Membrane bending is critical for the stability of voltage sensor segments in the membrane

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ABSTRACT

The interaction between membrane proteins and the surrounding membrane is becoming increasingly appreciated for its role in regulating protein function, protein localization, and membrane morphology. In particular, recent studies have suggested that membrane deformation is needed to stably accommodate proteins harboring charged amino acids in their transmembrane (TM) region, since it is energetically prohibitive to bury charge in the hydrophobic core of the bilayer. Unfortunately, current computational methods are poorly equipped for describing such deformations, since atomistic simulations are often too short to observe large-scale membrane reorganization and most continuum approaches assume a flat membrane. Previously, we developed a method that overcomes these shortcomings by using elasticity theory to characterize equilibrium membrane distortions in the presence of a TM protein, while using traditional continuum electrostatic and nonpolar energy models to determine the energy of the protein in the membrane. Here, we linked the elastostatics, electrostatics and nonpolar numeric solvers to permit the calculation of energies for non-trivial membrane deformations. We then coupled this procedure to a robust search algorithm that identifies optimal membrane shapes for a TM protein of arbitrary chemical composition. This advance now permits us to explore a host of biological phenomena that were beyond the scope of our original method. We show that the energy required to embed charged residues in the membrane can be highly non-additive, and our model provides a simple mechanical explanation for this non-additivity. Our results also predict that isolated voltage sensor segments do not insert into rigid membranes, but membrane bending dramatically stabilizes these proteins in the bilayer despite their high charge content. Additionally, we use the model to explore hydrophobic mismatch with regard to nonpolar peptides and mechanosensitive channels. Our method is in quantitative agreement with molecular dynamics simulations at a tiny fraction of the computational cost.