Fusion vs. endocytosis in receptor/coreceptor-mediated entry of enveloped viruses

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***Short Abstract* — Viral infection requires that host cell receptors and possibly coreceptors bind to glycoproteins, or ``spikes,'' on the viral membrane. Both fusion and endocytosis have been observed to be viable entry pathways for many viruses. We develop a stochastic model for the entry of viruses that require receptor engagement for endocytosis and coreceptor engagement for fusion. In this model, coreceptors bind only to viral spikes that have a receptor bound. The relative probabilities of viral entry by fusion and endocytosis are computed as functions of the receptor and coreceptor binding rates, and number of spikes.**

I. Introduction

THE entry of enveloped viruses into cells requires topological changes in the membranes of both the virus and host cell. Entry mechanisms are usually classified as either being endocytotic, or being initiated by membrane fusion. In fusion, the virus membrane becomes contiguous with the cell membrane. In endocytosis, the host cell internalizes the virus by wrapping it in an endosomal vesicle.

A number of viruses are known to enter cells via either fusion or endocytosis [1,2]. HIV is one such virus, and requires a receptor, CD4, for endocytosis, and both CD4 and a coreceptor, usually CXCR4 or CCR5 to fuse with the host cell membrane[3,4]. HIV infects cells with which it fuses, and is typically inactivated upon endocytosis[4].

Previous work[5] has examined the dynamics of viral entry when a single type of cell receptor binds viral spikes, deforming the membrane *and* promoting fusion. In this work, we develop a stochastic model that describes viral entry when a receptor binds to viral spikes to deform the membrane, and a co-receptor must bind to the spikes to promote fusion. The selection of entry pathway is computed as a function of the kinetic rates in the model.

II. Mathematical Model

We assume that receptors on a host cell membrane bind to spikes uniformly distributed on the virus surface. We define a ``contact line'' on the virus below which all spikes are occupied by a receptor and above which no spike is occupied. The instantaneous receptor binding rate is proportional to the number of spikes within a distance l above the contact line. After receptor binding, coreceptors may bind to the receptor-spike complex. Each spike can bind at most one receptor and one coreceptor, and a spike can bind a coreceptor only after it has bound a receptor. The coreceptor binding rate is thus proportional to the number of spikes with a receptor, but no coreceptor bound. Because of binding energies are ~10-20 kT [6], we do not consider unbinding of receptors or coreceptors. The virus may undergo fusion while partly or fully wrapped, with a rate proportional to the number of bound coreceptors. Once the virus becomes fully wrapped, it undergoes endocytosis at a constant rate. We solve the resulting master equations numerically and obtain an analytic solution in the limit where the number of viral spikes is large.

III. Results/Conclusions

In our model, viruses enter the host cell via either fusion or endocytosis. Therefore, it is sufficient to consider only the probability that the virus undergoes endocytosis. For the virus to undergo endocytosis: 1- it must become fully wrapped, and 2- once it becomes fully wrapped, endocytosis must occur with a faster rate than fusion. We first derive conditions, which depend on the receptor and coreceptor binding rates, and on the fusion rate, that the virus becomes fully wrapped (condition 1). When coreceptor binding is fast compared to receptor binding, condition 1 is independent of the coreceptor binding rate. When coreceptor binding is slow compared to receptor binding, condition 1 depends on the coreceptor binding rate and slow coreceptor binding can compensate for a large fusion rate, increasing the probability that the virus becomes fully wrapped. We additionally find the conditions under which a fully wrapped particle ultimately enters the cell via endocytosis. This (condition 2) depends on the fusion rate, the endocytosis rate, the coreceptor binding rate, and the number of viral spikes. Finally, we investigate the dependence of the mean time to entry and the mean number of receptors and coreceptors bound at entry on model parameters.

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