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Influenza Viral Membrane Deformation Due to Refolding of HA-Protein: Two-dimensional Model and Analysis

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Abstract. In this paper we study influenza viral membrane deformation related to the refolding of Hemagglutinin (HA) protein. The focus of the paper is to understand membrane deformation and budding due to experimentally observed linear HA-protein clusters, which have not been mathematically studied before. The viral membrane is modeled as a two dimensional incompressible lipid bilayer with bending rigidity. For tensionless membranes, we derive an analytical solution while for membrane under tension we solve the problem numerically. Our solution for tensionless membranes shows that the height of membrane deformation increases monotonically with the bending moment exerted by HA-proteins and attains its maximum when the size of the protein cluster reaches a critical value. Our results also show that the hypothesis of dimple formation proposed in the literature is valid in the two dimensional setting. Our comparative study of axisymmetric HA-clusters and linear HA-clusters reveals that the linear HA-clusters are not favorable to provide a sufficient energy required to overcome an energy barrier for a successful fusion, despite their capability to cause membrane deformation and budding.

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1 Introduction

An influenza virus first attaches to a host cell surface via a sialic acid binding site and

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then enters the cell by endocytosis process. In the cytoplasm of the cell, when pH-value is lowered, hemagglutinin (HA) protein anchored in the viral membrane undergoes a conformational change [7,11,13]. HA is a trimer of three monomers anchored in the membrane, connected to each other forming a triple-stranded α-helical coiled-coil. During conformational change, recruitment of additional residues to the coiled-coil as well as tilting of the HA-molecule take place [2, 6, 7, 18, 32, 35]. This process exerts force on the membrane. As a result, the membrane deforms leading to a budding to mediate efficient virus-cell fusion.

A study of pre-fusion membrane deformation and budding is important in order to understand the fusion of two membranes, which is the key stage for virus infection and replication. Understanding the role of HA-protein in deforming membrane is useful for various purposes such as disease control and drug/vaccine design. Recently, an antibody has been identified, which can recognize a highly conserved helical region in the membrane-proximal stem of HA1/ HA2 [10, 30]. This antibody is found to be capable of neutralizing the viruses behind bird flu and the 1918-19 flu pandemic along with some of the common strains that cause seasonal flu, by blocking conformational rearrangements associated with membrane fusion. Since the helix identified by that antibody and fusion peptides of HA, which enter the target cell membrane are highly conserved among influenza viruses of different strains, vaccines or/and drugs targeting these regions of HA causing fusion inhibition are more efficient to disable multiple varieties of the flu virus [10,30], which becomes more important during influenza pandemic. It is thus becoming more essential to understand membrane deformation and budding mechanism governed by HA-protein.

Even though the deformation of membrane due to HA-protein is very important, few attempts have been made to quantitatively study this process. In [18], it was hypothesized that the activated HA-protein can produce viral membrane dimples surrounded by a ring-like cluster of HA. They have assumed that the top of the dimple is a segment of perfect sphere connected to a funnel of a catenoid form (an axisymmetric surface with zero mean curvature). Similarly, in [19], HA has been assumed to produce a perfectly spherical top of the dimple. In [25], the formation of a dimple was also favored as a mechanism for membranes to make intimate contact which leads to subsequent fusion between membranes. For an axisymmetric membrane, we have computed numerically the formation of the dimple caused by a ring-like HA-protein cluster [36].

In reality, the distribution of HA-proteins depends on membrane compositions, and especially a quit distinct distribution has been observed between lipid rafts (microdomains enriched in sphingomyelin and cholesterol) and nonraft regions of the membrane [16, 20, 31]. It was found experimentally in [16, 20, 31] that they typically form clusters in the raft-associated membrane sections while nonraft HA distributed mostly randomly at the plasma membrane. It has been estimated that as mush as $\sim$ 50% of the cellular membrane exists as lipid rafts [20]. Furthermore, experimental evidence shows that influenza virus buds from rafts while nonraft HA contains reduced amount of infectivity because HA clusters in rafts provide a sufficient con-