Measurement and Application of Inter- and Intramolecular Forces

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Several microscopic techniques have recently been developed that are capable of directly measuring the forces between single molecules with a force sensitivity approaching a single hydrogen bond. Molecular force measurements are providing new insight into the structure and function of proteins, nucleic acids and their assemblies. Atomic force microscopy (AFM), one of these techniques, has the potential to develop beyond a specialized research instrument into a powerful tool for screening combinatorial libraries now in use in pharmaceutical research. Unfortunately, the configuration of the probe, force and displacement transducers in the AFM makes this measurement cumbersome, rendering this technique practically impossible. We will describe a microfabricated instrument that is capable of direct force measurements on massive ligand-receptor arrays, describe patterning to assemble spatially defined arrays and demonstrate its use on model systems. These innovations provide a promising approach to surmount the analytical bottleneck that currently limits combinatorial approaches to drug design. We will also describe the development of several chemical sensing techniques based on force differentiation and force amplification.

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