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Editorial

The Evolution of Sub-diffraction Chemical Imaging from Nanoscale to AI

Published as part of Chemical & Biomedical Imaging special issue "Sub-diffraction Chemical Imaging".

Cite This: *Chem. Biomed. Imaging* 2024, 2, 731−732

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A central theme of chemical imaging is the visualization of chemistry *in situ* in functional materials and *in vivo* in a living system. To achieve this, technologies with exceptional detection sensitivity and spatial resolution are essential for resolving specific chemicals at the nanoscale. As we celebrate the 10th anniversary of the Nobel Prize in Chemistry awarded for super-resolved fluorescence microscopy, the field's remarkable advancements become clear. Over the past 10 years, novel microscopies that break light diffraction limits continue to be invented. These include, for example, mid-infrared photothermal microscopy that breaks the diffraction limit in IR imaging, and expansion microscopy that allows super-resolution fluorescence imaging on a conventional microscope. Meanwhile, researchers have much increased the speed of structural illumination microscopy (SIM) and single molecule localization microscopy (SMLM), and pushed the resolution limit of stimulated emission depletion (STED) microscopy to angstrom scale. In parallel, data science and artificial intelligence (AI) are elegantly applied to break the diffraction limits of images recorded on a conventional microscope. These innovations have enabled very exciting applications, including the study of single particle catalysis, biomolecule trafficking inside a live cell, dynamic imaging of cellular organelles, and many others.

This special issue published in *Chemical & Biomedical Imaging*, titled "Sub-diffraction Chemical Imaging", begins with a comprehensive review by Chen et al., who dive into super-resolution microscopy techniques like STED, SIM, and SMLM (DOI: 10.1021/cbmi.4c00019). These methods have been game-changers in our ability to see biological processes at the nanoscale and have laid the groundwork for even more innovations. Tipping and Graham emphasize the integration of chemical specificity into sub-diffraction imaging through advancements in stimulated Raman scattering (SRS) microscopy (DOI: 10.1021/cbmi.4c00057). SRS allows researchers to probe biological structures and cellular interactions with chemical fingerprints. Extending the exploration of Raman-based imaging techniques, Smith et al. tackle the challenges of imaging in tricky, scattering-prone environments with their development of low-frequency interferometric impulsive stimulated Raman scattering (ISRS) imaging (DOI: 10.1021/cbmi.4c00020). This technique makes Raman imaging more robust and precise, even in complex samples. Murakami et al. combine ultrabroadband coherent anti-Stokes Raman scattering (CARS) with multivariate analysis to create detailed molecular fingerprints of brain tissues, capturing a wide range of molecular vibrations and refining them into distinct chemical components (DOI: 10.1021/cbmi.4c00034).

The evolution of sub-diffraction imaging continues with various creative integrations. Lin and Wang demonstrate the power of merging sub-diffraction imaging with single-molecule FRET to study molecular interactions within cellular machinery (DOI: 10.1021/cbmi.4c00010). Greaves et al. apply scattering-type scanning near-field optical microscopy (s-SNOM) to map mesoporous silica nanoparticles in glioma cells, highlighting the potential for combining detailed chemical and topographical analysis in therapeutic contexts (DOI: 10.1021/cbmi.4c00053). As these core techniques continue to evolve, their applications in biological and material sciences have become increasingly diverse. Sharma et al. showcase how single-molecule imaging plays a crucial role in understanding prokaryotic genome maintenance (DOI: 10.1021/cbmi.4c00037), while Lacen and Lee review methods for studying chromatin dynamics, emphasizing the value of integrating super-resolution microscopy with live-cell imaging (DOI: 10.1021/cbmi.4c00033). These applications reveal how sub-diffraction imaging is helping us understand dynamic molecular behaviors and complex cellular processes, shedding new light on gene regulation and disease mechanisms.

To push the capabilities of sub-diffraction imaging even further, researchers are increasingly turning to data science and AI. Zhang et al. discuss how machine learning is being integrated with tissue clearing and expansion microscopy, making it possible to image large-scale biological tissues and gain critical insights into complex tissue structures, both healthy and diseased (DOI: 10.1021/cbmi.4c00013). Reihani-saransari et al. explore how machine learning improves cancer diagnostics' accuracy and efficiency through advanced imaging technologies (DOI: 10.1021/cbmi.4c00031). Additionally, Antarasen et al.'s work on cross-correlation methods in fcsSOFI (DOI: 10.1021/cbmi.4c00032) and Kenkel and Bhargava's modeling of thermoelastic responses in IR imaging

Received: October 18, 2024
Accepted: October 21, 2024
Published: October 29, 2024

(DOI: 10.1021/cbmi.4c00018) further illustrate how data-driven approaches are not just pushing the boundaries of what is possible in sub-diffraction imaging, expanding its relevance and application across various scientific fields.

This Virtual Special Issue on Sub-diffraction Chemical Imaging highlights the incredible strides made in overcoming diffraction limits over the past decade. From groundbreaking advancements in imaging techniques to their innovative applications in biology and material sciences, and the integration of AI and data science, these articles showcase the transformative potential of these technologies. As these innovations continue to unfold, they promise to lead to even more breakthroughs in understanding complex molecular and structural processes, opening up new paths for discovery in a wide range of scientific disciplines.

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https://doi.org/10.1021/cbmi.4c00079
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