Poster E-11

Simulation of Amino Acid Solvation Structure in Transmembrane Helices and Implications for Membrane Protein Folding

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Short Abstract: We report on extensive molecular dynamics simulations used to quantitativly study the atomic scale structure and dynamics of interactions between hydrophilic residues in transmembrane helices and the bilayer environment. The main conclusion is that hydrophilic residues retain solvation water in amounts that correlate well with experimental hydrophobicity scales.

Long Abstract:

Membrane proteins play key roles in a wide range of processes in the cell, including transport and signaling. The classical view has long been that exposed residues are almost exclusively hydrophobic due to the non-polar lipid membrane environment. There are however transmembrane helices containing charged and polar amino acids and it has been shown experimentally by e.g. Hessa et al. [1] that it is possible to incorporate these hydrophilic amino acids into the membrane as long as they are counterbalanced by enough surrounding hydrophobic residues. Several studies have investigated interactions between membrane proteins and lipid bilayers in the context of integration of polar and charged amino acids in transmembrane segments and the effects this might have on structure and stability. Polar residues in transmembrane segments tend to be less mutable, indicating their structural and functional importance [2], they have e.g. been shown both to drive association of transmembrane helices in the membrane [3] and bind Heme groups in Cythochrome C oxidase [4]. Studies on existing structures of membrane proteins have shown that the side chains of polar residues located in lipid bilayers tend to be directed away from the membrane core [5, 6], a phenomenon referred to as snorkeling. Snorkeling causes a N to C-terminal composition bias since most polar amino acids are better able to snorkel their polar atoms away from the membrane core at the N-terminus than at the C-terminus [5]. It has also been observed that polar amino acids can form hydrogen bonds with lipid head groups and intramembrane solvation water [7], but to our knowledge the phenomenon has not yet been further evaluated or quantified.

Here, we report on extensive molecular dynamics simulations (3.5 microseconds of aggregated time) used to quantitativly study the atomic scale structure and dynamics of interactions between hydrophilic residues and the bilayer environment. The structural effects of amino acid substitutions in transmembrane helices have been evaluated and quantified using a model system similar to experimental ones [8, 1]. Results have been classied not only for all amino acids, but also as a function of the z-position in the helix.

Polar and charged residues retain signicant amounts of solvation water, even to the extent where many of them exist in a microscopic water environment without major distortion of the

membrane. Both solvation water amounts and hydrogen bonding patterns exhibit clear position dependence; hydration water around amino acids in the headgroup region exchange rapidly with the bulk solvent, while water retained deeper into the membrane normally requires 5-10 nanoseconds (sometimes even < 15ns) for the exchange to happen. Basic sidechains are found to frequently form hydrogen bonds with lipid carbonyl groups, a pattern we also confirm by a narrower dip in their relative occurrence inside bilayers compared to acidic residues. Interestingly, this also seems to have caused a slight evolutionary pressure on the overall amino acid distribution in membranes proteins: after subtracting the general positive-inside trend, the basic sidechains exhibit an increased relative occurrence at exactly the same z-coordinates as where the carbonyl groups are located.

Both snorkeling effects as well as N-C terminal composition bias are reproduced by simulations. Further, when pairs of charged residues are introduced close to the center of transmembrane helices, the strong snorkeling preference in combination with their relative locations will cause free helices to tilt (charges on opposite sides) or bend (charges on same side).

The total amount of hydration water retained around different types of amino acid side chains correlate well both with the experimental Wimley-White (water-octanol) [9] and the in vivo Hessa/von Heijne hydrophobicity scales [1]. In other words, these results strongly support the hypothesis that even the translocon mediated membrane protein insertion does not involve any active selection filter, but merely acts as a catalyzer to remove the entropic barrier associated with insertion.

In addition, the retained water has quite interesting implications for membrane helix aggregation. Moderately polar individual helices might actually be more water-solvated than previously thought, at least in the sense that there are significant amounts of water present around them. This raises the possibility of a split-timescale aggregation process, where even loose membrane helix contact can lead to a rapid reduction in water-lipid surface (and associated drop in free energy), followed by slower sidechain packing and eventual water expulsion.

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