1 Basic Principles of Chemical Force Microscopy

1.1 Chemical Sensitivity in Scanning Probe Microscopy Measurements

Intermolecular forces impact a wide spectrum of problems in condensed phases: from molecular recognition, self-assembly, and protein folding at the molecular and nanometer scale, to interfacial fracture, friction, and lubrication at a macroscopic length scale. Understanding these phenomena, regardless of the length scale, requires fundamental knowledge of the magnitude and range of underlying weak interactions between basic chemical functionalities in these systems (Figure 1). While the theoretical description has long recognized that intermolecular forces are necessarily microscopic in origin, experimental efforts in direct force measurements at the microscopic level have been lagging behind and have only intensified in the course of the last decade. Atomic force microscopy (AFM)\(^1,2\) is an ideal tool for probing interactions between various chemical groups, since it has pico-Newton force sensitivity (i.e., several orders of magnitude better than the weakest chemical bond\(^3\)) and sub-nanometer spatial resolution (i.e., approaching the length of a chemical bond). These features enable AFM to produce nanometer to micron scale images of surface topography, adhesion, friction, and compliance, and make it an essential characterization technique for fields ranging from materials science to biology.

As the name implies, intermolecular forces are at the center of the AFM operation. However, during the routine use of this technique the specific chemical groups on an AFM probe tip are typically ill-defined. To overcome this inherent limitation of the AFM, Lieber and coworkers introduced the concept of chemical modification of force probes to make them sensitive to specific molecular interactions\(^4\). By using chemically-functionalized tips, a force microscope can be transformed into a tool that can (i) quantify forces between different molecular groups, (ii) probe surface free energies on a nanometer scale, (iii) determine pK\(_a\) values of the surface acid/base groups locally, and (iv) map the spatial distribution of specific functional groups and their ionization state. This ability to discriminate between chemically distinct functional groups has led the Lieber group to name the variation of force microscopy carried out with specifically functionalized tips “chemical force microscopy” (CFM)\(^4\).
1.2 Measuring Interaction Forces with an Atomic Force Microscope

A typical force microscope consists of an integrated cantilever-tip assembly interacting with the sample surface, a detector that measures the displacement of the cantilever and feedback electronics to maintain a constant imaging parameter such as tip-sample separation or force (Figure 2). The integrated cantilever-tip assemblies can have single or V-shaped beams and normal spring constants, \( k_z \), in the range of 0.01–100 N/m. By far, the most popular and versatile detection scheme in AFM is optical lever deflection. In this scheme, the vertical displacement due to normal forces and lateral twist due to friction of the cantilever are measured using a quadrant photodiode, as shown in Figure 2. Force values are determined from the normal displacement, \( D_z \), of the cantilever from its rest position. With an instrumental sensitivity on the order of 0.1 Å, minimal forces in the range of \( 10^{-13} \)–\( 10^{-8} \) N (depending on the cantilever stiffness) can be measured. Hence, AFM can in principle measure molecular interactions ranging from weak van der Waals (<\( 10^{-12} \) N) to strong covalent (\( 10^{-7} \) N) bonds. In practice, the displacement (and corresponding force) sensitivity is limited by thermally excited cantilever vibrations, optical and electronic noise. If the measurements are conducted in ambient air or liquids, the thermal noise is especially important. For example, cantilever quality factors drop from \( 10^3 \)-\( 10^5 \) in vacuum to \( 10^0 \)-\( 10^2 \) in fluids due to hydrodynamic damping. The thermal noise limited minimal force is then on the order of 1–20 pN at room temperature. Use of specially designed small cantilevers for AFM can push the force detection threshold to even lower values.

AFM measures the magnitude of intermolecular interactions by performing a force-distance measurement, commonly referred to as an F-D curve or simply as a “force curve” (Figure 3). In these measurements, the deflection of the cantilever is recorded during the sample approach-withdrawal cycle. The magnitude of the jump in the retraction trace corresponds to the adhesion between functional groups on the tip and sample surfaces. The observed deflection of the cantilever is converted into a force of adhesion using the cantilever spring constant.

The sphere-on-flat tip-sample geometry of the typical AFM force measurement does not correspond to the interaction between two molecules, as shown in Figure 1. However, the general features of the interaction potential are the same; that is, the potential has a minimum and increases nonlinearly from this minimum (Figure 3). If the cantilever were infinitely stiff, the probe deflection would have simply traced the gradient of the interaction potential (of course, an infinitely stiff cantilever would not have generated any measurable deflection, making such an experiment fairly useless). In practice, the molecular force gradients are higher than the stiffness of the typical cantilevers over a substantial part of the intermolecular force profile; therefore, most AFM cantilevers experience mechanical...