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From high-throughput imaging to functional insight: lensless imaging moves beyond structure

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Abstract

Lensless imaging offers a scalable, hardware-light route to optical microscopy but has largely remained structural. In a recent study, Wang et al. demonstrate that molecular specificity can be intrinsically encoded and computationally recovered within a fully lensless framework. This work reframes lensless imaging from scaling structure to encoding function, highlighting an emerging paradigm in which optical simplicity and information completeness are co-designed through optics and computation.

The rapid expansion of imaging scale has become a defining feature of modern optical imaging. Across biomedical microscopy, digital pathology, and large-area biological screening, increasing emphasis has been placed on imaging efficiency: higher resolution, wider fields of view (FOV), extended depth of field, and scalable acquisition of centimeter-scale samples. These demands have driven the development of imaging systems with ever-growing space–bandwidth products (SBP), enabling the observation of complex biological organization beyond isolated microscopic fields [1–3]. To address this challenge, a broad class of computational imaging strategies has emerged. Synthetic aperture approaches [4–6], most notably Fourier ptychographic microscopy [2, 7], have demonstrated that spatial resolution and FOV need not be fundamentally traded off when spatial-frequency information is multiplexed in acquisition and recovered computationally. Related developments based on non-interferometric synthetic aperture imaging and diffraction tomography have further extended these concepts into three-dimensional (3D), label-free imaging regimes [8–10]. In parallel, lensless imaging techniques, including contact microscopy [11], in-line holography [12, 13], transport-of-intensity equation [14–16], and coded ptychographic imaging [17, 18], have pushed scalability even further by eliminating objective lenses altogether, enabling compact, wide-field, and mechanically simple imaging platforms [19]. Alongside these system-level advances, quantitative phase imaging has matured into an enabling label-free modality that complements high-throughput pipelines with quantitative, physically grounded contrast [20].

Despite their diversity, these approaches share a common motivation: to image more, faster, and across larger areas. In this sense, much of modern high-throughput computational imaging can be viewed as an answer to a single engineering question—*how to maximize effective information capacity under physical, optical, and*

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practical constraints. Yet as these methods mature, an increasingly evident limitation has emerged. While structural information can now be acquired at unprecedented scale, the recovered contrast remains predominantly morphological, offering limited insight into molecular composition or biochemical function. This limitation is particularly consequential at the mesoscale, where cells, tissues, and heterogeneous biological assemblies span millimeters to centimeters and biological interpretation is often tied to biochemical composition rather than geometry alone. Molecular specificity—central to pathology, cytology, and mechanistic biology—is therefore typically reintroduced through exogenous labels or stains, most prominently fluorescence probes and histochemical dyes [21–24]. Although powerful, such approaches impose practical constraints, including sample preparation time, potential perturbation of native biological states, and limited scalability for rapid, high-throughput, or in situ analysis.

Lensless imaging occupies a unique yet paradoxical position within this landscape: it is intrinsically scalable and hardware-light, yet historically dominated by structural readouts. The absence of imaging lenses simplifies system design but also removes conventional pathways for spectral discrimination and contrast engineering, leaving a persistent gap between imaging scale and biochemical interpretability. This tension raises a fundamental question for the field: *can lensless imaging evolve from a structural modality into a functional one, without sacrificing its defining advantages of scalability and simplicity?* Addressing this challenge requires a conceptual shift—from viewing lensless imaging as a reduced form of conventional microscopy to treating it as an information-engineering problem in its own right. A unifying insight across the evolution of lensless imaging is that optical elements are not eliminated, but replaced by structured modulation and computation. Transport-of-intensity frameworks demonstrated that axial intensity variations can encode phase gradients and enable quantitative reconstruction without interferometry [10, 15, 16]. Coded diffraction and ptychographic modulation further established that spatial resolution, depth of field, spectral diversity, and 3D refractive index can be recovered through deliberate information multiplexing and redundancy in measurement space [25–28]. In this view, imaging performance is determined not solely by optical formation, but by how effectively information is redistributed between physical acquisition and computational reconstruction.

Within this paradigm, a natural next question emerges: *can molecular specificity itself be treated as an encodable and recoverable degree of freedom?* A compelling affirmative answer is provided by the recent work of Wang et al. [29]. In their report in *eLight*, the authors introduce the deep-ultraviolet ptychographic pocket-scope (DART), a handheld, lensless imaging system that integrates intrinsic molecular spectroscopy into a high-throughput computational imaging framework (Fig. 1a). Rather than relying on external labels, DART exploits the strong and distinct absorption signatures of biomolecules in the deep-ultraviolet (DUV) spectral range, where nucleic acids and proteins exhibit pronounced intrinsic contrast [30–36]. Unlike conventional DUV microscopy, which relies on specialized optical components that limit FOV and compromise portability, DART uniquely unifies lensless imaging, compact system design, and molecular spectroscopy within a single platform. Using modified sensors to capture wavelength-resolved diffraction patterns, the system applies computational ptychographic reconstruction to achieve sub-micrometer spatial detail across large FOV in a portable form factor (Fig. 1b). By illuminating samples at selected wavelengths (266 nm and 280 nm—corresponding to strong absorption by DNA and proteins) and combining lensless acquisition with ptychographic reconstruction, DART recovers quantitative molecular mass distributions with femtogram-level sensitivity across centimeter-scale FOV and millimeter-scale depth of field (Fig. 1c, d). Because molecular contrast arises directly from wavelength-selective absorption, biochemical specificity is obtained at the moment of image acquisition, rather than inferred through post hoc staining or data-driven appearance mapping. This enables explainable virtual staining, grounded in direct measurements of molecular content rather than black-box deep learning, while avoiding perturbations associated with exogenous probes.

The significance of DART lies not merely in the use of DUV illumination. Deep-ultraviolet microscopy has long been recognized as a powerful route to label-free molecular imaging and mass mapping [30–33], with subsequent efforts extending DUV methods toward hematology analysis, histopathological phenotyping, and multispectral virtual staining grounded in intrinsic spectroscopic signatures [34–36]. However, conventional implementations typically rely on specialized optical components that constrain FOV, limit scalability, and introduce substantial chromatic and geometric aberrations. What distinguishes DART is the demonstration that quantitative spectroscopic molecular imaging can be achieved within a fully lensless, coded system, while preserving the scalability and robustness required for mesoscale imaging. This conceptual advance is inseparable from more than a decade of systematic development in coded-surface-based lensless imaging by Prof. Guoan Zheng's group at the University of Connecticut. Through a sequence of influential works [17, 18, 37–42], this body

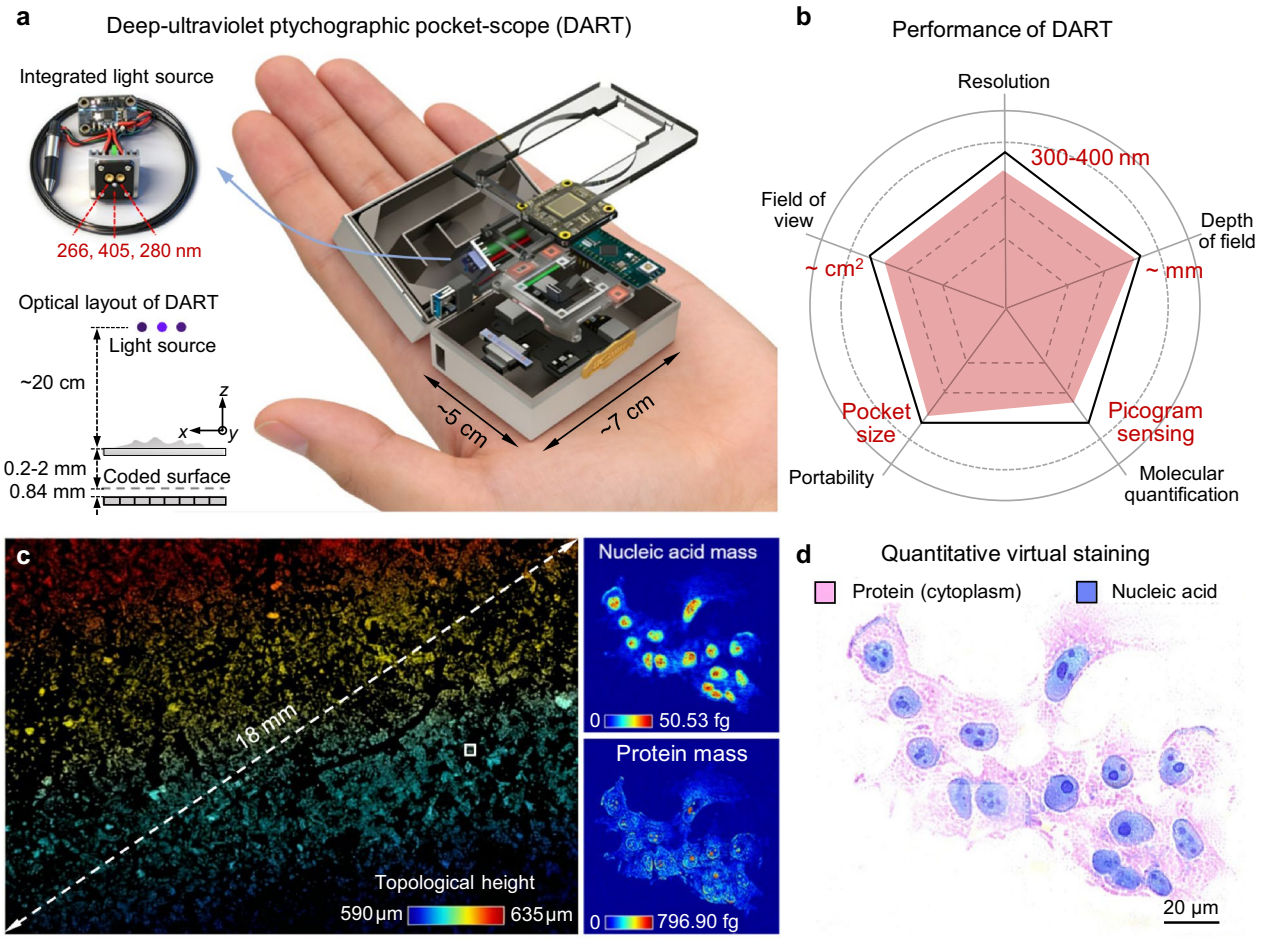

Fig. 1 Deep-Ultraviolet Ptychographic Pocket-Scope (DART) and its performance in label-free molecular imaging. **a** Schematic of the DART device, including its integrated light source (266 nm, 405 nm, and 280 nm) and optical layout, showcasing the compact design with key dimensions. **b** Performance radar chart of DART, highlighting its resolution, field of view, depth of field, molecular quantification capability, and portability. **c** Label-free subcellular imaging with DART: molecular distribution of nucleic acids (top right) and proteins (bottom right) in a sample, with molecular sensitivity down to picogram levels. **d** Quantitative virtual staining

of research established coded modulation not as an auxiliary technique for compensating missing optics, but as a general and scalable platform for information multiplexing. Collectively, these studies positioned coded modulation and computational inversion as foundational design principles for lensless imaging, reframing the field as an information-complete measurement problem rather than a hardware-limited modality.

Seen in this broader context, DART represents a natural yet decisive milestone along this trajectory. It is the first demonstration that a coded-surface lensless system can robustly support quantitative DUV spectroscopic imaging under partially coherent and non-ideal illumination conditions—regimes that have traditionally posed severe challenges for lensless platforms. Particularly notable is the introduction of virtual error bins, which explicitly model source incoherence and system imperfections as independent computational channels. Rather than suppressing or calibrating out these effects, DART incorporates them directly into the reconstruction framework. This error-aware strategy transforms long-standing limitations of portable lensless imaging into tractable degrees of freedom, reinforcing the information-centric philosophy that has underpinned coded-surface approaches from their inception. At a broader methodological level, DART resonates with the general principle of information multiplexing in ptychography [25, 26] and with multispectral ptychographic modulation strategies that co-design spectral diversity and super-resolved reconstruction [27]. It also aligns with ongoing progress toward depth-multiplexed and multi-slice ptychography for optically thick or stacked

specimens [37, 43, 44], as well as with emerging directions that introduce additional physical channels, such as polarization-sensitive coded ptychography [45] or chemically specific vibrational contrast within ptychographic frameworks [46]. Viewed together, these developments suggest a unifying theme: coded surfaces and computational inversion are evolving into a common language for encoding and decoding increasingly rich physical information within lensless architectures.

Beyond its immediate technical achievements, DART points toward a broader redefinition of lensless imaging itself. Over the past decade, the field has largely addressed the challenges of structural scalability: high resolution, wide FOV, high throughput, and compact form factors are no longer exceptional. As these structural capabilities approach practical saturation, **the limiting factor for impact shifts from how efficiently images are acquired to what information those images are fundamentally capable of conveying**. DART exemplifies a transition from structural scalability to functional completeness, demonstrating that molecular specificity need not be sacrificed for throughput, portability, or system simplicity. Looking further ahead, the coded-surface, information-centric paradigm underlying DART provides a natural pathway for integrating additional physical dimensions, such as polarization, angular diversity, and chemically specific spectroscopic contrast, within compact, deployable, lensless platforms. In this sense, DART does not merely add a new capability to the lensless imaging toolbox. It signals a maturation of the field, in which the long-standing emphasis on hardware minimalism gives way to a more ambitious objective: **information completeness at scale**. If this trajectory continues, lensless imaging may ultimately reshape not only how large biological specimens are imaged, but how optical systems are designed to access structure, composition, and function as co-equal— and co-engineered—dimensions of biological understanding.

Author contributions
J.Q. and J.S. prepared the manuscript. C.Z., Q.C., J.Q. and J.S. revised the manuscript.

Data availability
Not applicable.

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