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# Chemical Force Microscopy: Probing Chemical Origin of Interfacial Forces and Adhesion

D. V. Vezenov, A. Noy, P. Ashby

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# **Chemical Force Microscopy: Probing Chemical Origin of Interfacial Forces and Adhesion**

Dmitri V. Vezenov<sup>1a</sup>, Aleksandr Noy<sup>2</sup>, Paul Ashby<sup>3</sup>

*<sup>1</sup>Department of Chemistry and Chemical Biology, Harvard University, 12 Oxford St.,  
Cambridge, MA 02138, <sup>2</sup>Chemistry and Materials Sciences, Lawrence Livermore National  
Laboratory, L-234, Livermore, CA 94550, and <sup>3</sup>MIT Media Laboratory, 20 Ames Street  
Cambridge, MA 02139*

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<sup>a</sup> E-mail: [dvezenov@gmwgroup.harvard.edu](mailto:dvezenov@gmwgroup.harvard.edu)

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## **1. Chemical Force Microscopy: Motivation and Application to Adhesion Sciences.**

Solid-fluid interfaces occupy a prominent place in condensed matter sciences, since many of the important molecular events in chemistry, physics and biology are interfacial in nature [1]. Examples of such processes span length scales of many orders of magnitude: from the fracture of materials, wetting and lubrication on a macroscopic scale; to self-assembly and colloidal interactions on the mesoscopic scale; to molecular recognition, protein folding and membrane interactions at the nanoscopic scale. This vast array of phenomena initially appear complex and diverse; yet their outcomes are largely determined by the adhesive interactions among molecular assemblies that comprise the surfaces and surrounding fluid phase.

Adhesion forces are mediated by both specific and non-specific interactions. Potential technological and scientific benefits, which stem from gaining control over these interactions, are enormous. For instance, much of the current progress in nanotechnology hinges upon the bottom-up approaches that utilize precisely tailored intermolecular interactions to form higher-order structures [2]. The molecular-level organization of the interfaces and their binding of solvent play an important role in shaping the strength and distance scale of adhesive forces. Although often poorly understood, adhesion in general influences a widely diverse set of industrial applications from airplanes to paints to biosensors [3].

Understanding adhesion phenomena requires intimate knowledge of the intermolecular forces from which they arise. Historically, these forces have been inferred from macroscopic measurements and phenomena such as adsorption calorimetry, surface tension studies, pressure induced chemical or vibrational line shifts, equilibrium constants, virial coefficients, and elastic moduli [1, 3-5]. Although indirect measurements have provided significant information, the true

nanoscopic nature of the interaction is accessible only through a direct measurement. At present, our progress in understanding adhesive interactions at the interfaces is closely linked to the development of the physical techniques for measuring such interactions. Typical chemical bond strength ranges from 10 pN for a very weak Van der Waals bond to 2-10 nN for a strong covalent bond [4]. The interaction strength also varies significantly depending on the properties of the surrounding medium. Therefore, an ideal technique for measuring interactions at the interfaces must be capable of measuring forces in the pN to nN range with a sub-nanometer distance resolution under a variety of environmental conditions and solvent media.

Only in recent decades have techniques for elucidating the molecular origin of forces been developed. Specifically, chemical force microscopy (CFM) [6] uses the high precision and nanometer scale probe of atomic force microscopy (AFM) [7] to measure molecular and interfacial interactions. AFM uses nanometer-size probe tips mounted on flexible cantilevers with spring constants ranging from 0.01 N/m to 100 N/m. These springs, coupled with Angström-level positioning precision of the microscope, provide a natural ability to measure forces in the 50 pN – 100 nN range. However, use of standard commercial AFM tips as force probes is quite limited, since a generic chemical composition of a silicon nitride or a silicon (common materials in the microfabrication process) tip does not allow researchers to measure specific interactions such as, for example, molecular recognition forces involving organic functional groups. Thus, the tip-sample interaction is typically not well-defined, and even though image contrast is observed, most AFM images are devoid of chemical information.

Chemical force microscopy addresses these problems by introducing chemical modification of the AFM probes [6, 8]. Well-defined chemical interactions are created by coating the interacting surfaces with self-assembled monolayers (SAMs) terminated with specific

organic functional groups. Such modification transforms the AFM from a tool for measuring interactions of silicon needles with surfaces to a tool for measuring specific well-defined chemical interactions [9]. Careful design of the probe coating can also retard contaminations, control the number of the interacting molecules, and even separate different types of interactions spatially. This review presents the progress in applying CFM techniques for measuring equilibrium and time-dependent force profiles of molecular interactions, which led to a greater understanding of the origin of interfacial forces in adhesion. Measurements of the force profiles with chemically modified probes are more appropriately termed “chemical force spectroscopy” (CFS) (where the spectrum is a “force versus probe-surface distance” dependence), while the term “chemical force microscopy” (CFM) implies chemically sensitive *imaging* with such probes. While both names have been used interchangeably in the literature to describe the force-distance experiments, we will use the above nomenclature to make the distinction.

## **2. Probing Potential Energy Surfaces with Chemical Force Spectroscopy (CFS).**

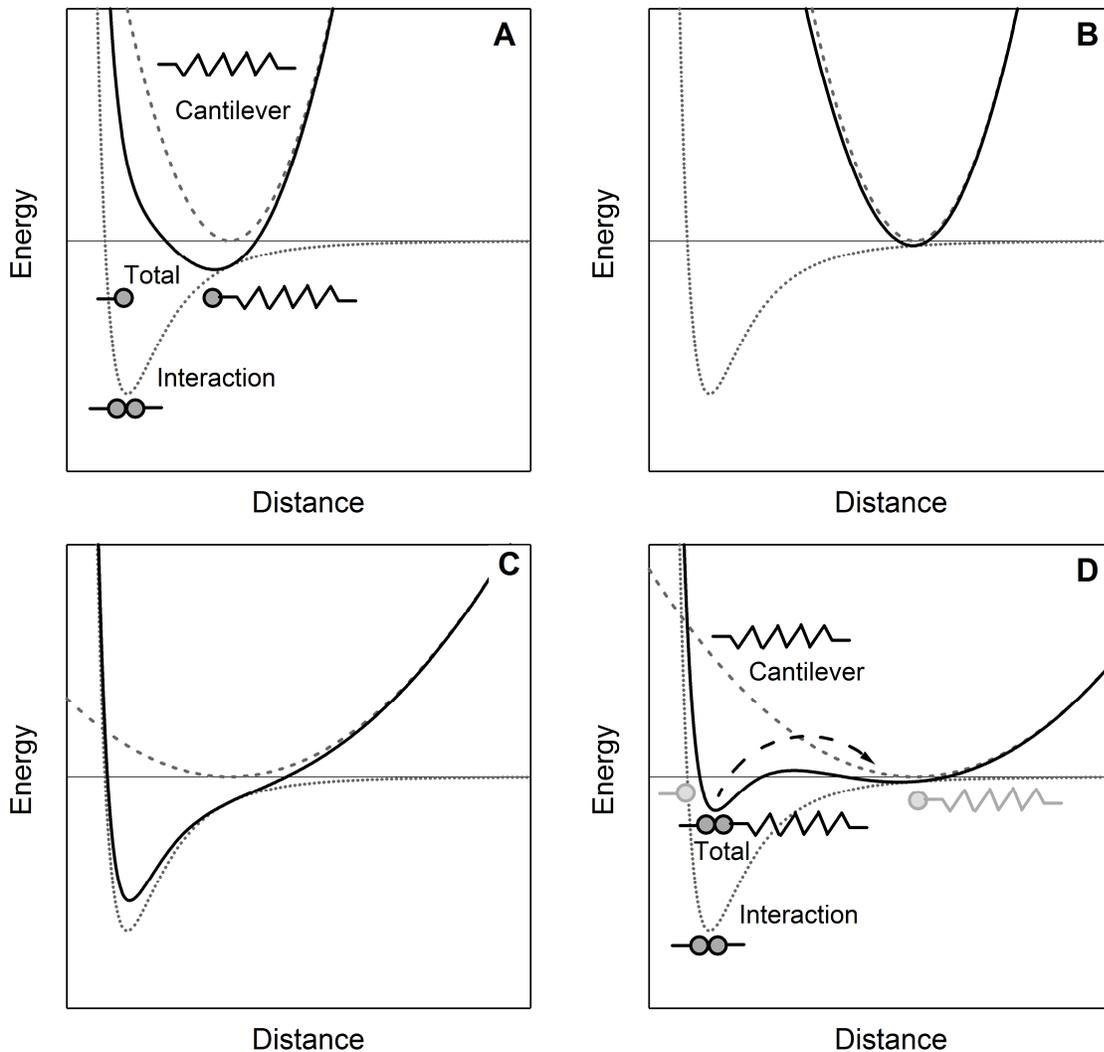
Before we discuss probe modification strategies, we need to review the basic physics of the interaction force measurements with a force microscope. The AFM can provide critical information about potential energy surfaces through the measurement of the force profiles. An equilibrium force profile is a derivative of a one-dimensional slice of the potential energy surface, where the reaction coordinate is defined by the pulling direction. The potential energy surface, which determines both energetics and dynamics of the interaction, can then be reconstructed by integration. The force acting on a modified AFM cantilever consists of the cantilever restoring (spring) force and the force originating from the interactions between the functional groups of the tip and the sample. In the simplest case, we can represent the tip-sample interaction with a single-well potential, and assume a parabolic potential of a Hookean spring for

the cantilever. The overall potential of the system, which determines equilibrium position of the cantilever, is a sum of these two potentials (Figure 1). A simple analysis shows that depending on the cantilever stiffness the system can behave in two very different ways: 1) For stiff cantilevers, the spring potential is so steep that it prevents formation of any secondary minima at all separations. Therefore, as the cantilever approaches and retracts from the surface, the forward and reverse curves coincide, and the probe can trace the entire potential energy well (Figure 1 A, B). 2) When the cantilever spring is soft, the parabolic potential is shallow and a secondary minimum can emerge at certain separations, leading to sudden jumps of the cantilever towards the surface during approach and away from the surface during retraction (Figure 1 C, D). The resulting hysteresis in the approach-retraction cycle obscures most of the potential energy well and allows mapping only of the regions close to the very top and very bottom of the energy well where the gradient of the interaction potential is weaker than the cantilever spring. Unfortunately, the second situation is overwhelmingly prevalent in the CFM measurements due to steep potential energy gradients typical of the surface forces and the limitations imposed by the AFM sensitivity and noise levels. Practically, it means that a large portion of the CFM measurements is restricted to characterization of maximum interaction force, or the pull-off force, which is manifested by a sharp jump in the retrace portion of the force-distance curve. Fortunately, as we will show, these measurements can still extract a wealth of information about intermolecular interactions.

### **3. CFM Studies of Fundamental non-Covalent Interactions.**

The fundamental CFM results obtained in the Lieber group were detailed in our earlier review article [9], which is a good starting point on the basics of the CFM technique; therefore

**Figure 1. Schematic potential energy surface diagram showing loading of a chemical bond (dotted curve potential) by an external spring (dashed curve potential). The total energy profile of the system is a sum of the two potentials (shown as a solid curve).**



only a brief summary will be given here. Lieber and co-workers showed that CFM can discriminate interactions between apolar and polar (hydrogen-bonding) groups, such as  $-\text{CH}_3$ ,  $\text{COOH}$  [6, 8]. Histograms of adhesion force observed in repeated pull-off measurements in ethanol for the tips and samples terminating with these groups clearly showed that probe functionalization influences the interaction strength. The trends observed in these experiments followed our intuitive expectations – hydrogen bonding  $\text{COOH}$  groups show stronger adhesion than the  $\text{CH}_3$  groups that can only interact through van der Waals interactions. Further studies extended this approach to a large number of different functionalities and solvents [9]. The advantage of direct force measurements with CFS was demonstrated for high-energy interfaces (such as  $\text{COOH}$  or  $\text{OH}$  groups in ethanol or water), where surface energies are not available by conventional contact angle measurements by virtue of complete wetting. The most striking feature of these CFS results is that they clearly showed that a simplistic model based solely on the predominant type of chemically specific forces, that act between the functional groups attached to surfaces of the tip and sample, cannot adequately describe the trends that govern the interaction strength. Instead, if we want to rationalize and quantitatively predict these trends, a detailed analysis of the thermodynamics and kinetics of the interactions is necessary. We will outline the main approaches to this analysis in the Section 5 of this review.

CFM approach was also useful for investigating double-layer interactions in aqueous solutions. Water is by far the most important solvent due to its role in biological and colloidal systems. A large number of surface functional groups can ionize in water giving rise to electrochemical interactions. Charging of the surface functional groups is accompanied by the redistribution of the counterions in solution, giving rise to the double layer forces. Vezenov et al. showed that chemically-modified AFM tips and samples can probe the changes in solid-liquid

surface free energies with pH [10]. By monitoring the adhesive force with an ionizable AFM probe, the authors detected changes in surface charge induced by the dissociation of acidic (COOH) or basic (NH<sub>2</sub>) groups on the surface. Variations in the sign and magnitude of the force indicated changes in the surface charge. Importantly, this work showed that an abrupt transition in the tip-sample force – from attractive to repulsive – occurred at a certain pH, attributed to the pK<sub>a</sub> of the functional groups on the surface. Researchers termed such data “force titration curves”. As expected, non-ionizable functional groups did not produce force titration curves. Instead, they showed an approximately constant, finite adhesive interaction throughout the whole pH range. The use of probes terminating in hydrophilic non-ionizing groups (such as OH-groups) as pK probes for unknown surface functionalities was also demonstrated. This new method of “chemical force titration” (CFT) provided a convenient way to determine pK<sub>a</sub> of the surface groups, potentially with a nanometer scale lateral resolution.

Contact angles (CAs) measured using buffered solution droplets on the same surfaces also showed a sharp transition (an increase in wettability) as the droplet pH was changed. Both local force microscopy measurements using a modified probe tip and macroscopic wetting studies provided very similar values for the pK<sub>1/2</sub> (=pH at which adhesion or CA are halved or doubled) of the surface amine group for disordered amine-terminated siloxane SAMs, although these values were 6 pK units lower than the typical bulk solution values. Vezenov et al also used CFT to determine pK values for COOH-terminated surfaces and found that the pK<sub>1/2</sub> of the surface-confined carboxylic acid is ~5.5 – very similar to the pK<sub>a</sub> of the COOH functionality in aqueous solution. Similar results for these groups were obtained by Van Der Vegte and Hadziioannou [11], and by He et al [12].

Noy et al also demonstrated that CFS is well suited to probe single molecule forces and elasticity of synthetic DNA oligomers [13]. While adhesive interactions between biological molecules is an important topic in the force spectroscopy literature, we will for the most part leave this subject out of the scope of this review and focus on simpler organic, or “soft matter”, systems of SAMs. Applications of CFM to polymers also deserve a separate summary (e.g. see work by the Vancso group [14-21]). In addition, while CFM uses chemical sensitivity of friction forces to map the distribution of the chemical functionality on the surface [9], we will only mention relevant studies in the context of adhesive contact between functionalized tips and samples.

#### **4. Chemical Functionalization of Force Probes.**

Formation of thiol self-assembled monolayers on gold coated tips has become the most widely used method for chemical modification of AFM tips since the introduction of chemical force microscopy by the Lieber group [6, 8, 22]. Several other methods for covalent attachment of functionalized monolayers have been investigated in detail since then (Table 1): 1) formation of siloxane self-assembled monolayers on silicon nitride AFM probes with [23] and without [24] surface oxide layer and on tungsten probes [25]; 2) attachment of alkyl monolayers on silicon probes with direct Si-C bond [26], and 3) functionalization of carbon nanotube (NT) probes [27, 28]. We found that the use of silver instead of gold produces similar results in CFS [29]. Fresh thiol SAM can be prepared on regenerated Au-coated tips after of a removal of organic monolayer in plasma oxidation followed by a reduction of the Au surface in hot (65° C) ethanol [30]. CFM was further advanced in the Lieber laboratory by using carbon NTs as AFM probes [27] and a review of this work is available [31]. The small size of the

**Table 1. Methods for chemical modification of the AFM probes.**

Probe material	Treatment	Attached molecule/group	Conditions	Ref
Si or SiN <sub>x</sub>	Cr(Ti)/Au	HS-(CH <sub>2</sub> ) <sub>n</sub> -X	1 mM in ethanol, 1-24h	[6, 9]
Si or SiN <sub>x</sub>	Cr(Ti)/Ag	HS-(CH <sub>2</sub> ) <sub>n</sub> -X	1 mM in ethanol, 1-24h	[29]
SiN <sub>x</sub>	O <sub>3</sub> 30 min, 0.5 M NaOH 20 min, 0.1 M HCl 10 min, 0.5 M NaOH 10 min Dry 120 °C, 10 min	Cl <sub>3</sub> Si-(CH <sub>2</sub> ) <sub>n</sub> -CH=CH <sub>2</sub>	1 mM dehydrated toluene, 4 h, 10-30 min at 120 °C	[9, 23]
SiN <sub>x</sub>	Piranha solution (H <sub>2</sub> SO <sub>4</sub> -30% H <sub>2</sub> O <sub>2</sub> , 7:3), 110 °C, 15-20 min 49% HF, 1 min	Cl <sub>3</sub> Si-(CH <sub>2</sub> ) <sub>17</sub> -CH <sub>3</sub> Cl <sub>3</sub> Si-(CH <sub>2</sub> ) <sub>11</sub> -Br	2-5 mM in hexadecane-chloroform (4:1 vol.), ~12 h	[24]
Si	8% NH <sub>4</sub> F 1 min	CH <sub>2</sub> =CH-(CH <sub>2</sub> ) <sub>9</sub> -CH CH <sub>2</sub> =CH-(CF <sub>2</sub> ) <sub>9</sub> -CF <sub>3</sub>	neat, UV light, 2 h	[26]
Si	Piranha solution (H <sub>2</sub> SO <sub>4</sub> -30% H <sub>2</sub> O <sub>2</sub> , 7:3), 80 °C 2% HF, 1 min	CH <sub>3</sub> O(CH <sub>2</sub> CH <sub>2</sub> O) <sub>3</sub> - -(CH <sub>2</sub> ) <sub>9</sub> -CH=CH <sub>2</sub>	degassed 0.1 M in freshly distilled mesitylene under N <sub>2</sub> , reflux, 2 h	[32]
W	Electrochemical etch, 2M KOH, 6V <sub>ac</sub> Preheat 1600 °C	Cl <sub>3</sub> Si-(CH <sub>2</sub> ) <sub>17</sub> -CH <sub>3</sub>	0.2-0.5% in hexadecane(70%)-chloroform(30%), 18 h	[25]
Carbon nanotube (NT)	Bias voltage between NT and Nb substrate in O <sub>2</sub> atmosphere	-COOH -CONH-C <sub>6</sub> H <sub>5</sub> -CONHCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	Shortened NT, as is NT + 5 mM benzylamine NT + 5 mM ethylenediamine in pH 6 buffer containing 50 mM carbodiimide, 2h	[27, 28, 31]
	N <sub>2</sub> atmosphere	-NH <sub>2</sub>	Shortened NT as is	
	H <sub>2</sub> atmosphere	=CH <sub>2</sub> , -CH <sub>3</sub>	Shortened NT as is	

probe and the capability of chemical functionalization make nanotube tips ideal for trying to achieve the ultimate lateral resolution in CFM; however, the commercial availability and mass-production of such probes remain a problem.

## 5. Theoretical Models of CFS.

### 5.1. Thermodynamic Model of Quasi-static CFS.

#### 5.1.1. Contact Mechanics Approach to Tip-Surface Contact in CFM.

Although force microscopy with sharp probes approaches the limit of point contact, in actual CFM experiments the number of interacting molecular species remains on the order of tens to hundreds, unless carbon nanotube probes are used. An attempt to estimate the number of molecular contacts found that continuum contact mechanics theories provided a surprisingly reasonable framework for interpretation of CFM data even at the nanoscopic level.

When coming into contact, two elastic bodies of curvatures  $R_1$  and  $R_2$  and effective radius  $R$ :

$$R = (1/R_1 + 1/R_2)^{-1} \quad [1]$$

deform due to both repulsive forces (Born repulsion) within the area of contact and due to attractive forces near the edge of the contact zone and outside it. Since Born repulsion is extremely steep, the interatomic distances within the contact zone differ little and this area can be considered to be a flat circle of radius  $a$ . For repulsive-only interactions (Hertz model), the dependence of the contact area size,  $a$ , on an external load,  $P$ , is well-known:

$$a^3 = \frac{RP}{K}, \quad [2]$$

$$\text{where } K = \frac{4}{3} \left( \frac{1 - \nu_1^2}{E_1} + \frac{1 - \nu_2^2}{E_2} \right)^{-1} \quad [3]$$

is the effective elastic constant of the system ( $\nu$  is the Poisson ratio and  $E$  is the Young's modulus). Inclusion of more realistic potentials is not straightforward, because interaction force

depends on the intermolecular separation, in other words, it is defined by the surface profile of the deformed sphere, which in turn depends on the interaction force. One can decouple the force-surface profile dependency by assuming that 1) the profile is not changed because of the presence of attractive forces outside the contact zone or 2) attractive forces act only within the contact area (zero range forces). The first option means that the forces are based on the Hertz result and leads to DMT (Derjaguin, Muler, and Toporov) model of adhesion [33]: the radius  $a$  and the stress distribution are given by Hertz equations with external load substituted by the total force, which includes adhesion  $F_a$ ,  $P+F_a$ . The force of adhesion is then given by  $F_a = 2\pi RW_{132}$ , where  $W_{123}$  is the thermodynamic work of adhesion, given by a balance of surface free energies  $W_{132}=\gamma_{13}+\gamma_{23}-\gamma_{12}$ .

The second choice, implemented in the JKR (Johnson, Kendall and Roberts) model,[34] results in a different stress distribution: compressive in the center of the contact zone, changing to tensile when approaching the boundary (and zero outside the contact circle). Using the energy minimization approach, JKR predicted that the contact radius is derived from Hertz equation when the external load  $P$  is substituted by an apparent load  $P_1$ :

$$a^3 = \frac{RP_1}{K} \quad P_1 = P + 3\pi W_{132}R + \sqrt{6\pi W_{132}RP + (3\pi W_{132}R)^2} \quad [4]$$

Alternatively, the problem of separation of the two surfaces can be treated within the formalism of the linear fracture mechanics: the mechanical energy made available through the crack growth, the energy release rate  $G$ , is used to overcome the surface energy of newly created surfaces  $W_{132}$  (so-called Griffith criterion for stability of the crack:  $G = W_{132}$ ). This leads to an equation for the energy release rate equivalent to the energy balance result [35]:

$$W_{132} = G = \frac{(P_1 - P)^2}{6\pi RP_1} = \frac{(Ka^3/R - P)^2}{6\pi Ka^3} \quad [5]$$

The requirement for  $P_I$  to remain real results in the JKR expression for the force of adhesion:

$$F_a = \frac{3}{2} \pi R W_{132} \quad [6]$$

JKR theory predicts a finite radius of contact under zero external load and when surfaces

separate:  $a_{0(\text{JKR})} = \left( \frac{6\pi W_{132} R^2}{K} \right)^{1/3}$  and  $a_{s(\text{JKR})} = \frac{a_{0(\text{JKR})}}{4^{1/3}} \approx 0.63 a_{0(\text{JKR})}$ , respectively. Dividing the contact

area at pull-off,  $a_s$ , by the area occupied by a single functional group allows an estimate of the number of molecular contacts to be made. Corresponding quantities for DMT theory are

$a_{0(\text{DMT})} = \left( \frac{2\pi W_{132} R^2}{K} \right)^{1/3}$  and  $a_{s(\text{DMT})} = 0$ . The estimate of the number of molecular contacts must

consider the range of intermolecular forces  $z_0$ .

The two models differ substantially in predicted contact area, force of adhesion and surface profile. After some heated debate in the literature, numerical calculations based on Lennard-Jones potential showed [36] that the DMT and JKR results correspond to the opposite ends of a spectrum of a non-dimensional parameter (so-called Tabor elasticity parameter):

$$\mu = \left( \frac{16 R W^2}{9 K^2 z_0^3} \right)^{1/3} \quad [7]$$

where  $z_0$  is the equilibrium distance in the Lennard-Jones potential. This parameter asserts the relative importance of the deformation under surface forces: for  $\mu < 0.1$  the DMT model is appropriate, for  $\mu > 5$  the JKR model applies. Although the JKR model predicts infinite stresses at the perimeter of the contact zone, whereas DMT model predicts discontinuous stress, no discontinuity was observed in the numerical results.

To avoid self-consistent calculations based on a specific potential, Maugis produced an analytical solution to this problem [35] by using Dugdale approximation that the adhesive stress

has a constant value  $\sigma_0$  (theoretical stress) until a separation  $h_0 = W/\sigma_0$  is reached at radius  $c$ , whereupon it falls to zero (Figure 2). The net force is given by ( $m = c/a$ ):

$$\bar{P} = \bar{a}^3 - \lambda \bar{a}^2 \left( \sqrt{m^2 - 1} + m^2 \arccos(1/m) \right), \quad [8]$$

where  $\lambda$  is a measure of the ratio of the elastic deformation to the range of surface forces and  $\bar{a}$  and  $\bar{P}$  are the scaled radius of the contact zone and external load:

$$\lambda = 2\sigma_0 \left( \frac{RK^2}{\pi W} \right)^{1/3} = 1.16\mu \quad \bar{a} = \frac{a}{(\pi WR^2 / K)^{1/3}} \quad \bar{P} = \frac{P}{\pi WR} \quad [9]$$

The elasticity parameter  $\lambda$  is related to  $m$  through:

$$\frac{1}{2} \lambda \bar{a}^2 \left[ (m^2 - 2) \arccos(1/m) + \sqrt{m^2 - 1} \right] + \frac{4}{3} \lambda^2 \bar{a} \left[ \sqrt{m^2 - 1} \arccos(1/m) - m + 1 \right] = 1 \quad [10]$$

When  $\lambda$  is increased,  $m \rightarrow 1$  and the JKR limit is recovered:

$$\bar{P} = \bar{a}^3 - \sqrt{6\bar{a}^3} = \bar{P}_1 - \sqrt{6\bar{P}_1}. \quad [11]$$

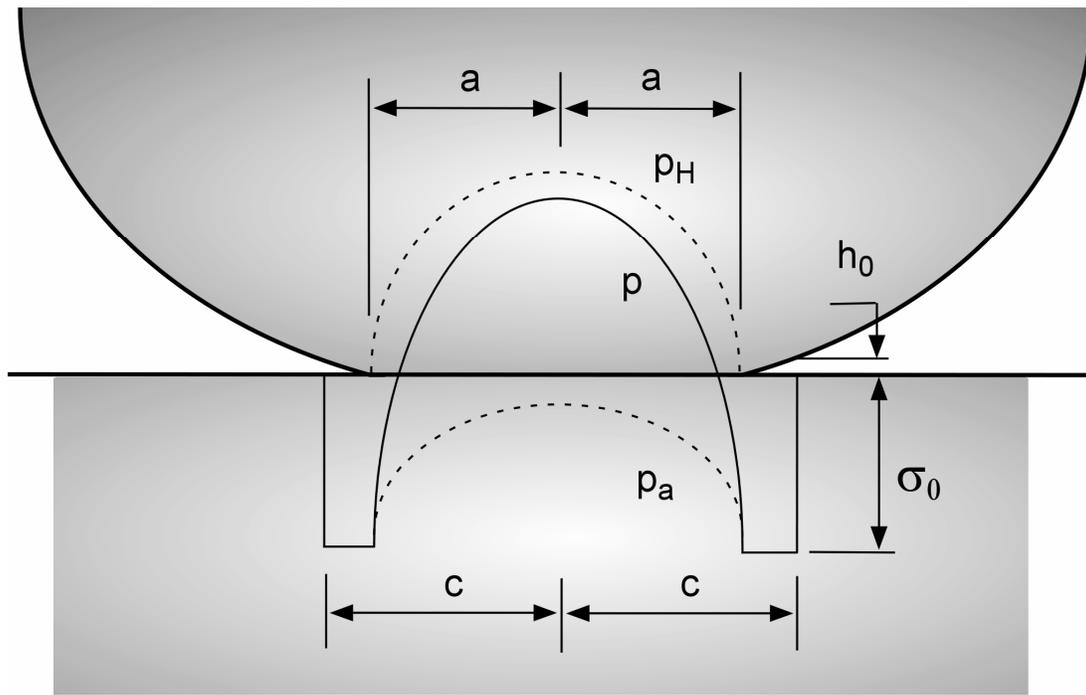
When  $\lambda$  is decreased,  $m \rightarrow \infty$  and the DMT limit is achieved:

$$\bar{P} = \bar{a}^3 - 2. \quad [12]$$

The Maugis-Dugdale (MD) model is an accurate representation of the adhesion in the presence of a liquid meniscus (constant pressure inside the meniscus). Knowing the functional form of the contact area dependence on the load is crucial to interpretation of friction data, which will depend on both shear strength of the contact and its size. The difficulty with MD theory is that it does not easily lend itself to fitting experimental data. This issue was addressed by Carpick et al. [37] who demonstrated that a simple general equation:

$$\frac{a}{a_{0(\alpha)}} = \left( \frac{\alpha + \sqrt{1 - P/F_{a(\alpha)}}}{1 + \alpha} \right)^{2/3} \quad [13]$$

**Figure 2.** The Maugis-Dugdale stress distribution is a sum of two terms: the Hertz pressure  $p_H$  acting on the area of radius  $a$  and adhesive tension  $p_a$  acting on the area confined by radius  $c$ .



closely approximates Maugis' solution and can be used to fit experimental data on contact area (friction). Numerical results are then used to obtain the Tabor parameter from the fitting parameter  $\alpha$  ( $\alpha = 0$  corresponds exactly to DMT case,  $\alpha = 1$  corresponds exactly to JKR case).

Development of the contact mechanics models and adhesion techniques over the past few years prompted Johnson to construct an “adhesion map” of the applicability of particular models depending on the parameter  $\mu$  and applied forces [38]. In the CFM, high modulus materials ( $\approx 100$  GPa) and tip radii  $\approx 100$  nm result in  $\mu < 1$ , thus CFM experiments fall into a “transition” zone. Johnson notes, however, that from comparison with numerical calculations for  $\mu < 0.3$ , the compliance of adhesive contact and computed contact radii are well represented by the JKR equation. Therefore, it appears that JKR equations give good predictions even under conditions well outside the expected JKR zone. We note that it is impossible to place a given system in the respective contact mechanics regime based on the adhesion force measurement alone, since contact area is not measured independently. An estimate of the Tabor elasticity parameter is preferred in this case, although this approach still needs to make assumptions about effective elastic constant of the monolayer/substrate system.

### 5.1.2. Intermolecular Force Components Theory

The sphere-on-flat tip-sample geometry of the AFM does not correspond to the interaction between two atoms. The Lennard-Jones potential typically used to represent interaction between molecular species (with minimum energy  $\epsilon_0$ ):

$$\frac{F_{\text{molec}}(z)}{\epsilon_0/r_0} = 12 \left[ - \left( \frac{z}{z_0} \right)^{-7} + \left( \frac{z}{z_0} \right)^{-13} \right] \quad [14]$$

has to be modified for the CFM geometry to account for multiple intermolecular pairs. The fundamental  $1/z^7$  law of attraction for dispersion forces between molecules was first derived by

London based on second order perturbation theory. An alternative approach by Dzyaloshinskii, Lifshitz and Pitaevskii (DLP) [39] relates van der Waals (vdW) forces to bulk spectroscopic properties of materials. However, quantum field theory of DLP produces an analytically useful result only in the case of vdW pressure between two semi-infinite dielectric slabs separated by a third medium:

$$f(z) = -\frac{A}{6\pi} \frac{1}{z^3} \quad [15]$$

where  $A$  is the (non-retarded) Hamaker constant, which relates to a detailed dielectric behavior through a complete electromagnetic spectrum.

The two methods (macro and microscopic) converge in Hamaker's approach: from the power law for intermolecular interactions,  $F_{\text{molec}}(z) = -C/z^7$ , the macroscopic vdW force, between bodies 1 and 2 with molecular densities  $\rho_1$  and  $\rho_2$ , can be obtained by volume integration of the pairwise interactions:

$$f(z) = -\frac{\pi\rho_1\rho_2 C}{36z^3}, \text{ where } \rho_1\rho_2 C = 6A/\pi^2. \quad [16]$$

Thus, London's result for interactions across vacuum ( $\alpha$  is atomic polarizability) [40]:

$$U_{\text{molec}}(12) = -\frac{3}{4\pi} h \frac{v_{e1}v_{e2}}{v_{e1} + v_{e2}} \frac{\alpha_1\alpha_2}{z^6} \quad [17]$$

leads to a geometrical mean combining rule for the corresponding Hamaker constants ( $v_{e1} \approx v_{e2}$ ) and surface free energies for bodies interacting via van der Waals forces:

$$A_{132} = \pm\sqrt{A_{131}A_{232}} \text{ and } \gamma_{12}^{\text{vw}} = \sqrt{\gamma_1^{\text{vw}}\gamma_2^{\text{vw}}}. \quad [18]$$

The pull-off forces, as described in the contact mechanics models, depend on the surface energetics through the thermodynamic work of adhesion. In associating solvents and for polar surfaces, it is important to take a proper account of both additive (symmetric) van der Waals

interactions and complimentary (asymmetric) electron donor-acceptor interactions (hydrogen bonding). Donor-acceptor or Lewis acid-base interactions are short-ranged (contact) forces and are not accounted for in London or Lifshitz treatment of weak intermolecular forces. These interactions, however, influence thermodynamic data, and thus must be included in computational models for analysis and prediction of physico-chemical properties, for example, in solvation models and the linear free energy relationship approaches.

Hydrogen bonding interactions operate over the background of omnipresent dispersion forces. While the dispersion forces for dielectrics are often very similar in magnitude, the hydrogen bonding interaction differentiates various classes of organic functional groups quite dramatically. One can compare, for example, boiling points of homologous hydrocarbons and alcohols or adhesion forces between CH<sub>3</sub>/CH<sub>3</sub> and COOH/COOH pairs.

Various scales for acidity exist. Acid-base interactions (or hydrogen bonding) can be treated as the formation of a complex (however weak) and one can draw parallels with Klopman's theory of chemical reactivity based on the concept of charge and frontier-controlled reactions [41]. Perturbation theory predicts that the energy of the two systems *R* and *S*, interacting through atoms *r* and *s*, is given by the sum of 1) the contribution  $\alpha_{RS}$  from the total electronic charge density,  $\sum_i (c_r^i)^2$ , or charge-controlled effects and 2) the contribution  $\beta_{RS}$  from the frontier (lowest unoccupied and highest occupied molecular orbitals) electron density,  $(c_i^k)^2$ , or covalent-type effects:

$$\Delta E = \Delta E_{\text{charge}} + \Delta E_{\text{frontier}} = \left( \sum_m^{\text{occupied}} (c_r^m)^2 \sum_n^{\text{unoccupied}} (c_s^n)^2 \right) \alpha_{RS} + (c_r^m)^2 (c_s^n)^2 \beta_{RS} \quad [19]$$

Therefore, this approach argues for separation of interactions at interfaces into two terms, due to total electron density and due to more localized interactions. The form of the equation also

suggests that each term can be represented as a product of the parameters corresponding to individual interacting molecular species. Drago has proposed and successfully used an equation of this type to *quantitatively* predict enthalpies of formation for weak acid-base complexes in solution [42].

A successful scale of the same type for the strength of acid-base interactions was included in the theory of surface free energy proposed by Fowkes, van Oss, Chaudhury and Good (FOCG) [5]. They recognized that two values of polar surface tension component are needed to represent electron accepting and electron donating abilities in combining relations. In this model, the total surface tension of a polar system is separated into van der Waals,  $\gamma^{vW}$ , and Lewis acid,  $\gamma^+$ , and Lewis base,  $\gamma^-$ , components:

$$\gamma_{\text{total}} = \gamma^{vW} + \gamma^{\text{AB}} \quad [20]$$

where  $\gamma^{\text{AB}} = 2\sqrt{\gamma^+\gamma^-}$ . For cross-interactions, combining rules apply:

$$\gamma_{12} = \sqrt{\gamma_1^{vW}\gamma_2^{vW}} + \sqrt{\gamma_1^+\gamma_2^-} + \sqrt{\gamma_2^+\gamma_1^-} \quad [21]$$

and the solid-liquid interfacial tension is then given by:

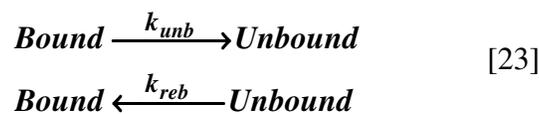
$$\begin{aligned} \gamma_{\text{SL}} &= \gamma_{\text{SV}} + \gamma_{\text{LV}} - 2\left(\sqrt{\gamma_{\text{SV}}^{vW}\gamma_{\text{LV}}^{vW}} + \sqrt{\gamma_{\text{LV}}^+\gamma_{\text{SV}}^-} + \sqrt{\gamma_{\text{SV}}^+\gamma_{\text{LV}}^-}\right) = \\ &= \left(\sqrt{\gamma_{\text{SV}}^{vW}} - \sqrt{\gamma_{\text{LV}}^{vW}}\right)^2 + 2\left(\sqrt{\gamma_{\text{SV}}^+\gamma_{\text{SV}}^-} + \sqrt{\gamma_{\text{LV}}^+\gamma_{\text{LV}}^-} - \sqrt{\gamma_{\text{LV}}^+\gamma_{\text{SV}}^-} - \sqrt{\gamma_{\text{SV}}^+\gamma_{\text{LV}}^-}\right) \end{aligned} \quad [22]$$

The interpretation of adhesion measurements in liquids can be complicated if all components are involved in acid-base interactions. Although there is no solid fundamental theoretical basis for applying the geometric mean combining rule for interactions of acid-base type (unlike for vdW interactions), the FOCG model has been successfully used in examining surface energies in polymer systems and organic liquids using CFM.

## 5.2. Kinetic Model of CFS.

### 5.2.1. Dynamics of Tip-Sample Interactions.

The thermodynamics models summarized in the previous section clearly show that we expect CFM measurements to be sensitive to the interfacial free energy, i.e. specific type of the intermolecular interactions. A detailed analysis of these measurements, however, is more complicated, because they involve multiple chemical bonds, which are not always loaded by macroscopic springs in an equilibrium manner. To extract quantitative information about intermolecular interactions from these measurements, we need to provide a rigorous *time-dependent* model description of the CFM experiment. In the Section 1 we have briefly touched on the dynamics of the cantilever-sample system. We now need to consider how loading by an AFM cantilever changes the tip-sample interactions. We assume that the tip-sample interaction is described by a single potential well (which we will call a “bond potential”), and the cantilever behaves as an ideal Hookean spring represented by a parabolic potential. Addition of the cantilever potential to the bond potential, leads to the emergence of a secondary minimum on the potential energy surface, which typically represents the unbound state (Figure 1B). The dynamics of the system are then determined by the transition from the primary minimum to this secondary minimum. Let us consider how external loading force changes the thermodynamics and kinetics of the transition between bound and unbound states. In the most general case, the dynamics of this two-well system involves two elementary first order processes - unbinding and rebinding - with each process characterized by a rate constant.



As Bell showed in his pioneering work [43], loading the system in the direction of unbound state lowers the barrier to unbinding and simultaneously raises the barrier to rebinding. Consequently, loading leads to the amplification of unbinding rate constant,  $k_{unb}$ , and retardation of the rebinding rate constant,  $k_{reb}$ :

$$k_{unb} = k_{unb}^0 \cdot e^{\frac{F \cdot x_{\beta}^{\rightarrow}}{k_B T}} \quad [24]$$

$$k_{reb} = k_{reb}^0 \cdot e^{\frac{-F \cdot x_{\beta}^{\leftarrow}}{k_B T}} \quad [25]$$

where  $x_{\beta}^{\rightarrow}$  denotes the distance to the transition state from the bottom of the primary well and  $x_{\beta}^{\leftarrow}$  is the corresponding distance from the bottom of the secondary, cantilever-induced potential well. One of the key points is that the distance  $x_{\beta}^{\leftarrow}$  is mostly determined by the cantilever potential (Figure 1), which can cause surprising variations in unbinding dynamics. Stiff springs place the secondary well relatively close to the transition barrier, while shallow potentials of weak springs place the secondary minimum far away. Equation 25 then predicts that the rebinding process becomes extremely slow when the bond is stretched by a soft spring. Another key point is that in most CFM experiments the loading force rarely stays constant during the loading process and almost always ramps up linearly, as the piezo scanner retracts from the surface at a constant speed.

A simple qualitative analysis shows that the unbinding transition can happen in two different regimes, as determined by the rate of bond loading. Under slow loading of the bond, the unbinding proceeds as an equilibrium process and the force necessary to break the adhesive junction is simply determined by the energy balance between bound and unbound states.

Alternatively, if the loading rate is comparable with the rate of at least one of the processes described by the Equations 23, the system never reaches equilibrium and the unbinding proceeds under kinetic control. One direct consequence of this conclusion is that the unbinding force becomes very dependent on *how* the bond is loaded; in other words, the loading history starts to play a critical role. Before we consider these regimes in more details, we note that equilibrium unbinding imposes extremely restrictive conditions on the system. In particular, to achieve equilibrium we need to load the bond slower than the rebinding rate – the situation, which does not happen often due to the exponential retardation of the rebinding rate by the external load. The Equation 25 indicates that for realistic loading rates the best chance to observe the equilibrium unbinding is with the systems that feature deep bond potentials (i.e. large  $k_{reb}^0$ ) and short distances from the secondary well to the transition state. In practical terms, it means that we can observe equilibrium unbinding only in multi-bond systems stretched slowly by stiff springs, although even in this case the system should transition into the non-equilibrium unbinding regime with increase of the loading rate. As a general rule, most of the single-molecule bond measurements always happen in non-equilibrium regime. Tethering interacting molecules to the AFM tip with long flexible linkers, which is a popular technique for studying biological interactions, also leads to non-equilibrium unbinding [44, 45]. In this case the bond is effectively stretched by the entropic elasticity of the polymer tether, which is equivalent to a very weak spring.

### 5.2.2. Non-Equilibrium Unbinding: Kinetic Model of Bond Strength.

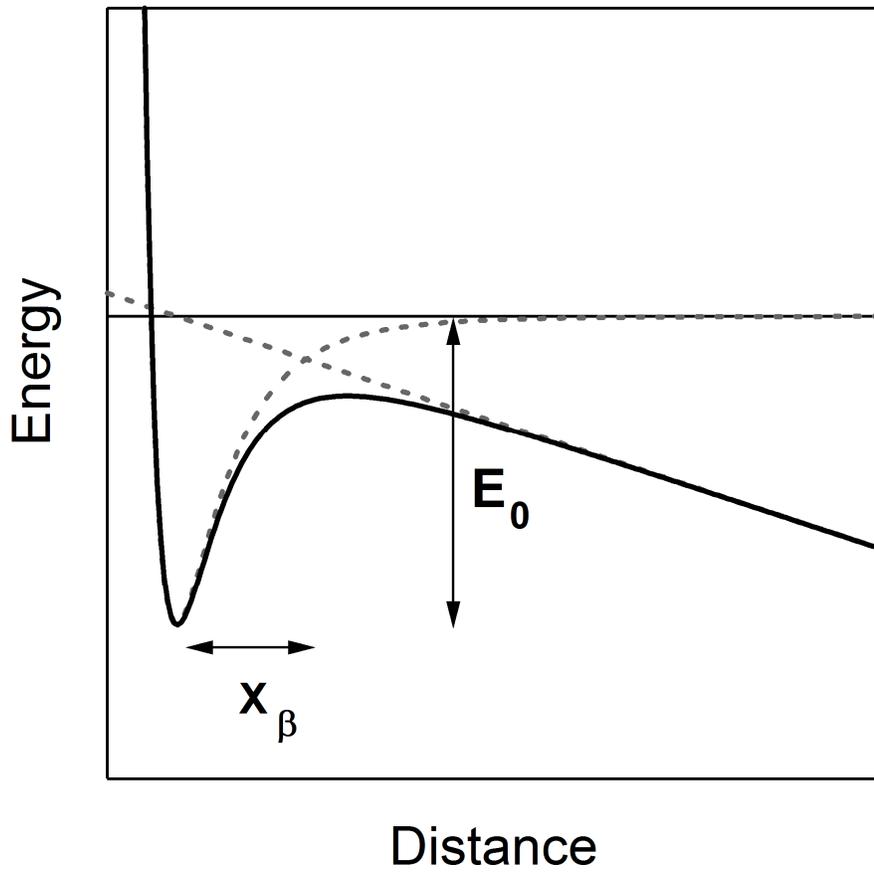
As mentioned in the section 5.2, we typically encounter non-equilibrium unbinding when strong chemical bonds are stretched with soft springs which place the probe-induced energy minimum far away from the transition state. This situation is common for routine CFM adhesion

measurements; therefore, we will consider it in detail. Figure 3 shows the energy diagram for this case, which is somewhat simpler than the generalized energy diagram presented on the Figure 1. In this case, the spring potential is so shallow that any significant movement along the reaction coordinate does not change the applied force appreciably. Therefore, we can approximate the potential of the cantilever by a linear function instead of a parabola. In this case, the external force lowers the energy barrier simply by tilting the interaction potential (Figure 3).

E. Evans and coworkers [46] developed a detailed description of the unbinding process in this regime based on Kramers' theory of thermally-assisted barrier crossing in liquids [47]. Evans' model describes an irreversible escape from the bound state as the potential tilts under the influence of the external loading force. This model completely neglects rebinding; therefore, the magnitude of thermal fluctuations and the interaction parameters define a finite lifetime of the adhesive bond in the absence of loading force. Loading the bond amplifies the escape rate exponentially, according to the Equation 24, and as the result, the system has a higher probability to reach the top of the barrier and escape from the well. The loading force increases linearly with time during a typical AFM experiment; therefore, the potential landscape is constantly changing as the loading force keeps tilting the barrier. Qualitatively, at lower applied forces the barrier is still too high for the thermally-activated transition to happen and at higher applied forces the transition has most likely happened already. In other words, the unbinding of a chemical bond under external load does happen in a fairly narrow range of the applied forces, which ultimately defines the bond strength that we register in the experiment.

Quantitative analysis verifies this intuitive picture. Evans and Ritchie [46] solved the kinetic equations for the case of linear loading at constant rate,  $r_f$ , to find the most probable

**Figure 3. An energy diagram illustrating the effect of the external loading force on the interaction potential in the case of loading a sharp barrier with a weak spring.**



detachment force. They obtained the following expression for the pull-off force [48]:

$$f_{\text{pull-off}} = \frac{k_B T}{x_\beta} \ln \left( \frac{r_f}{r_0} \right) \quad [26]$$

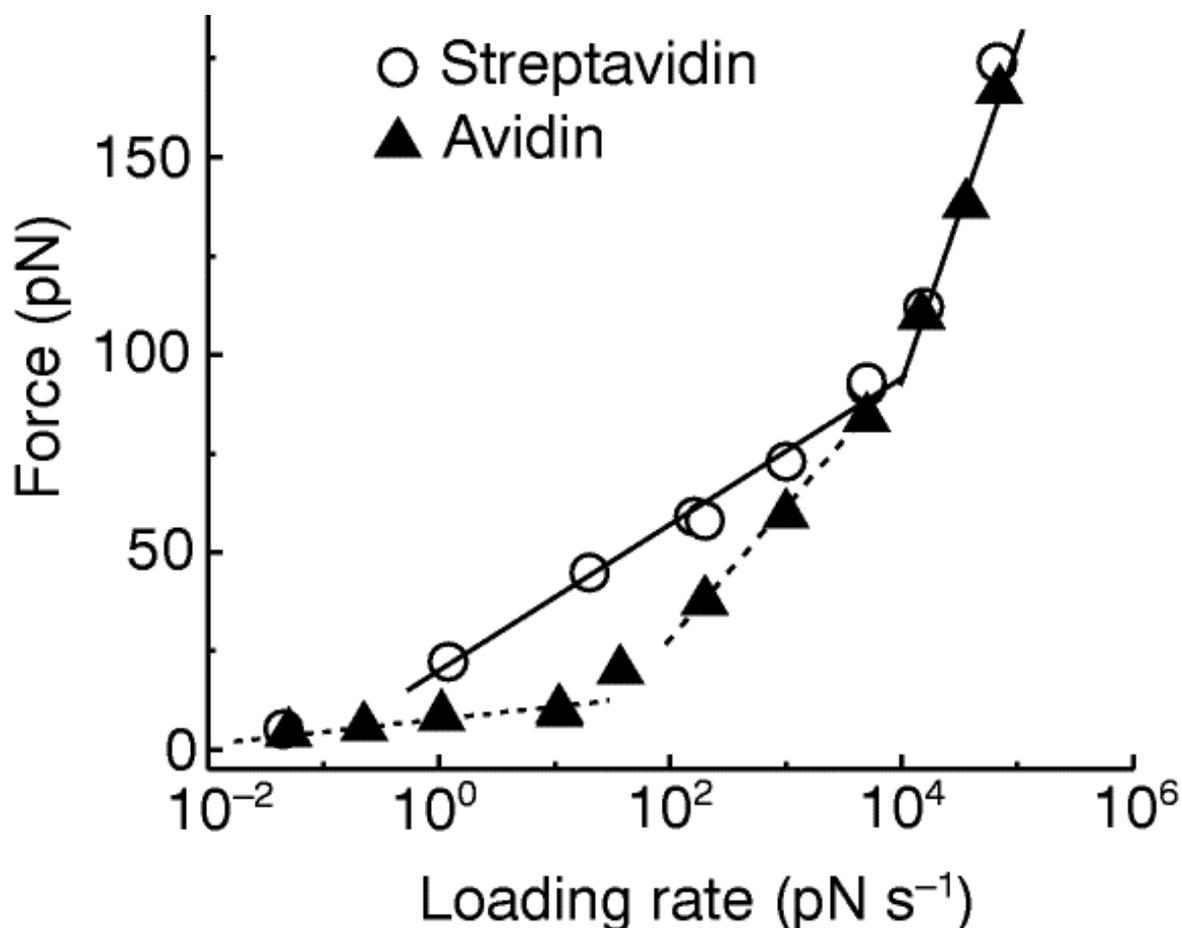
where  $r_0$  is defined as:

$$r_0 = \frac{k_B T}{x_\beta} \cdot \frac{1}{\tau_D \exp \left( \frac{E_0}{k_B T} \right)} \quad [27]$$

Here  $\tau_D$  represents the inverse of the diffusion-limited attempt frequency,  $E_0$  is the depth of energy well, and  $x_\beta$  is the distance to the transition state. Immediately, we can see from Equation 26 that the pull-off force increases logarithmically as the loading rate  $r_f$  increases. Thus, bond strength can vary quite significantly over a wide range of loading rates. Moreover, the slope of this dependence provides the value of the distance to the potential barrier,  $x_\beta$ . Evans and coworkers [49] demonstrated this behavior in a *dynamic force spectroscopy* experiment by measuring the interaction between biotin ligands and avidin or streptavidin proteins over many decades of loading rate (Figure 4). Subsequently, researchers used dynamic force spectroscopy to study energy landscapes of single bonds for a number of interactions between biological and chemical species, such as DNA [50, 51], RNA [52], proteins and ligands [53, 54], and enzymes and drugs [55]. Table 2 summarizes some of these results.

Chemical force microscopy often involves studying multiple individual bonds connected in parallel. Evans and Williams considered the kinetics of the bond rupture in such systems [44, 45]. We can simplify the analysis by assuming that all the bonds are correlated, i.e. they share a single reaction coordinate. Then the system can be analyzed as a single “macro-bond” with the total potential equal to the sum of the potentials of individual components [45]. For the serial loading of  $N$  identical bonds Evans and Williams obtained the following expression for the

Figure 4. Dynamic force spectroscopy measurements of the strength of biotin–streptavidin (circles) and biotin-avidin (triangles) bonds. Biotin-streptavidin data show activation barriers at 0.5 nm and 0.12 nm. Biotin-avidin pair also shows an inner barrier at 0.12 nm; but the outer barrier shifts to 0.3 nm (dashed line). In addition, at very low loading rates the biotin-avidin force spectrum exhibits a low-strength regime (dashed line) that corresponds to a barrier at 3 nm. From reference [56] with permission.



unbinding force:

$$f_{pull-off} = \frac{k_B T}{x_\beta} \ln \left( \frac{r_f}{r_0} N \exp \left( \frac{(N-1)E}{k_B T} \right) \right) \quad [28]$$

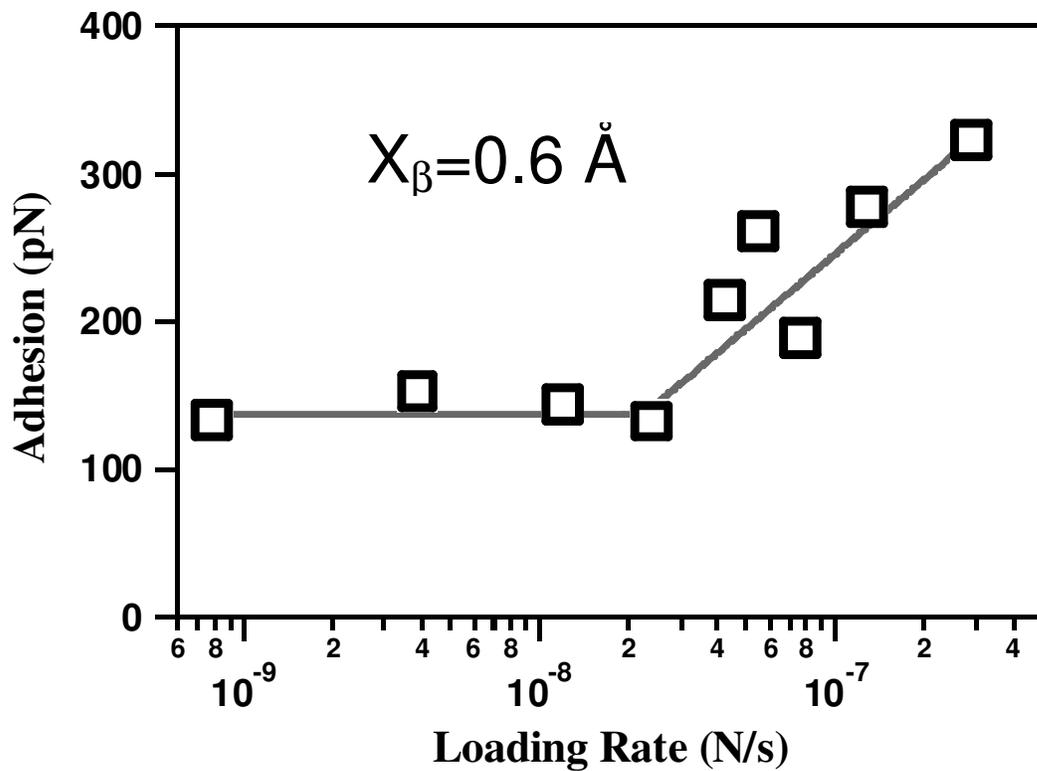
Qualitatively, in case of parallel loading of N bonds the binding force is only slightly smaller than N times single bond strength. One of the most important features of this case is that the distance scale of the interactions is unchanged, i.e. the width of the potential for the “macro-bond” is still equal to the width of the potential for a single bond. Moreover, the scaling of the bond strength with the loading rate predicted by the kinetic model for a single bond case is still valid.

We can use the dynamic force spectroscopy measurement to determine the width of the interaction potential using CFM experiments that provide an almost ideal parallel loading case due to the configuration constraints imposed by the rigid self-assembled monolayers. Noy and coworkers [57] demonstrated such measurement for the interactions of COOH-terminated surfaces (Figure 5), and for interactions of mica surface with Si<sub>3</sub>N<sub>4</sub>-terminated probe. Remarkably, both cases show the distinctive behavior predicted by our analysis. When the tip-sample junction was loaded slowly, the unbinding force was virtually independent of the loading rate, indicating unbinding in the equilibrium regime. As the loading rate increased further, the system transitioned to the non-equilibrium unbinding leading to a characteristic exponential increase in the binding force with the loading rate. The measured slope of this increase provides the distance to the transition state of 0.6 Å for the interactions between COOH functionalities. The distance to the transition state is significantly shorter than the values typically observed for interactions between biological macromolecules (Table 2), which is reasonable to expect considering the size difference. Interestingly, this value is comparable to the barrier width *per*

**Table 2. Interaction potential parameters for various single bond systems determined using dynamic force spectroscopy.**

<b>Experimental System</b>	<b><math>X_{\beta}</math>, nm</b>	<b><math>K_{off}</math>, s<sup>-1</sup></b>	<b>Reference</b>
12-mer DNA	0.58		[50]
12-mer RNA	0.67	0.39	[52]
12-mer RNA with UCU bulge	0.37	7.94	[52]
10,20, and 30-base pair DNA	0.7+0.07·n, n: number of bp.	$10^{3-0.5 \cdot n}$	[51]
Titin I27 domains	0.32	$2.9 \cdot 10^{-4}$	[53]
Immunobiotin-Streptavidin	0.57	0.2	[54]
	0.13	69	
Dihydrofolate reductase/ methotrexate	0.3		[55]

Figure 5. Binding forces between COOH-modified probe and sample in ethanol plotted as a function of loading rate. Lines indicate fits according to Equation 25 in the equilibrium and non-equilibrium unbinding regimes.



*base pair* ( $0.7\text{\AA}$ ) obtained by Strunz et al. in the DNA unbinding experiments [51]. It is tempting to assign the value obtained in the CFM experiment to the hydrogen bond potential, but, as we will show in the Section 7, the interpretation is more complicated.

## **6. Validity of Contact Mechanics Description of CFM Experiments.**

Although the theoretical framework of contact mechanics was applied to interpretation of CFS results since its original report [6], it is remarkable that one can even turn to continuum models as a valid approach for interpretation of experiments conducted at the nanometer scale, when only a limited number (tens to hundreds) of molecular species participate in the formation of the contact. Several issues can cast doubt on applicability of continuum mechanics down to the nanometer scale regime. Do SAM-coated tips and samples follow JKR model of adhesion? How significant is the idealization of the tip and sample shapes? Can one accurately determine effective radius of the CFM probes? What is the effective elastic constant in the system? Do the relationships and trends predicted by the contact mechanics model hold in experimental observations? Several experiments reported in the last few years confirmed, in a systematic manner, the general validity of the contact mechanics description of the CFM experiments.

### **6.1. Determination of the Tip Radius.**

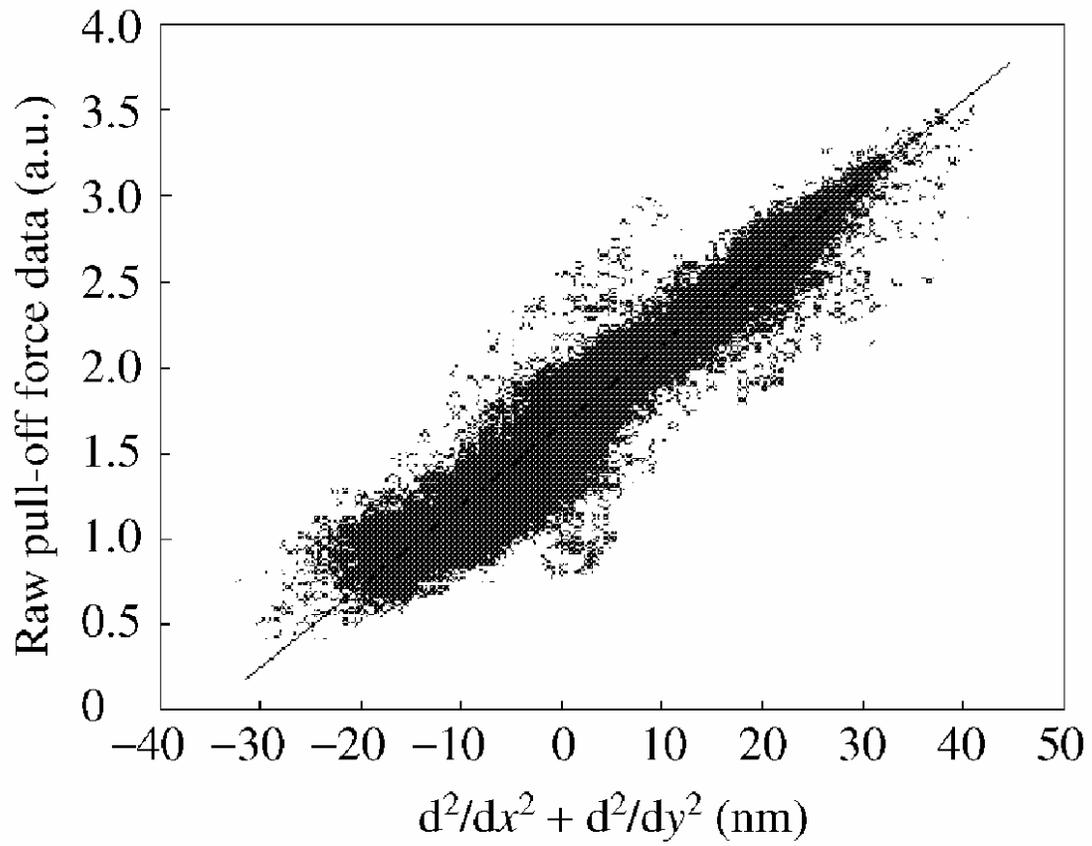
Three methods for tip characterization have been applied in CFM: 1) tip imaging using scanning electron microscopy provides a direct measure of the radius and is the most common approach [9, 58-60]; 2) “standard” system (e.g.  $\text{CH}_3\text{-H}_2\text{O-CH}_3$ ) provides the benchmarked work of adhesion to define effective tip radius from adhesion force measurements and selected contact mechanics model, e.g.  $R = F_a / (3\pi W_{123})$  [61, 62]; 3) tip characterizers, such as sharp Si spikes [60] on a flat surface, atomically sharp features on the (305) face of  $\text{SrTiO}_3$  [63], or the sample itself [32], are used to image tip shape with a scanning probe microscope, and tip radius

is found with blind tip reconstruction algorithms based on image morphology operations. The results from the latter method were compared with the estimates from the direct SEM imaging of the tips by Tormoen et al [60], who found an excellent agreement between the two techniques.

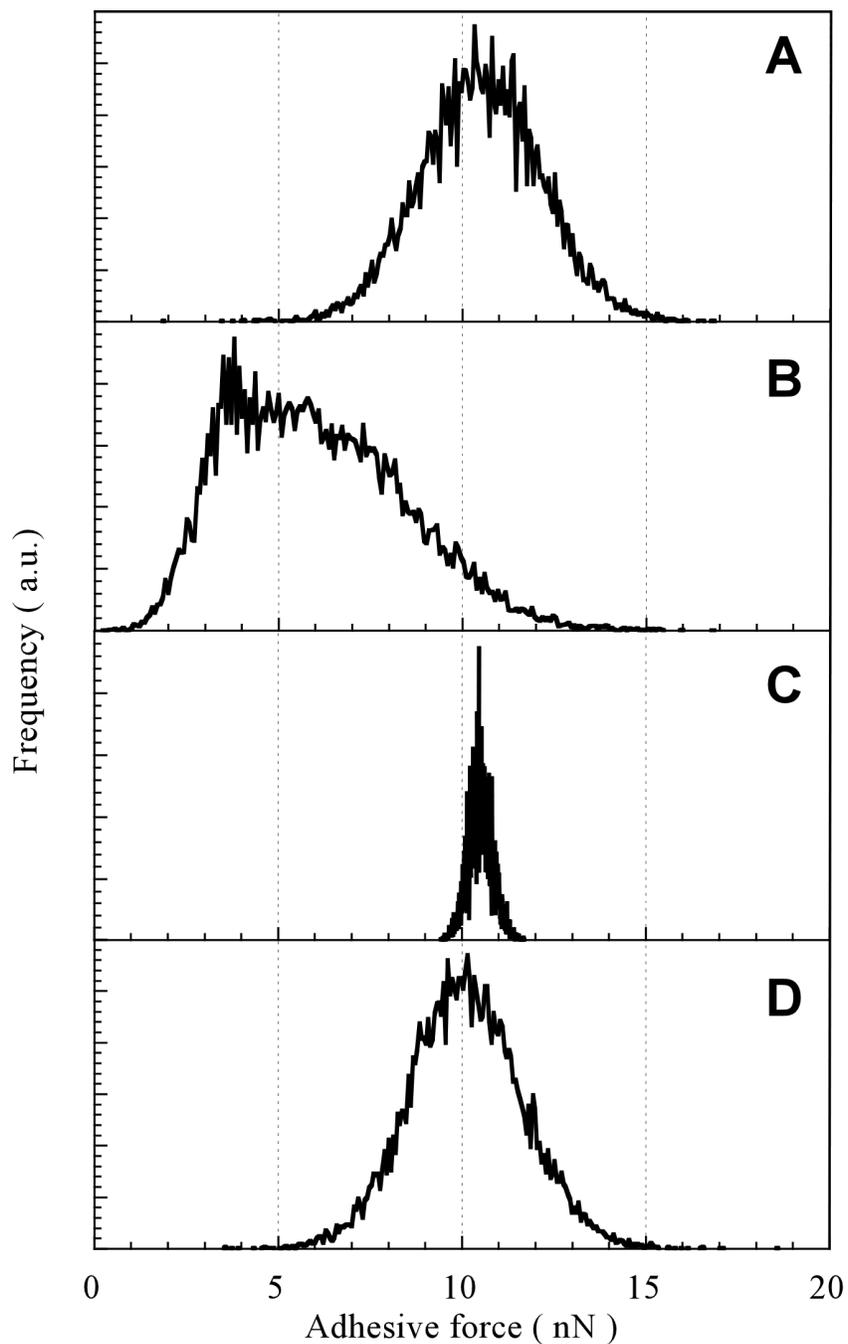
### **6.2. Effect of the Substrate and Tip Curvature: Scaling of Adhesion with Effective Tip Radius.**

One of the advantages of using point probe experiments in adhesion studies is that the requirements to the surface quality in order to achieve molecularly smooth contact are reduced by virtue of nanometer size dimensions of the contact. Contact mechanics predicts that pull-off forces in CFS are directly proportional to effective radius defined by Equation 1. One can immediately recognize, however, that substrate roughness, e.g. local variations in the substrate radius of curvature will affect the magnitude of adhesion. For example, analysis of force and topography maps from AFM measurements on a chemically homogeneous, hydrophobic sample - silanized etched silicon [64]– showed unambiguous direct correlation between substrate's local curvature and the force of adhesion (Figure 6). Performing CFS on HS(CH<sub>2</sub>)<sub>15</sub>COOH/HS(CH<sub>2</sub>)<sub>15</sub>COOH pair in ethanol, McKendry et al. observed [65] a greater than a factor of two reduction in the width of adhesion force distribution, when they switched from polycrystalline Au substrates to predominantly single crystalline annealed Au on mica substrates. A similar observation was made in the work of Fujihira et al [66], who measured adhesion in water and used the same HS(CH<sub>2</sub>)<sub>19</sub>CH<sub>3</sub> terminated tip on several HS(CH<sub>2</sub>)<sub>15</sub>CH<sub>3</sub> modified substrates: 1) 11-nm sputtered Au film, 2) 110-nm sputtered Au film, and 3) annealed Au(111) on mica. A direct correlation was observed in cross-sections taken from topography and adhesion maps. The width of the distribution ( $\sigma_F$ ) and mean force was dramatically affected by the nature and quality of the Au layer:  $\sigma_F$  was 2 nN, 3 nN, and 0.45 nN for substrates (1)-(3),

**Figure 6. Relationships between adhesion and the second derivative of substrate topography (silanized etched Si). Reproduced from reference [64].**



**Figure 7.** Histograms of adhesive force mappings using the same CH<sub>3</sub>-terminated tip on HS(CH<sub>2</sub>)<sub>19</sub>CH<sub>3</sub> SAMs formed on: (A) 11 nm thick sputtered gold, (B) 110 nm thick sputtered gold, (C) 100 nm thick thermally evaporated Au(1 1 1) on mica, and (D) same as (A). The sequence of CFS measurements was (A)-(B)-(C)-(D). Reproduced from reference [66] with permission.



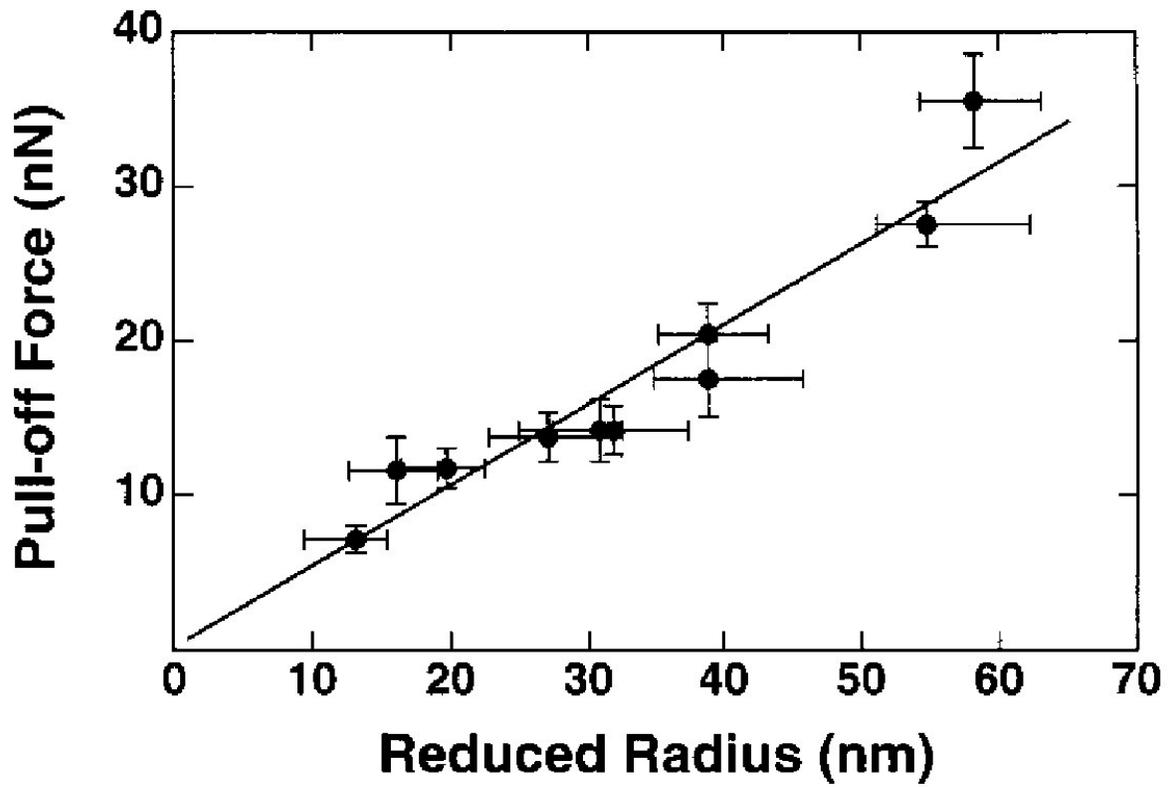
respectively. Au substrates presenting large areas of the (111) face had the same mean value of adhesion, while having a factor of five smaller standard deviation. This finding demonstrates that the width of local curvature distribution of the substrate is a primary factor responsible for the width of adhesion force distributions for chemically identical tip-sample combinations. Thus, one needs to exercise caution in statistical treatments of force fluctuations in CFS – a significant contribution to  $\sigma_F$  could arise from the distribution of asperity curvature at pull-off.

Skulason and Frisbie probed systematically [58] the relationship between the tip radius and force of adhesion,  $F_a$ , measured in CFS of hydrophobic contacts ( $\text{CH}_3/\text{CH}_3$ ) in water. For tip radii ranging from  $R=15$  nm to 125 nm, they observed a remarkably good *linear correlation between mean  $F_a$  and  $R$* . Moreover, when they also considered substrate roughness (radius of curvature of Au grains) in defining effective radius (Equation 1), the linear fit had a zero intercept, as expected from the predictions of contact mechanics models (Figure 8). From the slope of the least-squares linear fit,  $0.52\pm 0.05$  N/m, and value for thermodynamic work of adhesion in the  $\text{CH}_3\text{-H}_2\text{O-CH}_3$  system,  $103$  mJ/m<sup>2</sup>, one can derive the value of the coefficient in the equation for the force of adhesion –  $(1.59\pm 0.15)\pi$ , very close to the  $1.5\pi$  value of the JKR model.

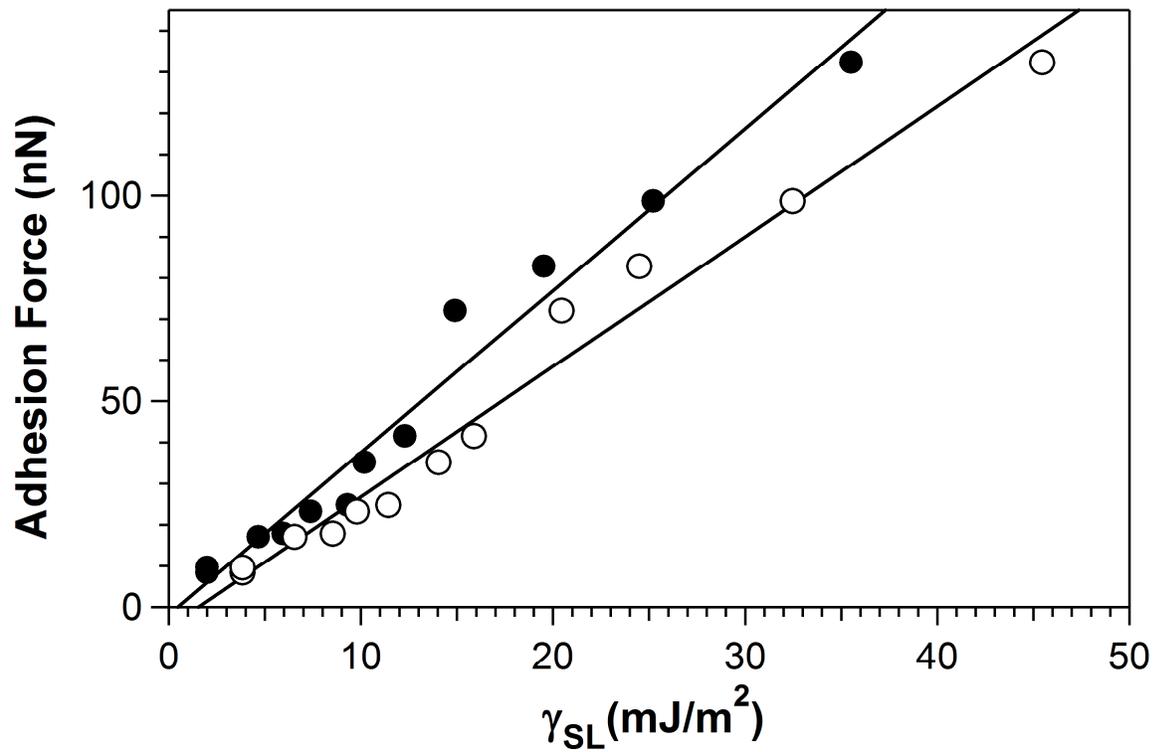
### **6.3. Scaling of Adhesion Force with Interfacial Free Energy.**

To preserve geometrical parameters of the system, researchers used the same tip-sample pair both terminating in  $\text{CH}_3$  groups and determined force of adhesion in a series of methanol-water mixtures, where interfacial free energy could be varied by changing the composition of the solvent [29]. Combining results from the adhesion force measurements with the contact angle data on these low-energy  $\text{CH}_3$  monolayers, Vezenov et al observed that there is a direct, *linear correlation between adhesion forces and corresponding surface free energy* values determined

Figure 8. Plot of mean pull-off force versus reduced tip radius, taking into account roughness of the substrate (bars are estimated maximum and minimum radius or width of force distributions, line is a linear least-squares fit). Reproduced from reference [67] with permission.



**Figure 9.** Adhesion between -CH<sub>3</sub>-terminated tips and samples versus solid-liquid surface free energy determined from advancing (open symbols) and receding (closed symbols) contact angles, ( $\gamma_{SV}=19.3 \text{ mJ/m}^2$  for CH<sub>3</sub>SAM). Adopted from reference [29].



with contact angles (Figure 9). The interfacial surface energy for identical non-polar surface groups was found not to exceed 2 mJ/m<sup>2</sup> in these experiments.

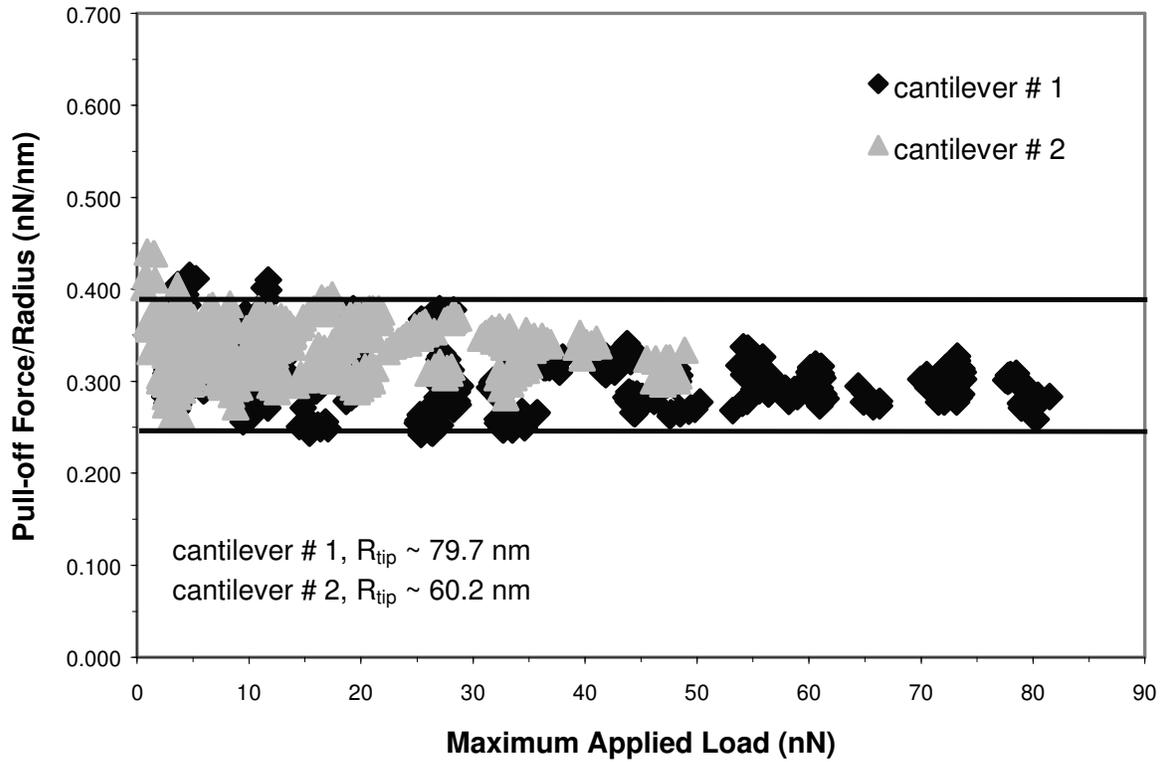
#### **6.4. Change of Contact Area with Applied Load.**

The main weakness of CFS in deriving adhesion values is its inability to obtain independent measure of the contact area. Frequently, a tip-sample friction force is assumed to provide a simultaneous measurement of the contact area on assumption that friction is proportional to the actual contact area and interfacial shear stress for corresponding functional group pairs [68]:

$$F = \tau_0 \pi a^2 \quad [29]$$

On the basis of general relationship between radius of the area of contact and external load (Equation 13), one expects a non-linear relationship between friction force and applied load. Surprisingly, most of the reported experimental friction-load curves in chemical force microscopy showed approximately linear behavior [9, 69-71]. Vezenov et al speculated [63] that the apparent linear form of these curves was due to the averaging of multiple single-asperity contacts occurring when a friction force is averaged over a path of several micrometers in a typical measurement. The non-linear JKR-like behavior was detectable only for relatively blunt tips when large forces for hydrophobic SAMs in water turned substrate imperfections into secondary effects [63]. This observation is also consistent with the CFS results by Beach et al [72], who found that, for SAMs on polycrystalline Au(111) surface, higher maximum applied load (i.e. force just before the tip direction is reversed) reduces the effect of the substrate roughness, so that the spread in adhesion values narrows (Figure 10). Researchers indeed demonstrated non-linear relationship between friction and applied load in methanol-water mixtures using methyl terminated siloxane SAMs on smooth Si substrates and silicon nitride

**Figure 10. Normalized pull-off force vs maximum applied load. Lines highlight the range of pull-off force values. Reproduced from reference [72].**



tips [63]. The adhesion increased with higher water content; however, interfacial shear stress, determined by fitting to contact mechanics model, remained constant.

### **6.5. Effect of Chain Packing.**

The degree of packing in the SAM is affected by the anchoring mechanism and defect density and is different in thiolates on Au, trichlorosilanes on Si, and trimethoxysilanes on Si. The tilt angle of alkyl chains with respect to substrate is influenced by the anchoring group density in these SAMs. Ellipsometry results on thicknesses of these monolayers - 2.2 nm, 2.4 nm, and 1.9 nm, respectively - were consistent with an all-trans conformation and expected trend in tilt angles - 30°, 10° and 40°, respectively. The orientation of the terminal group is, therefore, expected to be different for the three types of the SAMs. Adhesion forces measured between HS(CH<sub>2</sub>)<sub>17</sub>CH<sub>3</sub>/Au tips and HS(CH<sub>2</sub>)<sub>17</sub>CH<sub>3</sub>, Cl<sub>3</sub>Si(CH<sub>2</sub>)<sub>17</sub>CH<sub>3</sub>, and (CH<sub>3</sub>O)<sub>3</sub>Si(CH<sub>2</sub>)<sub>17</sub>CH<sub>3</sub> monolayers in water were sensitive to SAM internal organization [73]. The adhesion results obtained with three different probes, while nominally reflecting methyl-methyl interactions in water, displayed a trend that paralleled the quality of organization of the SAMs: adhesion forces ratios were 1/(0.797±0.005)/(0.687±0.006) for HS-, Cl<sub>3</sub>Si-, and (CH<sub>3</sub>O)<sub>3</sub>Si- anchor groups, correspondingly (the error is the standard deviation of the mean for different tips). Contact angles, measured 111°, 110°, and 108° on the same series of samples, were less sensitive to the type of SAMs. Thus, different chain packing and orientation of the terminal group of the self-assembled monolayer can lead to measurable differences in the pull-off forces determined by CFS. The use of work of adhesion in a “reference“ system, such as methyl-methyl contacts in water (W=103 mJ/m<sup>2</sup>), to determine effective tip radius [61, 62] should be used with caution, because nominally the same interface can produce different apparent work of adhesion.

## 7. Role of the Solvent.

Lieber et al advanced surface free energy arguments to explain the magnitudes of adhesion forces measured between organic functional groups in ethanol [6, 8]. We also suggested [9] that surface tension component (STC) theory [5] can be useful in explaining CFM data in various solvents. Several authors published systematic studies that used STC interpretation to rationalize the CFS results in liquids and air. Clear and Nealey measured adhesion forces between HS(CH<sub>2</sub>)<sub>17</sub>CH<sub>3</sub> modified Au-coated probes and CH<sub>3</sub> and COOH-terminated siloxane monolayers on Si substrates in a range of solvents [62]. They generally found good agreement between work of adhesion for CH<sub>3</sub>/CH<sub>3</sub> interface in a number of solvents obtained experimentally with CFS, contact angle measurements, and values calculated from the STC model.

Vezenov et al observed [29] that adhesion measured by CFS did not correlate with solvents polarity defined through dipole moments or dielectric constant, nor did it correlate with cohesion energy of the solvent (Hildebrand parameter [74]). A good correlation was observed, on the other hand, with the STC model predictions. The methanol-water mixture provided a simple way to generate similar solvents that span a large range of hydrogen bonding ability. With a non-polar SAM, the force of adhesion increased monotonically in mixed solvents of higher water content; whereas, with a polar SAM (one having a hydrogen bonding component) higher water content led to decreased adhesion compared to non-polar counterpart. Overall, surface tension component interpretation of the CFS data in solvents showed that competition between hydrogen bonding within the solvent and hydrogen bonding of surface groups and the solvent provided the main contribution to adhesion forces between organic functional groups in liquids.

When adhesion data are taken with the same tip-sample pair,  $\gamma_{SL}$  and, hence,  $F_a$  are directly proportional to  $\gamma_{LV}\cos\theta$ :

$$F_a = 2n\pi R\gamma_{SL} = 2n\pi R(\gamma_{SV} - \gamma_{LV} \cos \theta) \quad [30]$$

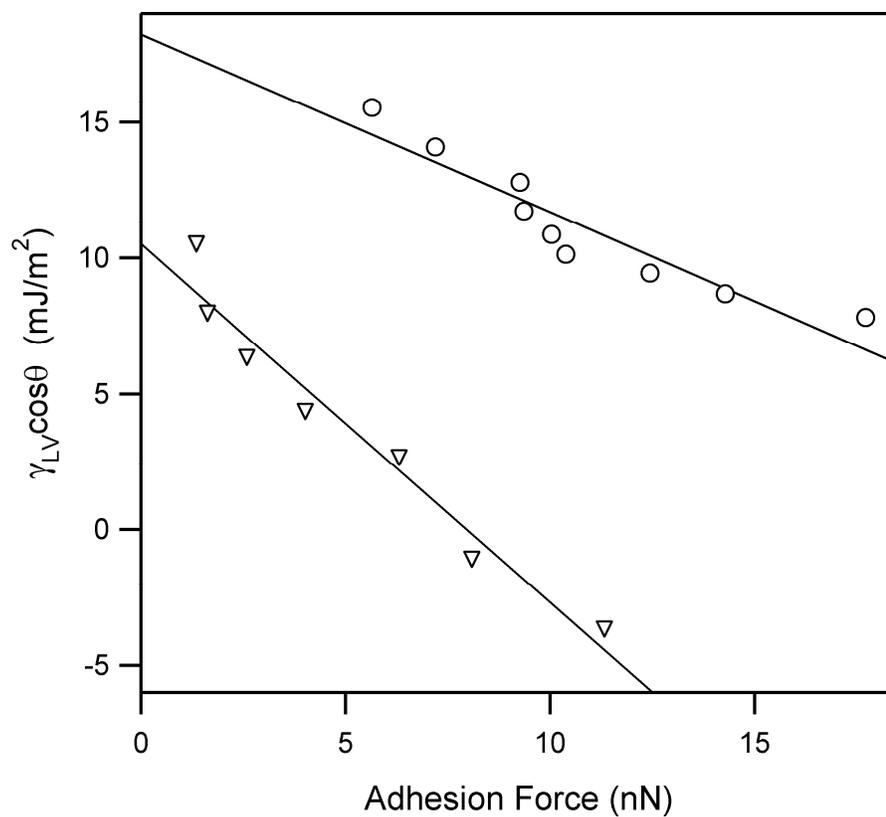
Plots of  $\gamma_{LV}\cos\theta$  versus  $F_a$  extrapolated to zero adhesion force yield  $\gamma_{SV}$  (assuming  $\gamma_{ST}\approx 0$  for the same groups). This approach for non-polar SAMs in methanol-water mixtures (Figure 11) yielded a value of  $\gamma_{SV}=18.5 \text{ mJ/m}^2$  for  $\text{CH}_3$ -terminated SAM and  $10.8 \text{ mJ/m}^2$  for  $\text{CF}_3$ -terminated SAM [29].

Solvents that are able to form strong interfacial bonds can display two adhesion minima: 1) one corresponding to contact between the groups of the tip and the first solvation shell of the surface, when the maximum load on the tip in contact is small, and 2) the second, deeper, minimum corresponding to contact between the tip and the surface groups, when the maximum load is high ( $>0.5 \text{ nN}$ ) and solvation shell is fully penetrated. For OH-OH pair in octanol, the CFS gives  $\gamma_{SL}=0.16 \text{ mJ/m}^2$  and  $0.60 \text{ mJ/m}^2$ , respectively, for the two minima [59].

An inspection of the work of adhesion values for the similar systems (same functional group pairs in the same solvent) presented in Table 3 reveals some spread in reported values. The discrepancies can be attributed partly to differences in the structural properties of SAMs (e.g. thiols vs. siloxanes) and partly to the errors in determination of the tip radii (reported accuracy is on the order of 10-30%). Several groups, however, reported consistent surface free energy values for a few select interfaces and these values are also in good agreement with corresponding contact angle data and STC estimates. These values are for  $\text{CH}_3$  SAMs in water ( $44\text{-}55 \text{ mJ/m}^2$ ), hexadecane ( $0.4 \text{ mJ/m}^2$ ), decane ( $0.2 \text{ mJ/m}^2$ ) and perfluorodecaline ( $1.9 \text{ mJ/m}^2$ ) and  $\text{CF}_3$  SAMs in hexadecane ( $6.8 \text{ mJ/m}^2$ ), and perfluorodecaline ( $1.0 \text{ mJ/m}^2$ ).

The more interesting experiments involve COOH and OH groups in both non-polar and

**Figure 11. Plots of  $\gamma_{LV}\cos\theta_{adv}$  versus adhesion force for the determination of  $\gamma_{SV}$  values for SAMs terminating in  $\text{CH}_3$  (circles) and  $\text{CF}_3$  (triangles) groups. Values of  $\gamma_{SV}=18.5$  (for  $\text{CH}_3$ ) and  $\gamma_{SV}=10.8$   $\text{mJ/m}^2$  (for  $\text{CF}_3$ ) are determined by extrapolation to zero adhesion force. Reproduced from reference [29] with permission.**



Solvent		$\gamma_{LV}$ mJ/m <sup>2</sup>	$\gamma^{LW}$ mJ/m <sup>2</sup>	$\gamma^{AB}$ mJ/m <sup>2</sup>	$W_{132}$ SCT <sup>a</sup>	$W_{132}$ CA <sup>a</sup>	$W_{132}$ CFS <sup>b</sup>	Ref
Tip=Au/HS(CH <sub>2</sub> ) <sub>17</sub> CH <sub>3</sub> Sample=Si/Cl <sub>3</sub> Si(CH <sub>2</sub> ) <sub>17</sub> CH <sub>3</sub>	Hexadecane	27.7	27.7	0	1.5	0.82	4.1 <sup>b</sup>	[62]
	Ethanol	22.8	20.1	2.7	5.4	3.7	3.3 <sup>b</sup>	
	1,2-Propanediol	38	25	13	26.7	6.5	20.7 <sup>b</sup>	
	1,3-Propanediol	49	28	21	43.6	26.7	41.5 <sup>b</sup>	
	Water	72.8	21.8	51	102.2	93.1	102.9 <sup>b</sup>	
Tip=Au/HS(CH <sub>2</sub> ) <sub>17</sub> CH <sub>3</sub> Sample=Au/HS(CH <sub>2</sub> ) <sub>17</sub> CH <sub>3</sub>	Decane	23.9	23.9	0	0.5		0.34 <sup>b</sup>	[29]
	Benzene	28.9	27.1	1.8	4.9		0.39 <sup>b</sup>	
	Methanol	22.6	18.5	4.1	8.2		4.5 <sup>b</sup>	
	Ethanol	22.8	20.1	2.7	5.4		2.1 <sup>b</sup>	
	Propanol	23.3	21.1	2.2	4.5		1.6 <sup>b</sup>	
	Butanol	25.0	24.6	0.4	1.4		1.7 <sup>b</sup>	
	Hexanol	25.8	25.8	0	0.9		2.1 <sup>b</sup>	
	DMF	36.7	36.7	0	5.5		5.3 <sup>b</sup>	
	acetonitrile	29.3	29.3	0	2.1		10.6 <sup>b</sup>	
	DMSO	44	36	8	21.2		14.9 <sup>b</sup>	
	1,2-Ethandiol	48.2	29	19.2	40.4		26.5 <sup>b</sup>	
	Water	72.8	21.8	51	102.2		102.9 <sup>b</sup>	
	Water	72.8	21.8	51	102.2		110	
	Air <sup>e</sup>				19.3	19.3	18.5	
Tip=Au/HS(CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub> Sample=Au/HS(CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub>	Hexadecane	27.7	27.7	0	1.5		0.8	[59]
	Perfluorodecaline	18.2	18.2	0	3.4 <sup>c</sup>		3.8	
	Water	72.8	21.8	51	102.2		92	
Tip=Au/HS(CH <sub>2</sub> ) <sub>2</sub> (CF <sub>2</sub> ) <sub>7</sub> CF <sub>3</sub> Sample=Au/HS(CH <sub>2</sub> ) <sub>2</sub> (CF <sub>2</sub> ) <sub>7</sub> CF <sub>3</sub>	Hexadecane	27.7	27.7	0	13.8 <sup>c</sup>		13.6	[59]
	Perfluorodecaline	18.2	18.2	0	3.4		2.0	[29]
	Air <sup>e</sup>				11	11	10.8	
Tip=Au/HS(CH <sub>2</sub> ) <sub>17</sub> CH <sub>3</sub> Sample=Si/Cl <sub>3</sub> Si(CH <sub>2</sub> ) <sub>6</sub> COOH	Hexadecane	27.7	27.7	0			4.6	
	Ethanol	22.8	20.1	2.7			2.1	
	1,2-Propanediol	38	25	13			4.9	
	1,3-Propanediol	49	28	21			6.0	
	Water	72.8	21.8	51			0.9	
Tip=Au/HS(CH <sub>2</sub> ) <sub>15</sub> COOH Sample=Si/Cl <sub>3</sub> Si(CH <sub>2</sub> ) <sub>6</sub> COOH	Hexadecane	27.7	27.7	0			19.6	[62]
	Ethanol	22.8	20.1	2.7			10.1	
	1,2-Propanediol	38	25	13			16.0	
	1,3-Propanediol	49	28	21			6.0	
	Water	72.8	21.8	51			1.7	
Tip=Au/HS(CH <sub>2</sub> ) <sub>10</sub> COOH Sample= Au/HS(CH <sub>2</sub> ) <sub>10</sub> COOH	Water	72.8	21.8	51			12.0	[59]
Tip=Au/HS(CH <sub>2</sub> ) <sub>10</sub> COOH Sample= Au/HS(CH <sub>2</sub> ) <sub>19</sub> CH <sub>3</sub>	Water	72.8	21.8	51			17.2 <sup>b</sup>	[59]
Tip=Au/HS(CH <sub>2</sub> ) <sub>10</sub> COOH Sample= Au/HS(CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub>	Water	72.8	21.8	51			36.0	[59]
Tip=Au/HS(CH <sub>2</sub> ) <sub>11</sub> OH Sample= Au/HS(CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub>	Hexadecane	27.7	27.7	0			0.6	[59]
	Water	72.8	21.8	51			28	
Tip=Au/HS(CH <sub>2</sub> ) <sub>11</sub> OH Sample= Au/HS(CH <sub>2</sub> ) <sub>11</sub> OH	Hexadecane	27.7	27.7	0			4.6	[59]
	Dodecane <sup>d</sup>	25.4	25.4	0			4.4	
	Perfluorodecaline <sup>d</sup>	18.2	18.2	0			3.8	
	Ethanol <sup>d</sup>	22.8	20.1	2.7			0.41	
	Octanol	27.5	27.5	~0			1.2	
	Water	72.8	21.8	51			3.2	

- <sup>a</sup>  $\gamma_{LV}=19.3 \text{ mJ/m}^2$  is assumed for CH<sub>3</sub>-terminated SAMs. CAs on a planar thiol SAM are used to estimate of W.
- <sup>b</sup>  $\gamma_{SL}=102.9 \text{ mJ/m}^2$  is assumed for CH<sub>3</sub>-terminated SAMs in contact with water to determine tip radius.
- <sup>c</sup> to account for non-ideality in the dispersion interaction between fluoro- and hydrocarbon groups, Good-Crivalco parameter  $\Phi$  was set to 0.91 according to Good.
- <sup>d</sup> scaled to work of adhesion in hexadecane, ratios were determined experimentally by exchanging solvent in the liquid cell and keeping the same tip-sample pair
- <sup>e</sup> extrapolated from combined CFS and CA data for a methanol-water series

hydrogen-bonding solvents. The acid-base components of surface free energy of these SAMs are not readily available from contact angle measurements, because most test liquids will completely wet such surfaces. The CFS in these systems can potentially provide, along with a dispersion component, the values of  $\gamma^+$  and  $\gamma^-$ , which together will completely characterize adhesion between these SAMs and other organic surfaces. For example, STC treatment of  $W_{\text{HO/HD/OH}}$  and  $W_{\text{HO/HD/CH}_3}$  value listed in Table 3 using Equation 22 and assuming  $\gamma_{\text{OH}}^{\text{LW}} \approx \gamma_{\text{CH}_3}^{\text{LW}} \approx 19.3 \text{ mJ/m}^2$  and taking  $\gamma_{\text{CH}_3/\text{H}_2\text{O}} \approx 51 \text{ mJ/m}^2$ , yields  $\gamma_{\text{OH}}^{\text{AB}} \approx 1.1\text{-}1.5 \text{ mJ/m}^2$ . On the other hand, if for the same monolayers we used work of adhesion values found with CFS in water (Table 3), we would obtain  $\gamma_{\text{OH}}^{\text{AB}} \approx 24.6 \text{ mJ/m}^2$ . Warszynski et al argued [59] that the discrepancy can be resolved if one assumes that in combining relationships (Equation 21) one needs to take the values for free energy of solids saturated with respective liquids. Possible rearrangement of surface groups in response to different environment is another plausible explanation. In addition, STC model has been shown to have internal inconsistencies and CFS could be a powerful tool to explore them. Clearly, the  $\gamma^{\text{AB}}$  values for high surface energy groups are not available by other means (e.g. contact angle measurements); in these situations, CFS can be used as an independent method to construct the respective acid-base scales. It also can provide insights in the behavior of surface groups in contact with varying liquid medium. A systematic study that takes advantage of CFS to derive STCs in a self-consistent way, however, is lacking in the present literature.

## 8. Control of Adhesion with Mixed SAMs and Mixed Solvents.

Brewer and Leggett [70] used mixed monolayers of  $\text{HS}(\text{CH}_2)_{11}\text{CH}_3$  and  $\text{HS}(\text{CH}_2)_{11}\text{OH}$  thiols to derive surfaces of controlled surface free energies. Adhesion between these mixed SAM substrates and  $\text{CH}_3$  or  $\text{COOH}$  functionalized tips in ethanol displayed approximately linear

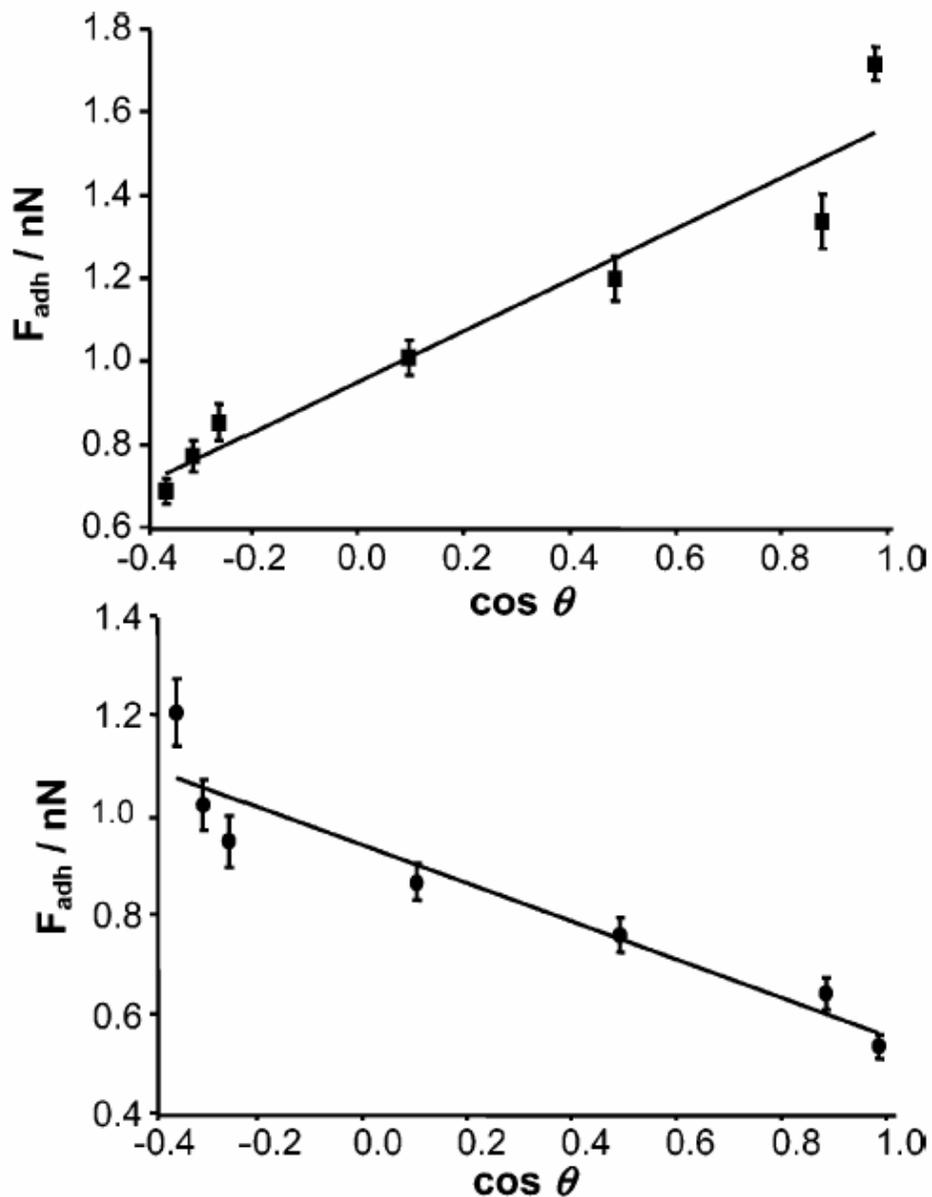
dependence on the contact angle of water with these surfaces (e.g. fraction of hydrogen-bonding component). Adhesion force between COOH tips and samples in ethanol increased with greater content of polar component in the SAM, whereas adhesion measured with CH<sub>3</sub> tips dropped for SAMs with higher fraction of OH groups (Figure 12). Pull-off forces for these mixed monolayer surfaces displayed broadened distributions compared to adhesion distributions of individual homogenous SAMs, with some indications of bimodal nature for these distributions. While no phase separation could be observed in friction force images, the lateral resolution of pull-off experiments could be better due to reduced contact radius at pull-off versus that at low loads (~10 nN) during friction force imaging, calculated 1 nm vs. 2.4 nm for tip radius used. Thus, CFS appears to be sensitive to nanometer (or sub-nanometer) spatial heterogeneity in surface composition.

Vezenov et al. used mixed COOH-CH<sub>3</sub> SAMs to vary surface free energy of the probes for CFS of epoxy polymer [29]. Adhesion forces in water between epoxy polymer and CFM tips functionalized with mixed SAMs showed a direct correlation with the work of adhesion calculated on the basic STC theory and contact angle measurements of the polymer on these SAM surfaces. Use of methanol-water mixtures to obtain solvents of continuously varying hydrogen-bonding ability was also demonstrated. While these mixed systems appear to behave as pseudo averaged homogenous systems, the questions remain regarding the quantitative magnitude of corresponding effects reflecting underlying molecular heterogeneity (adsorption and phase-separation).

## **9. Entropic Solvation Barriers Probed by Chemical Force Spectroscopy.**

As the previous sections showed, solvation plays a very important role in shaping the

Figure 12. Variation in the mean pull-off force as a function of  $\cos\theta$  ( $\theta$  is the CA of water) for mixed monolayers of  $\text{HS}(\text{CH}_2)_{11}\text{OH}$  and  $\text{HS}(\text{CH}_2)_{11}\text{-CH}_3$  on gold using a carboxylic acid-terminated tip (top) and a methyl-terminated tip (bottom). Reproduced from reference [70] with permission.



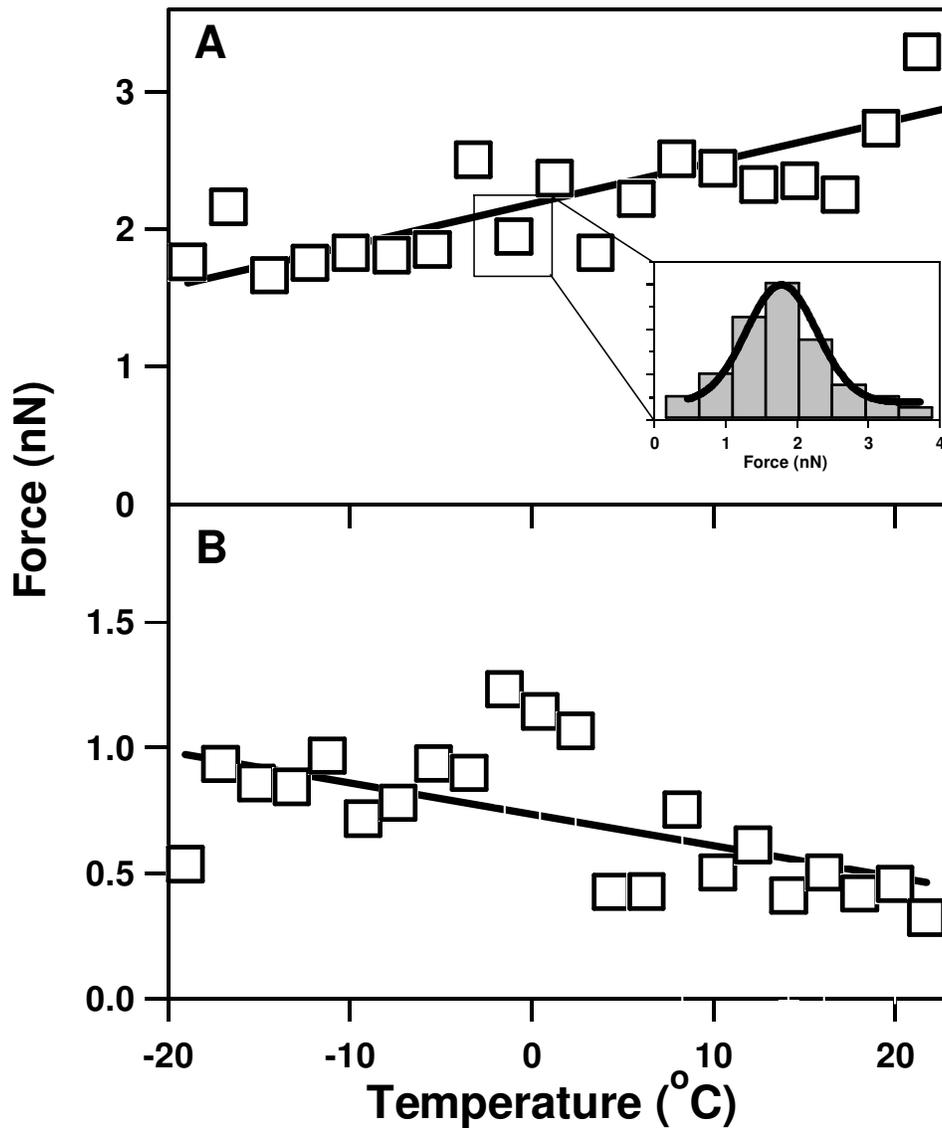
interactions between chemically-modified probes and surfaces. Surface tension component model provides the quantitative framework for predicting binding forces. However, we can gain a deeper understanding of the origin of such forces if we consider the temperature dependence of the tip-sample interaction strength. Noy and co-workers [57, 75] studied the strength of the interactions between several different surfaces as a function of temperature. Intuitively, we expect the binding force to decrease as the temperature increases and the thermal fluctuations gain more energy to break the bond. Surprisingly, the researchers observed that for interactions between COOH-terminated surfaces in a polar, hydrogen-bonding solvent the interaction strength *increased* with the temperature (Figure 13A). This behavior was also present for interactions of other hydrophilic functionalities in polar solvents. Conversely, when the liquid medium was switched to a non-polar solvent (hexane) the temperature trend reversed (Figure 13B). Researchers attributed this behavior to the large negative entropy accompanying ordering of solvent molecules at the interfaces [75]. This negative entropy destabilizes the unbound state and leads to the observed counterintuitive temperature dependence. Non-polar solvents do not tend to form ordered layers and thus do not contribute to these *entropic* solvation barriers.

A kinetic model (Section 5.2.2) can provide a quantitative interpretation of this phenomenological picture. If we separate the energy barrier into enthalpic and entropic components,  $E_0 = \Delta H - T\Delta S$ , and substitute Equation 27 into Equation 26, we can represent the temperature dependence of pull-off forces in a much more revealing form,

$$f_{pull-off} = \frac{\Delta H}{x_\beta} - \frac{\Delta S}{x_\beta} T - \frac{k_B T}{x_\beta} \ln \left[ \frac{k_B T}{r_f \tau_D x_\beta} \right] \quad [31]$$

The first two terms in Equation 31 describe the enthalpic and the entropic contribution to

**Figure 13. (A) Binding force as a function of temperature for interactions of COOH-modified probe and sample in ethanol. Inset shows a binding force histogram at one temperature point. (B) Binding force as a function of temperature for the interactions of COOH-modified probe and sample in hexane.**



the bond strength and the third term describes the contribution of thermal motion to the bond strength. In other words, the first two components describe the true energy-barrier contribution and the (always negative) third component describes the “thermal weakening” of a bond caused by the thermal fluctuations helping the system to get over the activation barrier.

Equation 31 highlights another bit of non-trivial physics of chemical bond behavior under external load. The third term in the Equation 31 (“thermal weakening”) always increases in magnitude as the temperature increases, leading to the overall decrease in the observed force, in full agreement with the intuitive picture of bond “loosening”. Yet, the entropic term can lead to either increase or decrease in the overall interaction force depending on the sign on the entropy change for the unbinding process. Therefore, for the cases when the energy barrier has a large entropy component (i.e. in cases of entropic interactions) we expect the bond strength to increase with the temperature. The relative magnitude of the entropic and the kinetic terms in Equation 31 defines two regimes of bond rupture: 1) thermally-dominated kinetics where the kinetic weakening leads to decrease in the observed bond strength with the increase in temperature and 2) barrier-dominated kinetics where the entropic term overwhelms the kinetic term and leads to an increase in interaction strength with increase in temperature. Furthermore, Equation 31 also indicates that the entropic regime of unbinding must exist only over a limited range of temperatures. As the temperature increases, kinetic term which increases as  $T \cdot \ln T$  will overwhelm the entropic term which increases only linearly. For the entropic forces caused by the ordering of the solvent molecules at the surface this cross-over point simply corresponds to the situation when the thermal motion becomes too strong and overwhelms molecular ordering in the solvent layers.

## 10. Force Titrations.

The ionization (charged) state of the surfaces is of fundamental interest in colloidal stability and particle adhesion to surfaces [1, 3]. Since our original report [10], the concept of chemical force titrations (CFT) has been refined and expanded. In CFT, one probes pH dependence of adhesion forces between basic or acidic functional groups, or more generally, dependence of adhesion forces between ionizable groups and concentration of counterions.

Several aspects were investigated: 1) large  $pK_a$  shifts of amine-terminated SAMs; 2) observation of inverted CFT curves for aromatic amines; 3) effect of ionic strength (IS) on the shape of the CFT curves and peak positions; 4) ion adsorption/binding. Table 3 summarizes the results of CFT for several functional groups. Li demonstrated the local character of  $pK_a$  measurements with CFT by observing  $pK_{1/2}$  of 5.6 for COOH SAM on micropatterned substrates (1-2  $\mu\text{m}$  regions), for which contact angle titration showed a transition at  $pK_{1/2}=11.0$  [76]. Vancso group reported a remarkable spatial resolution of *ca.* 50 nm for CFTs of plasma treated polymer substrates [16, 18].

(3-aminopropyl)triethoxysilane (APTES) monolayers were observed to have unusually large  $pK_a$  shift of *ca.* 7 pK units (IS=0.01M) [10], although similarly large forces and  $pK_a$  shifts at high IS ( $10^{-2}$  M) were found in thiolate long-chain ( $-(\text{CH}_2)_{11}-$ ) SAM pairs bearing amine functionality [11]. The large shift and high adhesion in neutral state were attributed to a disordered structure of the siloxane monolayer. The quality of the APTES modified on  $\text{SiO}_2/\text{Si}$  substrates was improved with a new vapor-phase deposition procedure that used refluxing APTES/xylene solution below suspended substrate [77]. This silanization method gave reproducible monolayers with a higher  $pK_{1/2}$  and factor of three lower forces. On the other hand, increasing the chain length from 2 to 11 methylene units of analogous amine-terminated thiol SAM did not result in significant  $pK_{1/2}$  changes at low IS ( $10^{-4}$  M), however,  $F_a$  increased with

switching to a short-chain pair (Table 3) [78]. A second drop in adhesion for NH<sub>2</sub>-terminated thiol SAMs was observed at high pH and attributed to the ionizable oxidized sulfur-containing groups at the interface. The infra-red spectroscopy of these SAMs provided evidence for the presence of S-O moieties, possibly from exposure and subsequent oxidation of surface thiol groups, resulting from the competition between amine and thiol groups for binding to Au.

CFT of basic functional groups, in which a nitrogen atom is involved with aromatic functionality (either as being part of the aromatic ring, as in 4-mercaptopyridine (HS-Py), or through conjugation, as in 4-aminothiophenol (HS-Ph-NH<sub>2</sub>)), produced high adhesion force at low pH and low/repulsive forces at high pH – contrary to expectations based on their charged state [79, 80]. To explain this phenomenon, *ab initio* calculations of surface charges were carried out for APTES, HS-Ph-NH<sub>2</sub>, and HS-Py molecules [81]. Surface charges (in units of electron charge) for these groups were, respectively, 0.606, 0.607, and 0.035 in the protonated state, and -0.09, -0.298, and -0.909 in the neutral state. Highly polarized state of Py groups together with efficient charge dispersion in Py-H<sup>+</sup> is consistent with repulsion between the neutral Py groups and attraction between charged Py-H<sup>+</sup> groups observed in CFTs. Significant surface charge of Ph-NH<sub>2</sub> groups is responsible for low adhesion at high pH. Protonated Ph-NH<sub>3</sub><sup>+</sup> groups, however, carry the same charge as primary amine APTES. Since some fraction of neutral groups carrying comparable and opposite surface charge (-0.3 vs 0.6) is available at low pH, the observed adhesion reflects the interaction between surfaces with reduced overall charge and having a distribution of positive (due to Ph-NH<sub>3</sub><sup>+</sup>) and negative (due Ph-NH<sub>2</sub>) local charge.

CFT at low IS (<10<sup>-4</sup> M) resulted in another type of unusual behavior: instead of a sigmoidal transition from the high adhesion between neutral groups to low adhesion (or repulsion) between charged groups, Smith et al. observed a peak in adhesion force at

intermediate pH for COOH [82-84], PO(OH)<sub>2</sub> [83-85] and NH<sub>2</sub> [78] groups. Their interpretation of 10 to 20-fold increase of adhesion between hydrophilic groups centers on a hypothesis of formation of “strong hydrogen bonds” between neutral and charged groups representing a conjugated acid/base pair, e.g. carboxyl and carboxylate. For a given fraction  $\beta$  of dissociated groups, the total adhesion force is comprised of two contributions from N groups: 1) “weak” hydrogen bonds between neutral groups (e.g. COOH/COOH) with a single force value of  $f_{hb}$  and 2) “strong” ionic hydrogen bonds (e.g. COOH/COO<sup>-</sup>) that are a factor of  $m$  stronger:

$$F_a = N f_{hb} [2(1 - \beta) \beta m + (1 - \beta) (1 - \beta) m] \quad [32]$$

Smith et al. were able to reproduce the shape of the CFT peak with the equation above for HS(CH<sub>2</sub>)<sub>15</sub>COOH SAMs resulting in a fitted value  $m \approx 16$  (Figure 14), although for shorter HS(CH<sub>2</sub>)<sub>10</sub>COOH SAM, the observed peak was wider than predicted [82]. Since the relevant forces reflect the energy balance for interactions between groups on the tip and sample as well as these same surface groups and the solvent, one needs to take these arguments as reflecting the difference in the strength of respective hydrogen bonds between carboxylate anion and carboxylic acid group, on one hand, and carboxylate anion and water, on the other hand. Differences in hydrogen bond strength could partly reflect differences in the dielectric constant of the environment surrounding charged groups, when exposed to water, or when sandwiched between organic SAMs. Similar shape of CFT curves was observed for (HS(CH<sub>2</sub>)<sub>11</sub>O)<sub>2</sub>PO(OH) modified tips and surfaces [86]. One caveat of this model is that while the peak in adhesion force is predicted for  $\beta = 1/2$ , the  $pK_{1/2}$  values should be more appropriately treated as pH values where adhesion force takes  $1/2$  its maximum value, rather than pH for the degree of dissociation of 0.5 for surface groups. An analysis of the non-contact regime of CFT with force feedback showed that the surface potential of COOH groups at pH=7 reflects the maximum  $\beta$  value of

about 15% [87], while surface charge calculation gives the  $pK_a$  of 7.7. Simultaneous analysis of contact (adhesion) and non-contact (double layer) forces appears to be the most consistent way for determining the  $pK_a$  of surface functional groups.

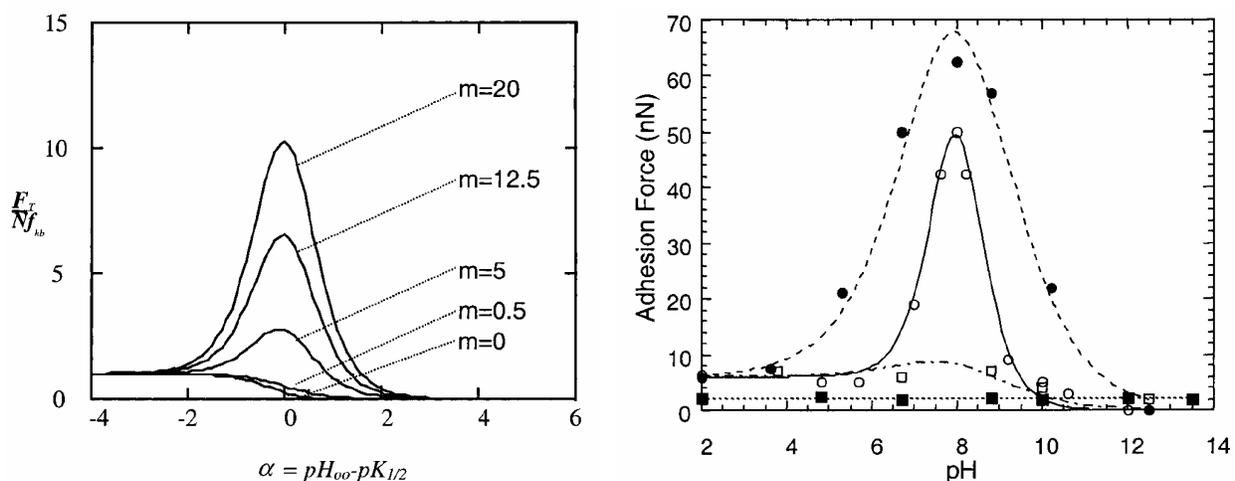
CFT of neutral surfaces that can form complexes with ions from solution can result in a sandwich-type interfacial bond: adhesion between methylsulfanyl groups on the tip and sample in solution of  $AgNO_3$  (IS=0.1M,  $KNO_3$ ) showed a peak at  $p[Ag^+]=2$ , while adhesion between similarly prepared hexyl monolayers was insensitive to variations in  $Ag^+$  concentration [88]. A model of binding was proposed that involved formation of 1:2 interfacial complexes,  $R(CH_3)S-Ag^+-S(CH_3)R$ , that promoted strong interfacial bonds at low concentration of silver ions. At high concentration ( $>10^{-2}$  M) of  $Ag^+$ , the surface coverage increased (approached saturation): competitive repulsion from  $R(CH_3)S-Ag^+/Ag^+-S(CH_3)R$  interactions resulted in a sharp drop in adhesion. Interestingly, detailed analysis of non-contact regime in CFTs on nominally neutral surfaces - hydrophobic, methyl-terminated, and hydrophilic, ethylene oxide-terminated, revealed that both interfaces undergo complex charging as a function of solution pH (Table 3) via adsorption of hydronium and hydroxyl ions [89].

**Table 3. Shapes of chemical force titration curves and apparent  $pK_{1/2}$  values for chemically modified tips and samples (IS = ionic strength).**

Functional group		IS, M	Curve shape/ $F_a$ trend (low-high pH)	$pK_{1/2}$ or $pK_{peak}$	$pK_{bulk}$	Ref.
surface	tip					
H <sup>+</sup> binding / Basic groups						
(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	10 <sup>-1</sup>	Sigmoid low-high	5.3 <sup>a,b</sup>		[88]
(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> NH <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>11</sub> OH	10 <sup>-2</sup>	Sigmoid: zero-high	7.4		[77]
HS(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	10 <sup>-4</sup>	Peak: low-high-low	5.1 <sup>c</sup>	10.54(C <sub>3</sub> )- 10.64(C <sub>11</sub> )	[78]
HS(CH <sub>2</sub> ) <sub>2</sub> NH <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>11</sub> NH <sub>2</sub>	10 <sup>-4</sup>		6.3 <sup>c</sup>		
HS(CH <sub>2</sub> ) <sub>11</sub> NH <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>11</sub> NH <sub>2</sub>	10 <sup>-4</sup>		6.1 <sup>c</sup>		
HS(CH <sub>2</sub> ) <sub>11</sub> NH <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>11</sub> NH <sub>2</sub>	10 <sup>-1</sup>		Sigmoid: zero-high		
(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> N <sub>2</sub> C <sub>3</sub> H <sub>2</sub>	(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> N <sub>2</sub> C <sub>3</sub> H <sub>2</sub>	10 <sup>-1</sup>	Sigmoid low-high	4.1 <sup>b</sup>		[88]
HSC <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	HSC <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	10 <sup>-2</sup>	Sigmoid: high-low	5.3	4.87	[79]
HSC <sub>5</sub> H <sub>5</sub> N <sup>d</sup>	HSC <sub>5</sub> H <sub>5</sub> N <sup>d</sup>	10 <sup>-2</sup>	Sigmoid: high-low	5.5	5.23	[90]
HS(CH <sub>2</sub> ) <sub>10</sub> C <sub>9</sub> H <sub>6</sub> N <sup>c</sup>	HS(CH <sub>2</sub> ) <sub>10</sub> C <sub>9</sub> H <sub>6</sub> N <sup>c</sup>	10 <sup>-2</sup>	Peak: low-high-low	5.3		
HS(CH <sub>2</sub> ) <sub>10</sub> C <sub>9</sub> H <sub>6</sub> N <sup>c</sup>	HS(CH <sub>2</sub> ) <sub>11</sub> OH	10 <sup>-2</sup>	Peak: low-high-zero	5.2	4.90	[80]
HS(CH <sub>2</sub> ) <sub>11</sub> OH	HS(CH <sub>2</sub> ) <sub>10</sub> C <sub>9</sub> H <sub>6</sub> N <sup>c</sup>	10 <sup>-2</sup>	Peak: low-high-zero	5.4		
H <sup>+</sup> binding / Acidic groups						
HS(CH <sub>2</sub> ) <sub>10</sub> COOH	HS(CH <sub>2</sub> ) <sub>10</sub> COOH	10 <sup>-1</sup>	Sigmoid: high-zero	5.0		[82]
HS(CH <sub>2</sub> ) <sub>10</sub> COOH	HS(CH <sub>2</sub> ) <sub>10</sub> COOH	10 <sup>-2</sup>		5.4-5.6		[76]
HS(CH <sub>2</sub> ) <sub>10</sub> COOH	HS(CH <sub>2</sub> ) <sub>10</sub> COOH	10 <sup>-4</sup>	Peak: low-high-zero	6.3	4.78(C <sub>2</sub> )- 4.96 (C <sub>9</sub> )	[82]
HS(CH <sub>2</sub> ) <sub>10</sub> COOH	HS(CH <sub>2</sub> ) <sub>10</sub> COOH	10 <sup>-7</sup>		8.0		
HS(CH <sub>2</sub> ) <sub>15</sub> COOH	HS(CH <sub>2</sub> ) <sub>15</sub> COOH	10 <sup>-7</sup>		8.0		
HS(CH <sub>2</sub> ) <sub>3</sub> COOH	HS(CH <sub>2</sub> ) <sub>10</sub> COOH	10 <sup>-7</sup>		Sigmoid: high-low		
HS(CH <sub>2</sub> ) <sub>3</sub> COOH	HS(CH <sub>2</sub> ) <sub>3</sub> COOH	10 <sup>-7</sup>	Plateau	-		
HS(CH <sub>2</sub> ) <sub>11</sub> OPO(OH) <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>11</sub> OPO(OH) <sub>2</sub>	10 <sup>-1</sup>	Double Sigmoid: high-low-lower	(1) 4.6 (2) 7.7	(1) 2.16 (2) 7.21	[82, 85]
HS(CH <sub>2</sub> ) <sub>11</sub> OPO(OH) <sub>2</sub>	HS(CH <sub>2</sub> ) <sub>11</sub> OPO(OH) <sub>2</sub>	10 <sup>-4</sup>	Double Peak: low-high-low-high-low	(1) 4.6 (2) 8.4	(H <sub>3</sub> PO <sub>4</sub> )	
(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	10 <sup>-3</sup> - 10 <sup>-7</sup>		5.0		
(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	1	Peak: low-high-zero	4.5	(1) 3.8	
(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	HS(CH <sub>2</sub> ) <sub>15</sub> COOH	10 <sup>-3</sup> - 10 <sup>-7</sup>		4.0	(2) 6.2 (AMP <sup>f</sup> )	
O <sub>2</sub> Fe-OH (iron hydroxide colloid)	(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	10 <sup>-2</sup> - 10 <sup>-7</sup>	Triple Peak	(1) 5.5 (2) 7.5 (3) 12.0	(1) 7.0 (2) 11.0 (Fe(OH) <sub>2</sub> )	[86]
(O <sub>2</sub> Fe-O) <sub>2</sub> PO(OH) (iron hydroxide colloid coprecipitated with HPO <sub>4</sub> <sup>2-</sup> )	(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	10 <sup>-3</sup> - 10 <sup>-7</sup>	Peak: low-high-zero	5.0	-	
O <sub>2</sub> Fe-OPO(OCH <sub>3</sub> ) <sub>2</sub> (iron hydroxide colloid coprecipitated with (OCH <sub>3</sub> ) <sub>2</sub> PO(OH))	(HS(CH <sub>2</sub> ) <sub>11</sub> O) <sub>2</sub> PO(OH)	10 <sup>-3</sup> - 10 <sup>-7</sup>	Plateau: broad peak	6.0	-	
H <sup>+</sup> and OH <sup>-</sup> binding / absorption to neutral groups						
HS(CH <sub>2</sub> ) <sub>15</sub> CH <sub>3</sub>	HS(CH <sub>2</sub> ) <sub>15</sub> CH <sub>3</sub>	10 <sup>-3</sup>	Sigmoid: attraction- repulsion	4.0	-	[89]
HS(CH <sub>2</sub> ) <sub>11</sub> (OCH <sub>2</sub> CH <sub>2</sub> ) <sub>3</sub> OCH <sub>3</sub>	HS(CH <sub>2</sub> ) <sub>15</sub> CH <sub>3</sub>	10 <sup>-3</sup>	Sigmoid: repulsion- attraction-repulsion	(1) 4.5 (2) 7.5	-	
Ag <sup>+</sup> binding						
(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	10 <sup>-1</sup>	Plateau	-		[88]
(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> SCH <sub>3</sub>	(CH <sub>3</sub> O) <sub>3</sub> Si(CH <sub>2</sub> ) <sub>3</sub> SCH <sub>3</sub>	10 <sup>-1</sup>	Peak: low-high-low	2	-	

- a) independent of counterion:  $\text{Cl}^-$  or  $\text{NO}_3^-$
- b) a second drop in  $F_a$  is observed at  $\sim \text{pH}=12$  and attributed to ionization of Si-OH groups
- c) a second drop in  $F_a$  is observed at  $\sim \text{pH}=10$  and attributed to ionization of  $-(\text{SO})\text{OH}$  groups
- d) pyridine
- e) quinoline
- f) 3'-Adenosine monophosphate

**Figure 14.** (Left) The adhesion force titration curve is modeled as a linear combination of two types of hydrogen bonds – strong ionic and weak neutral bonds. CFTs are plotted for different values of  $m$ , the ratio of the strength of these two bonds.  $\text{pH}_\infty$  is the pH of the bulk solution, and  $\text{p}K_{1/2}$  is defined as the pH at which half of the surface groups are ionized. The peak in CFT observed for the low electrolyte concentration is reproduced with values of  $m=15-20$ , whereas the sigmoidal step at high ionic strength is reproduced by  $m\sim 0$ , i.e., no strong hydrogen bonds formed (e.g. because of the interaction of buffer ions with the ionized acid groups in the SAMs). (Right) Effect of SAM packing on CFT curves in very low electrolyte concentration buffer ( $10^{-7}$  M) for tip and substrate modified with  $\text{HS}(\text{CH}_2)_{15}\text{COOH}$  (16:16, open circles),  $\text{HS}(\text{CH}_2)_{10}\text{COOH}$  (11:11, solid circles),  $\text{HS}(\text{CH}_2)_{10}\text{COOH}$  and  $\text{HS}(\text{CH}_2)_3\text{COOH}$  (11:3, open squares), and  $\text{HS}(\text{CH}_2)_3\text{COOH}$  (3:3, solid squares). The 16:16 peak is accurately fitted by Equation 32, yielding a value of  $m=16$ , while the rest of the curves (11:11, 11:3, and 3:3 data) are only guides to the eye. Reproduced from reference [82] with permission.



## 11. Mapping of Full Intermolecular Potentials using Chemical Force Microscopy

Conventional chemical force microscopy measurements probe only a portion of the force profile where the spring stiffness is larger than the second derivative of the potential energy profile (see Section 2). Removing this restriction and probing the full potential energy profile is clearly important for realizing the full potential of chemical force microscopy for probing intermolecular interactions. Such attempts fall into two different categories: (1) dynamic measurements and (2) quasi-static measurements. Dynamic measurements use non-equilibrium experimentals to extract information about equilibrium potential energy surface. One such example is dynamic force spectroscopy (DFS) reviewed in Section 5.2.2. DFS measurements are quite powerful; however they require large number of individual pull-off force measurements and thus depend on having robust CFM probes that can survive thousands of force curve cycles. Another example is the use of the Jarzynski equality (Equation 33) [91, 92] to extract equilibrium potential energy profiles:

$$e^{\frac{-\Delta G}{k_r T}} = \left\langle e^{\frac{-W_i}{k_r T}} \right\rangle \quad [33]$$

This remarkable thermodynamic equality postulates that an equilibrium free energy difference ( $\Delta G$ ) can be recovered by using *Boltzman-weighted averaging* of non-equilibrium work values ( $W_i$ ); thus, Jarzynski equality opens up a possibility of obtaining equilibrium energy values from experiments that involve energy dissipation along non-equilibrium pathways. Jarzynski equality has only recently been introduced into the force spectroscopy realm [92], and it is yet unclear whether it will provide a robust solution for CFM.

Quasi-static measurements, on the other hand, have enjoyed considerable and prolonged attention in CFM applications. In a typical quasi-static measurement the cantilever spring stiffness is always above the potential energy gradient, eliminating cantilever jumps. Historically, the sensitivity tradeoff associated with using very stiff cantilevers motivated researchers to design feedback systems that dynamically stiffened the AFM cantilever as it sampled the interaction potential. The first successful such attempt was an Interfacial Force Microscope (IFM) developed by J. Houston's group [93]. Houston and Kim wrote an excellent review article [94] on CFS performed with IFM, using tips and samples modified by SAMs. IFM used specially-designed teeter-type force sensors and capacitive feedback to balance the attractive tip-sample forces. Unfortunately, capacitive feedback can be difficult to work with in fluid environments and particularly in ionic solutions.

More recently Pethica and co-workers [95] and Lieber and co-workers [87] used magnetic feedback mechanism to stabilize the AFM probe against an external force gradient. Ashby et al used magnetically-stabilized cantilevers to examine interactions between probe and surfaces modified with COOH and OH groups [87]. These measurements, as well as analysis of jump-to-contact distances for CH<sub>3</sub> groups in methanol-water mixtures [29], showed that the interaction potential is described well by the van der Waals interactions with Hamaker constant of  $1-1.2 \cdot 10^{19}$  J. Interestingly, these measured values were close to the Hamaker constant for the gold-gold interactions, suggesting that the long-term interactions between modified probes and samples had a large contribution from probe and sample material, rather than from pure chemical interactions of terminal functionalities. Unfortunately, magnetic feedback also introduced additional noise and failed to control the cantilever motion near the resonance [96].

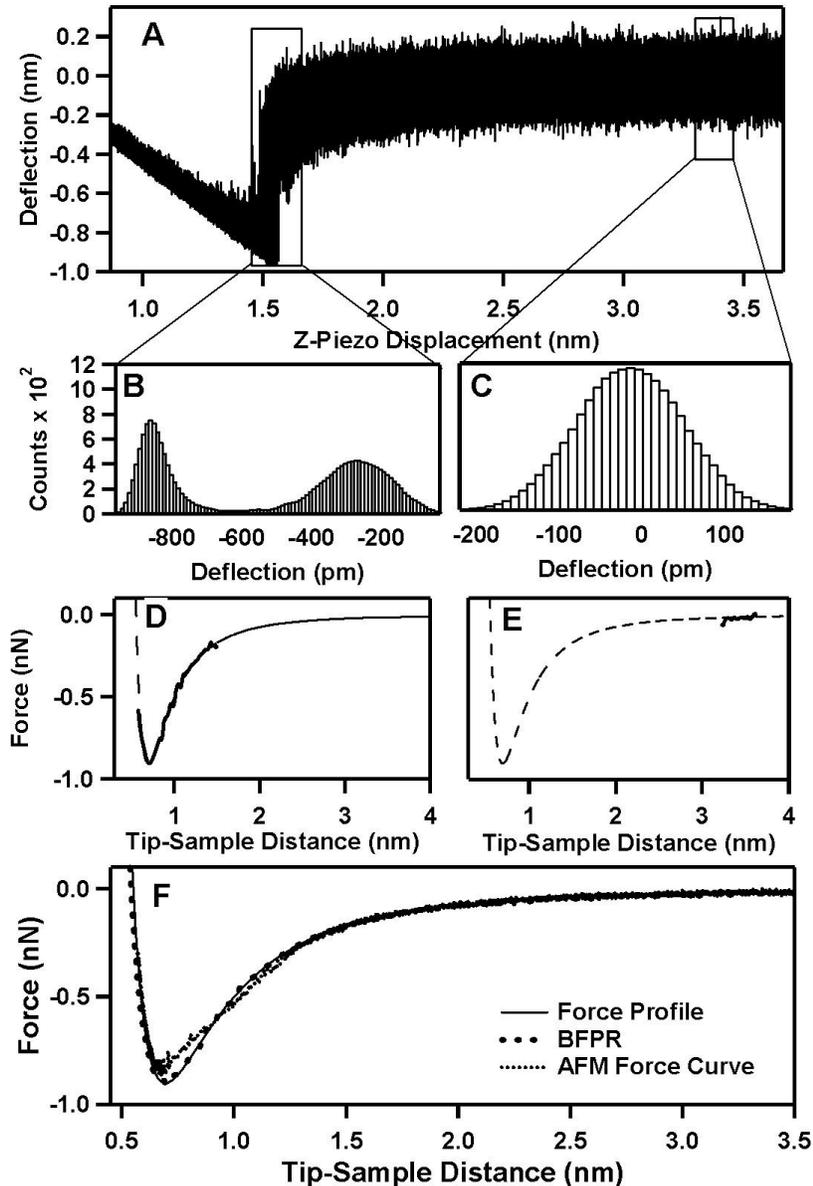
Later Ashby and Lieber designed another technique for extracting equilibrium potential profiles from the force microscopy measurements [96]. This time their technique relied on using very stiff cantilevers (1-10N/m), to eliminate instabilities. Using these cantilevers required extensive modification to the AFM hardware in order to increase detection sensitivity by an order of magnitude [96]. Ashby et al also noticed that as the cantilever approaches the surface, its movement becomes anharmonic due to the influence of the interaction potential. In this situation simple DC averaging of the cantilever movement typical for conventional force curve measurements distorts the true interaction potential and underestimates potential energy gradients. To recover true interaction potential from the AFM measurements Ashby et al, introduced the *Brownian force profile reconstruction* (BFPR) technique [97].

BFPR harnesses thermal vibrations of the cantilever to probe the interaction potential. As the cantilever vibrates in the proximity of the sample, it encounters different regions of the interaction potential. Ordinarily, this information is lost in the DC averaging, yet it can be recovered by oversampling the deflection signal at frequency higher than thermal resonance frequency. A histogram of the probe position taken from a region of such “noisy” force curve contains the information about the sum of the interaction potential and the harmonic cantilever potential well. Specifically, the histogram of the cantilever positions is populated according to the Boltzman-weighted distribution:

$$p(\mathbf{x}) = p_0 \cdot e^{-\frac{U_{ts}(\mathbf{x}) + U_{cant}(\mathbf{x})}{k_B T}} \quad [34]$$

where  $U_{ts}$  refers to the potential of the tip-sample interactions and  $U_{cant}$  refers to the cantilever spring potential. Inverting the position histogram according to the Equation 34 produces the sum of two potentials (Figure 15A-C). The cantilever potential can then be recovered from a section

**Figure 15. Computer simulation illustrating BFPR procedure. (A) Force curve sampled at four times the resonant frequency to include all cantilever thermal noise. (B, C) Histograms of sections of force curve marked by boxes in A. (D, E) Force profile sections (solid lines) calculated from the histograms B, C superimposed with the force profile used in the simulation (dashed lines). (F) Comparison between the results of BFPR, standard CFM force curve, and the force profile used in the simulation. Reproduced from [97].**



of the force curve recorded far away from the surface. Subtraction of the cantilever potential then recovers a small section of the interaction potential near the average tip-sample separation at this point (Figure 15D, E). Researchers also developed an algorithm which “stitched” these pieces to recover the full potential energy profile (Figure 15F, G).

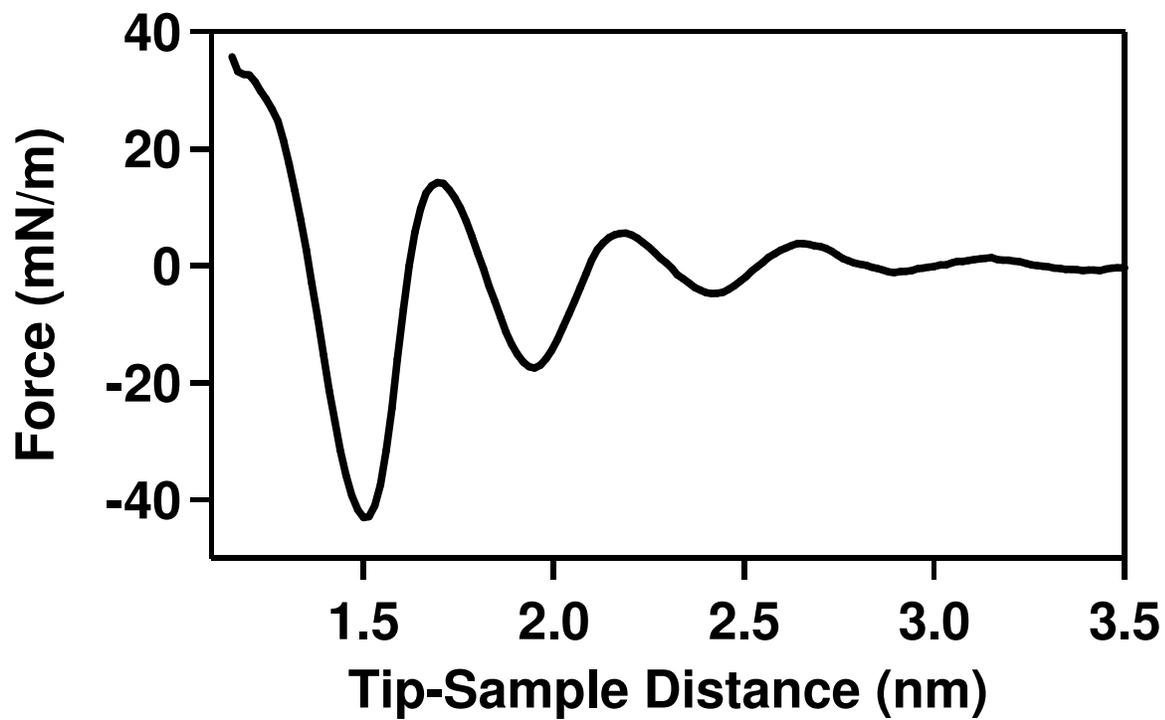
Ashby demonstrated BFPR utility by reconstructing the normalized force profile of nonanol between two hydrophobic surfaces, a CH<sub>3</sub> terminated thiol tip and HOPG surface. (Figure 16). The measurement showed that structural forces from nonanol solvation layers dominate these interactions. The reconstructed profile clearly shows the periodic potential due to the squeezing of the sequential nonanol layers out of the tip-sample gap. These measurements unambiguously demonstrate structural forces in a truly nanoscale system.

Ashby et al. has also developed another technique to quantify tip-sample dissipative interactions, this time using highly non-equilibrium tip-sample interactions in tapping mode [96, 98]. This method calculates the energy dissipation in the probe-sample junction at every point in the tapping mode image. Energy dissipated per cantilever tap improves upon simple phase imaging by removing contributions from the sample topography and is a better way to characterize tip-sample interactions. Ashby et al further investigated dissipative interactions by solving the equation of motion for tip-sample interaction force to measure advancing and receding force profiles during tapping mode. This technique allows the direct observation of adhesion hysteresis in force profiles of dissipative intermolecular interactions.

## **12. Modeling of CFS Experiments.**

In the last few years, several publications on atomistic simulations of CFS appeared in the literature, using both molecular dynamics (MD) and pseudo-equilibrium simulations. The theoretical work on modeling the contact between SAMs during load-unload cycle provided

**Figure 16.** Average reconstructed force profile for the interactions of two hydrophobic surfaces in 1-nonanol. The force profile has a period of 4.5 Å, the molecular diameter of 1-nonanol.

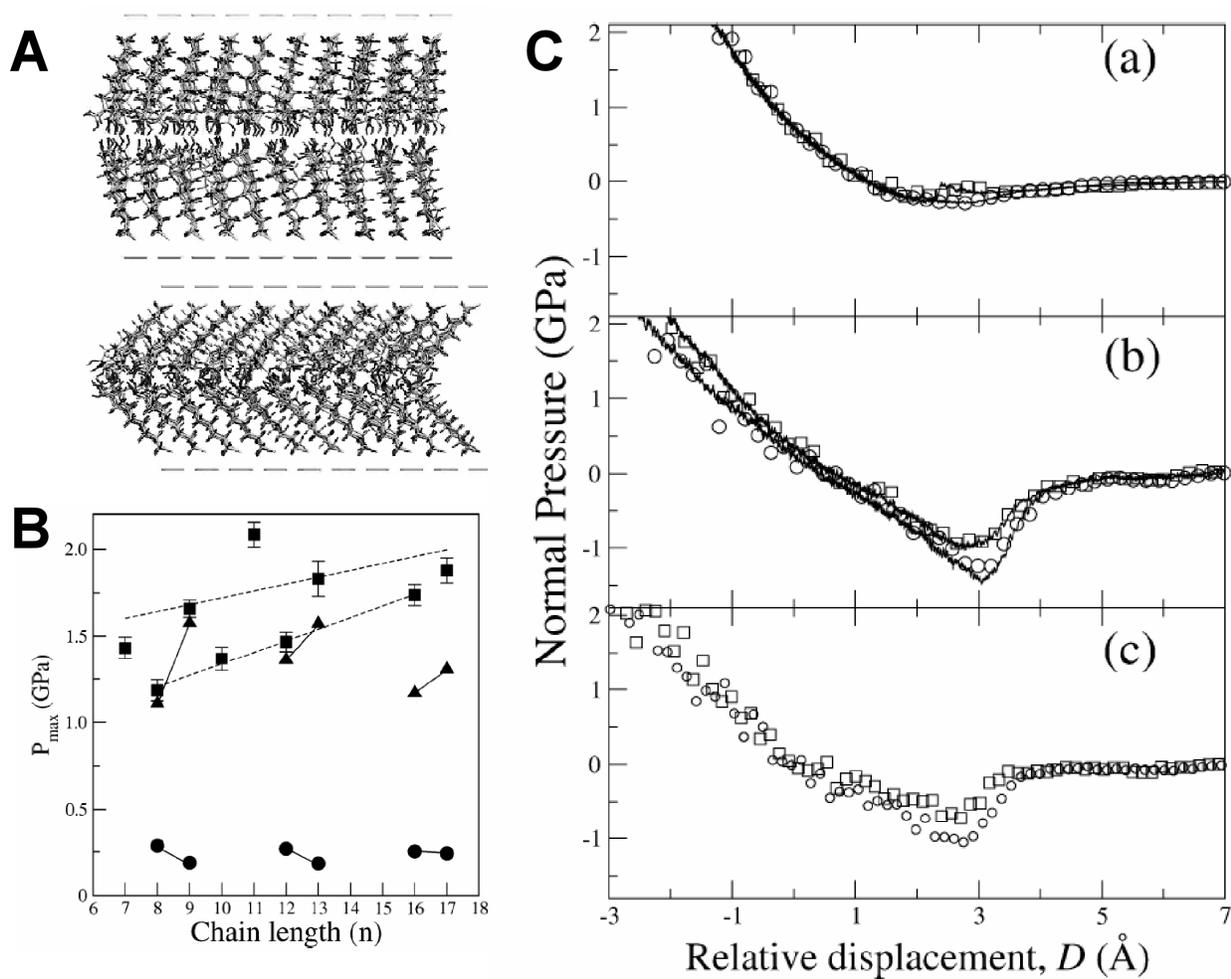


unprecedented molecular level details of intermolecular interactions and rearrangements in the course of a typical CFS experiment. All simulations are done in vacuum and most appropriately compared to results in dry air. The experimental loading rates,  $\sim 10^{-6}$  m/s, are unfeasibly slow for simulation, which are done at  $10^0$ - $10^1$  m/s. Near attractive potential well, a hysteresis is observed in MD [99, 100] due to slow relaxation of collective motion within the SAMs.

Park et al [99] analyzed 1) the effect of the terminal groups on adhesion, and 2) the chain length and even-odd effects by performing MD simulations for compression-decompression of flat  $\text{HS}(\text{CH}_2)_n\text{X}$  monolayers bearing  $\text{X}=\text{CH}_3$ ,  $\text{OH}$  ( $n = 8,9,12,13,16,17$ ) and  $\text{COOH}$  ( $n = 7-13,16,17$ ) functional groups (Figure 17A). Methyl terminated SAMs of all chain lengths indeed showed significantly lower adhesion (Figure 17C) than their respective counterparts with polar groups – the attractive minima for  $\text{COOH}$ ,  $\text{OH}$ , and  $\text{CH}_3$  SAMs ( $n = 8$ ) were  $1.3\pm 0.06$ ,  $1.1\pm 0.06$ , and  $0.28\pm 0.06$  GPa, correspondingly (surface free energies of 135, 116, and  $10.1 \text{ mJ/m}^2$  – *our integration* of data in [99]). Explicit MD calculation showed that for  $\text{OH}$  and  $\text{COOH}$  groups H-bonding does occur, is directional and requires appropriate geometry for the end groups of both surfaces. The tilt angle of thiolate SAMs affects the relative positioning of the functional groups at the interface and, thus, makes a difference in H-bonding between even and odd chain lengths (Figure 17B). The simulation found greater attraction for odd  $n$  chain lengths, in contrast to IFM measurement where even  $n$  resulted in larger adhesion. The  $\text{COOH}$  SAMs also displayed significant chain-length dependence (dashed lines in Figure 17B). Tilt angle for polar SAMs adjusted significantly to maximize hydrogen bonding – it was lower than the equilibrium value of  $30^\circ$  in attractive region and higher than  $30^\circ$  in the compression region.

Since the characteristic relaxation of the SAM in response to perturbation by the moving tip is fast, the equations of motion for the CFM tip and the SAM film ( $\text{HS}(\text{CH}_2)_8\text{X}$ ) could be

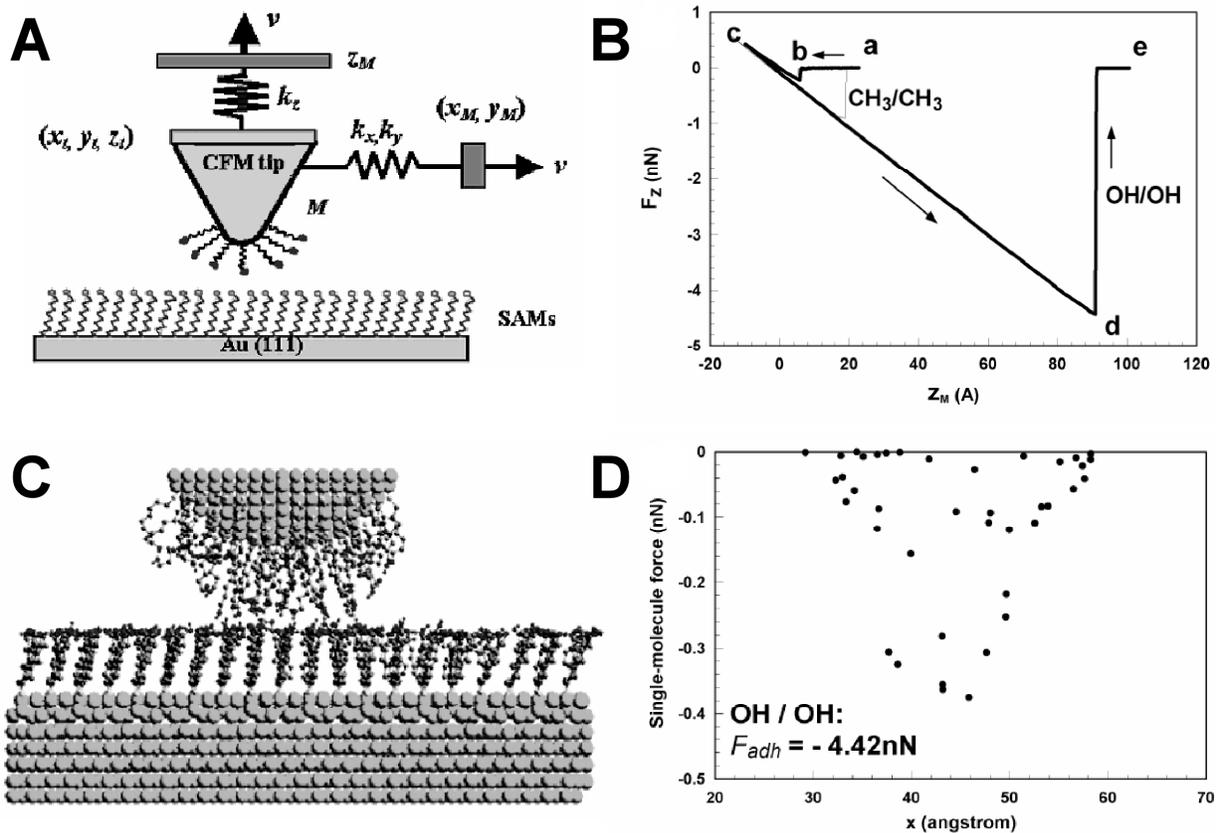
**Figure 17. (A) Structure of HS(CH<sub>2</sub>)<sub>8</sub>COOH SAMs at the maximum attraction and at a highly compressed position. (B) Chain length dependence of maximum attractive normal pressure for HS(CH<sub>2</sub>)<sub>n</sub>X, X=CH<sub>3</sub> (circles), OH (triangles), COOH (squares). Solid lines connect even: odd pairs for CH<sub>3</sub> and OH. Dashed lines are least-squares fit to the even and odd *n* for COOH SAMs. (C) Compression(squares)/decompression(circles) curves (X=(a) CH<sub>3</sub>, (b) COOH, and (c) OH). Adopted from reference [99] with permission.**



integrated separately. This hybrid approach (Figure 18A) [100] allows for a complete simulation of the force curve as it obtained in the CFS experimentally (Figure 18B). In this case, MD also reveals an order of magnitude difference in the force of adhesion between non-polar CH<sub>3</sub> and polar OH groups (0.9 vs. 4.42 nN for 3 nm tip). These forces provided the surface free energy estimates of 32 and 157 mJ/m<sup>2</sup> for CH<sub>3</sub> and OH surfaces, respectively, using the JKR model of contact mechanics (the respective Tabor elasticity parameter is ~0.5-2.2 assuming E=1-10 GPa). These values are consistent with IFM measurements for CH<sub>3</sub> and COOH terminated SAMs in dry nitrogen, 30 and 114 mJ/m<sup>2</sup>, although somewhat high value for  $\gamma_{\text{CH}_3}$  could imply a disordered interface exposing CH<sub>2</sub> groups as found in MD simulations of planar SAMs described above. Interestingly, the calculated values for  $\gamma_{\text{CH}_3}$ =32 mJ/m<sup>2</sup> (JKR model) and 24 mJ/m<sup>2</sup> (DMT model) are very close to the recent results from CFS measurements for HS(CH<sub>2</sub>)<sub>15</sub>CH<sub>3</sub> in air: 32.4-35.9 mJ/m<sup>2</sup> (JKR model) and 24.3-26.9 mJ/m<sup>2</sup> (DMT model) [72]. The simulations allowed analyzing the distribution of the overall adhesion force among individual molecular chains/groups in the contact zone. Single molecule forces were distributed quite unevenly (Figure 18 D), a fact that should be taken into account in statistical treatment of adhesion force distributions. Consistent with the view that surface free energy was largely responsible for the adhesion, 95% of the load-bearing capacity at pull-off fell on the first four segments (CH<sub>3</sub> and CH<sub>2</sub> groups) in the case of CH<sub>3</sub> SAMs, and 86% of the total load was borne by the OH group alone in the contact between OH terminated SAMs.

Patrick et al noted [101] that forces experimentally measured by CFS are cumulative effects of multiple simultaneous interactions averaged over the characteristic measurements time, which is much longer than respective time scale for atomic/molecular motion. Therefore, atomic-level understanding of processes within tip-sample junction is necessary to validate the

**Figure 18.** (A) Mechanical model for the simulation setup (support position coordinates are  $(x_M, y_M, z_M)$ , tip radius  $R=3$  nm). (B) Force-distance for the OH/OH and CH<sub>3</sub>/CH<sub>3</sub> contact pairs. (C) Molecular configurations for the OH terminated SAMs at a pull-off stage. (D) Single-molecule force distributions over SAM chains on the CFM tip at the pull-off stage OH/OH contact. Adopted from reference [100] with permission.

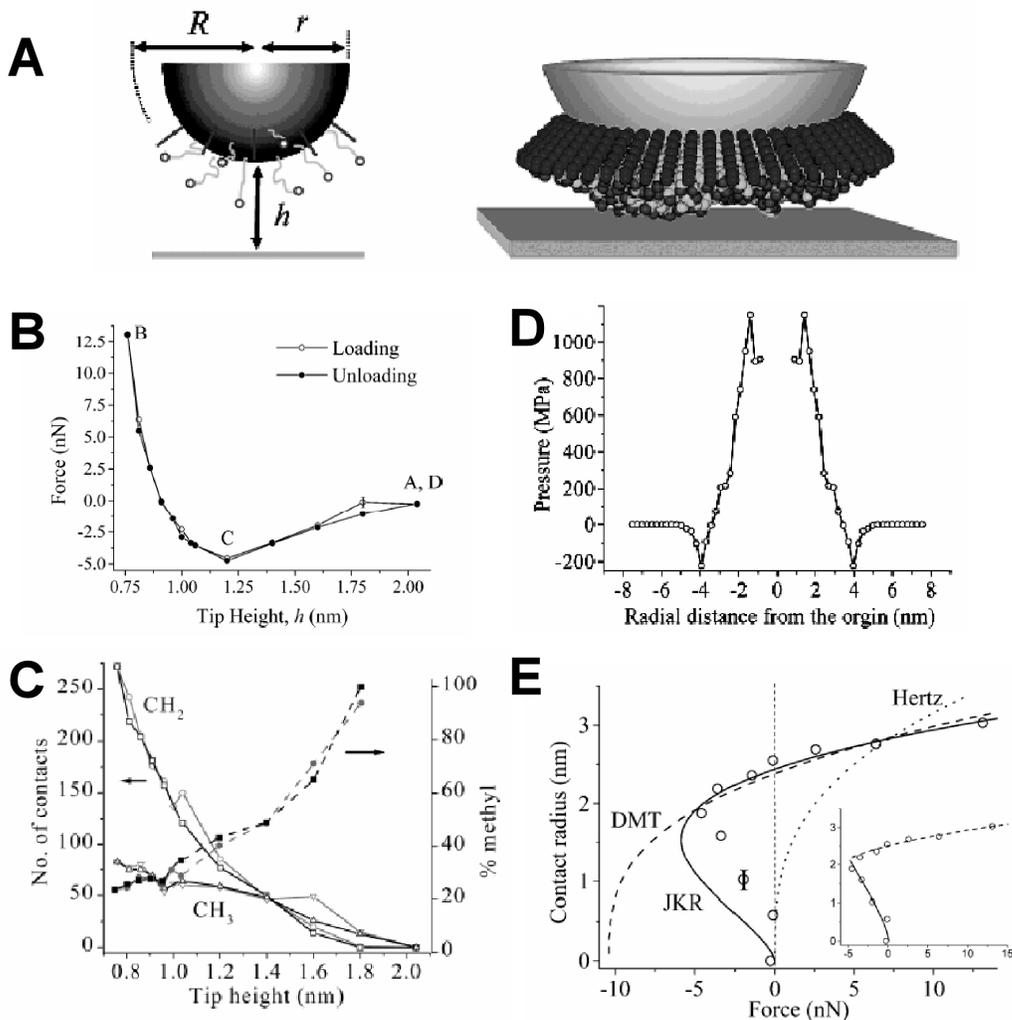


continuum mechanics models under the circumstances, when interactions are expected to be dominated by discrete molecular events. Patrick used pseudo-equilibrium MD simulations of HS(CH<sub>2</sub>)<sub>11</sub>CH<sub>3</sub> SAM coated sphere interacting with a perfectly flat wall (Figure 19A) to assess the applicability of the contact mechanics models to CFM setup [101]. The force profile in this case was fully reversible, with no hysteresis between approach and withdrawal paths (Figure 19B). The chemical composition of the contact changed with fraction of methyl-wall contacts dropping at decreasing tip-wall separations (Figure 19C). The pull-off force in these simulations corresponded to an arrangement when 2/3 of all contacts were due methylene groups. This observation is consistent with discussed above hybrid simulation for CH<sub>3</sub>/CH<sub>3</sub> contacts that found a surface energy of 32 mJ/m<sup>2</sup>, which is more typical of the methylene-rich surface.

The time-average stress distribution was similar to that expected for Maguis-Dugdale model (compare Figure 19D and Figure 2). The contact mechanics models performed poorly, however, when fitted to the whole of the contact area vs. applied load data, with JKR model providing the best overall agreement (Figure 19E). Interestingly, the simulations not only detected the change in the number of methyl contacts, but also highlighted the decrease in the number of gauche defects and an almost 2 orders of magnitude drop in the atomic self-diffusion coefficient after the point of zero force [101]. Both of these effects signify solidification of the SAM film under stress. Therefore, the failure of the models to account for the variability of the elastic modulus of the SAM resulted in discrepancies between fitting results under compressive and tensile forces. When the assumption of constant compliance was dropped, the agreement between MD simulations and JKR model improved, giving K=13 GPa for the SAM in the solid state and K=0.8 GPa for the fluid state (Figure 19E insert).

Molecular dynamic simulations of CFM experiments produced molecular level picture on

**Figure 19.** (A) The simulation setup of asperity ( $r=5$  nm,  $R=6.53$  nm) interacting with a flat wall. (B) Interaction force between the tip and wall at different stylus heights during both loading and unloading. (C) Changes in the chemical composition of the contact with loading. (D) Stress (the normal component of the SAM-wall force per unit area) distribution (averaged over 1-1.5 ns) on the planar wall in compressed state corresponding to point B in (B). Negative values correspond to attractive forces. Data at the center of the contact are omitted, because a bald spot in the film developed there producing large uncertainties in the stress. (E) Maugis theories were fit to the measured relationship between contact radius and force. Simulation data are shown as open circles. The best fit in the Maugis-Dugdale theory was found to coincide with the JKR limit. Also shown for comparison is the best fit in the DMT limit. Insert: fitting results after dividing the simulation data into two subsets – before and after the point of maximum adhesion – and fitting each separately to the JKR model, using a single, fixed value for the  $W$ , while the compliance was allowed to vary. Adopted from reference [101] with permission.



dynamics of interactions within the tip-sample junction. The results reinforced the central role played by hydrogen-bonding interactions in defining the value of adhesion force in these monolayer systems. The distribution of forces among molecular segments, the chain movement from equilibrium positions in isolation, the varying chemical nature of contacts could all be visualized and analyzed in detail. The numerical results were generally in a very good agreement with the values obtained in corresponding CFS experiments, while contact mechanics appeared to describe well the averaged values of contact area and adhesion forces in this system, provided that behavior of the SAM under stress is treated appropriately. While Leng and Jiang [100] found good agreement between experiment and adhesion values obtained from MD simulations and JKR theory, they did not analyze the relationship between contact area and applied load. On the other hand, Patrick et al [101] tried to derive an estimate of the work of adhesion independent from the use of the contact mechanics and found a poor agreement. It seems more appropriate to try to arrive at an estimate of the work of adhesion by using the approach of Park et al [99] to derive the stress-distance curves for planar surfaces, in which case  $W$  is obtained by direct integration without additional assumptions. Generally, good agreement between CFS modeling and experimental data is encouraging future elaborate comparisons and suggesting that well-defined CFS experiments can serve to verify corresponding force fields. Finally, most CFS data was accumulated in liquids and while simulation in liquids are much more complex, it will be very illuminating to address additional issues of dissecting the contributions from the solvent media to overall forces as discussed in Sections 7-10.

### **13. High-throughput CFM**

Reliable determination of the interaction forces requires collecting large statistical sets, which often include hundreds or thousands of individual pull-off measurements. Any potential

application, requiring screening of large arrays of molecules, for example, a  $10^4$  ligand library, must then collect at least  $10^6$  force curves. The failure rate of modified AFM cantilevers observed so far in conventional CFM experiments makes this type of measurement quite challenging. Extending CFM into the realm of practical applications would require using out-of-the-box approaches. One possibility is to focus on determination of equilibrium potential energy curves, similar to the BFPR approach, which we described in the previous section. However, BFPR would typically require careful matching of the cantilever stiffness to the interaction potential, which would be difficult to adjust on-the-fly for array screening. Another possibility is to increase the throughput of the CFM measurements drastically. Pulsed force mode (PFM) measurements [102] allow researchers to collect adhesion force data at the rates approaching 1kHz, which is almost close to the natural limit for the adhesion measurement speed (as set by the AFM piezo resonance frequency). PFM measurements thus can provide high-throughput screening capability; however, they still must rely on robust cantilever functionalization.

Green and co-workers designed an interesting scheme to implement AFM screening of combinatorial libraries [103]. Their *inverted CFM* design utilizes an inverted configuration with a tipless cantilever contacting a sample consisting of a microfabricated array of functionalized tips. This configuration possesses several significant advantages over conventional CFM. First, it uses a very robust cantilever, which essentially consists of a large flat functionalized surface area. If one of the functionalized tips on the sample fails, researchers can simply move the cantilever to the next tip in the array. Second, every measurement uses the same cantilever. This configuration eliminates one of the major error sources in the AFM measurement- cantilever spring constant determination uncertainty, and simplifies comparison between measurements done with different tips. Third, this configuration gives researchers the ability to quickly screen

a large number of tips, providing a tool for averaging out variations in probe size and shape. Green and co-workers also suggest using microfluidics and microcontact printing as possible techniques or creating libraries of probes bearing different functionalities [103].

## **14. Conclusions.**

Experimental methods of measuring intermolecular interactions have had several recent developments which have improved our understanding of chemical forces. First, they allowed direct exploration of the role that different functionalities, solvents and environmental variables play in shaping the strength of intermolecular interactions. Chemical force microscopy approach, in particular, became an extremely effective tool for exploring the contributions of each of these factors. Second, CFM studies clearly debunked the naïve notion that intermolecular interaction strength is determined only by the nature of the interacting groups. These studies showed that the interaction strength between two chemical species must always be considered in context of the environment surrounding these species. Third, CFM studies highlighted the critical role solvent plays in shaping intermolecular interactions in condensed phases.

Emerging kinetic view of the intermolecular interactions introduced a completely new paradigm for understanding these interactions. Kinetic modeling showed that the measured interaction strength depends not only on the energy landscape of the system, but also on the loading history prior to the bond break-up. This new paradigm refocused our attention to the energy landscape as a fundamental characteristic of the interaction. Moreover, dynamic force spectroscopy, derived from kinetic models, allowed direct characterization of the geometry of the potential energy barrier, while some other methods attempt to probe the equilibrium energy landscape directly. Further investigations of the interactions in different systems, especially

interactions between biomolecules, will uncover many interesting characteristics of intermolecular potentials. These studies have the potential to reveal, for the first time, a true picture of the energy landscapes of adhesion processes in complex chemical and biological systems.

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