Computational modeling of adhesive contact between a virus and a cell during receptor driven endocytosis

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The present contribution deals with the viral entry into a cell dictated by the change of the receptor density. While the receptors of the virus are considered to be fixed on its surface, the ones of the cell are mobile within its membrane. Upon contact, a locally increased receptor density of the cell is required, which causes it to diffuse towards the virus. The membrane inflicts and forms an envelope around the virus in the contact zone. The described problem is simulated on the basis of the assumption that the differential equation typical of the heat transport is suitable to describe the diffusion of receptors. Furthermore, two boundary conditions are proposed. The first condition deals with the balance of fluxes on the front of the adhesion zone, where the velocity is supposed to be proportional to the gradient of the chemical potential. The second condition represents the energy balance equation with contributions due to the binding of receptors, the free energy of the membrane, its curvature and the kinetic energy due to the motion of the front. The selected numerical example shows the change of the receptor density over the membrane as well as the motion of the front of the adhesion zone. Special attention is paid to the mobility of the receptors.

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1 Introduction

One of the main mechanisms used by viruses in order to enter a cell is receptor driven endocytosis [1]. During this process the virus connects its receptors to the receptors of the cell. This causes the cell membrane to bend and to build a vesicle around the virus. The process is characterized by the ability of the receptors of the cell to move freely within its membrane, while the receptors of the virus are fixed and occur with a much higher density. Upon contact, the virus dictates the required receptor density for bonding, thus causing the receptors of the cell to move towards the contact area. As a consequence, the contact area grows while the local receptor density of the cell changes, resulting in a moving boundary problem.

2 Endocytosis as moving boundary problem

At the beginning of the process a virus connects to the cell and splits the cell membrane into two areas separated by an adhesion front. These two areas are characterized by the distribution of the receptor density $\xi(x, t)$. In the contact area the cell receptor density matches the constant receptor density of the virus $\xi(x, t) = \xi_{eq}$. In the area in front of the adhesion zone the density is a function of position and time $\xi(x, t)$ with its minimum at the adhesion front, where $\xi(x, t) = \xi_+$. Since the cell size is orders of magnitudes larger than the virus size, the density profile remains unchanged far away from the contact area $\lim_{x \to \infty} \xi(x, t) = \xi_0$. The motion of the receptors on the cell surface is based on the diffusion differential equation depending on the mobility $m$, i.e.

$$\frac{\partial \xi}{\partial t} = m \frac{\partial^2 \xi}{\partial x^2}. \tag{1}$$

A solution of this partial differential equation requires additional boundary conditions. The conservation of binders is considered first. It states that the amount of receptors required for the advancement of the adhesion front has to be equal to the amount of receptors provided by the flux. Following Fick’s first law, the diffusion equation leads to the first boundary condition

$$(\xi_{eq} - \xi_+) v_+ - m \left[ \frac{\partial \xi}{\partial x} \right]_+ = 0, \tag{2}$$

which depends on quantities related to the adhesion front [2]. Here, $v_+$ denotes the velocity of the front. For the second boundary condition an approach considering the energetic aspects of the front motion is chosen [3]. The front movement, represented by the kinetic energy $E_{kin} = \frac{1}{2} k T \xi_{eq} v_+^2$ is caused by the difference in the energy in front of and behind the front, each consisting of several contributions denoted by superscript "-" behind the front and superscript "+" in front of the front. Thus,

$$E^-_b + E^-_e + E^-_nu - E^+_b + E^+_e + E^+_nu = E_{kin}. \tag{3}$$

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Behind the front, $E_b^- = - k T C_b \xi_{eq}$ denotes a reduction in the free energy due to the binding of receptors, with $k$ being the Boltzmann constant, $T$ the absolute temperature and $C_b$ a reduction factor. The term $E_c^- = k T \xi_{eq} \ln \left( \frac{\xi_{eq}}{\xi_0} \right)$ represents the energy associated with the entropy of receptors. Here, the initial binder density $\xi_0$ is adopted as a reference value. The term $E_v^- = \frac{1}{2} k T B \kappa^2$ represents the energy related with bending, where $\kappa$ is the curvature of the membrane and where $B$ is the bending stiffness. In front of the front $E_c^+ = k T \xi_v \ln \left( \frac{\xi_v}{\xi_{eq}} \right)$ represents the energy associated with the entropy of receptors. The term $E_v^+ = \frac{1}{2} k T \xi_v v_i^2$ represents the kinetic energy of the receptors in front of the front moving towards the adhesion area, with $v_i$ being their corresponding velocity. Finally, the second boundary condition is expressed in terms of the receptor density $\xi(x,t)$ and the front velocity $v_r$ by

$$
\left[ - \xi_{eq} C_b + \xi_{eq} \ln \left( \frac{\xi_{eq}}{\xi_0} \right) + \frac{1}{2} B \kappa^2 \right] - \left[ \xi_v \ln \left( \frac{\xi_v}{\xi_{eq}} \right) + \frac{1}{2} k T \xi_v v_i^2 \right] = \left[ \frac{1}{2} \xi_{eq} v_i^2 \right].
$$

The corresponding non-linear system of equations is implemented by using the finite difference method and is solved numerically by a Newton Raphson scheme.

### 3 Numerical results

The chosen numerical example models the uptake of a spherical virus. Due to the symmetry of the virus and the contact cell area, the simulation is performed in 2D, but a 3D extension is rather straightforward. The evolution of the receptor profile of the cell as well as the motion of the adhesion front are shown in Fig. 1. At the beginning of the process the receptor density at the front experiences a strong decrease and reaches $\approx 50\%$ of its initial value after 300 time steps. This decrease weakens as the time progresses. During the whole process the adhesion front advances continuously, while its velocity decreases towards a limit value. The numerical results are strongly influenced by the mobility parameter $m$ which measures how fast the cell can provide receptors to the adhesion zone. Further important factors are the initial receptor density of the virus as well as the cell [3].

![Fig. 1: Receptor density over the cell surface for the time steps 0 - 1500. Chosen process parameters are $m = 1\mu m^2/s$, $C_b = 5$, $B = 30$, $\xi_{eq} = 4800 \, 1/\mu m^2$, $\xi_v = 1000 \, 1/\mu m^2$, virus diameter $D = 0.05\mu m$.](image)

### 4 Conclusions

The present study focuses on the simulation of the influence of the binder mobility in the viral entry driven by receptor diffusion. The process is described by a diffusion differential equation accompanied by two boundary conditions. The two boundary conditions describe the flux balance and the energy balance at the adhesion front. The proposed moving boundary problem enables an efficient numerical simulation of the process and provides the basis for the consideration of additional relevant aspects. Bending of the cell in front of the adhesion front and an alternative expression for bending lipid bilayers are envisaged as topics of our future work.

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