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Single-molecule force spectroscopy: Practical limitations beyond Bell's model

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A B S T R A C T

Single-molecule force spectroscopy experiments, and a number of other physical systems, are governed by thermally activated transitions out of a metastable state under the action of a steadily increasing external force. The main observable in such experiments is the distribution of the forces, at which the escape events occur. The challenge in interpreting the experimental data is to relate them to the microscopic system properties. We work out a maximum likelihood approach and show that it is the optimal method to tackle this problem. When fitting actual experimental data it is unavoidable to assume some functional form for the force-dependent escape rate. Focusing on escape processes over a single activation barrier, we consider a quite general and common such functional form and demonstrate by means of data from a realistic computer experiment that the maximum number of fit parameters that can be determined reliably is three. They are related to the force-free escape rate and the position and height of the activation barrier. Furthermore, the results for the first two of these fit parameters show little dependence on the assumption about the manner in which the barrier decreases with the applied force, while the last one, the barrier height in the absence of force, depends strongly on this assumption.

1. Introduction

A quite remarkable experimental achievement of the last decade is the direct observation of chemical dissociation at the single-molecule level by applying time-dependent external forces on the pico-Newton scale. This technique is called dynamic force spectroscopy or single-molecule force spectroscopy and reviewed e.g. in Refs. [1,2]. It allows to extract kinetic constants and energy landscape parameters of various interactions like antibody-antigen recognition [3] or protein-DNA interactions [4]. Also the dynamics of various other experimental systems are governed by thermally activated transitions out of a metastable state over a potential barrier, whose height decreases in time due to a steadily increasing external force. Examples include the polarization reversal in nanomagnets [5], friction at the atomic scale [6–8], and phase jumps in Josephson junctions [9,10]. In all these cases, the knowledge of the force-dependent rate out of the metastable state can be exploited to characterize the system studied. The main theme of the present work is how to perform such a characterization in the most optimal way and to point out the limitations even of such an optimized procedure under practical conditions.

A typical experimental setup is schematically sketched in Fig. 1: the single chemical bond of interest, e.g. in a ligand-receptor complex, is connected via two linker molecules with the tip of an AFM (atomic force microscope) cantilever (or some other micromechanical tool) and a piezoelectric element. The latter is employed for "pulling down" the attached linker molecule at some constant velocity, leading to an elastic reaction force of the cantilever, determined from the deflection of a laser beam. The main quantity of interest is the magnitude of the force at the moment when the bond breaks.

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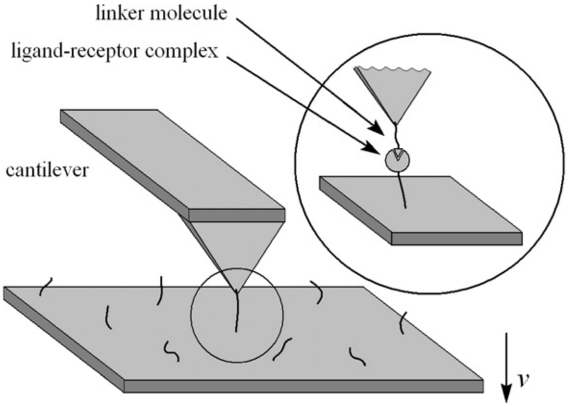

Fig. 1. Schematic illustration of a single-molecule force spectroscopy experiment. Receptor and ligand are connected via suitable linkers to the surface and the AFM tip, respectively. The distance of the tip from the surface can be controlled with a piezoelectric element (not shown). When pulled down at constant speed an (approximately linearly) increasing force acts on the bond which can be measured through the deflection of the cantilever.

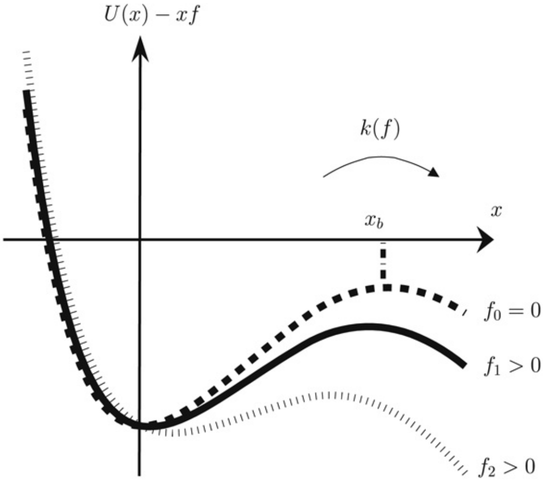

Fig. 2. Schematic illustration of the total relevant potential energy landscape $U(x) - xf$ of a receptor-ligand-bond as function of the reaction coordinate x without and with externally applied bias forces $f_1 < f_2$. For low forces the main effect is that the energy barrier $E_b(f)$ is lowered by an amount $\Delta E_b \simeq x_b f$, where x_b is the distance between potential well and barrier at zero force. For larger forces this distance decreases.

The theoretical interpretation of the observed rupture forces is a non-trivial task for the following reasons. Upon repeating the same experiment with the same pulling velocity, the rupture forces are found to be distributed over a wide range, contrary to what one would naively expect for a purely mechanical breaking of a compound object at some fixed, "critical" strain force. A further theoretical challenge represents the experimental finding that for different pulling velocities different such distributions are obtained. Hence, neither a single rupture event nor the average rupture force at any fixed pulling velocity can serve as a meaningful characteristics of a given chemical bond strength. Major steps in solving the puzzle are due to Bell [11] and to Evans and Ritchie [12], recognizing that a forced bond rupture event is a thermally activated decay of a metastable state that can be described within the general framework of Kramers reaction rate theory [13]. Subsequently, their basic theoretical approach has been extended and refined in several important directions, see e.g. Refs. [1,2,14–27].

Following Evans and Ritchie [12,1], a single-molecule dissociation process is viewed as thermally activated escape of a reaction coordinate x over a potential barrier, see Fig. 2. Given the one-dimensional potential landscape along the reaction coordinate, the dissociation rate $k(f)$ for an instantaneous force f (projected onto the direction of the reaction coordinate) can be written according to Kramers reaction-rate theory [13] in the form

$$k(f) = \omega(f)\ \exp(-E_b(f)/k_B T), \tag{1}$$

where the pre-exponential factor $\omega(f)$ has the intuitive meaning of an "attempt frequency" and the exponentially leading Boltzmann–Arrhenius factor contains the relevant potential barrier $E_b(f)$ against escape, Boltzmann's constant k_B, and the temperature T.

In dynamic force spectroscopy experiments, the rate at which the force increases is much slower than all other relevant molecular relaxation processes. Due to this separation of time scales [13], the reaction kinetics can be very accurately