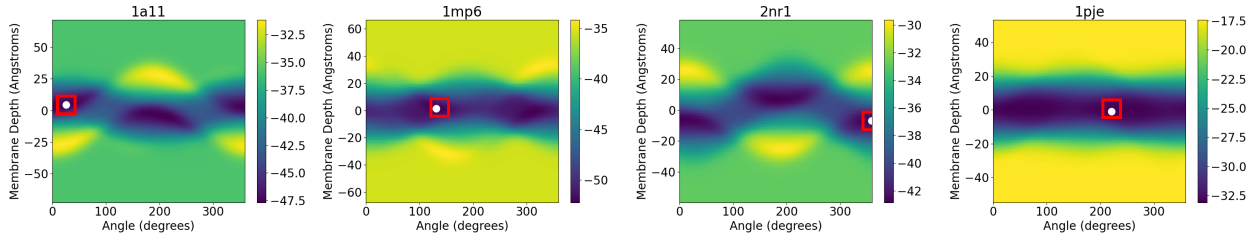
Scientific test: mp_f19_energy_landscape

FAILURES

None

RESULTS



AUTHOR AND DATE

Rebecca F. Alford (ralford3@jhu.edu)

PI: Jeffrey J. Gray (Johns Hopkins ChemBE)

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PURPOSE OF THE TEST

The purpose of this test is to evaluate the scientific performance of franklin2019, the default energy function for membrane protein structure prediction and design. Specifically, the computed insertion depths and tilt angles of 5 peptides are compared to experimental values.

BENCHMARK DATASET

The benchmark dataset includes five transmembrane peptides. Each peptide has an NMR structure and a tilt angle measured by solid-state NMR. The first four targets (2nr1, 1a11, 1mp6, and 1pje) were taken from [1]. The fifth target, WALP23 was taken from [2].

1. Ulmschneider MB, Sansom MSP, Di Nola A (2005) "Evaluating tilt angles of membrane-associated helices: comparison of computational and NMR techniques" Biophys J 90(5): 1650-1660

2. Holt A, Koehorst RBM, Rutters-Meijneke T, Gelb MH, Rijkers DTS, Hemminga MA, Antoinette-Killian J (2009) "Tilt and rotation angles of a transmembrane model peptide as studied by fluorescence spectroscopy" Biophys J 97(8): 2258-2266

The input files are the PDB coordinates for each peptide downloaded from the Protein Databank. Instead of spanfiles, we specify the "single_TM_mode" option, indicating that the protein is a single-TM segment. The PDB coordinate files were cleaned using the `clean_pdb.py` script.

PROTOCOL

This scientific benchmark identifies low-free energy peptide orientation by calculating an energy landscape: a mapping between all possible orientations relative to the membrane and their energies. Orientation is defined by two coordinates: distance between the center of the membrane and center-of-mass of the peptide, and (2) angle between the membrane normal and helical axis. The protocol first applies side-chain packing and minimization to resolve steric clashes in the peptide structure. Then, rigid body moves are applied to sample all combinations of angle and depth values. Membrane depth values are sampled between -60Ã… and 60Ã… with a 1Ã… step size and tilt angles are sampled between 0-360 degree with a 1 degree step size.

For each peptide, the protocol takes approximately 1-2 CPU hours (for a total 10 CPU hours).

The membrane energy landscape sampling protocol is described in:

(Alford, R. F., Fleming, P. J., Fleming, K. G. & Gray, J. J. Protein Structure Prediction and Design in a Biologically Realistic Implicit Membrane. Biophys. J. 118, 2042â€“2055 (2020).)

PERFORMANCE METRICS

There are two key performance metrics for this test. The first is the water-to-bilayer partitioning energy of the peptide, calculated as the energy difference between a peptide submerged in water and a peptide oriented vertically in the membrane. The test passes if the calculated partitioning energy is within +/- 1REU of the calculated value from the franklin2019 score function.

The second metric is the minimum energy tilt angle and membrane depth. The test passes if the calculated orientation is within +/- 2Ã… and +/- 10Ëš of the experimentally determined orientation as defined in the cutoffs file.

KEY RESULTS

The white dots in the plots are the computed minima in the energy landscape, not the experimentally determined values. The result.txt file contains which measurements are failing, if any. The water-to-bilayer partitioning energy, delta G should be less than 0 for all peptides to ensure that the peptides partition into the membrane. Further, the low-energy peptide orientations should generally be between 0-45 degrees tilted relative to the membrane normal and no more than +/- 5Ã… from the membrane center. Exceptions here are WALP23 with an 82Ëš angle and 2nr1 with a distance of 6.7Ã… from the membrane center. Note that these values have been experimentally determined.

DEFINITIONS AND COMMENTS

The membrane normal and center, in addition to the coordinate frame setup are described in:

Alford RF, Koehler Leman J, Weitzner BD, Duran AM, Tiley DC, Elazar A, Gray JJ (2015) "An integrated framework advancing membrane protein modeling and design" PLoS Comput. Biol. 11 (9):e1004398.

LIMITATIONS

Better quantification metrics for the full energy landscape would be beneficial. WALP23 was taken out because it fails hard in angle_min and moderately in z_min. The data remains in the scientific test code even though it is neither tested nor plotted. It would be beneficial if this could be looked at.