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RESEARCH BRIEFING

Digital array modulation microscopy (DaMo): three-dimensional super-resolution imaging with suppressed background

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Introduction

Digital array modulation microscopy (DaMo) combines Gaussian illumination modulation with digital detection modulation to achieve heterodyne detection imaging with 100% contrast [1]. This method improves the signal-to-background ratio (SBR) by a factor of 1284, increases the reconstruction speed by over 100-fold, and eliminates the reconstruction artifacts commonly observed in conventional super-resolution structured illumination microscopy (SR-SIM), while achieving lateral and axial resolutions of 100 nm and 300 nm, respectively.

Motivation

SR-SIM plays a critical role in organelle research due to its excellent fluorophore compatibility and high-speed imaging capability. However, conventional SR-SIM has long been plagued by two major challenges. First, in wide-field imaging mode, out-of-focus background and noise are readily amplified during frequency-domain reconstruction, introducing severe artifacts such as honeycomb and stripe patterns that compromise image fidelity and resolution. Second, the reconstruction algorithm relies heavily on extensive Fourier transforms and iterative optimization, resulting in low computational efficiency and severely limiting imaging throughput. Existing algorithmic or deep learning-based denoising methods cannot fundamentally eliminate the sources of artifacts and often result in the loss of genuine structural information from weak signals. Therefore, there is an urgent need for a novel super-resolution (SR) imaging technique that can suppress background noise at the physical level while enabling fast, high-fidelity reconstruction.

Solution

This study proposes a novel imaging method termed digital array modulation microscopy (DaMo) [1]. Based on an off-axis imaging framework [2], DaMo combines the inherent Gaussian illumination generated by the objective focus with digital modulation using an array detector. This approach achieves sinusoidal modulation heterodyne detection with 100% contrast without relying on any physical modulation device. The design maximizes the allocation of energy to high-frequency components while effectively suppressing out-of-focus background at the physical level through the confocal effect of line illumination.

In terms of the reconstruction algorithm, DaMo introduces the single-spectrum reconstruction (SSR) algorithm. By exploiting the Hermitian symmetry of the modulated spectrum, SSR reconstructs a complete SR image using only half of the spectrum, transforming the originally complex iterative frequency-domain process into a straightforward linear computation. To accommodate various application needs, the SSR algorithm offers three operational modes: SSR-HS (speed-prioritized), SSR-HC (contrast-prioritized), and SSR-HF (fidelity-prioritized).

In simulation experiments with background interference, DaMo achieves an image fidelity with a Pearson correlation coefficient of 0.99 ± 0.01 and a reconstruction speed of 75.7 frames per second (for 256×256 pixels), which is two orders of magnitude faster than existing state-of-the-art methods. *In situ* comparative results from three-dimensional imaging of intact cells, DaMo improves the SBR by a factor of 1,284, achieves lateral and axial resolutions of 100 nm and 300 nm, respectively, and demonstrates artifact-free reconstruction.

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Significance

DaMo establishes a new paradigm in SR imaging that simultaneously achieves high resolution, speed, SBR, and versatility. This method requires no additional modulation devices nor any reliance on post-acquisition image enhancement, representing a more intrinsic and reliable imaging approach.

In terms of biological applications, DaMo exhibits strong cross-scale imaging capabilities. In living cells, it successfully captures the dynamic assembly of actin filaments and the stepwise fusion process involving five filopodia. In whole-cell smears, DaMo accomplishes three-color SR imaging and reconstruction of over ten thousand asynchronously growing cells within just 20 min, for the first time statistically revealing the evolution of mitochondrial morphology across different phases of the cell cycle. At the tissue level, DaMo performs rapid three-color SR imaging of a complete 10 mm × 10 mm mouse small-intestinal section and enables region-specific quantitative analysis of mitochondrial pathology in an inflammatory model.

By bridging the cross-scale observation link from subcellular organelles to tissue architecture, DaMo provides new technological support for cutting-edge fields, including cell biology, developmental biology, neuroscience, drug screening, and clinical pathological diagnostics, and holds promise for advancing the deep application of high-content SR imaging analysis across a broader range of scientific questions.

Behind the paper

The inspiration for this study can be traced back to the line illumination modulation (LiMo) microscope developed earlier by our team [3]. During the LiMo work, we unexpectedly discovered that when the array detector and line illumination form a pixel-level one-to-one correspondence, the system inherently possesses a capability for "digital modulation" [2]. This prompted us to consider whether it might be possible to completely abandon traditional physical modulation devices and achieve SR imaging solely through digital means.

This idea seemed somewhat unorthodox at the time, as high-quality physical modulation has long been considered indispensable in the field of SR imaging. We devoted considerable effort to repeated theoretical analysis and experimental validation, ultimately proving that, through clever system design, virtual sinusoidal modulation with 100% contrast is not only feasible but also capable of fundamentally resolving the persistent artifact issues of conventional SIM. The discovery of the single-spectrum reconstruction algorithm was, to some extent, serendipitous. While analyzing the symmetry of the modulated spectrum, we realized that perhaps only half the data would suffice. After countless rounds of derivation and validation, this intuition eventually evolved into a concise yet powerful algorithm. We hope that DaMo will provide life science researchers with a truly user-friendly, artifact-free, and high-throughput SR imaging tool.

Author contribution All authors read and approved the final manuscript.

Declarations

Competing interests The authors declare that they have no competing interests.

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