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Mechanics and physics of HIV virus interaction with cell membranes

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ABSTRACT

A key step in the HIV infection process is the fusion of the virion membrane with the target cell membrane and the concomitant transfer of the viral RNA. Experimental evidence appears to suggest that the fusion is preceded by considerable elastic softening and thinning of the cell membranes and the formation of well-defined pores. What are the precise mechanisms underpinning the elastic softening of the membrane upon peptide insertion? A clear understanding of this could potentially pave the way for intelligent drug design to combat the epidemic caused by this deadly virus. State-of-the-art experiments to understand the HIV peptide insertion with T-cell membranes have been conducted recently. Using diffuse X-ray scattering, they deduced the bending modulus of the membranes upon HIV fusion peptide addition. Depending on the type of membrane, they found that the bending modulus (i.e., the property which dictates how resistant a membrane is to mechanical bending) can reduce between 3 and 13 times. This enormous mechanical softening greatly facilitates the subsequent fusion and infection process. Although the experimental findings are quite interesting, very little atomistic insights were gleaned. In short, modeling or simulations are necessary to interpret the aforementioned experiments and then provide guidelines for computationally driven rationale drug design. Predicated on the hypothesis that understanding, at the atomistic level, the membrane softening due to HIV peptide insertion will enable countermeasures, we have conducted large-scale molecular dynamics simulations on the interaction between HIV fusion peptide and cell membrane. Such simulations require modeling millions of atoms that interact with each through a complicated set of forces. The dynamics of such an ensemble was then studied and interpreted. For example, although the experiments were able to measure the overall reduction in bending modulus of the membrane – upon interaction with the HIV peptide – the key physics lies in what is happening locally at the peptide–membrane insertion interface. What exactly happens there that causes an overall softening of the membrane? In principle, insertion of rigid proteins or peptide in membranes ought to stiffen the membrane not soften it thus rendering the experimental observations even more perplexing. To this end, we have devised a numerical “experiment” which involves (computationally) sticking a needle into the membrane region of interest. Through derived theoretical formulae, and observation of the response of the atoms in the simulation when subject to the needle probe, we estimated the elastic behavior of a small and local patch of the membrane as opposed to the entire membrane itself. This, and the direct observation of the atomic behavior, allowed us to understand precisely what occurs at the peptide–membrane interface.