP) to Nrf2. Chromatin immunoprecipitation study showed that overexpression of p65 also increased the MafK-associated histone deacetylase 3 (HDAC3) and reduced acytilation of histone H4 in chromatin level.

In summary, two mechanisms were found to coordinate the p65-mediated repression of ARE:

1. p65 selectively deprives CBP, the co-activator of Nrf2, from Nrf2 by competitive interaction with the CH1-KIX domain of CBP, which results in inactivation of Nrf2. The inactivation depends on PKA catalytic subunit-mediated phosphorylation of p65 at S276.
2. p65 promotes recruitment HDAC3, the co-repressor, to ARE by facilitating the interaction of HDAC3 with either CBP or MafK, leading to local histone hypoacetylation.

This investigation revealed the participation of NF-κB p65 in the negative regulation of Nrf2-ARE signaling, and may provide a new insight into a possible role of NF-κB in suppressing the expression of anti-inflammatory or anti-tumor genes.