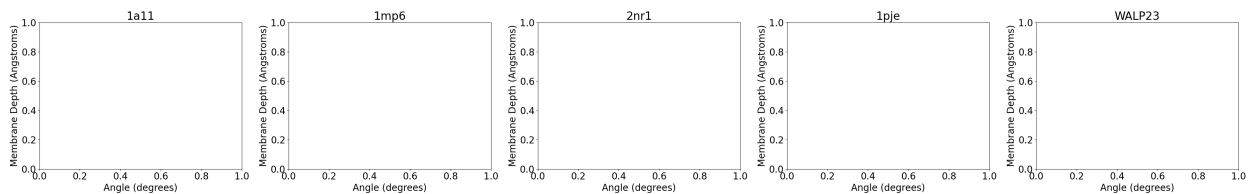# Scientific test: mp_f19_energy_landscape

FAILURES

None

RESULTS

AUTHOR AND DATE

THE RESULTS OF THIS TEST ARE NOW MOVED TO mp_f19_tilt_angle TEST.

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Test created 6/6/19 and then editted on 05/11/21

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.

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, WALP3. 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 three coordinates: distance between the center of the membrane and center-of-mass of the peptide, and (2) angle between the membrane normal and the axis of the peptide and (3) azimuthal angle rotation about the axis of the peptide. 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 the two angles and the depth values. Membrane depth values are sampled between -60Ã… and 60Ã… with a 1Ã… step size, the tilt angles are sampled between 0-180 degree with a 1 degree step size, and the azimuthal angles are sampled between 0-360 degree with a 45 degree step size. The energy landscape shown here is obtained by minimizing over all azimuthal angles. The energy landscapes were also found to be symmetrical about the tilt angle of 90 degrees and the center of the membrane.

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:

3. Alford RF, Samanta R, Gray JJ (2021) "Diverse scientific benchmarks for implicit membrane energy functions" Journal of Chemical Theory and Computation (under review)

4. Alford RF, Fleming PJ, Fleming KG, Gray JJ (2020) "Protein structure prediction and design in a biologically-realistic implicit membrane" Biophys J 180(8): 2042-2055

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 previously calculated value. 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 previously calculated orientation. In addition, the energy landscape mapping will be plotted and checked through visual inspections.

KEY RESULTS

The white dots in the plots are the computed minima in the energy landscape, and where applicable the experimentally measured orientations are shown in red triangle. The black dashed lines are the constant

franklin2019 energy lines. In addition, each grid point is colored by the franklin2019 energy, with low energies in blue and the higher in yellow.

In The water-to-bilayer partitioning energy, delta G should be less than 0 for all peptides. Further, the low-energy peptide orientations should be between 0-45 degrees tilted relative to the membrane normal and no more than +/-5Ã… from the membrane center. The results are compared to two prior membrane energy functions, a knowledge-based model and an organic-solvent based model in [4].

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.

Alford RF, Samanta R, Gray JJ (2021) "Diverse scientific benchmarks for implicit membrane energy functions" Journal of Chemical Theory and Computation (under review)

LIMITATIONS