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Pulling-induced rupture of ligand-receptor bonds between a spherically shaped bionanoparticle and the support

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ABSTRACT

Contacts of biological or biologically-inspired spherically shaped nanoparticles (e.g., virions or lipid nanoparticles used for intracellular RNA delivery) with a lipid membrane of cells are often mediated by multiple relatively weak ligand-receptor bonds. Such contacts can be studied at a supported lipid bilayer. The rupture of bonds can be scrutinized by using force spectroscopy. Bearing a supported lipid bilayer in mind, the author shows analytically that the corresponding dependence of the force on the nanoparticle displacement and the effect of the force on the bond-rupture activation energy are qualitatively different compared to what is predicted by the conventional Bell approximation.

1. Introduction

Since the seminal experiments by Gaub's and Lieber's groups [1,2], force spectroscopy has attracted attention as an effective tool allowing one to scrutinize bonds in biological macromolecules, e.g. proteins and DNA, attached to a support (reviewed in [3–5]). Such measurements, based on pulling fragments of a macromolecule or macromolecular complex apart, have become possible with the development of low-stiffness cantilevers [3]. Nowadays, the experiments of this type are often performed on the lipid membrane of cells (see, e.g., articles [6–8], reviews [5,9,10], and references therein).

The interpretation of the force-spectroscopy experimental data customarily involves analytical expressions describing the effect of pulling on the rate constants of bond rupture and formation (reviewed in [3,4,11]). In this area, the generic treatment belongs to Bell [12] who was interested in ligand-receptor-mediated adhesion between cells or cells to surfaces. Assuming each bond to be equally stressed and referring to the kinetic concepts of the strength of solids (or more specifically to [13]), he reasonably neglected the effect of force on the rate of bond formation and proposed the following expression for the rate constant of rupture of a bond

$$k_{\rm off} = k_{\rm off}^{\circ} \exp\left(\frac{\gamma F}{N k_{\rm B} T}\right), \tag{1}$$

where F is the total applied force, N is the number of bonds, γ is a parameter (length) characterizing the intermolecular interaction potential, and $k_{\rm off}^{\circ}$ is the rate-constant value corresponding to the no-force case ($F = 0$). Physically, $\gamma F/N$ represents the force-related reduction of the activation energy for rupture of a bond.

The available justifications and extensions of Eq. (1) are focused primarily on the rupture of a single bond (i.e., on $N = 1$ as reviewed in [3,4,11]; see also e.g. Refs. [14–20]) and bonds in a polymer chain (see e.g. Refs. [21–23]). In particular, the rupture of a single bond was described in detail in terms of the conventional theory of chemical rate processes or, more specifically, in the framework of the Kramers theory [14,15]. In this approach, the force-induced increase of $k_{\rm off}$ is also related primarily to the reduction of the activation energy for the bond rupture, i.e., to $\Delta E_{\rm a}$. The value of $\Delta E_{\rm a}$ is, however, calculated in more detail by employing the combined bond-cantilever potential energy which is constructed as a function of the coordinates characterizing a bond and cantilever. The generic expression for this energy is as follows [14]

$$U(x) = U_{\circ}(x) + \kappa (vt - x)^2/2, \tag{2}$$

where x is the coordinate characterizing a bond, vt is the coordinate characterizing the equilibrium position of a cantilever, $U_{\circ}(x)$ is the energy profile for the bond formation in the no-force case,

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and $\kappa(vt-x)^2/2$ is the effective harmonic bond-cantilever interaction energy (κ is the corresponding force constant). The simplest physically reasonable expression for the former energy is

$$U(x)=\begin{cases} kx^2/2 & \text{for } x\le x_\ddagger, \\ -\infty & \text{for } x>x_\ddagger, \end{cases} \tag{3}$$

where $x_\ddagger$ is the critical coordinate for rupture. For this and other energy profiles, the effect of the force on the rupture rate constant was shown to be close to that predicted by Bell [Eq. (1)] provided the force is low or, in other words, the device stiffness is small, $\kappa \ll k$ [14] (reviewed in [11]).

The contacts of biological nanoparticles (e.g. virions of typical size from 60 to 150 nm [24]) with a lipid membrane of cells are often mediated by multiple relatively weak ligand-receptor bonds. Each ligand-receptor pair typically form a relatively short chain (with length appreciably shorter than the particle radius). Such multivalent ligand-receptor-mediated interaction is also of high current interest in the context of fabrication of a new generation of drugs based on intracellular RNA delivery by biologically inspired nanoparticles of size 50–150 nm [25–27]. Now, atomic force in combination with confocal microscopy allows one to track events of binding of such nanoparticles directly on cells [28,29]. In basic studies, the multivalent interaction can be explored at the level of individual nanoparticles also on a supported lipid bilayer (the fabrication of such bilayers is reviewed in [30,31]) by employing optical tracking under stagnant or flow conditions (Refs. [32] and [33], respectively). Potentially, the force spectroscopy can be used in this case as well. In the latter context, it is of interest to scrutinize theoretically how multiple bonds between a nanoparticle and a supported lipid bilayer can be ruptured by the force applied to a nanoparticle.

In an ensemble of bonds, in general, the rupture of a bond depends on the conditions determined by the state of other bonds, and the whole rupture process can be viewed as a series of sequential events of rupture of individual bonds. Thus, to describe the whole process, one should first of all scrutinize rupture of individual bonds. As already noticed above, it was done already by Bell [12] who proposed to use Eq. (1) in this context. In his model, (i) the bonds are considered to be located between two rigid flat areas so that the locations of bonds are geometrically equivalent, (ii) the total applied force is assumed to be equally distributed among the bonds so that the force acting on a bond is equal to F/N, and (iii) the rate of rupture of a bond is postulated to be determined by the latter force, i.e., the interplay of bonds is reduced to equal partitioning of the total applied force. Later on, the force-induced rupture of multiple bonds was theoretically analyzed in other works [34–38] with emphasis on the kinetics of sequential rupture events. The rupture of individual bonds was described analytically by accepting approximations (i)–(iii) explicitly or with minor modifications [34–36] or numerically by using molecular dynamics [38].

Physically, the validity of approximations (ii) and (iii) is open for debate even if one accept approximation (i). In the case of biological or biologically inspired nanoparticles contacting a flat supported lipid bilayer, the applicability of approximation (i) is not obvious, while approximations (ii) and (iii) are not applicable because the shape of such particles are usually close to spherical and the locations of bonds are geometrically not equivalent. Herein, our goal is to scrutinize what may happens beyond approximations (i)–(iii). Following this line, we analyze first the bonds between flat contact areas (Sec. 2) and then bond-mediated contact of a spherically shaped nanoparticle with a flat surface representing a supported lipid bilayer (Sec. 3). The focus is on rupture of individual bonds or, more specifically, on the force-related reduction of the activation energy of rupture events. The model we employ includes a set of elastic chains acting in parallel (this orientation of bonds is likely in the case of nanoparticles). Although, as already noticed, the models with this orientation of bonds have already been analyzed in the literature, the aspects we discuss are novel.

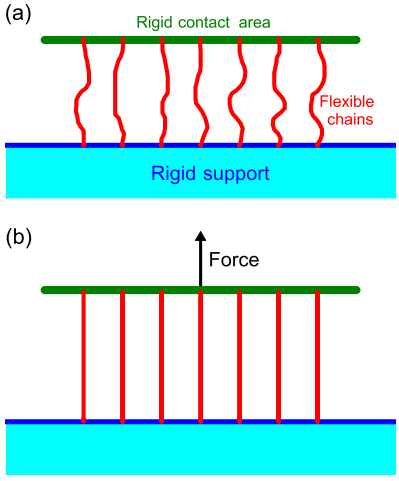

Fig. 1. Scheme illustrating two flat rigid contact areas, linked by flexible elastic chains, (a) without and (b) with the external force.

2. Bonds between flat contact areas

In this section, we focus on the simplest model implying that (i) two flat rigid contact areas are linked by N equivalent flexible elastic chains (Fig. 1), (ii) each chain is formed by two sub-chains representing a ligand and receptor, and (iii) the bonds in sub-chains are strong so that their rupture is negligible. To make the equations compact, the bonds in sub-chains are considered to have equal stiffness, k. The corresponding displacements are designated as x_{ij}, where $i\le N$ and $j\le n$ (n is the number of bonds of this type in a chain). The bond between two sub-chains is associated with the ligand-receptor contact. The latter bonds are assumed to be relatively weak with stiffness $k_*<k$ and displacements x_{*i} ($i\le N$). Under pooling conditions, they are subjected to rupture.

In the absence of the external force [Fig. 1(a)], the potential energy of the chains is represented in the harmonic approximation,

$$U=\sum_{i=1}^{N}\sum_{j=1}^{n} kx_{ij}^2/2+\sum_{i=1}^{N} k_* x_{*i}^2/2. \tag{4}$$

The use of this expression implies, as already noticed, that the chains are flexible. Physically, this means that we neglect the chain bending energy and do not impose restrictions on the relative orientation of displacements. The entropy related to different orientation of displacements is neglected as well because the number of bonds in each chain is considered to be relatively small ($n<10$).

Under the pulling conditions, the unbroken chains are assumed to be oriented in parallel [Fig. 1(b)]. Mathematically, the latter means that the displacements are constrained as

$$\sum_{j=1}^{n} x_{ij}+x_{*i}=X, \tag{5}$$

where X is the displacement of the right-hand-side contact area or, in other words, the total displacement. To calculate the displacements, we first assume that any given time the system is close to full equilibrium, which is reached at equal displacements, $x_{ij}\equiv x$ and $x_{*i}\equiv x_*$. Employing these conditions, we rewrite (5) as

$$nx+x_*=X \tag{6}$$