IMAGING

AFM in a split second

A new development in high-speed atomic force microscopy enables microsecond resolution.

Just like the organisms they build, biological macromolecules are highly dynamic. They change conformation, associations with interaction partners, or both, and insight into these processes is crucial for a complete understanding of their functions. Consequently, researchers have developed a number of techniques to probe these phenomena, each with its own strengths and limitations.

X-ray crystallography and electron microscopy can yield biomolecular structures with astonishing spatial resolution, but these models are static snapshots. Conversely, several light microscopy techniques, such as fluorescence resonance energy transfer and fluorescence correlation spectroscopy, allow one to track the dynamics of single molecules, at the expense of spatial resolution. Nuclear magnetic resonance spectroscopy and high-speed atomic force microscopy (HS-AFM) offer both structural and dynamic information, yet they are not well suited to tackle many experimental questions.

The advantages of HS-AFM include the ability to visualize unlabeled molecules in native conditions and manipulate the sample throughout the experiment, as well as to image with up to ~0.1-nm spatial resolution along the vertical axis and ~100-ms temporal resolution. George Heath and Simon Scheuring at Weill Cornell Medical College pushed the boundaries of HS-AFM further to achieve microsecond temporal resolution.

During AFM imaging, a sharp tip in intermittent contact with the sample scans along an *x*–*y* grid. To improve temporal resolution, the authors halted the scanning in one or both directions, probing the sample's height along a single line every 0.5–1 ms or at a fixed position every ~10 µs. The methods are thus termed HS-AFM line scanning or HS-AFM height spectroscopy, respectively.

Heath and Scheuring used their approach to assess calcium-triggered lipid-bilayer binding, diffusion, and oligomerization of annexin V (a protein that assembles around lesions in cell membranes). The method is poised to find wide-ranging applications in studies of oligomerization and conformational dynamics of membrane proteins.

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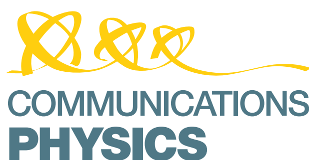
Research papers

Heath, G. R. & Scheuring, S. High-speed AFM height spectroscopy reveals µs-dynamics of unlabeled biomolecules. *Nat. Commun.* **9**, 4983 (2018).



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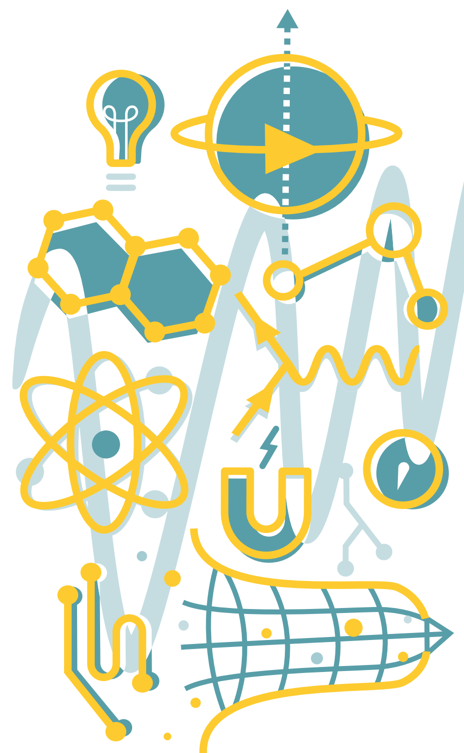

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