**Incorporating Proteins into Geometrically Complex, Cell-Scale Membrane Models for Molecular Dynamics Simulations**

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**Abstract**

The membranes that surround cells and organelles play a vital role in biological function, acting as semipermeable barriers that separate and protect cells and organelles from their surroundings. Molecular dynamics (MD) simulations provide the means to investigate the fundamental molecular mechanisms that give rise to membranesâ€™ biological functions, but it is exceedingly difficult to build MD models that capture cellular membranesâ€™ immense scales and complex geometries. To address this challenge, we previously introduced software called xMAS (Experimentally-Derived Membranes of Arbitrary Shape) Builder, and we used it to generate a ~4.5 billion atom (~1.9Î¼mÂ³) model of a piece of the endoplasmic reticulum with a helicoidal shape called a Terasaki ramp. In previous work, we also ran a long-term equilibrium MD simulation on a smaller test system to demonstrate that xMAS Builder produces stable, high quality models. Used to develop and test the base capabilities of xMAS Builder, these previous models were somewhat limited in that they were composed entirely of lipids. We now introduce an updated xMAS Builder capable of incorporating proteins into its membrane models. In xMAS Builderâ€™s approach, proteins are automatically placed on a mesh representing the surface of the membrane, lipids are carefully filled in around the proteins using coarse-grained simulation-based techniques, and a sophisticated restrained equilibration procedure is used to ensure the quality and stability of the final model. With this new capability, xMAS Builder can now produce cellular membrane models that provide compelling insight into the complex molecular interactions between proteins, lipids, and the cellular environment which ultimately give rise to membrane structure and biological function.