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Atomic force microscopy from nanoscale imaging to holistic exploration

David Alsteens, Ernst Meyer, Daniel J. Müller & Christoph Gerber

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Forty years after its invention, atomic force microscopy has evolved from a simple surface imaging tool into one of the most versatile measurement platforms in nanoscience. This Comment traces the key innovations.

Four decades ago, Gerd Binnig, Calvin F. Quate and Christoph Gerber reported a deceptively simple idea: dragging a sharp tip across a surface and measuring the forces it encounters[1]. That idea became atomic force microscopy (AFM), which today is used across physics, chemistry, biology, materials science and engineering. Its capacity to simultaneously characterize structural, mechanical, chemical and electronic properties at the nanoscale, under conditions ranging from ultrahigh vacuum to physiological liquids, has made it an indispensable platform for both fundamental research and industrial applications, including semiconductor metrology[2]. That a single instrument can serve such diverse communities, forty years on, is a testament not to a single breakthrough but to a sustained sequence of innovations by a user society across scientific disciplines.

The challenge that launched AFM

By the mid 1980s, scanning tunnelling microscopy (STM) had already begun to revolutionize surface science. STM could resolve individual atoms, but it relied on a tunnelling current between tip and sample, restricting it to conductive and semiconductive surfaces. This was a severe limitation: the vast majority of technologically and biologically relevant materials — including polymers, ceramics, biological membranes and insulating thin films — remained beyond reach. What was needed was a scanning probe microscope that could image any surface, regardless of its electrical conductivity.

The first AFM (Fig. 1) addressed this challenge by replacing the tunnelling current with a direct measurement of tip–sample forces, as reported in *Physical Review Letters* in 1986[1]. By mounting a diamond tip on a cantilever and detecting its deflection, it was demonstrated that surfaces could be traced molecularly or even atomistically through mechanical interaction alone, opening the door to nanoscale imaging of virtually any material[2].

The first version of AFM introduced the conceptual architecture that every subsequent implementation has followed[1]. Its three essential elements, which define a modular measurement platform of remarkable generality, are: a compliant cantilever acting as a force sensor (in the original implementation, a handcrafted strip of gold foil with a manually glued diamond tip and poorly defined spring constants); a sensitive readout of its deflection (provided initially by a secondary STM); and piezoelectric tubes for precise tip–sample positioning.

From the outset, both the static operation of the cantilever tip in continuous contact with the sample surface (known as contact mode) and the principles of dynamic detection were outlined, foreshadowing the operational diversity that would later expand AFM's reach[1]. Because the method rests on forces rather than currents, it applies in principle to any surface, conductive or insulating, hard or soft, in vacuum, ambient atmosphere or liquid — a scope unattainable by STM. Equally consequential was the design's modularity: cantilevers, detection schemes, actuators, feedback electronics and operating modes could each be refined or exchanged independently of the underlying concept, inviting successive contributions from a broad scientific and technical community.

Innovation in cantilevers and detection

Two advances in the late 1980s proved transformative. First, the development of optical beam deflection, which bounces a laser off the cantilever back onto a segmented photodiode, replaced the cumbersome STM-based readout with a compact, sensitive and easily aligned detection scheme that has become the standard today. Second, advanced microfabrication techniques borrowed from the semiconductor industry enabled batch production of silicon and silicon nitride cantilevers with precisely controlled dimensions, resonance frequencies, spring constants and tip shapes[2]. Together, these innovations turned AFM from a one-of-a-kind laboratory curiosity into a reproducible, commercially viable instrument. By the early 1990s, commercial AFMs were entering laboratories worldwide, and the user community expanded rapidly beyond surface physics into chemistry, biology and materials science.

Dynamic modes and new environments

In early AFM systems, the forces in contact mode were destructive of samples, and proved difficult for users to control. This drawback motivated the development of dynamic operating modes, which expanded AFM's reach. In tapping (intermittent-contact) mode, the cantilever oscillates near its resonance frequency and touches the surface only briefly at the bottom of each oscillation cycle, dramatically reducing lateral forces and enabling non-destructive imaging of soft and loosely bound samples, which was a breakthrough for polymer and biological studies[3]. Non-contact frequency-modulation AFM, pioneered in ultrahigh-vacuum environments, achieved true atomic resolution on insulating surfaces by tracking tiny shifts in the cantilever's resonance frequency[4]. The introduction of tuning-fork-based qPlus sensors further enhanced force sensitivity and stiffness control, enabling sub-molecular imaging of chemical bonds and charge distributions with ångström precision[5,6]. In parallel, fluid cells and environmental chambers extended operation to liquids, controlled atmospheres and a wide temperature range, making AFM uniquely suited for studying biological processes under near-physiological conditions and materials under operationally relevant environments.

From imaging to manipulation and multiparametrization

Beyond imaging, AFM evolved into a tool for directly measuring and manipulating matter at the single-molecule level[7]. In single-molecule

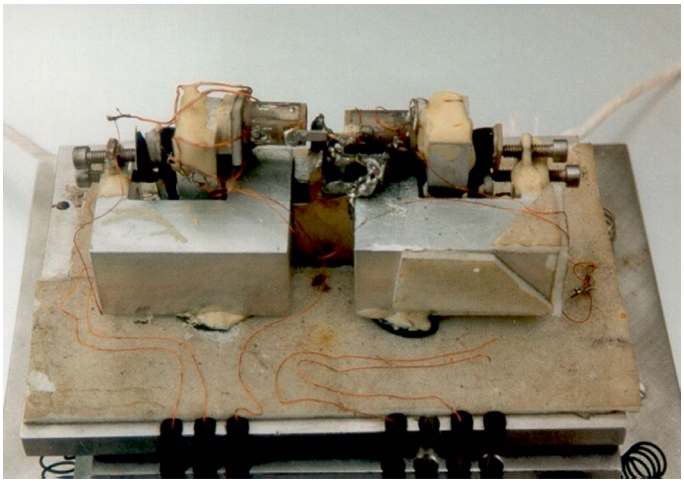

Fig. 1 | The first atomic force microscope. The instrument rests on a stacked vibration-isolation stage of metal plates with Viton damping elements. Two machined blocks on the upper plate carry the central measurement assembly, in which a soft cantilever with the force-sensing tip is positioned beneath a sharp tunnelling tip; the tip-to-cantilever tunnelling current served as the deflection sensor. Viton spacers in the machined blocks damp mechanical vibrations at high frequencies and decouple the cantilever, the STM tip and the AFM sample. Squeezing the Viton damping elements by means of a mechanically driven differential screw system allowed a highly accurate approach of the integrated tube piezos to scan the AFM tip across the sample surface and yielded a high mechanical eigenfrequency of the setup.

force spectroscopy, the cantilever tip is used to stretch individual proteins, nucleic acids or receptor–ligand complexes. Such measurements are used to explore the mechanical stability, folding pathways and binding kinetics of single biomolecules, a quantitative information inaccessible to any ensemble technique[3,8]. By functionalizing the tip of the AFM cantilever either physically, biologically or chemically it can be turned into a nanotool to directly image complex samples and quantify multiple parameters, thus opening new dimensionalities of sample characterization, manipulation and understanding[3,7,9]. At the temporal extreme, high-speed AFM pushed frame rates from minutes to milliseconds, enabling real-time observation of molecular motors, protein assemblies and enzymatic activity under near-native conditions, effectively turning AFM into a nanoscopic video camera for the molecular machinery of life[3,9]. Moreover, combining these approaches with multifrequency and off-resonance methods further advanced quantitative multiparametric imaging, allowing researchers to extract mechanical, chemical and biological maps simultaneously with topography in a single AFM scan.

Technological integration and complementary characterization

A further leap came from coupling AFM with complementary analytical techniques. Tip-enhanced Raman spectroscopy and AFM-based infrared nanospectroscopy (AFM-IR) added chemical fingerprinting to topographic imaging, enabling the identification of molecular species with nanometre-scale spatial resolution[10]. Correlative platforms that combine AFM with fluorescence microscopy, scanning electron microscopy and helium-ion microscopy now furnish multidimensional datasets richer than any single technique can provide[3,9]. In electrochemistry, operando AFM maps local charge-transfer kinetics and interfacial restructuring at electrode surfaces under working conditions. In surface chemistry, tip-induced manipulation directs bond formation and breakage with single-bond precision[5]. Living cellular systems, observed with such multiple microscopic approaches, could be better analysed in their complexity, manipulated at molecular precision, and have physiological and pathophysiological functionalities discovered[3,8]. Meanwhile, nanomechanical cantilever array sensors combined with microfluidic devices have extended AFM principles into diagnostics, detecting masses and molecular interactions with sensitivities that rival established clinical assays. Collectively, these advances have transformed AFM from a single-channel imaging tool into a multitechnological measurement platform[9].

David Alsteens[1], Ernst Meyer[2], Daniel J. Müller[3] ✉ & Christoph Gerber[2]

[1]Louvain Institute of Biomolecular Science and Technology, Université catholique de Louvain, Louvain-la-Neuve, Belgium. [2]Swiss Nanoscience Institute (SNI), Department of Physics, University of Basel, Basel, Switzerland. [3]Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland.
✉e-mail: daniel.mueller@bsse.ethz.ch

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Competing interests

The authors declare no competing interests.

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