SPARCOM: Sparsity Based Super-Resolution Correlation Microscopy

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Abstract—In traditional optical imaging systems, the spatial resolution is limited by the physics of diffraction. The information on sub-wavelength features is carried by evanescent waves, never reaching the camera, thereby posing a hard limit on resolution: the so-called diffraction limit. Modern microscopic methods enable super-resolution, by employing florescence techniques. State-of-the-art localization based fluorescence sub-wavelength imaging techniques such as PALM and STORM achieve sub-diffraction spatial resolution of several tens of nano-meters. However, they require tens of thousands of exposures, which limits their temporal resolution. We have previously proposed SPARCOM (sparsity based super-resolution correlation microscopy), which exploits the sparse nature of the fluorophores distribution, alongside a statistical prior of uncorrelated emissions, and showed that SPARCOM achieves spatial resolution comparable to PALM/STORM, while capturing the data hundreds of times faster. Here, we provide a rigorous and thorough mathematical formulation of SPARCOM, which in turn leads to an efficient numerical implementation, suitable for large-scale problems. We further extend our method to a general framework for sparsity based super-resolution imaging, in which sparsity can be assumed in other domains such as wavelet or total-variation, leading to better reconstructions and faster computations. As such, SPARCOM may facilitate super-resolution imaging and capturing of intra-cellular dynamics within living cells.

Index Terms—Fluorescence, High-resolution imaging, Compressed sensing, Correlation.

I. INTRODUCTION

SPATIAL resolution in diffractive optical imaging is limited by one half of the optical wavelength, known as Abbe’s diffraction limit [1], [2]. Modern microscopic methods enable super-resolution, even though information on sub-wavelength features is absent in the measurements. One of the leading sub-wavelength imaging modalities is based on fluorescence (PALM [3] and STORM [4]). Its basic principle consists of attaching fluorescent molecules (point emitters) to the features within the sample, exciting the fluorescence with short-wavelength illumination, and then imaging the fluorescent light. PALM and STORM rely on acquiring a sequence of diffraction-limited images, such that in each frame only a sparse set of emitters (fluorophores) are active. The position of each fluorophore is then found through a super-localization procedure [5]. Subsequent accumulation of single-molecule localizations results in a grainy high-resolution image, which is then smoothed to form the final super-resolved image. The final image has a spatial resolution of tens of nanometers.

A major disadvantage of these florescence techniques is that they require tens of thousands of exposures. This is because in every frame, the diffraction-limited image of each emitter must be well separated from its neighbors, to enable the identification of its exact position. This inevitably leads to a long acquisition cycle, typically on the order of several minutes [4]. Consequently, fast dynamics - even at video rates - cannot be captured by PALM/STORM.

To reduce acquisition time, an alternative technique named SOFI (super-resolution optical fluctuation imaging) was proposed [6], which uses high fluorophore density, and eventually reduces integration time. In SOFI, the emitters usually overlap in each frame, so that super-localization cannot be performed. However, the emitted photons from each emitter, which are uncorrelated between different emitters, are captured over a period of several frames by the camera. Hence, consecutive frames contain information in the pixel-wise temporal correlation between them. The measurements are processed such that correlative information is used, enabling the recovery of features that are smaller than the diffraction limit by a factor of $\sqrt{2}$. By calculating higher order statistics (HOS) in the form of cumulants [7] of the time-trace of each pixel, a theoretical resolution increase equal to the square root of the order of the statistics can in principle be achieved. Using the cross-correlation between pixels over time, it is possible to increase the resolution gain further, to an overall factor that scales linearly with the order of the statistical calculation [8].

SOFI enables processing of images with high fluorophore density, thus reducing the number of required frames for image recovery and achieving increased temporal resolution over localization based techniques. However, at least thus far, the spatial resolution offered by SOFI does not reach the level of super-resolution obtained through STORM and PALM, even when using HOS. The use of HOS can in principle increase the resolution, but higher (than the order of two) statistical calculations require an increasingly large number of frames for their estimation, degrading temporal resolution. Moreover, SOFI suffers from a phenomenon known as dynamic range expansion, in which weak emitters are masked in the presence of strong ones. The effect is worsened as the statistical order increases, which in practice limits the applicability of SOFI to second order statistics and a moderate improvement in spatial resolution.

Recently, we proposed a method for super-resolution imag-
In our previous work, we have shown that our method achieves spatial resolution similar to PALM/STORM, while acquiring the data hundreds of times faster, by performing sparse recovery on correlation information. Mathematically, SPARCOM recovers the support of the emitters, by recovering their variance values. Sparse recovery from correlation information was previously proposed to improve sparse recovery from a small number of measurements \cite{1, 2, 3}. When the non-zero entries of the sparse signal are uncorrelated, support size recovery can be theoretically increased up to \(O(M^2)\), where \(M\) is the length of a single measurement vector. In SPARCOM we use similar concepts to enhance resolution and improve SNR (signal to noise ratio) in optical imaging. By performing sparse recovery on correlation information, SPARCOM enjoys the same features of SOFI, i.e. fast frame capturing rate of high fluorophore density frames and the use of correlative information, while offering the possibility of achieving single-molecule resolution comparable to that of PALM/STORM, which may facilitate super-resolution imaging of dynamic processes within living cells. Moreover, by relying on correlation information only, SPARCOM overcomes the dynamic range problem of SOFI when high-order statistics are used, and results in improved image reconstruction.

In this paper, we focus on three major contributions with respect to our previous work. The first is to provide a thorough and detailed formulation of SPARCOM, elaborating on its mathematical aspects. Second, we provide several extensions of SPARCOM, when super-resolution is considered in additional domains such as the wavelet or discrete cosine transform domains, as well as providing scenarios in which such reconstructions are beneficial. Lastly, we show how SPARCOM exploits structural information to achieve a computationally efficient implementation. This goal is achieved by considering the SPARCOM reconstruction model in the sampled Fourier space, which leads to fast image reconstruction, suitable for large-scale problems.

The rest of the paper is organized as follows: Section II presents the problem and explain the key idea of SOFI. In Section III we formulate our proposed solution. A Detailed explanation of our algorithm, implementation and additional extensions to super-resolution in an arbitrary bases are provided in Sections IV and V. Simulation results are demonstrated in Section VI.

Throughout the paper, \(x\) represents a scalar, \(x\) represents a vector, \(X\) a matrix and \(I_{N \times N}\) is the \(N \times N\) identity matrix. The notation \(\| \cdot \|_p\) represents the standard \(p\)-norm and \(\| \cdot \|_F\) is the Frobenius norm. Subscript \(x_i\) denotes the \(i\)th element of \(x\) and \(x_i\) is the \(i\)th column of \(X\). Superscript \(x^{(t)}\) represents \(x\) at iteration \(t\), \(T^*\) denotes the adjoint of \(T\), and \(\tilde{A}\) is the complex conjugate of \(A\).

II. PROBLEM FORMULATION AND SOFI

Following \cite{4, 5}, the acquired fluorescence signal in the object plane is modeled as a set of \(L\) independently fluctuating point sources, with resulting fluorescence source distribution

\[
J(r, t) = \sum_{k=0}^{L-1} \delta(r - r_k)s_k(t).
\]

Each source (or emitter) has its own time dependent brightness function \(s_k(t)\), and is located at position \(r_k \in \mathbb{R}^2, k = 0, \ldots, L - 1\). The acquired signal in the image plane is the result of the convolution between \(J(r, t)\) and the impulse response of the microscope \(u(r)\) (also known as the point spread function (PSF)),

\[
f(r, t) = \sum_{k=0}^{L-1} u(r - r_k)s_k(t).
\]

Due to the propagation of light, the microscope can be considered as a spatial low-pass filter (LPF) \cite{6}, so that \(f\) consists of frequencies below the cutoff of the PSF. We assume that the measurements are acquired over a period of \(t \in [0, T]\). Ideally, our goal is to recover the locations of the emitters, \(r_k\) and their variances with high spatial resolution and short integration time. The final high-resolution image is constructed from the recovered variance value for each emitter.

To proceed, we assume the following:

\begin{itemize}
  \item **A1** The locations \(r_k, k = 0, \ldots, L - 1\) do not depend on time.
  \item **A2** The brightness is uncorrelated in space, namely, \(E\{s_i(t_1)s_j(t_2)\} = 0\), for all \(i \neq j\), and for all \(t_1, t_2\).
  \item **A3** The brightness functions \(s_k(t), k = 0, \ldots, L - 1\) are wide sense stationary with \(E[s_k(t)] = E[s_k(t + \tau)] = g_k(\tau)\), where \(\hat{s}_k(t) = s_k(t) - E[k]_k\).
\end{itemize}

Using assumptions A2 and A3, the autocorrelation function at each point \(r\) can be computed as

\[
G_f(r, \tau) = E\{\hat{f}(r, t)\hat{f}(r, t + \tau)\} = \sum_{k=0}^{L-1} u^2(r - r_k)g_k(\tau),
\]

where \(\hat{f}(r, t) = f(r, t) - E[f(r, t)] = \sum_{k=0}^{L-1} u(r - r_k)s_k(t)\). The final SOFI image is the value of \(G_f(r, 0)\) at each point \(r\), where \(g_k(0)\) represents the variance of emitter \(s_k\). We see from \(2\) that the autocorrelation function depends on the PSF squared. If the PSF is assumed to be Gaussian, then this calculation reduces its width by a factor of \(\sqrt{2}\). However, the final SOFI image retains the same low resolution grid as the captured movie. Similar statistical calculations can be performed for adjacent pixels in the movie leading to a simple interpolation grid with increased number of pixels in the high-resolution image, but at the cost of increased statistical order using cumulants \cite{7}. Higher order statistics reduce the PSF size further but at the expense of degraded SNR and dynamic range for a given number of frames \cite{8}.

In the next section we provide a rigorous and detailed description of our sparsity based method, first presented in \cite{9}, for estimating \(r_k\) and \(g_k(0)\) on a high resolution grid. We rely on correlation only without resorting to higher order statistics, thus maintaining a short acquisition time, similar to correlation-based SOFI. In contrast to SOFI, we exploit the sparse nature of the emitter’s distribution and recover a high-resolution image on a much denser grid than the camera’s grid. This leads to spatial super-resolution without the need to perform interpolation using higher order statistics \cite{8}.
III. SPARCOM

A. High resolution representation

To increase resolution by exploiting sparsity, we start by introducing a Cartesian sampling grid with spacing $\Delta_L$, which we refer to as the low-resolution grid. The low-resolution signal $f[m\Delta_L, n\Delta_L, t]$ can be expressed over this grid as

$$ f[m\Delta_L, n\Delta_L, t] = \sum_{k=0}^{L-1} u[m\Delta_L - m_k, n\Delta_L - n_k]s_i(t), \quad m, n = 0, \ldots, M - 1, $$

where $r_k = [m_k, n_k]^T \in \mathbb{R}^2$. We discretize the possible locations of the emitters $r_k$, over a discrete Cartesian grid $i, l = 0, \ldots, N - 1, L < N$ with resolution $\Delta_H$, such that $[m_k, n_k] = [i_k, l_k]\Delta_H$ for some integers $i_k, l_k \in [0, \ldots, N - 1]$. We refer to this grid as the high-resolution grid.

The latter discretization implies that (3) is sampled (spatially) over a grid of size $M \times M$, while the emitters reside on a grid of size $N \times N$, with the $i$th pixel having a fluctuation function $s_i(t)$ (only $L$ such pixels actually contain fluctuating emitters, according to (3)). If there is no emitter in the $i'l$th pixel, then $s_{il}(t) = 0$ for all $t$. We further assume that the PSF $u$ is known.

Rewriting (3) in Cartesian form with respect to the grid of emitters yields,

$$ f[m\Delta_L, n\Delta_L, t] = \sum_{i=0}^{N-1} \sum_{l=0}^{N-1} u[m\Delta_L - i\Delta_H, n\Delta_L - l\Delta_H]s_{il}(t). $$

(4)

For simplicity we assume that $\Delta_L = P\Delta_H$ for some integer $P \geq 1$, and consequently $N = PM$. In addition, it holds that

$$ m\Delta_L - i\Delta_H = (mP - i)\Delta_H. $$

Omitting the spacing $\Delta_H$, we can rewrite (4) as

$$ f[mP, nP, t] = \sum_{i,l=0}^{N-1} u[mP - i, nP - l]s_{il}(t). $$

(5)

B. Fourier analysis

We next present (6) in the Fourier domain, which will lead to an efficient implementation of our method.

Since $y[m, n, t] = f[mP, nP, t]$ is an $M \times M$ sequence, denote by $Y[k_m, k_n, t]$ its $M \times M$ two dimensional discrete Fourier transform (DFT). Performing an $M \times M$ two dimensional DFT on $y[m, n, t]$ yields

$$ Y[k_m, k_n, t] = \sum_{m, n=0}^{M-1} f[mP, nP, t]e^{-j\frac{2\pi m k_m}{M}}e^{-j\frac{2\pi n k_n}{M}} = \sum_{i=0}^{N-1} \sum_{l=0}^{N-1} s_{il}(t) \sum_{m, n=0}^{M-1} u[m\Delta_L - i\Delta_H, n\Delta_L - l\Delta_H]e^{-j\frac{2\pi m k_m}{M}}e^{-j\frac{2\pi n k_n}{M}}, $$

where we defined $\tilde{m} = mP$ and $\tilde{n} = nP$ and $k_m, k_n = 0, \ldots, M - 1$. Next, consider $\tilde{m}, \tilde{n} = 0, \ldots, N - 1$ and define the $N \times N$ sequence

$$ \tilde{u}[\tilde{m}, \tilde{n}] = \begin{cases} u[\tilde{m}, \tilde{n}], & \tilde{m}, \tilde{n} = 0, P, \ldots, N - P, \\ 0, & \text{else}, \end{cases} $$

(6)

where $u$ is the discretized PSF sampled over $M \times M$ points of the low-resolution grid. We can then equivalently write

$$ Y[k_m, k_n, t] = \sum_{i,l=0}^{N-1} s_{il}(t) \sum_{\tilde{m}, \tilde{n}=0}^{N-1} \tilde{u}[\tilde{m}, \tilde{n}]e^{-j\frac{2\pi \tilde{m} k_m}{M}}e^{-j\frac{2\pi \tilde{n} k_n}{M}}. $$

(7)

By defining $p = \tilde{m} - i$ and $q = \tilde{n} - l$, (7) becomes

$$ Y[k_m, k_n, t] = \tilde{U}[k_m, k_n] \sum_{i,l=0}^{N-1} s_{il}(t) e^{-j\frac{2\pi k_m p}{M}}e^{-j\frac{2\pi k_n q}{M}}, $$

(8)

with

$$ \tilde{U}[k_m, k_n] = \sum_{p, q=0}^{N-1} \tilde{u}[p, q]e^{-j\frac{2\pi k_m p}{M}}e^{-j\frac{2\pi k_n q}{M}}. $$

(9)

Note that $\tilde{U}[k_m, k_n]$ is the $N \times N$ two-dimensional DFT of the $N \times N$ sequence $\tilde{u}$, evaluated at discrete frequencies $k_m, k_n = 0, \ldots, M - 1$. From (6) and (7), it holds that $\tilde{U}[e^{-j\frac{2\pi k_m p}{M}}, e^{-j\frac{2\pi k_n q}{M}}] = U[e^{-j\frac{2\pi k_m p}{M}}, e^{-j\frac{2\pi k_n q}{M}}]$ for $k_m, k_n = 0, \ldots, M - 1 (N = PM)$, where $U$ is the $M \times M$ two-dimensional DFT of $u$ sampled on the low-resolution grid.

Denote the column-wise stacking of each frame $Y[k_m, k_n, t]$ as an $M^2$ long vector $y(t)$. In a similar manner, $s(t)$ is a length-$N^2$ vector stacking of $s_{il}(t)$ for all $i, l$. We further define the $M^2 \times M^2$ diagonal matrix $H = \text{diag} \{U[0,0], \ldots, U[M-1, M-1]\}$. Vectorizing $u$ yields

$$ y(t) = H(F_M \otimes F_M)s(t) = As(t), \quad A \in \mathbb{C}^{M^2 \times N^2}, $$

(10)

where $s(t)$ is an $L$-sparse vector and $F_M$ denotes a partial $M \times N$ DFT matrix whose $M$ rows are the corresponding $M$ low frequency rows from a full $N \times N$ discrete Fourier matrix.

Define the autocorrelation matrix of $y(t)$ as

$$ R_y(\tau) = E\left\{y(t) - E[y(t)]\right\}y(t + \tau) - E[y(t + \tau)]y(t)\right\}^H. $$

(11)

From (10),

$$ R_y(\tau) = A R_s(\tau) A^H. $$

(12)

Under assumption $A^2 R_s(\tau)$ is a diagonal matrix. Therefore, (12) may be written as

$$ R_y(\tau) = \sum_{i=0}^{N^2} a_i a_i^H r_{s_i}(\tau), $$

(13)

with $a_i$ being the $i$th column of $A$, $r_s(\tau)$ the $i$th entry of $r_{s_i}(\tau)$. By taking $\tau = 0$ we estimate the variance of $s_{il}(t)$, $i, j = 0, \ldots, N - 1$ (as written in assumption A3). It is also possible to take into account the fact that the autocorrelation matrix $R_y(\tau)$ may be non-zero for $\tau \neq 0$; for simplicity we use $\tau = 0$. The support of $r_{s_i}(\tau)$ is equivalent to the support of $s(t)$, which in turn indicates the locations of the emitters on a grid with spacing $\Delta_H$. Thus, our high resolution problem reduces to recovering the $L$ non-zero values of $r_{s_i}(0)$ in (13).
C. Sparse recovery

SPARCOM is based on (13), taking into account that \( x = r_s(0) \) is a sparse vector. We therefore find \( x \) by using a sparse recovery methodology. In our implementation of SPARCOM we use the LASSO formulation (13) to construct the following convex optimization problem

\[
\min_{x \geq 0} \lambda \|x\|_1 + \frac{1}{2} \left\| R_y(0) - \sum_{l=1}^{N^2} a_l a_l^H x_l \right\|^2_F, \quad \text{(F-LASSO)}
\]

with a regularization parameter \( \lambda \geq 0 \) and \( x_l \) denoting the \( l \)th entry in \( x \). We note that it is possible to write a similar formulation to (F-LASSO) accounting for \( \tau > 0 \) (without the non-negativity constraint). Other approaches to sparse recovery may similarly be used.

We solve (F-LASSO) iteratively using the FISTA algorithm (14), (15), (16), which at each iteration performs a gradient step and then a thresholding step. By performing the calculations in the DFT domain, we can calculate the gradient of the smooth part of (F-LASSO), that is the squared Frobenius norm, very efficiently. We discuss this efficient implementation in detail in Section V.

To achieve even sparser solutions, we implement a re-weighted version of (F-LASSO) (17).

\[
x^{(p+1)} = \arg\min_{x^{(p)} \geq 0} \lambda \|W^{(p)} x^{(p)}\|_1 + \frac{1}{2} \left\| R_y(0) - \sum_{l=1}^{N^2} a_l a_l^H x_l^{(p)} \right\|^2_F,
\]

where \( W \) is a diagonal weighting matrix and \( p \) denotes the number of the current reweighting iteration. Starting from \( p = 1 \) and \( W = I \), where \( I \) is the identity matrix of appropriate size, the weights are updated after a predefined number of FISTA iterations according to the output of \( x \) as

\[
W_i^{(p+1)} = \frac{1}{|x_i^{(p)}| + \epsilon}, \quad i = 1, \ldots, N^2,
\]

where \( \epsilon \) is a small non-negative regularization parameter. After updating the weights, the FISTA algorithm is performed again.

In practice, for a discrete time-lag \( \tau \) and total number of frames \( T \), \( R_y(\tau) \) is estimated from the movie frames using the empirical correlation

\[
R_y(\tau) = \frac{1}{T - \tau} \sum_{t=1}^{T-\tau} (y(t) - \bar{y})(y(t + \tau) - \bar{y})^H,
\]

with

\[
\bar{y} = \frac{1}{T} \sum_{t=1}^{T} y(t).
\]

In the following sections we elaborate on our proposed algorithms for solving (F-LASSO) and the reweighted scheme (14). In particular, we explain how they can be implemented efficiently and extended to a more general framework of super-resolution under assumptions of sparsity.

Before proceeding, we briefly address the question of how many point emitters can be recovered within a single diffraction limited spot, from a theoretical point of view. The authors of (18) considered stable recovery of positive point sources from low pass measurements. By solving a simple convex optimization problem in the noiseless case, they show that a sufficient condition for recovery is that \( \|x\|_0 < M/2 \), where \( M \) is the number of low-pass measurements, without any regard to where the sources are on the high resolution grid. In the presence of noise, such a condition is not sufficient and it is important to know how regular the positions of the emitters are, or how many spikes are clustered together within a diffraction limited, or resolution cell (see Definition 1 in (18) for a proper definition of regularity). The bounds given in (18) are with respect to specific theoretical PSFs. For example, the authors of (19) found that the length of the resolution cell in the case of a 1D Gaussian kernel is \( 1.1/\sigma \), where \( \sigma \) is the standard deviation of the Gaussian.

Since we aim to recover the variance of each emitter, we deal with the recovery of positive quantities, where now the desired signal is the variance of the emitters, and not their actual intensities. Thus, similar to the work of (11), in the noiseless case we theoretically expect to recover up to \( O(M^2) \) emitter locations instead of \( M/2 \) for the same number of measurements. In the presence of noise, the emitters must be regular with respect to the squre diffraction limited spot.

IV. PROXIMAL GRADIENT DESCENT ALGORITHMS

A. Variance recovery

Problem (F-LASSO) can be viewed as a minimization of a decomposition model

\[
\min_{x \geq 0} \lambda g(x) + f(x),
\]

where \( f \) is a smooth, convex function with a Lipschitz continuous gradient and \( g \) is a possibly non-smooth but proper, closed and convex function. Following (15) and (16) we adapt a Fast-Proximal algorithm, similar to FISTA, to minimize the objective of (F-LASSO), as summarized in Algorithm I. Solving (F-LASSO) iteratively involves finding Moreau’s proximal (prox) mapping (20), (21) of \( g \) for some \( \alpha \geq 0 \), defined as

\[
\text{prox}_{\alpha g}(x) = \arg\min_{u \in \mathbb{R}^n} \left\{ \alpha g(u) + \frac{1}{2} \|u - x\|_2^2 \right\}.
\]

For \( g(x) = \|x\|_1 \), \( \text{prox}_{\alpha g}(x) \) is given by the well known soft-thresholding operator,

\[
\text{prox}_{\alpha \|\cdot\|_1}(x) = \text{Proj}_{\alpha} \left( x \right) = \max\{\|x\| - \alpha, 0\} \cdot \text{sign}(x),
\]

where the multiplication, max and sign operators are performed element-wise. In its simplest form, the proximal-gradient method calculates the prox operator on the gradient step of \( f \) at each iteration.

Denoting

\[
f(x) = \frac{1}{2} \left\| R_y(0) - \sum_{l=1}^{N^2} a_l a_l^H x_l \right\|^2_F,
\]

and differentiating it with respect to \( x \) yields

\[
\nabla f(x) = Mx - v,
\]

where \( v = [a_1^H R_y(0) a_1, \ldots, a_{N^2}^H R_y(0) a_{N^2}]^T \), \( M = |A^H A| \) and we have used the fact that \( x \) is real since it
represents the variance of light intensities. The operation $|·|^2$ is performed element-wise. The Lipschitz constant $L_f$ of $f(x)$ is readily given by $L_f = ||M||_2$, corresponding to the largest eigenvalue of $M$, since by (18)

$$||\nabla f(x) - \nabla f(y)||_2 \leq ||M||_2 ||x - y||_2.$$ 

Calculation of (18) is the most computationally expensive part of Algorithm 1. Since $M$ is of dimensions $N^2 \times N^2$, it is usually impossible to store it in memory and apply it straightforwardly in multiplication operations. In Section V, we present an efficient implementation that overcomes this issue, by exploiting the structure of $M$. We also develop a closed form expression for $L_f$. 

Algorithm 1 Fast Proximal Gradient Descent for SPARCIM

Input: $L \geq L_f, R_y(0), \lambda > 0, K_{max}$

Initialize $x_1 = x_0 = 0, t_1 = 1$ and $k = 1$

while $k \leq K_{max}$ or stopping criteria not fulfilled do

1: $\nabla f(z_k) = Mz_k - v$

2: $x_k = T_k(z_k - \frac{1}{2} \nabla f(z_k))$

3: Project to the non-negative orthant $x_k(k_k < 0) = 0$

4: $t_{k+1} = 0.5(1 - \sqrt{1 + 4t_k^2})$

5: $z_{k+1} = x_k + \frac{t_{k+1}}{t_{k+1}}(x_k - x_{k-1})$

6: $k ← k + 1$

end while

return $x_{K_{max}}$

Implementing the re-weighted $l_1$ minimization of (14) involves calculation of the following element-wise soft-thresholding operator

$$T_kW_i(x_i) = \max\left\{ |x_i| - \frac{\lambda}{t_i} W_i, 0 \right\} \cdot \text{sign}(x_i),$$ (19)

with $W_i$ being the current value of the $i$th entry of the diagonal of the weighting matrix $W$. The re-weighting procedure is summarized in Algorithm 2.

Algorithm 2 Iterative re-weighted Fast Proximal Gradient for (F-LASSO)

Input: $L \geq L_f, R_y(0), \lambda > 0, \epsilon > 0, P_{max}$

Initialize Set iteration counter $l = 1$ and $W^1 = I$

while $p \leq P_{max}$ or stopping criteria not fulfilled do

1: Solve (F-LASSO) using Algorithm 1 with (19)

2: Update weights for $i = 1, \ldots, N^2$

$$W_i^{(p+1)} = \text{diag}\left\{ \frac{1}{|x_i^p| + \epsilon}, \ldots, \frac{1}{|x_{N^2}^p| + \epsilon} \right\},$$

3: $p ← p + 1$

end while

return $x_{P_{max}}$

B. Regularized super-resolution

Recall that to achieve super-resolution we assumed that the recovered signal is sparse. Such an assumption arises naturally in the context of fluorescence microscopy, in which the imaged object is labeled with fluorescing molecules such that the molecular distribution or the desired features themselves are spatially sparse. In [9], we exploit both the uncorrelated emissions of the emitters and their sparse distribution within the images. But, in some scenarios (e.g., imaging of thick, two-dimensional objects) the assumption of sparse emitter distribution is insufficient to produce a clear and smooth image. In many cases, the sought after signal has additional structure which can be exploited alongside sparsity, especially since attaching fluorescing molecules to sub-cellular organelles serves as means to image these structures, which are of true interest. Thus, when considering sparsity based super-resolution reconstruction, we can consider a more general context of sparsity within the desired signal.

Consider the general decomposition model

$$\min_{x \geq 0} \lambda g(x) + f(x).$$

The choice of the regularization function $g$ can be extended beyond the common $l_1$ norm. The use of different regularizers implies different prior assumptions on the structure of $x$ and in turn leads to different image reconstructions. This section explores an extension for (F-LASSO) in which sparsity is assumed not in the correlation-image itself, but rather in different bases such as a tight wavelet frame, discrete cosine basis and with additional regularizers such as total-variation (TV) (see e.g., [22], [23]) which is known to produce piecewise smooth reconstructions. In Section VI, we show several reconstructions under such different priors and discuss their benefits.

In the general context of sparse recovery, two common formulations are often considered [10], [24], known as the synthesis and analysis formulations. In the next sections, we consider unitary transformations such that the analysis and synthesis problems admit the same solution. For convenience, we focus on the analysis formulation.

1) Total variation super-resolution imaging: We first modify (F-LASSO) to incorporate a total-variation regularization term on $x$, that is, we assume that the reconstructed super-resolved correlation-image is piece-wise constant:

$$\min_{x \geq 0} \lambda \text{TV}(x) + \frac{1}{2} \left\| R_y(0) - \sum_{l=1}^{N^2} a_l x_l \right\|_F^2.$$ (F-TV)

We follow the definition of the discrete TV(x) regularization term as described in [25], for both the isotropic and anisotropic cases. The proximity mapping $\text{prox}_{\alpha\text{TV}}(x)$ does not have a closed form solution in this case. Instead, the authors of [25] proposed to solve $\text{prox}_{\alpha\text{TV}}(x)$ iteratively. The minimizer of (15) is the solution to a denoising problem with the regularizer $\alpha g(\cdot)$ on the recovered signal. In particular, $\text{prox}_{\alpha\text{TV}}(x)$ is the denoising solution with a prior of total-variation. Many total-variation denoising algorithms exist (e.g., [22], [23], [26] and [27]), thus any one of them can be used to calculate the proximity mapping iteratively. In particular, we chose to follow the fast TV denoising method suggested in [23] and denoted as Algorithm GP. The algorithm accepts an observed image, a regularization parameter $\lambda$ which balances between the level of...
sparsity and compatibility to the observations and a maximal number of iterations $N_{max}$. The output is a TV denoised image. Thus, as summarized in Algorithm 3, each iterative step is composed of a gradient step of $f$ and a subsequent application of Algorithm GP.

Algorithm GP already incorporates a projection onto box constraints, which also includes as a special case the non-negativity constraints of (F-TV). Hence we have omitted the projection step in Algorithm 3. Since the solution of the proximty operator is the solution to a denoising procedure, any denoising technique can be theoretically used to produce super-resolved images which correspond to different priors.

Algorithm 3 Fast Proximal Gradient Descent for (F-TV)

**Input:** $L \geq L_f$, $R_g(0), \lambda > 0$, $K_{max}, N_{max}$

Initialize $z_1 = x_0 = 0$, $t_1 = 1$ and $k = 1$

while $k \leq K_{max}$ or stopping criteria not fulfilled do

1: $\nabla f(z_k) = Mz_k - v$

2: $x_k = \text{GP}(z_k - \frac{1}{\lambda} \nabla f(z_k), \lambda, N_{max})$

3: $t_{k+1} = 0.5(1 + \sqrt{1 + 4t_k^2})$

4: $z_{k+1} = x_k + \frac{t_k}{t_{k+1}}(x_k - x_{k-1})$

5: $k \leftarrow k + 1$

end while

return $x_{K_{max}}$

2) Analysis type super-resolution imaging: In many scenarios, additional priors can be exploited alongside sparsity, to achieve sub-wavelength resolution. Examples include wavelet transforms and the discrete cosine transforms (DCT). In general, the problem we wish to solve is

$$
\min_{x} \lambda||T^*x||_1 + \frac{1}{2}||R_g(0) - \sum_{l=1}^{N^2} a_l a_l^H x_l||_F^2,
$$

Where $T \in \mathbb{C}^{M \times N}$ is some known transformation. In general, the prox mapping of the regularization term $||T^*x||_1$ does not admit a closed form solution. The authors of [28] suggested to approximate the generally non differentiable function $f(x) + g(T^*x)$ with a surrogate differentiable function, thus alleviating the need to calculate the prox mapping of the non-differentiable term $g(T^*x)$. The smooth surrogate function used is the Moreau envelope of $g$ [20], given by

$$
g_\mu(x) = \min_{u} \left\{ g(u) + \frac{1}{2\mu}||u - x||_2^2 \right\}.
$$

We therefore propose a smooth counterpart to (F-LASSO),

$$
\min_{x \geq 0} f(x) + g_\mu(T^*x),
$$

with $f(x)$ given by (17) and $g_\mu(x)$ given by

$$
g_\mu(T^*x) = \min_{u} \left\{ \lambda||u||_1 + \frac{1}{2\mu}||u - T^*x||_2^2 \right\}.
$$

The gradient of (F-SM) is now a combination of the gradients of $f(x)$ and $g_\mu(x)$, with

$$
\nabla g_\mu(T^*x) = -\frac{1}{\mu}T(T^*x - \tau_\mu(T^*x)).
$$

Using [20] we have modified the SFISTA algorithm in [28] to solve (F-SM), as summarized in Algorithm 4. Note that the Lipschitz constant of $f(x) + g_\mu(T^*x)$ is given by $L_f + \frac{||T||_2^2}{\mu}$.

Algorithm 4 Fast Proximal Gradient descent for (F-SM)

**Input:** $L \geq L_f$, $R_g(0), \lambda > 0$, $K_{max}$

Initialize $z_1 = x_0 = 0$, $t_1 = 1$ and $k = 1$

while $k \leq K_{max}$ or stopping criteria not fulfilled do

1: $\nabla f(z_k) = Mz_k - v$

2: $\nabla g_\mu(T^*x_{k-1}) = \frac{1}{\mu}T(T^*x_{k-1} - \tau_\mu(T^*x_{k-1}))$

3: $y_k = z_k - \frac{1}{\lambda} (\nabla f(z_k) + \nabla g_\mu(T^*x_{k-1}))$

4: $t_{k+1} = 0.5(1 + \sqrt{1 + 4t_k^2})$

5: $z_{k+1} = x_k + \frac{t_k}{t_{k+1}}(x_k - x_{k-1}) + \frac{r_k}{t_{k+1}}(y_k - x_k)$

6: $k \leftarrow k + 1$

end while

return $x_{K_{max}}$

V. EFFICIENT IMPLEMENTATION

Solving (F-LASSO), (F-TV) and (F-SM) in practice can be very demanding in terms of numerical computations, due to the large dimensions of the reconstructed super-resolved image. Consider for example an input movie with frames of size $64 \times 64$ pixels and a reconstructed super-resolved image of size $512 \times 512$ pixels (an eight-fold increase in the density of the high-resolution grid compared to the low-resolution captured movie). Calculating $R_g(0)$ yields a covariance data matrix of size $64^2 \times 64^2$ and $R_x(0)$ is of size $512^2 \times 512^2$ pixels (though in practice its a diagonal matrix with a diagonal of length $512^2$ pixels). The exponential growth in the problem dimensions on the one hand and the diagonal structure of the covariance matrix of the super-resolved image on the other, prompts the search for an efficient implementation for Algorithms [1]4. We now show that by considering the signal model in the spatial frequency domain as in [5], an efficient implementation based on FFT and IFFT operations is possible.

A. Frequency domain structure

Recall that

$$
\nabla f(x) = Mx - v,
$$

with $M = \left| A^H A \right|^2$, $A = H(F_M \otimes F_M)$ and $v = \left[a_{1}^H R_g(0)a_{1}, \ldots, a_{N^2}^H R_g(0)a_{N^2}\right]^T$. Reconstruction of a super-resolved image of size $N \times N$ dictates that $M$ will be of size $N^2 \times N^2$. In most cases, it is impossible to store $M$ in memory or perform matrix-vector multiplications. Instead, we exploit the special structure of $M$ to achieve efficient matrix-vector operations without explicitly storing it.

Figure 1a illustrates the structure of $M$ for two formulations: Figure 1a shows the structure of $M$ if we do not consider performing an FFT on $F$. In this case, the $n$-th column of $A \in \mathbb{R}^{M \times N^2}$ contains the vectorized $M \times M$ PSF centered at the high resolution pixel $ij$, $i,j \in [0, \ldots, N-1]$. Figure 1b illustrates the structure of $M$ in the spatial-frequency domain, derived from (8). In both cases, $M$ is of size $64 \times 64$ pixels.
and is generated from a PSF of size 4 × 4 pixels. Both figures represent a reconstruction of a 64 × 64 super-resolved image.

Figure 1b implies that the spatial-frequency formulation of M has a cyclic structure. This special structure will play a crucial role in our algorithm, as it leads to efficient implementation of matrix vector multiplications. More specifically, in Appendix A we show that M is block circulant with circulant blocks (BCCB) [29]. Figure 1b can be divided into 8 × 8 blocks (the different blocks are marked with rectangles of different colors to illustrate the block circular structure of the matrix), each block of size 8 × 8 pixels. As can be seen, M is circulant with respect to the blocks and each block is also circulant.

Similar to circulant matrices which are diagonalizable by the DFT matrix, BCCB matrices are diagonalizable by the kronecker product of two DFT matrices of appropriate dimensions. Such structure allows the implementation of a fast matrix-vector multiplication using FFT and inverse FFT operations without the need to store M in memory. In the following sections we describe the implementation of (18) in detail, by defining several operators which play a crucial role in its calculation.

B. Efficient Implementation of Mx

We first define \( \mathcal{M}(x) \), which takes \( x \in C^{N^2} \) and transforms it into a matrix \( X \in C^{N \times N} \), that is

\[
X = \mathcal{M}(x).
\]

This operation is performed using a column-wise division from top to bottom of \( x \). Upon dividing \( x \) into \( N \) sub-vectors of length \( N \) each, the \( i \)th column of \( X \) corresponds to the \( i \)th sub-vector of \( x \). Similarly, we denote the vectorization of \( X \in C^{N \times N} \) which stacks the columns of \( X \) by

\[
x = \text{vec}(X) = \mathcal{V}(X).
\]

Here, \( x \) is a vector of length \( N^2 \), whose \( i \)th sub-vector of length \( N \) corresponds to the \( i \)th column of \( X \).

In Appendix A we show that \( M \) is an \( N^2 \times N^2 \) BCCB matrix with blocks of size \( N \times N \). It is well known that such a matrix is diagonalizable by the kronecker product of two discrete \( N \times N \) Fourier matrices \( F_2 = F \otimes F \) [29], so that

\[
M = F_2^H \Lambda F_2
\]

with \( \Lambda \) a diagonal matrix containing the eigenvalues of \( M \) on its diagonal. To compute \( Mx \) we therefore need to calculate the eigenvalues of \( M \), and apply \( F_2 \) and \( F_2^H \) on a given vector. Now,

\[
F_2x = (F \otimes F)x = \mathcal{V}(FM(x)F^T).
\]

The matrix \( FM(x)F^T \) corresponds to applying the FFT on each column of \( M(x) \), and then again over the rows of the result. In MATLAB, \( F_2x \) is easily performed by reshaping \( x \) to \( M(x) \), applying the \texttt{fft2} command on \( M(x) \) and vectorizing the result. Similarly, calculation of the 2D inverse FFT of an \( N \times N \) matrix \( X_T \) is equivalent to \( \frac{1}{M}F^H X_T F \) and is easily implemented in MATLAB with the \texttt{fft2} command.

To compute the eigenvalues of \( M \) efficiently, we first need to be able to compute \( Ax \) and \( A^Hx \) for some \( x \in C^{N^2} \).

1) Calculation of \( Ax \): Recall that

\[
A = H(F_M \otimes F_M),
\]

where \( F_M \in C^{M \times N} \) denotes a partial Fourier matrix, corresponding to the low-pass values of a full \( N \times N \) Fourier matrix. The operator \( Ax \) corresponds to taking \( X = M(x) \), calculating \( F_MXF_M^T \), vectorizing the result and multiplying by \( H \). Denote,

\[
F_{M_2}(X) = F_MXF_M^T.
\]

The application of \( F_M \) on an \( N \times N \) matrix \( X \) can be implemented by performing an FFT on each column of \( X \) and taking only the first \( M \) rows of the result. Similarly, calculation of \( XF_{M_2}^T = (F_MX^T)^T \) is done by performing an FFT on each row of \( X \), taking the first \( M \) rows of the result and performing the transpose operation.

Equation (25) implements a partial 2D-FFT operation on \( X \), where the full 2D-FFT operation is written as \( FXF^T \) with an \( N \times N \) discrete Fourier matrix \( F \). The multiplication \( Ax \) can then be summarized as follows,

\[
Ax = H \cdot \mathcal{V}(F_{M_2}(M(x))).
\]

Since \( H \) is a diagonal matrix, the matrix-vector multiplication in (26) corresponds simply to multiplying the diagonal of \( H \) and the corresponding vector. If instead of a vector \( x \) we perform \( AZ \) on some matrix \( Z \in C^{N^2 \times N} \), then the operation is performed on each column of \( Z \).

2) Calculation of \( A^Hx \): For \( x \in C^{M^2} \),

\[
A^Hx = (F_{M}^H \otimes F_{M}^H)H^Hx = (F_{M}^H \otimes F_{M}^H)z.
\]

Upon reformulating \( z \) as an \( M \times M \) matrix \( Z = M(z) \), we have

\[
\mathcal{M}(A^Hx) = F_{M}^HZF_M.
\]

Since \( F_M^H = N F_M \) and \( F_{M}^HZF_M \) corresponds to performing an inverse FFT on the zero-padded columns of \( Z \) and multiplying by \( N \). We denote the result as \( Y \). Next, notice that \( YF_M = (F_M^T Y^H)^H \). Since the DFT matrix is a symmetric matrix, the second step involves performing an FFT on the
zero-padded columns of $Y^H$ and finally, taking the Hermitian operation. By denoting $F^H_{M_2}(X) = F^H_{M}X\bar{F}_M$ we can write

$$A^Hx = \mathcal{V}(F^H_{M_2}(\mathcal{M}(H^Hx))).$$

(27)

If instead of a vector $x$ we perform $A^H(Q)$ on some matrix $Q \in \mathbb{C}^{M \times N}$, then the operation is performed on each column of $Q$.

3) Calculation of the eigenvalues of $M$: To calculate the eigenvalues of $M$, denoted by $\lambda$, note that from (23)

$$\frac{1}{N}F_2m_1 = \Lambda f_1,$$

which implies that $\frac{1}{N}F_2m_1 = \Lambda f_1$ with $m_1$ and $f_1$ being the first columns of $M$ and $F_2$, respectively. Since $f_1$ is a vector of ones, we have

$$\frac{1}{N}F_2m_1 = \lambda,$$

with $\lambda = \text{diag} \{A\}$. To compute $m_1$ we note that since $M = |A^HA|^2$, $m_1 = |A^HA|^2$ where $a_1$ is the first column of $A$. From the definition of $A$, $a_1 = h$, where $h = \text{diag} \{H\}$, and therefor $m_1 = (F^H_{M_2} \otimes F^H_M)h|^2{\lambda}$. In MATLAB, this can be implemented using $\text{fft} / \text{ifft}$ operations, as noted by the first two steps of Algorithm [5].

By denoting the $M \times M$ DFT of the PSF as $U$, it follows straightforwardly that $|M(m_1)| = Z = |F^H_{M_2}(U)|^2$, where the operation $|\cdot|^2$ is performed element-wise. After the calculation of $m_1$, finding $\lambda$ is straightforward, since

$$\mathcal{M}(\lambda) = S = FZF^T,$$

which can be computed using the 2D-FFT.

We can summarize the application of $M \times x$ in Algorithm [5] with $A \circ B$ representing the Hadamard element-wise product of two matrices $A$ and $B$, and the $\text{fft} / \text{ifft}$ operations performed columnwise.

Algorithm 5 Calculation of $Mx$

Input: The DFT of the PSF $U$ and $x$

Eigenvalues calculation:

1: Calculate $T = N \text{iff} \{ |U|^2 \} \text{ of length } N$
2: Calculate $E = \text{fft} \{ T^H \} \text{ of length } N$
3: Eigenvales calculation $S = F |E|^2 F^T \text{ using } \text{fft2}$

Application of $Mx$:

4: Calculate $Q = S \circ (FM(x)F^T)$
5: Calculate $Y = \frac{1}{N^2}F^HMQ\bar{F} \text{ using } \text{ifft2}$

return $Y = Mx$.

Algorithms [1,2] require the Lipschitz constant $L_f$ of $M$. This constant is readily given by noting that

$$L_f = \| M \|_2 = \max_i \lambda_i, \ i = 1, \ldots, N^2,$$

with $\lambda_i$ being the $i$'th entry of $\lambda$. The value $\max_i \lambda_i$ is calculated as part of Algorithm [5] and is given by

$$L_f = \max_{i,j} s_{ij}, \ i, j = 1, \ldots, N,$$

where $s_{ij}$ is the $ij$th entry of $S$ from line 2 in Algorithm [5].

C. Efficient calculation of $v$

The vector $v$ in (18) is the input data to Algorithms [1,2]. Its $i$th element is given by

$$v_i = a_i^H R_p(0) a_i, \ i = 0, \ldots, N^2 - 1,$$

with $a_i$ representing the $i$th column of $A$. Since $v$ is an $N^2$ long vector, calculating its entries strictly by applying $A^H$ and $A$ on $R_p(0)$ and taking the resulting diagonal is impractical as $N$ increases. Instead, it is possible to calculate its entries in two steps, as follows.

The application of $a_i$ on a matrix is very similar to the application of $A$, only for a specific index $i$. We may write $a_i$ more explicitly as

$$a_i = H(f_{k_i} \otimes f_{l_i}),$$

with $k_i = \lfloor \frac{i}{N} \rfloor$ and $l_i = i \mod N$. By using the previously defined operations, $v$ can be calculated as summarized in Algorithm [6]. This calculation needs to be performed only once, at the beginning of Algorithms [1,2].

Algorithm 6 Calculation of $v$

Input: $H$ and $R_p(0)$

Calculation of $Z^H = A^H R_p(0)$:

1: Calculate $Q = H^H R_p(0)$
2: For each column of $Q$, $q_i, i = 0, \ldots, M^2 - 1$:
3: Calculate $T_i = N \text{iff} \{ \mathcal{M}(q_i) \}$ of length $N$
4: Calculate $E_i = \text{fft} \{ T_i^H \}$ of length $N$
5: Take the $i$th column of $Z^H$ as $\mathcal{V}(E_i^H)$

Calculation of each element in $v$:

For each $i = 0, \ldots, N^2 - 1$:

1: $B = F^H \mathcal{M}(H^H z_i), \text{ with } z_i \text{ the } i \text{th column of } Z$
2: Calculate $u = Fb_{k_i}$, with $b_{k_i}$ the $k_i$th row of $B$
3: Take $u_i = u_{k_i}$, the $k_i$th entry of $u$.

return \( v \).

VI. SIMULATIONS

In this section we present several numerical simulations which show the benefits of SPARCOM. In [9] we presented on both simulations and experimental datasets the advantages of SPARCOM over SOFI, STORM and state-of-the-art high density techniques such as FALCON [30] and 3B [31]. The results presented in [9] show the dramatic improvement in the temporal resolution compared with these methods (200 faster than PALM/STORM), while retaining the best possible spatial resolution, as indicated by PALM/STORM (over 12000 frames). Furthermore, we quantified the number of accurately detected molecules as a function of increasing labeling density.

In this section, we provide further examples and characterization of SPARCOM. We start by providing an additional simulation to the results given in [9], showing the ability of SPARCOM in recovering fine features absent in the diffraction limited movie, as well as providing additional comparisons to an improved SOFI formulation, termed balanced SOFI (bSOFI) [36] and high emitter density STORM. This sub-diffraction object and its corresponding SPARCOM recovery serves as a basis for an additional sensitivity analysis of...
SPARCOM. The next simulation presents the key advantages of SPARCOM in scenarios where assuming sparsity in other domains than the image domain leads to improved recovery results. We finish by examining the reconstruction sensitivity of SPARCOM to the knowledge of the PSF, based on the first simulation. These aspects complement the demonstration and analysis performed in [9], thus giving the reader a more comprehensive understanding of SPARCOM and its applications.

A. Comparison of different super-resolution methods

We numerically simulated a movie of sub-wavelength features over 1000 frames with some additional out-of-focus features and Gaussian noise with SNR = 14.95dB,

$$\text{SNR} = 20 \cdot \log_{10} \frac{|Y_{\text{movie}}|_F}{|N_{\text{movie}}|_F},$$

were $Y_{\text{movie}}$ is an $M^2 \times T$ matrix, representing the entire blurred movie (each movie frame is column stacked as a single column in $Y_{\text{movie}}$) and $N_{\text{movie}}$ is the added noise to all the frames (same dimensions as $Y_{\text{movie}}$).

In Fig. 2a we show the simulated ground truth of the image with subwavelength features of size 512 $\times$ 512 pixels. The imaging wavelength is 800nm with a numerical aperture of 1.4. We simulated two movies. The first is composed of 1000 high emitter density frames, while the second is composed of 5000 low emitter density frames of the same features.

Figure 2 illustrates a single frame from the high density movie (each frame size is 64 $\times$ 64 pixels and the pixel size corresponds to 160nm), while Fig. 2b shows the diffraction limited image (a sum of all 1000 frames). The PSF (shown in Fig. 2a) after binning by a factor of 8 was generated using the freely available PSF generator [33], [34].

Figure 2c shows a smoothed ThunderSTORM reconstruction (freely available code) from the low emitter density movie. This image serves as a reference for the best possible reconstruction, when there are no temporal considerations. On the other hand, Fig. 2d depicts smoothed ThunderSTORM reconstruction, performed with the high density movie of 1000 frames. Since the ground truth is of size 512 $\times$ 512 pixels, the raw localizations image was resized to a 512 $\times$ 512 image and smoothed with a Gaussian kernel. Figures 2f and 2g show the second and forth order SOFI images respectively (absolute values, zero time-lag). SOFI reconstructions were performed using the freely available code of bSOFI [36], which also includes a Richardson-Lucy deconvolution step with the discretized PSF used in our method. Last, Fig. 2h displays the SPARCOM reconstruction (512 $\times$ 512 pixels) after smoothing with the same kernel used in Figs. 2f and 2g. Reconstruction was performed over 2000 iterations and with $\lambda = 10^{-3}$.

Note that the SOFI reconstructions do not compare in resolution to the STORM and SPARCOM recoveries. This additional comparison shows that, even when considering more advanced implementations of SOFI, such as bSOFI, the resolution increase does not match that of SPARCOM. Furthermore, it is evident that the SPARCOM recovery (Fig. 2i) detects the “cavities” within the hollowed features, similarly to low density STORM (2j). When high emitters density is used, Fig. 2j illustrates that STORM recovery fails and no clear depiction of these features is possible.

In order to further quantify the performance of SPARCOM, Fig. 2 presents selected intensity cross-sections along two lines. In both profiles (solid and dashed yellow lines in the panels of Fig. 2), several observations can be made. First, there is a good match between the locations and width of the SPARCOM (solid red) and low density STORM (dash dot green) recoveries with the ground truth (dashed blue), indicating that SPARCOM achieves a comparable spatial resolution to STORM, when there are no temporal constraints. Second, if temporal resolution is critical, then STORM fails (solid thin purple), detecting only a single, misplaced peak, compared with the two peaks of the ground truth. Finally, in this scenario, SOFI reconstruction (dot black) failed in achieving good recovery.

Figures 2 and 3 demonstrate that sparse recovery in the correlation domain achieves increased resolution with increased temporal resolution (5 times in this example) and detects the cavities within the sub-wavelength features which are absent in the low resolution movie, high density ThunderSTORM and SOFI reconstructions. This simulation adds upon the simulations presented in [9], by comparing SPARCOM with bSOFI, which adds additional steps to the original SOFI scheme, such as a deconvolution step, as well as demonstrating the disadvantages of PALM/STORM in the high labeling density scenario (which can lead to a reduction in the total acquisition time).

B. Super-resolution under different priors

Next, we tested our more general framework for super-resolution reconstruction. We simulated a movie of microtubulin over 1000 frames with Gaussian noise (SNR = 17.72dB). In Fig. 3a we show the simulated ground truth of size 512 $\times$ 512 pixels. The imaging wavelength is 800nm with a numerical aperture of 1.4. Figure 3b shows the positions of the emitters for the first frame in the movie, while Fig. 3c shows the diffraction limited image (a sum of all 1000 frames). Figure 3d shows a single frame from the simulated movie, where each frame size is 64 $\times$ 64 pixels and the pixel size corresponds to 160nm. We used the same PSF as before.

Figure 3e shows reconstruction in the 2D wavelet domain, while Fig. 3f considers reconstruction under the assumption of a sparse distribution of molecules (Algorithm 1, 2000 iterations, $\lambda = 10^{-4}$ and smoothed with the same kernel as before). For the wavelet reconstruction we used Algorithm 2 with 2000 iterations, $\lambda = 8 \cdot 10^{-4}$ and $\mu = 10^{-5}$. The wavelet and inverse-wavelet transform were implemented using the Rice Wavelet Toolbox V.3 [37], with 2 decomposition levels and a Daubechies scaling filter of 32 taps produced by the function daubcqf [38]. Figure 3g considers reconstruction in the 2D DCT domain, while Fig. 3h shows reconstruction under an isotropic TV assumption. The DCT reconstruction used Algorithm 3 with 2000 iterations, $\lambda = 5 \cdot 10^{-4}$ and $\mu = 10^{-5}$ and the isotropic TV recovery was performed using Algorithm 4 with 500 iterations and $\lambda = 10^{-4}$. Each denoising step (GP algorithm from [25]) used 100 iterations.
Fig. 2: Reconstruction performance comparison of different methods. Upper row: (a) Ground truth: high resolution image of simulated sub-wavelength features. (b) Single diffraction limited frame from the movie, created by convolving the movie of fluctuating point emitters according to the locations in (a) with the PSF and adding Gaussian noise. (c) Diffraction-limited image, taken by averaging all the frames in the movie. (d) ThunderSTORM recovery from 5000 low density frames. Lower row: recovered images from a noisy sequence of 1000 frames. (e) Smoothed ThunderSTORM. (f) Correlations SOFI (zero time-lag). (g) 4th order SOFI (in absolute value, zero time-lag). (h) SPARCOM recovery.

Fig. 3: Normalized cross-sections along the solid yellow line (left) and the dashed yellow line (right) of Fig. 2, comparing the ground truth (dashed blue, Fig. 2a), diffraction-limited image (solid yellow, Fig. 2c), ThunderSTORM using 5000 low density frames (dash dot green, Fig. 2d), ThunderSTORM using 1000 high density frames (solid thin purple, Fig. 2e), 4th order SOFI (dot black, Fig. 2g), and SPARCOM (solid red, Fig. 2h).

In Fig. 5 we show the normalized intensity profiles of the yellow lines in Fig. 4 comparing the reconstruction performance of the various algorithms used previously. It is clear that the diffraction limited profile (dashed orange) conceals two micro-tubules (solid black curve), which are distinguishable in all methods. However, the $l_1$ based reconstruction (i.e. sparsity assumption in the positions of the emitters) results in artifacts which gives the reconstructed image a grainy appearance and does not capture the true width of the micro-tubules. On the other hand, the wavelet and TV based images show the tubulin width more precisely, while DCT recovers a blurrier image of the micro-tubules.

Though this example is artificial, it serves to demonstrate that in some cases assuming sparsity in other domains than the original sparsity assumption may help produce reconstructions which are more faithful to the desired object and have smoother textures.

C. Sensitivity of reconstruction to the PSF

Knowledge of the PSF is crucial for all the algorithms presented in this work. In practice, this knowledge is often imperfect and the PSF is usually estimated from the data [8] or from a specific experiment used to determine it [39]. When measuring the PSF of the microscope in an experiment, the position of the emitters or beads may not be exactly in the focal-plane, but rather a few hundreds of nanometers above
Fig. 4: **Effect of out-of-focus PSF on the reconstruction. Upper row: unprocessed data.** (a) Ground truth: high resolution image of simulated micro-tubulin. (b) Positions of emitters in the first frame. (c) Diffraction-limited image. (d) Single diffraction limited frame. **Lower row: recovered images from a noisy sequence of 1000 frames.** (e) 2D wavelet reconstruction. (f) $l_1$ reconstruction. (g) 2D DCT reconstruction. (h) Isotropic TV reconstruction.

Fig. 5: Normalized cross-sections along the solid yellow line of Fig. 4, comparing the ground truth (solid black, Fig. 4a), diffraction-limited image (dashed yellow, Fig. 2c), 2D wavelet reconstruction (dashed green, Fig. 2e), $l_1$ reconstruction (blue dot, Fig. 2f), 2D DCT reconstruction (dash-dot pink, Fig. 2g), and isotropic TV reconstruction (orange solid x, Fig. 2h).

or below it. Hence, we tested the reconstruction performance of Algorithm 1 when used with different out-of-focus PSFs, to assess its robustness to inexact knowledge of the PSF. We used the same simulated data (and same SNR) as in Fig. 2 (which was generated with the PSF in Fig. 6d) and simulated several PSFs measured at different distances from the focal plane. All reconstructions were performed over 2000 iterations and with $\lambda = 10^{-3}$. Figures 6a-6d illustrate the different (binned) PSFs with varying distances from the focal plane, $z = 750, 500, 250, 0$ nm, respectively. Each PSF was generated using the PSF generator, and for $z = 500$ nm, the PSF width is twice the width of the in-focus PSF ($z = 0$ nm).

Figures 6e-6h show the reconstruction results when used with the PSFs in Figs. 6a-6d, respectively, while Figs. 7a-7d show a zoom-in on the area inside the yellow rectangles in Figs. 6a-6h. It is clear from both Figs. 6 and 7 that as the PSF widens, reconstruction quality degrades, but similar reconstruction results in this example are given even for a PSF that twice as wide ($z = 500$ nm) as the in-focus PSF ($z = 0$ nm). This observation suggests that SPARCOM is fairly
Fig. 6: **Reconstruction with out-of-focus PSFs.** **Upper row:** (a)-(d) show simulated PSFs at distances \( z = 750, 500, 250, 0 \) nm from the focal plane, respectively. The captured movie was generated with the PSF in (d). **Lower row:** (e)-(h) show the reconstructed images using Algorithm 1 for each of the PSFs (a)-(d), respectively. Yellow rectangles represent a magnified area shown in Fig. 7.

Fig. 7: (a)-(d) show a zoom-in on the yellow rectangular windows in Fig. 6(e)-Fig. 6(h).

Fig. 6: **Reconstruction with out-of-focus PSFs.** **Upper row:** (a)-(d) show simulated PSFs at distances \( z = 750, 500, 250, 0 \) nm from the focal plane, respectively. The captured movie was generated with the PSF in (d). **Lower row:** (e)-(h) show the reconstructed images using Algorithm 1 for each of the PSFs (a)-(d), respectively. Yellow rectangles represent a magnified area shown in Fig. 7.

VII. CONCLUSIONS

We have proposed SPARCOM, a method for super-resolution fluorescence microscopy with short integration time and comparable spatial resolution to state-of-the-art methods. By relying on sparse recovery and the uncorrelated emissions of fluorescent emitters, SPARCOM manages to reduce the total integration time by several orders of magnitudes compared to commonly practiced methods. In this paper, we developed a thorough and detailed mathematical formulation of our method, and showed that considering reconstruction in the sampled Fourier domain results in a special structure of the gradient, which leads to a numerically efficient implementation relying of FFT operations. Moreover, we explored additional extensions of SPARCOM to scenarios in which assuming sparsity in other domains than simply the locations of the emitters leads to better recovery results. We believe that these improvements may facilitate super-resolution imaging of dynamic processes within living cells and that the proposed framework can be extended to a much wider range of imaging modalities, as long as there are statistical priors to exploit alongside sparsity.
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APPENDIX A
PROOF OF MATRIX $M$ BEING BCCB
We begin by defining circulant and block circulant with circulant blocks (BCCB) matrices [29], [30].

Definition 1. A matrix $C \in \mathbb{C}^{N \times N}$ is said to be circulant if $C_{ij} = c_{(j-i) \mod N}$, $\forall i, j = 1, \ldots, N$, for some $c_i \in \mathbb{C}$, where $C_{ij}$ is the $ij$th entry of $C$.

Definition 2. A matrix is said to be block circulant with circulant blocks if it can be divided into $N \times N$ square blocks, where each block is circulant and the matrix is circulant with respect to its blocks, e.g.:

$$B = \begin{bmatrix} C_0 & C_{N-1} & \ldots & C_1 \\ C_1 & C_0 & \ldots & C_2 \\ \vdots & \vdots & \ddots & \vdots \\ C_{N-1} & C_{N-2} & \ldots & C_0 \end{bmatrix},$$

where each $C_i, i = 0, \ldots, N-1$ is an $N \times N$ circulant matrix.

A circulant matrix of size $N \times N$ is completely defined by its first column vector, and so has $N$ degrees of freedom. Similarly, a BCCB matrix of size $N^2 \times N^2$ is completely defined by its first column and has $N^2$ degrees of freedom. Denote the first column of $B$ as $b \in \mathbb{C}^{N^2}$, such that its $i$th element is denoted by $b_i$. In the following proof, we will show that the general element of $B$ and ($M$) can be represented by two independent sets of indices, the first corresponding to block circularity between $N \times N$ blocks and the second corresponding to circularity of the entries within each block. These two sets of indices correspond to partitioning $b$ into $N$ non-overlapping vectors, each of length $N$, the first set indicates which is the right partition and the second to the right element within that partition. For the general element of $B$, this property can be written more explicitly as,

$$B_{ij} = b_{((k_j - k_i) \mod N) \cdot N + (l_j - l_i) \mod N},$$

with $b_{ij} \in \mathbb{C}, i = k_i N + l_i, i = 0, \ldots, N^2 - 1$ (same for the index $j$), such that $l_i, l_j = 0, \ldots, N - 1$ correspond to the position of $C_i$ inside an $N \times N$ circulant block, and $k_i, k_j = 0, \ldots, N - 1$ correspond to one of the $N \times N$ blocks of $B$. Notice that by the above construction, the values of $k_i$ and $k_j$ are increased by one, every $N$ increments of $l_i$ and $l_j$.

We now prove that $M$ is a BCCB matrix.

Proof. Recall that $M = |A^H A|$ and that $\cdot$ is performed element-wise. We start by considering the structure of $A^H A$:

$$A^H A = (F_M^H \otimes F_M^H) H^H H (F_M \otimes F_M),$$

Diagonal matrix. Denoting the $m$th column of $F_M^H \otimes F_M^H$ by $\hat{f}_m, m = 1, \ldots, M^2$, we may write (30) equivalently as

$$A^H A = \sum_{m=1}^{M^2} h_m \hat{f}_m \hat{f}_m^H,$$

with $h_m$ the $m$th entry diagonal element of $H^H H$.

The $m$th column of $F_M^H \otimes F_M^H$ is the kronecker product of two columns from $F_M^H$, say $f_{m1}$ and $f_{m2}$, $m_1, m_2 \in 0, \ldots, M - 1, m = 0, \ldots, M - 1$. Replacing the summation over $m$ with a double sum over $m_1$ and $m_2$, (31) can be written more explicitly as

$$A^H A = \sum_{m_1=0}^{M-1} \sum_{m_2=0}^{M-1} (\hat{f}_{m1} \otimes \hat{f}_{m2})(\hat{f}_{m1}^H \otimes \hat{f}_{m2}^H) h_{(M-m_1+m_2)},$$

The $ij$th element of $M$ is derived directly from (32) and has the form

$$M_{ij} = \sum_{m_1=0}^{M-1} \sum_{m_2=0}^{M-1} \cos \frac{2\pi}{M} m_1 (k_j - k_i) \cos \frac{2\pi}{M} m_2 (l_j - l_i) h_{(M-m_1+m_2)},$$

with $k_i = \lfloor \frac{i}{N} \rfloor$ and $l_i = i \mod N$ (also for the index $j$). Note that the value of $k_i$ changes only between each $N \times N$ block, while the value of $l_i$ changes between the entries of each block. This construction directly implies that $i = k_i N + l_i$ (also for $j$), as indicated in (29).

It can now be observed that $M_{ij}$ is composed of two independent sets of indices. Since $M$ is of size $N^2 \times N^2$, we can divide it to $N \times N$ non-overlapping blocks of the same size (similar to Fig. 1). The first exponential term $e^{i \frac{2\pi}{M} m_1 (k_j - k_i)}$ corresponds to $M$ being a block circulant matrix with $N \times N$ blocks. This can be seen by the construction of $k_i$ and $k_j$, since $k_j - k_i \in \{-(N-1), \ldots, N-1\}$ and by the periodicity by $M$ of the exponential term.

The second set of indices, $l_j - l_i$ corresponds to each $N \times N$ block being circulant. This can be seen by the term $e^{i \frac{2\pi}{M} m_2 (l_j - l_i)}$, since $l_j - l_i \in \{-(N-1), \ldots, N-1\}$ and due to the periodicity by $N$ of the exponential. Thus, $M_{ij}$ has a structure similar to (29), with two independent sets of indices, the first corresponds to block circularity and the second to circularity within each block. Consequently, $M$ is a BCCB matrix.

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