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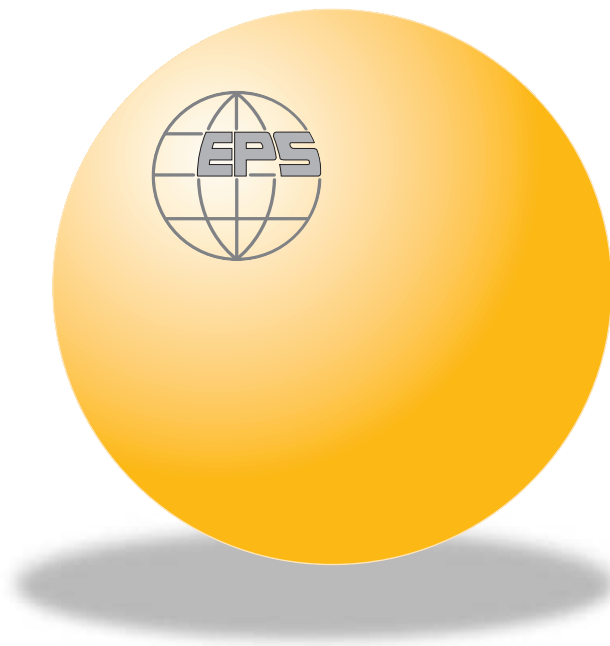
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Irreversible *vs.* reversible bridging: When is kinetics relevant for adhesion?

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Abstract. – We study theoretically the adhesion between two approaching surfaces, one containing tethered ligands and the other receptors. Using the reaction-diffusion formalism, we show that the range of adhesion ℓ_r is generally determined by a combination of tether dynamics, ligand-receptor affinity and experimental speed of approach v . Contrary to previous studies, we fully account for back reactions and are thus able to describe the crossover between irreversible adhesion at large affinities or high speed v and reversible adhesion at small affinities or low speed. We also briefly discuss the case of rupture and show that in the limit of irreversible adhesion the rupture occurs always at a *larger* distance than ℓ_r determined for approaching surfaces.

Understanding the mechanisms at work in the adhesion of two surfaces is a fundamental challenge in many fields [1–3]. Of obvious importance for the design of adhesives, glues and other sticking substances [4–6], the control of adhesion is crucial in the living realm where the communication, proliferation, differentiation and migration of cells is determined by the formation of specific bonds between the cell walls [7–9]. Adhesion studies have gained a renewed interest in biology and other soft matter since experiments related to polymer and surfactant interfaces started to unveil some of the key factors at play in the adhesive process [10–14]: bond structure and strength, spacer elasticity, loading rates. . . . It is surprising, however, that the bulk of the research effort was devoted to the separation of two surfaces previously brought together, particularly when one considers many practical situations where the structure of the interface and the conditions under which adhesion proceeds determine the very possibility of making the adhesive contact. In a recent series of experiments, Wong *et al.* [15,16] studied the adhesive forces between two opposing surfaces carrying tethered ligand-receptor pairs with a very strong affinity. They showed for the first time that the range of adhesion between the *approaching* surfaces is set, for such strong binders, by rare events associated with configurations where the polymer tether is extended many times beyond its characteristic size. The adhesion range between strongly binding, approaching surfaces is therefore dynamically controlled by the speed of approach or, equivalently, by the time available to perform the experiments. This contrasts with conditions at the other extreme of the affinity range, for weak enough binding where thermodynamic equilibrium prevails, making irrelevant any reference to the kinetics of

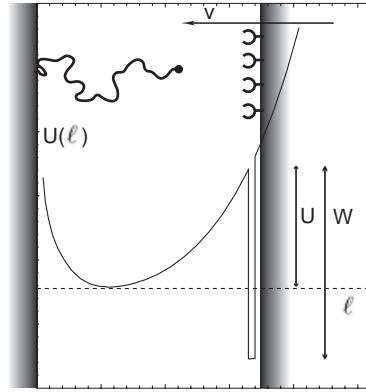


Fig. 1 – A typical experimental configuration for specific adhesion. The tether end moves in the polymer potential $U(\ell)$. The adhesion strength W is the measure of ligand-receptor affinity. The surfaces approach each other at speed v .

the spacer or to the dynamical conditions of the experiments. In this letter, we reconcile such opposite limits by studying the crossover from reversible to irreversible bridging, thus identifying the various roles played by the spacer, the ligand-receptor pair and the experimental conditions in determining the nature of the adhesive approaching process.

Figure 1 shows a typical adhesion configuration for specific binding. Two opposing surfaces at distance ℓ , carrying binding groups, approach each other at speed v . In general, at least one of the surfaces carries its binders tethered by flexible spacers. Experiments on model systems employ polymers as the tethering molecules. Actual synthetic or natural surfaces might carry less well-identified spacers, which will, notwithstanding, be characterized by some intrinsic flexibility and mobility. The spacer determines therefore the potential landscape available for the ligand in the absence of its receptor. For the usual cases where the spacer has the largest molecular weight, it also dominates the dynamic conditions under which the ligand moves in its landscape. The approaching surface will bring into play the third actor of this configuration by making available to the ligand the binding well associated with the presence of the receptors that it carries. For large spacers, this binding potential can also be represented as a structureless sink into which the ligand can fall. Staged in such manner, the physical situation at hand seems to fall into the classical set of problems concerned with the escape over a barrier by a Brownian particle, first treated by Kramers [17]. However, the movement of the ligand cannot be described by a simple diffusion in a potential. Indeed, the internal structure of the tether results in a many-mode dynamics, which needs to be fully accounted for.

We describe the local binding events and the dynamics of the tether within the framework of polymer reaction-diffusion theory. Contrary to previous work [16], we allow for back reactions to occur. A tethered binder, after crossing the gap between the surfaces, can either stay bound or be extracted from the ligand potential well by the pulling forces of the polymer. The distribution function Ψ of the grafted polymer end-to-end vector \mathbf{R} obeys the so-called reaction-diffusion equation

$$\mathcal{L}\Psi(\mathbf{R}, t) = -Q(\mathbf{R})\Psi(\mathbf{R}, t) + P(\mathbf{R}) \left[1 - \int dV \Psi(\mathbf{R}, t) \right], \quad (1)$$

where \mathcal{L} is the formal diffusion operator describing the multimode dynamics of the end-to-end vector, Q is a sink operator describing the on-rate of the binding events and P is a source term accounting for the rate at which an unbinding event occurs. For irreversible reactions one has $P = 0$. In this case, the fraction of tethered ends having reacted at time t ,

$\phi(t) = 1 - \int dV \Psi(\mathbf{R}, t)$ approaches unity for long times: $\phi(t \rightarrow \infty) = 1$.

In a reversible situation, P and Q are related quantities through $\int dV [Q(\mathbf{R})\Psi(\mathbf{R}, \infty) - P(\mathbf{R})\phi_{\text{eq}}] = 0$, where $\phi_{\text{eq}} \equiv \phi(t \rightarrow \infty)$ is the equilibrium amount of reacted ends. This is fixed by the values of the polymer and binding potentials —see fig. 1— according to

$$\phi_{\text{eq}}(\ell) = \frac{e^{W-U(\ell)}}{1 + e^{W-U(\ell)}}, \quad (2)$$

where all energies are written in units of $k_B T$. The definition of the range of adhesion ℓ_r depends on the character [18] of the experimental set. For simplicity, we define ℓ_r as the distance at which half of the chains have reacted, being however a trivial matter to adapt the formalism to other definitions of ℓ_r . It then follows from our definition and eq. (2) that the *equilibrium* range of adhesion ℓ_{eq} is given by the solution of $U(\ell_{\text{eq}}) = W$ (see fig. 2 for a typical shape of $\phi_{\text{eq}}(\ell)$). The characteristic length Δ_{eq} over which this function changes from zero to one is approximately given by $\Delta_{\text{eq}} \simeq \sqrt{2}/U'(\ell_{\text{eq}})$.

In the geometry considered here, we assume one of the surfaces to be homogeneously covered with binding sites. The adhesion well is thus only a function of z , the coordinate perpendicular to the walls. Given the relative dimensions of the polymer and of the ligand-receptor attraction range, we write the sink and source terms as $Q(\mathbf{R}) = q\delta(z-\ell)$ and $P(\mathbf{R}) = p\delta(z-\ell)$. The one-dimensional nature of the sink and source implies also a one-dimensional structure for the reaction-diffusion equation. Following de Gennes [19], we formally invert eq. (1) and obtain

$$\psi(z, t) = \psi_0(z) + \int_0^t dt' G(z, \ell; t-t') \times [-q\psi(\ell, t') + p\phi(t')], \quad (3)$$

where $\psi(z, t) = \int dx dy \Psi(\mathbf{R}, t)$ and G is the dynamic propagator associated with the diffusion operator through $\mathcal{L}G(z, z'; t-t') = \delta(t-t')\delta(z-z')$. The function $\psi_0(z)$ is the one-dimensional equilibrium distribution of the end-to-end vector in the absence of any reactions. The difficulty of solving the reaction-diffusion equation is now transferred into the determination of G , a quantity that can be obtained for a large class of linear problems. Equation (3) can be solved by Laplace transform leading to

$$\widehat{\phi}(s) = (\phi_{\text{eq}}/s) / (1 + \phi_{\text{eq}} s \widehat{h}(s)), \quad (4)$$

where the hat refers to Laplace-transformed functions $\widehat{\phi}(s) = \int_0^\infty dt \phi(t) \exp[-st]$, and the function $\widehat{h}(s)$, containing all the relevant information about tether dynamics, is given by $1 + s\widehat{h}(s) = s\widehat{G}(\ell, \ell, s)/\psi_0(\ell)$. We have taken the relevant limit of fast local reactions, $q \rightarrow \infty$, $p \rightarrow \infty$, with $q\psi(\ell, \infty) = p\phi_{\text{eq}}$, as required by the relation between P and Q previously stated. In general, the time evolution of the fraction of reacted ends can only be obtained by performing an evolved numerical Laplace inversion of eq. (4). However, for our purpose here it is sufficient to extract its long-time behavior by calculating the smallest pole of $\widehat{\phi}(s)$. This leads to an exponential variation,

$$\phi(t) = \phi_{\text{eq}} (1 - \exp[-t/\phi_{\text{eq}}\tau_{\text{ir}}]), \quad (5)$$

where ϕ_{eq} is the time-independent function of eq. (2). The characteristic time τ_{ir} [20] is given by the smallest pole of $\widehat{\phi}(s)$ in the absence of back-reactions, *i.e.* when $W \rightarrow \infty$ corresponding to $\phi_{\text{eq}} = 1$.

The result given in eq. (5) assumes the two walls to be at a fixed distance ℓ . For the system treated here, it is necessary to have the fraction of bound chains as a function of the distance between the walls when these *move* relative to each other at a certain speed. In principle, it is possible to exactly incorporate the moving walls in the reaction-diffusion equation (1): this is however complicated, and to avoid this we assume that the systems of interest have

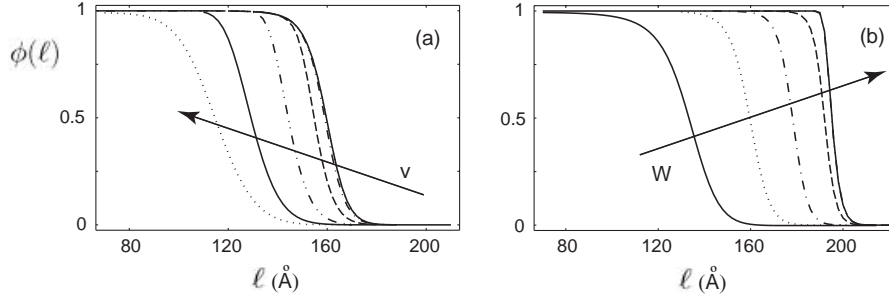


Fig. 2 – Fraction of bound chains ϕ as a function of the distance between surfaces ℓ (for $N = 100$ and equilibrium size $R_F = 66 \text{ \AA}$). Plot (a): fixed adhesion strength $W = 10k_B T$ for speeds (from right to left) $v = 1, 10^4, 10^5, 10^6, 10^7$ and $5 \times 10^7 \text{ \AA s}^{-1}$. The two lower speeds are coincident, indicating that for this chain and affinity, equilibrium conditions are reached for $v < 10^4 \text{ \AA s}^{-1}$. Plot (b): fixed speed $v = 1 \text{ \AA s}^{-1}$ and affinity (from left to right) $W = 5, 10, 15, 20, 25$ and $30k_B T$. For $W > 20$ the curves coincide, indicating that irreversible conditions are at work.

a speed of approach v which is small in comparison to the microscopic characteristic speed associated with the tethers (*e.g.*, the ratio between the radius of gyration and the Rouse or Zimm time). In this case, the time variation of the bound fraction ϕ can be converted into a space-dependent function by identifying $d\phi/dt = -v(\ell)d\phi/d\ell$ and using $d\phi/dt = (\phi_{\text{eq}} - \phi)/\tau_{\text{ir}}$, which follows from eq. (5). Solving the equation for $\phi_{\text{eq}} - \phi$ (with the boundary condition $\phi = 0$ as $\ell \rightarrow \infty$) leads, after some algebra, to

$$\phi(\ell) = \int_{\ell}^{\infty} d\ell'' \left(-\frac{d\phi_{\text{eq}}(\ell'')}{d\ell''} \right) \times \left(1 - \exp \left[-\int_{\ell}^{\ell''} \frac{d\ell'}{v(\ell')\phi_{\text{eq}}(\ell')\tau_{\text{ir}}(\ell')} \right] \right). \quad (6)$$

Equation (6) is our main result. It shows that the amount of chains bound under dynamic approach conditions is a combination of two factors, associated with the first and second terms of the integrand: the first is a reflection of thermodynamic equilibrium, while the second is controlled by dynamics through the combined effects of chain kinetics and speed of surface approach. In the limit of vanishing speed one naturally recovers from eq. (6) the equilibrium result $\phi(\ell) = \phi_{\text{eq}}(\ell)$. On the other hand, by formally taking the limit of infinite adhesion strength W , one recovers the irreversible result of ref. [16]. Equation (6) is a general result based only on the knowledge of the dynamic propagator G describing the movement of the reacting end. We now explicitly compute the bound chain fraction and the range of adhesion for the specific case where the tethers are polymer chains in a good solvent.

A theoretical evaluation of the potential energy associated with the extended position of the end-to-end vector needs to simultaneously account for the finite extensibility of the chain, for the excluded volume between monomers and for the impenetrability of the two confining walls. We met these conditions by performing Monte Carlo numerical simulations of a grafted pearl-bead polymer chain [16]. By keeping one surface fixed and allowing the other to move under a perpendicular force f , a force-distance curve can be extracted from the simulations, and the energy-distance curves obtained by integration. The curves diverge, as they should, at complete extension of the chains $\ell = Na$, where N is the index of polymerization and $a = 3.5 \text{ \AA}$ is the monomer size. For very large relative extensions, $\ell/Na \geq 0.8$, the forces are coincident with the analytical predictions of the freely hinged model for a polymer chain [16,21]. Moreover the point of zero force is at some finite distance from the wall due to entropic reasons. We used the values for the stretching energy from these numerical simulations when calculating τ_{ir} in eq. (6) to predict the range of adhesion for different speeds of approach v , adhesion strengths W and chain lengths N . Note that this optimizes a combination of static and

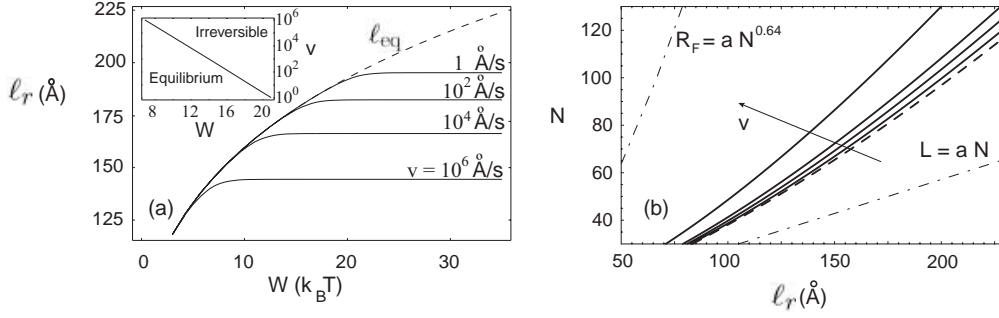


Fig. 3 – The behavior of the adhesion range. Plot (a): ℓ_r as a function of the adhesive strength W (for $N = 100$). For low enough speed of approach v and affinity W , the range is determined by the equilibrium condition $U(\ell_{eq}) = W$ (dashed curve). For high v and large W , ℓ_r saturates and becomes only a function of v . The inset to (a) shows the crossover line from reversible to irreversible adhesion (given by the point where ℓ_{eq} equals the plateau value of ℓ_r at a certain v). Plot (b): ℓ_r for polymers with different indices of polymerization N ($a = 3.5 \text{ \AA}$ and $W = 25k_B T$). The dashed curve is the equilibrium solution (equivalent to $v = 0$), and the full curves correspond, from right to left, to $v = 0.1, 1, 10$ and 10^4 \AA/s . The dot-dashed curves correspond to the total extension of the polymer and the equilibrium end-positions.

dynamic results from two different chain models: the exponential weight related to chain stretching is accurately accounted for by a finite extensibility model, and the multimode local dynamics close to the top of the potential barrier fully described by a polymer dynamic model accounting for hydrodynamic interactions.

Figure 2 shows the fraction of bound chains for a chain of one hundred monomers, $N = 100$, both for a given adhesion strength W at various speeds of approach and at constant speed for various values of the adhesion strength W . The Zimm time is $\tau_Z = \eta R_F^3 / k_B T$, with $\eta = 10^{-3} \text{ Pa s}$, the solvent viscosity, and $R_F = N^{3/5} a$ the Flory radius of the chain. This gives $\tau_Z \simeq 10^{-8} \text{ s}$ for a chain of 45 monomers and we therefore use for a chain of N monomers the value $\tau_Z = (N/45)^{9/5} \cdot 10^{-8} \text{ s}$. The characteristic speed v^* which emerges from our analysis corresponds to traveling one polymer distance in the Zimm time, thus roughly at 10^9 \AA s^{-1} . Note that typical experimental conditions in a SFA apparatus, for instance, correspond rather to 1 \AA s^{-1} . As can be seen from fig. 2a, an experiment performed at a small enough speed, $v/v^* \ll 1$, allows to reach the equilibrium value of ϕ , while increasing speeds reduce the range by a substantial amount. In this latter situation the chains do not have the time to reach across the gap into their equilibrium range position before the surfaces move into a smaller distance. For the case shown in the figure, with $N = 100$ and $W = 10k_B T$, speeds superior to $5 \times 10^3 \text{ \AA s}^{-1}$ result in a significant reduction of the adhesion range from its equilibrium value at $\ell_{eq} = 160 \text{ \AA}$. Given a typical experimental speed of 1 \AA s^{-1} , fig. 2b shows when the adhesion strength value W is high enough for the adhesion range to be independent of the actual W value, a situation we refer to as irreversible adhesion.

The respective importance of the speed of approach v and of the adhesive strength W is summarized in fig. 3a, where the adhesion range ℓ_r (given, as previously mentioned, by the position where $\phi(\ell) = 1/2$) of a polymeric tether with $N = 100$ is plotted as a function of the adhesive strength W for various speeds of approach. As explained before and now explicitly displayed in the figure, large enough values of W lead to a W -independent but v -dependent value of ℓ_r . It also becomes evident that in this latter regime ℓ_r depends weakly on the speed of approach, a fact that is reflected in the crossover line which divides the limits of

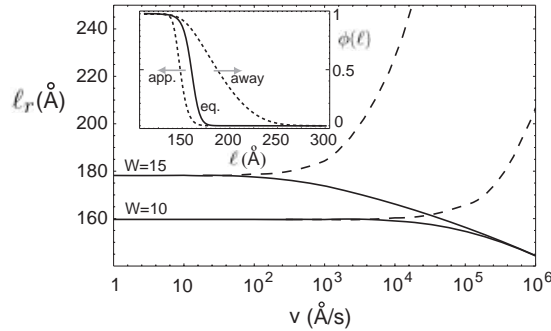


Fig. 4 – Range of adhesion as a function of the speed v for two surfaces approaching (full lines) and moving away from (dashed lines) each other (for $W = 10$ and $W = 15k_B T$). In equilibrium, ℓ_r does not distinguish the direction of v . Away from equilibrium, the range of adhesion for surfaces approaching each other is always *smaller* than for surfaces moving away from each other due to the hysteresis exhibited by $\phi(\ell)$ (shown at the inset for $v = 5 \times 10^5$ and $W = 10$).

equilibrium from irreversible adhesion (inset to fig. 3a). Finally, the index of polymerization of the polymer tethers and the strength of the ligand-receptor couples can be experimentally varied in an independent way, thus tuning the range of adhesion. We plot in fig. 3b the interaction range for a variety of chain lengths and fixed adhesion strength $W = 25k_B T$, at various approaching speeds. As expected, lower speeds and longer chains have larger adhesion range. Note also the concavity of the curves showing that longer chains bridge at smaller relative extensions than the shorter ones.

We now briefly study the onset of rupture when two bound surfaces are moved away from each other. Although this situation has been extensively studied in the past [10–14], it is of interest to see, on the one hand, how the formalism developed here applies to this case and, on the other hand, what differences and similarities emerge from a comparison between adhesion and rupture. One can derive the distance-dependent fraction of bound chains in the same fashion as eq. (6), except that now $d\phi/dt = v(\ell)d\phi/d\ell$ and $\phi = 1$ as $\ell \rightarrow 0$.

As one would suspect, away from equilibrium (*i.e.*, at high enough v) the behavior of $\phi(\ell)$ strongly depends on whether the two surfaces approach or move away from each other. When approaching at high enough speeds, as previously discussed, the tethered ligands do not have the time to bind the receptors in their equilibrium range position before the surfaces move into a smaller distance. This leads to a reduction of the range of interaction in comparison to the equilibrium value ℓ_{eq} . On the other hand, when the two surfaces move apart at high enough speeds, the bound ligand-receptor pairs do not have the time to *unbind* at the equilibrium range, leading to an *increase* of the range of adhesion in comparison to the equilibrium value. In other words, at high enough v , $\phi(\ell)$ exhibits a hysteresis (cf. inset to fig. 4), leading to different values of ℓ_r if the surfaces are approaching or moving away from each other. This is explicitly shown in fig. 4, where the range of adhesion is plotted as a function of v (for $W = 10$ and $W = 15$) for both cases discussed above. Note that this effect has been seen experimentally [15,16]. A more detailed account of the rupture within this framework will be given in a later publication.

In summary, we have shown that the adhesion between surfaces carrying tethered binding groups is controlled by a combination of the tether kinetics, the binding affinity and the speed at which the two surfaces approach (or move away from) each other. We identified and quantified the respective role of each of these factors within a new development in polymer reaction-diffusion theory that fully accounts for the possibility of back-reactions. The formal-

ism has the potential for many further developments, accounting, for instance, for in-plane heterogeneities in the distribution of binding sites or for solvent flow effects. Also, modification of the reaction scheme might be needed in some cases, as, for instance, to account for the competition of many chains trying to attach to a small number of sites. As more and more chains bridge, the amount of sites available for binding is reduced, implying a second-order reaction mechanism. Furthermore, it is important to stress that, although the formalism was devised within the context of tether ligand-receptor adhesion, it has applications in other systems like transient networks or polymer surfactant mixtures. The knowledge of the bridging probability, for instance, allows to compute in these systems rheological quantities such as the viscoelastic moduli $G'(w)$ and $G''(w)$.

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