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Quantum super-resolution microscopy by photon statistics and structured light

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Reaching high-resolution imaging of delicate samples at a low-intensity level is a major challenge in microscopy. Here, we present and experimentally implement an advanced quantum super-resolution imaging technique based on photon statistics measurement. Our reconstruction algorithm adapts to any kind of non-Poissonian emitters, outperforming the corresponding classical SOFI method, in particular in low-light conditions. It offers sub-diffraction resolution improvement that scales with the $\sqrt{j}$, where j is the highest-order central moments of the photocounts. More remarkably, we show that in combination with structured illumination, an improvement of $j+\sqrt{j}$ can be reached, providing a promising avenue for non-invasive super-resolution microscopy.

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1. INTRODUCTION

Improving spatial resolution is critical in current biological and medical research [1]. Within the principle of optical diffraction, Ernst Abbe initially identified the optical resolution limits as imposed by the numerical aperture of the objective and the wavelength of light [2]. For more than a century, it was considered an impassable limit. However, in the early 1990s, novel approaches broke beyond Abbe's limit by circumventing some of its underlying assumptions (explicit or implicit), among them the linear and static response of the sample to incident light, the far-field intensity detection, and uniform illumination. In particular, by exploiting the non-linear or randomly selective response of point-like fluorescence markers, pioneering techniques such as stimulated emission depletion (STED) microscopy and single-molecule localization microscopy (SMLM) have substantially advanced the field and demonstrated exceptional resolution enhancement [3–6]. However, biologists often demand live cell imaging technologies that provide high resolution while minimizing photodamage when using photosensitive samples, which limits the applicability of the aforementioned techniques in a biocompatible context [7–10].

A biocompatible super-resolution approach that does not require high illumination levels is super-resolution optical fluctuation microscopy (SOFI) [11–14], which exploits the natural or induced random fluctuation of fluorophores' brightness. However, as we will discuss later, SOFI, like some more advanced methods built on it (e.g., [15]), is based on a semi-classical model of light that only contemplates classical super-Poissonian emitters, does not take into account quantum fluctuation, and leads to a strongly limited resolution enhancement in low-light scenarios. In low-light regimes, photon quantization emerges, and a full quantum description is essential for optimal optical imaging [16,17], often exploiting quantum features such as entanglement [18,19] and squeezing [20]. This field, referred to as quantum imaging (see [21] for a recent review), has enabled advancements such as sub-shot-noise imaging and sensing [22–26], quantum-enhanced AFM [27], optical tweezers and non-linear microscopy [28,29], image distillation from noise [30], and imaging/spectroscopy with undetected photons [31–33] to cite a few.

The use of quantum anti-bunching in single-photon emitters to achieve super-resolution via higher-order photo-count correlation functions was first proposed in [34] and later experimentally demonstrated both in wide-field [35] and in confocal settings [36]. Those last methods can be seen as the equivalent of SOFI but for sub-Poissonian emitters.

This paper aims to introduce a full quantum method for super-resolution named quantum super-resolution imaging by photon statistics (QSIPS) that is based on a rigorous full quantum model describing the photon emission and detection. Our model yields a generalized SOFI approach that works optimally at any intensity level and with any non-Poissonian emitter, including single-photon emitters and any kind of blinking (photoswitching) fluorophores. Here, we present the model together with simulations and experimental results, demonstrating the superiority of our approach over traditional SOFI methodologies published in