characterizes the mechanism of HP35 folding. The three alpha helices in HP35 exhibit distinct patterns of formation, and each forms at a different stage in the folding process. The one-dimensional free energy profile is computed by integrating the mean force along the folding pathway and roughly two major energy barriers are observed. The biggest folding energy barrier is estimated to be 4.1 kcal/mol and the second one about 3.3 kcal/mol. The two major free energy barriers divide the whole folding process into three metastable states, namely the unfolded, native and a partially folded state in between, which is characterized by an aromatic core including residue Phe6, Phe10 and Phe17. This three-state picture is consistent with the biphasic kinetics inferred from previous laser temperature jump experiments and a recent computational study using temperature replica exchange MD simulations. Markov states model (MSM) is then built to estimate the rate of folding. We find that folding time scale implied from MSM is much faster than experimental folding time, although good Markovian behavior is observed in present model. Possbile reasons for this difference and alternative ways to improve the MSM are discussed.

3043-Pos Board B90
Protein Coarse-Grain Potentials for Folding Simulations
Marcos R. Betancourt.
IUPUI, Indianapolis, IN, USA.
Protein coarse-grained models are simplified representation of proteins that in principle can be used to perform long time scale simulations for the study of their folding dynamics, thermodynamics, and native structures. The main challenge in realizing these models is to find a physically accurate energy parameterization. Here two approaches are considered for this purpose. The first is the popular knowledge based potential approach, where the energies are extracted from the sequence and structure of known proteins. The advantages and limitations of this approach are examined from the perspective of minimal lattice models. It is concluded that this approach is less accurate in the determination of non-bonded interactions. The other approach involves the straightforward coarse-graining of individual residue pairs by performing molecular dynamics simulations. This approach does not suffer from the approximations involved in knowledge-based potentials and have the advantage that their quality can be controlled. The final energy model is built from a balanced combination of knowledge based potentials and coarse-grained interactions from molecular dynamics. Applications of this model to protein structure prediction are presented.

3044-Pos Board B91
Pressure-induced Structural Changes Of Amyloid-β Peptide:a Md Simulations Study
Jihua Wang, Xiuping Luo.
Key lab for bioinformatics in universities of Shandong, 253023, Dezhou, Shandong, China, Dezhou, China.
Major constituents of the amyloid plaques found in the brain of Alzheimer's patients are the 39-43 residue amyloid-β(Aβ)peptide. Extensive in vitro as well as in vivo biochemical studies have shown that 40- and 42-residue peptides play major roles in the neurodegenerative pathology of Alzheimer's disease (AD). It is known that Aβ40 and Aβ42 have obvious different conformation in its native state, even though they differ in only two (IA) amino acid residues at the C-terminal end. In this study, to characterize the pressure-induced structural changes in both Aβ40 and Aβ42 peptide monomers, we perform 6 independent long-time molecular dynamics (MD) simulations at variable pressure of 0.1Mpa, 200Mpa and 1000Mpa for total of 360ns. In aqueous solution, α-helix to β-sheet conformational transition for Aβ40 under the pressure of 200Mpa was observed, and higher pressures such as 1000Mpa could retain the unfolding rate of α-helix. However, the pressure-induced structural change of Aβ42 was different from Aβ40, under 200Mpa pressure, the β-sheet in Aβ40 of propensity increases, and the high pressure can restrain the Aβ42 to from β-sheet. The results of MD simulations are beneficial to understanding the mechanism of amyloid formation and designing the compounds for inhibiting the aggregation of Aβ and amyloid fibril formation.
Keywords: Amyloide-β peptide, Molecular dynamics simulation, conformational transition, Pressure

3045-Pos Board B92
Atomistic and Coarse-grained MD study on mutated alpha-Synuclein in Water Box
Hongyi Yang, James C. Patterson, James C. Patterson.
UAB, BIRMINGHAM, AL, USA.
Alpha-synuclein (αS) belongs to a natively unstructured protein family. The misfolded αS is recognized as a possible causative agent in the pathogenesis of Parkinson's disease (PD). Genetic studies have identified two dominant mutations A30P and A53T, which are associated with the early onset of PD. We show here that these two mutants observably affect the folding process of αS in a water box. Based on the NMR minimized average structure (PDB ID = 1XQ8) of the wild type (WT) αS, three mutated αS models are created: αS with mutation A30P; αS with mutation A53T; αS with mutation A30P and A53T. The WT αS model is also used for comparison. For each simulated system, which contains a monomeric protein and a water box, the temperature and pressure were set as constant: 300K and 1atm. Atomistic simulations were performed for 30 ns each, using CHARMM22/CMAP force field (MacKerell et al, 2004). Then, using the MARTINI force field v2.1 (Marrink et al, 2008), coarse-grained simulations were performed for 400ns each to simulate the conformation changes of αS over a longer time scale. The coarse-grained simulations demonstrate similar equilibrium structures for both mutated and WT αS systems. In addition, the atomistic simulations indicate that the two mutations significantly increase the rate of denaturation in the N terminus.

3046-Pos Board B93
Deciphering Protein Mechanical Stability By Comparing Different Folds
Morten Källberg, Georgi Z. Genchev, **Gamze Gürsoy**, Hui Lu.
University of Illinois at Chicago, Chicago, IL, USA.
Cellular functionality is in large dependent on the ability to respond properly to external stimuli thorough signaling networks. Traditionally, this concept has been described by means of chemical reaction pathways, however, lately it has become apparent that mechanical force also plays a crucial role in many physiological processes. Signal transduction is achieved by regulating the reversible folding and binding of single proteins. The combination of single molecule force measurement and computer modeling has been used successfully in studying such force induced protein signaling events. Steered molecular dynamics (SMD) is one of the most popular simulation methods used in such modeling.
In this work, we systematically use SMD to investigate the mechanical properties of a number of proteins involved in mechanical signaling events. Specifically, SMD illustrates the atomic level protein conformational changes induced by mechanical forces. These conformational changes have been used to propose means by which mechanical and chemical signals are interconnected to achieve regulatory ends. Additionally, we are able to compare the relative mechanical stability of different folds, thereby eluding to how certain folds are specifically tailored to withstand mechanical stress.

3047-Pos Board B94
Super-proteins From Fitness-threshold Selection Statistics
David Rodriguez-Larrea[1], Raul Perez-Jimenez[2], Inmaculada Sanchez-Romero[1], Rocio Arco-Gonzalez[1], Asuncion Delgado[1], Julio M. Fernandez[2], Josè Manuel Sanchez-Ruiz[1].
[1]University of Granada, Granada, Spain, [2]University of Columbia, New York, NY, USA.
It is in principle possible to assign a fitness value (organism reproductive rate) to every sequence of any given protein. The resulting fitness landscape can be regarded as the convolution of two mappings: one from genotype to phenotype with another mapping from phenotype to fitness. Despite this intrinsic complexity, we may expect organism fitness to depend on protein properties bearing upon catalysis, interactions with other molecules, stability, et cetera. However, the specific relation between fitness, sequence space, evolution and protein molecular properties is not understood, a fact which hampers efforts to tap the enormous potential for protein and organism engineering contained in the exponentially-growing sequence databases. Here we show that a simple evolutionary hypothesis on the statistics of purifying natural selection over a fitness threshold is operational and leads to protein multi-feature optimization. We thus obtain variants of E. coli thioredoxin showing simultaneous, large-scale optimizing modulations in stability, folding/unfolding kinetics, bulk-solvent oxidoreductase activity and the two chemically and evolutionary different mechanisms of enzymatic catalysis revealed by single-molecule force clamp spectroscopy. Furthermore, preliminary experiments suggest that these variants may induce in-vivo resistance to thermal and oxidative stresses. We anticipate, therefore, applications in fields that involve organism engineering (microbial biotechonology, synthetic biology).

3048-Pos Board B95
Molecular Modeling of Folding and Preferred Regioisomer Formation in α-Conotoxins
Aaron P. Osysko, Pedro L. Muíño.
Saint Francis University, Loretto, PA, USA.