AN APPROXIMATE EXPECTATION-MAXIMIZATION FOR TWO-DIMENSIONAL MULTI-TARGET DETECTION

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ABSTRACT

We consider the two-dimensional multi-target detection (MTD) problem of estimating a target image from a noisy measurement that contains multiple copies of the image, each randomly rotated and translated. The MTD model serves as a mathematical abstraction of the structure reconstruction problem in single-particle cryo-electron microscopy, the chief motivation of this study. We focus on high noise regimes, where accurate detection of image occurrences within a measurement is impossible. To estimate the image, we develop an expectation-maximization framework that aims to maximize an approximation of the likelihood function. We demonstrate image recovery in highly noisy environments, and show that our framework outperforms the previously studied autocorrelation analysis in a wide range of parameters. The code to reproduce all numerical experiments is publicly available at https://github.com/krshay/MTD-2D-EM.

Index Terms— Expectation-maximization, multi-target detection, cryo-electron microscopy.

1. INTRODUCTION

We study the multi-target detection (MTD) problem of estimating a target image $f : \mathbb{R}^2 \to \mathbb{R}$ from a noisy measurement that contains multiple copies of the image, each randomly rotated and translated [1, 2, 3, 4, 5, 6, 7]. We consider a measurement $M \in \mathbb{R}^{N \times N}$ of the form

$$M[\vec{\ell}] = \sum_{i=1}^{p} F_{\phi_i}[\vec{\ell} - \vec{\ell}_i] + \varepsilon[\vec{\ell}], \tag{1}$$

where $F_{\phi_i}[\vec{\ell}] := f_{\phi_i}(\vec{\ell}/n)$ is a discrete copy of f, rotated by angle ϕ_i about the origin; n is the radius of the image in pixels; $\{\phi_i\}_{i=1}^{p} \sim \text{Unif}[0, 2\pi)$ are uniformly distributed rotations; $\{\vec{\ell}_i\}_{i=1}^{p} \in \{n+1, \ldots, N-n\}^2$ are arbitrary translations; and $\varepsilon[\vec{\ell}]$ is i.i.d. Gaussian noise with zero mean and variance σ^2. The rotations, translations, and the number of occurrences of f in M, denoted by p, are unknown. Importantly, since the rotations are unknown, it is possible to reconstruct the target image only up to a rotation.

Following [3, 4, 5], we assume that the image f is supported on the unit disk $\{\vec{x} \in \mathbb{R}^2 : |\vec{x}| \leq 1\}$ and has a finite expansion in the basis of Dirichlet Laplacian eigenfunctions. In particular, the
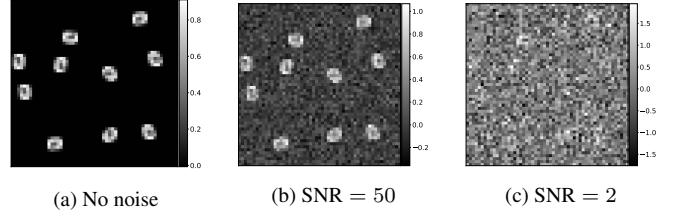
Fig. 1: Three measurements at different SNRs: (a) no noise; (b) SNR = 50; (c) SNR = 2. Each measurement contains multiple rotated versions of the target image. We focus on the low SNR regime (e.g., panel (c)) in which the locations and rotations of the image occurrences cannot be detected reliably.

image f can be expanded as

$$f(r, \theta) = \sum_{(\nu,q):\lambda_{\nu,q} \leq \lambda} \alpha_{\nu,q} \psi_{\nu,q}(r, \theta), \tag{2}$$

where $\psi_{\nu,q}(r, \theta) = J_\nu(\lambda_{\nu,q} r) e^{i\nu\theta}$, for $r \leq 1$, $\nu \in \mathbb{Z}_{\geq 0}$, J_ν is the ν-th order Bessel function of the first kind, $\lambda_{\nu,q} > 0$ is the q-th positive root of J_ν, λ is called the bandlimit frequency, and α is the vector of expansion coefficients. Hereafter, by estimating the image we mean estimating the vector of coefficients α. Notably, the basis of Dirichlet Laplacian eigenfunctions is steerable: rotating f is equivalent to modulating the expansion coefficients $\alpha_{\nu,q}$. Specifically, the expansion of the rotated image $f_\phi(r, \theta) := f(r, \theta + \phi)$ is given by

$$f_\phi(r, \theta) = \sum_{(\nu,q):\lambda_{\nu,q} \leq \lambda} \alpha_{\nu,q} \psi_{\nu,q}(r, \theta) e^{i\nu\phi}. \tag{3}$$

We focus on the well-separated case of the 2-D MTD problem, which was introduced in [3, 4]. In this case, each transaltion in the measurement M is separated by at least a full image diameter from its neighbors. Specifically, we assume

$$|\vec{\ell}_{i_1} - \vec{\ell}_{i_2}| > 4n, \quad \text{for all } i_1 \neq i_2. \tag{4}$$

Figure 1 presents an example of a measurement M at different signal-to-noise ratios (SNRs). We define $\text{SNR} := \frac{\|F\|_F^2}{A\sigma^2}$, where A is the area in pixels of F.

The MTD model serves as a mathematical abstraction of the cryo-electron microscopy (cryo-EM) technology for macromolecular structure determination [8, 9, 10]. In a cryo-EM experiment [11], individual copies of the target biomolecule are dispersed at unknown 2-D locations and 3-D orientations in a thin layer of vitreous ice,

from which 2-D tomographic projection images are produced by an electron microscope. It is necessary to keep the electron dose low in order to minimize irreversible structural damage. Consequently, the projection images are considerably noisy. In the current data processing pipeline of cryo-EM [12, 13, 14, 15], the 2-D projections are first detected and extracted from the micrograph, and later rotationally and translationally aligned to reconstruct the 3-D molecular structure. This approach fails for small molecules, which are difficult to detect and align [7, 8, 12, 16].

The MTD model was devised in [7] in order to study the recovery of small molecular structures using cryo-EM, below the current detection limit [17]. In [3, 4, 5], an autocorrelation analysis technique was devised for the 2-D MTD problem (1). Autocorrelation analysis is a special case of the method of moments, and it consists of finding an image that best matches the empirical autocorrelations of the measurement, thus bypassing detecting the locations and rotations of individual image occurrences. In this work, we propose to replace autocorrelation analysis by expectation-maximization (EM): a classical algorithm to compute the maximum likelihood estimator [18]. Similarly to autocorrelation analysis, the EM algorithm estimates the target image F directly by marginalizing over the translations and rotations.

Previous works demonstrated that EM outperforms autocorrelation analysis in terms of estimation accuracy for the 1-D MTD problem [2] as well as for the closely related multireference alignment model [19, 20]. EM is also the most popular computational framework for reconstructing molecular structures using cryo-EM, e.g., [14, 15]. Moreover, a recent paper [21] shows that likelihood optimization in the low SNR regime reduces to a sequence of least squares optimization problems that match the moments of the estimate to the ground truth moments one by one, and by that suggests that EM has the potential to surpass the estimation accuracy achieved by autocorrelation analysis.

At each iteration, EM assigns probabilities to all possible rotations and translations (see Section 2). Unfortunately, for the MTD model, the number of possible translations grows quickly with the measurement size, and therefore direct application of the EM algorithm to the MTD problem is computationally intractable, even for very small measurements. Thus, following [2], we suggest mitigating the computational burden by developing an EM algorithm that maximizes an approximation of the likelihood function. In the approximate EM scheme, the number of possible translations is linear in N^2, making the algorithm tractable.

The main contribution of this paper is in developing an approximate EM framework for the two-dimensional MTD problem; see Section 2. In Section 3, we demonstrate a successful reconstruction in noisy regimes. We also conduct extensive numerical experiments that demonstrate significant improvement in estimation accuracy compared to autocorrelation analysis. Section 4 concludes the paper and introduces future work. In particular, we discuss potential implications for the ongoing effort to estimate small molecular structures using cryo-EM [7].

2. APPROXIMATE EXPECTATION-MAXIMIZATION

Given a measurement M that follows the MTD model (1), the maximum marginal likelihood estimator (MMLE) for the vector of coefficients α, that represents the target image F (2), is the maximizer of the likelihood function $p(M|\alpha)$. The translations and rotations of the target images within the measurement are treated as nuisance variables. The EM algorithm estimates the MMLE by iteratively applying the expectation (E) and maximization (M) steps [18]. Specif-

ically, given the current estimate α_k, the E-step computes the expected log-likelihood function, where the expectation is taken over all admissible configurations of translations and rotations. The estimate is then updated in the M-step by maximizing the function with respect to α. Unfortunately, for the MTD model, the number of possible translations grows quickly with the problem size, rendering direct application of EM computationally intractable. Hence, based on [2], we suggest to apply EM to an approximation of the likelihood function, in which the number of possible translations is linear in N^2.

The approximate EM begins by partitioning the measurement M into $N_d = (N/L)^2$ non-overlapping patches; each patch is of size $L \times L$, where $L = 2n + 1$ is the diameter of the target image F. Then, we aim to estimate the image by maximizing the approximate likelihood function

$$p(M_0, M_1, \ldots, M_{N_d-1}|\alpha) \approx \prod_{m=0}^{N_d-1} p(M_m|\alpha), \qquad (5)$$

where M_m is the mth patch, and we neglect statistical dependencies between patches. Our approximate EM algorithm works by applying the EM algorithm to estimate the approximate MMLE of (5).

The separation condition (4) implies that each patch M_m can contain either no target image, a full rotated target image, or part of a rotated image; overall there are $(2L - 1)^2$ possible configurations. In particular, each patch can be modeled by

$$M_m = CT_{\vec{\ell}_m}ZF_{\phi_m} + \varepsilon_m, \quad \varepsilon_m \sim \mathcal{N}(0, \sigma^2 I_{L \times L}), \qquad (6)$$

where the operator Z zero-pads L entries to the right and to the bottom of the rotated copy of F, and $T_{\vec{\ell}_m}$ circularly shifts the zero-padded image by $\vec{\ell}_m = (\ell_{mx}, \ell_{my}) \in \mathbb{L} := \{0, 1, \ldots, 2L - 1\}^2$ positions, that is,

$$T_{\vec{\ell}_m}ZF_{\phi_m}[i, j] =$$
$$ZF_{\phi_m}[(i + \ell_{mx}) \bmod 2L, (j + \ell_{my}) \bmod 2L]. \quad (7)$$

The operator C then crops the first L entries in the vertical and horizontal axes, and the result is further corrupted by additive white Gaussian noise. In addition, since the EM algorithm assigns probabilities to different rotations (in the expectation step), we need to discretize the search space of rotations:

$$\phi_m \in \Phi := \left\{ k\frac{2\pi}{K} \right\}_{k=0}^{K-1}, \qquad (8)$$

where K is a parameter chosen by the user. Higher K means higher accuracy at the cost of running time (see Figure 4).

In the E-step, our algorithm calculates the expected log-likelihood function of the model (6)

$$Q(\alpha|\alpha_k) = \sum_{m=0}^{N_d-1} \sum_{\vec{\ell} \in \mathbb{L}} \sum_{\phi \in \Phi} p(\vec{\ell}, \phi|M_m, \alpha_k) \log p(M_m, \vec{\ell}, \phi|\alpha),$$
$$(9)$$

given the current estimate α_k, where

$$p(M_m|\vec{\ell}, \phi, \alpha) \propto \exp\left(-\frac{\|M_m - CT_{\vec{\ell}}ZF_\phi\|_{\text{F}}^2}{2\sigma^2}\right), \qquad (10)$$

with the normalization $\sum_{\vec{\ell} \in \mathbb{L}} \sum_{\phi \in \Phi} p(M_m|\vec{\ell}, \phi, \alpha) = 1$. Bayes'

rule dictates

$$p(\vec{\ell},\phi|M_m,\alpha_k) = \frac{p(M_m|\vec{\ell},\phi,\alpha_k)p(\vec{\ell},\phi|\alpha_k)}{\sum_{\vec{\ell}'\in\mathbb{L}}\sum_{\phi'\in\Phi}p(M_m|\vec{\ell}',\phi',\alpha_k)p(\vec{\ell}',\phi'|\alpha_k)},$$ (11)

which is the normalized likelihood function $p(M_m|\vec{\ell},\phi,\alpha_k)$, weighted by the prior distribution $p(\vec{\ell},\phi|\alpha_k)$. We assume that $p(\vec{\ell},\phi|\alpha_k) = p(\vec{\ell})p(\phi)$, namely, $\vec{\ell}$ and ϕ are independent of α_k and of each other. We also assume that the rotations are drawn from a uniform distribution in the set Φ from (8), and therefore

$$p(\vec{\ell},\phi|\alpha_k) = \rho[\vec{\ell}]\frac{1}{K},$$ (12)

where $\rho[\vec{\ell}]$ is the distribution of 2-D translations in (6) (which should be estimated simultaneously with α). We can rewrite (9) as (up to a constant):

$$Q(\alpha,\rho|\alpha_k,\rho_k) = \sum_{m=0}^{N_d-1}\sum_{\vec{\ell}\in\mathbb{L}}\sum_{\phi\in\Phi}p(M_m|\vec{\ell},\phi,\alpha_k)\rho_k[\vec{\ell}]$$
$$\times\left(\log p(M_m|\vec{\ell},\phi,\alpha) + \log\rho[\vec{\ell}]\right),$$ (13)

where $p(M_m|\vec{\ell},\phi,\alpha)$ is given by (10).

The M-step updates the image estimate and ρ by maximizing $Q(\alpha,\rho|\alpha_k,\rho_k)$ under the constraint that ρ lies on the simplex $\Delta_{2L\times 2L}$:

$$\alpha_{k+1},\rho_{k+1} = \arg\max_{\alpha,\rho} Q(\alpha,\rho|\alpha_k,\rho_k) \text{ s.t. } \rho\in\Delta_{2L\times 2L}.$$ (14)

The constrained maximization of (14) can be achieved with the unconstrained maximization of the Lagrangian

$$\mathcal{L}(\alpha,\rho,\eta) = Q(\alpha,\rho|\alpha_k,\rho_k) + \eta\left(1 - \sum_{\vec{\ell}\in\mathbb{L}}\rho[\vec{\ell}]\right),$$ (15)

where η is the Lagrange multiplier. As we will see next, the constraint is automatically satisfied at the maximum of the Lagrangian.

Since $Q(\alpha,\rho|\alpha_k,\rho_k)$ is additively separable for α and ρ, we maximize $\mathcal{L}(\alpha,\rho,\eta)$ with respect to α and ρ separately. At the maximum of $\mathcal{L}(\alpha,\rho,\eta)$, we have

$$0 = \frac{\partial\mathcal{L}}{\partial(\alpha)_{\nu,q}} = \sum_{m=0}^{N_d-1}\sum_{\vec{\ell}\in\mathbb{L}}\sum_{\phi\in\Phi}p(M_m|\vec{\ell},\phi,\alpha_k)\rho_k[\vec{\ell}]$$
$$\times\frac{\partial\log p(M_m|\vec{\ell},\phi,\alpha)}{\partial(\alpha)_{\nu,q}},$$ (16)

resulting in a set of linear equations which is solved to update α. In order to update ρ, we maximize $\mathcal{L}(\alpha,\rho,\eta)$ with respect to ρ:

$$0 = \frac{\partial\mathcal{L}}{\rho[\vec{\ell}]} = \sum_{m=0}^{N_d-1}\sum_{\phi\in\Phi}p(M_m|\vec{\ell},\phi,\alpha_k)\rho_k[\vec{\ell}]\frac{1}{\rho[\vec{\ell}]} - \eta,$$ (17)

for $\vec{\ell}\in\mathbb{L}$. We thus obtain the update rule for ρ as

$$\rho[\vec{\ell}] = \frac{1}{\eta}\sum_{m=0}^{N_d-1}\sum_{\phi\in\Phi}p(M_m|\vec{\ell},\phi,\alpha_k)\rho_k[\vec{\ell}],$$ (18)

Algorithm 1: Approximate EM for 2-D MTD

Input: measurement M; noise variance σ^2; initial guesses α_0 and ρ_0; parameter K (8); stopping parameter ϵ

Output: an estimate for α and ρ

1   set $k\to 0$;
2   calculate Q_0 according to (9) and set $Q_{-1}\to-\infty$;
3   **while** $Q_k - Q_{k-1} > \epsilon$ **do**
4   calculate $p(M_m|\vec{\ell},\phi,\alpha_k)$ according to (10) and ;
5   update α_{k+1} by solving (16);
6   update ρ_{k+1} according to (18);
7   calculate Q_{k+1} according to (9);
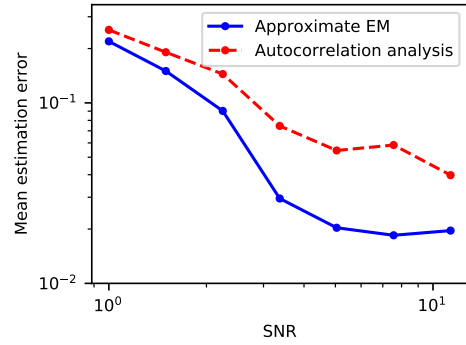8   set $k\to k+1$;

Fig. 2: The mean estimation error of recovering the target image F, as a function of the SNR, by approximate EM (Algorithm 1) and autocorrelation analysis.
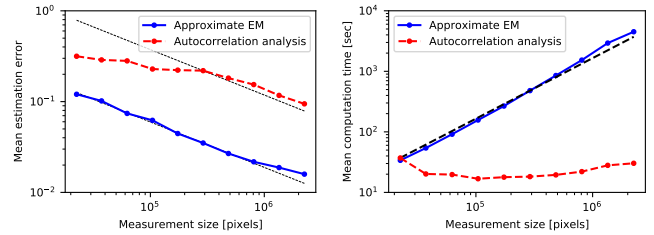

Fig. 3: The mean estimation error of recovering the target image F (left) and running time (right), as a function of measurement size N^2 by approximate EM and autocorrelation analysis. For the estimation error, the black dashed lines illustrate a slope of $-1/2$, as predicted by the law of large numbers. For the computation time, the black dashed line illustrates a slope of 1, implying a linear increase in computation time, as the number of patches $N_d = N^2/L^2$ grows linearly in N^2.

and $\eta = N_d$ from the normalization $\sum_{\vec{\ell}\in\mathbb{L}}\rho[\vec{\ell}] = 1$. The approximate EM algorithm is summarized in Algorithm 1.
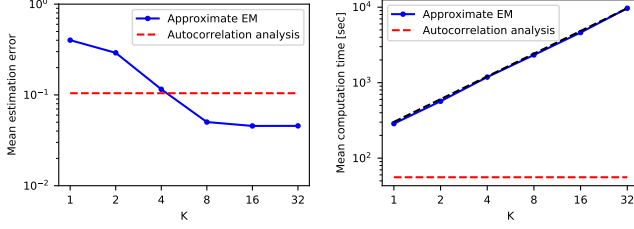
Fig. 4: The mean estimation error of recovering the target image F (left) and running time (right), as a function of K—the size of the search space of rotations (8)—by approximate EM. The recovery error and running time using autocorrelation analysis are marked by the dashed horizontal red lines. For the running time, the black dashed line illustrates a slope of 1, which implies a linear increase in computation time, as the number of computations per patch depends linearly on K. The results suggest that one can save running time by coarsely sampling the rotations without severely degrading the estimation quality.

3. NUMERICAL EXPERIMENTS

In this section, we present numerical results for the approximate EM described in Section 2. As a baseline, we compare the results against autocorrelation analysis with the first three autocorrelations based on the framework (and code) of [3, 4, 5]. To take the in-plane rotation symmetry into account, we measure the estimation error by

$$\text{relative error}_\alpha := \min_{\phi \in [0, 2\pi)} \frac{\|\alpha^* - \alpha_\phi\|_2}{\|\alpha^*\|_2}, \tag{19}$$

where α^* is the true vector of expansion coefficients, and α_ϕ is the vector of coefficients of the estimated image, rotated by angle ϕ. In all experiments, the measurements were generated according to (1) with density $\gamma = 0.04$, where $p = \gamma \frac{N^2}{L^2}$. The rotations were drawn from a uniform distribution on $[0, 2\pi)$, while the search space of the EM was discretized with a parameter K according to (8). The target images are of diameter $L = 5$ pixels. Each entry of the target images was drawn i.i.d. from a uniform distribution on $[0, 1]$. Then, each image was normalized such that $\|F\|_F = 10$, and expanded using its first 10 coefficients. The initializations of the EM and autocorrelation analysis iterations were drawn from the same distribution as the ground truth images, and $\gamma_{\text{init}} = 0.03$. If the algorithms were initialized from several random points, we calculated the estimation error of the image estimate whose final likelihood function is maximal (for approximate EM), or final objective function is minimal (for autocorrelation analysis). Figures 2, 3 and 4 present the mean error over 40 trials. The code to reproduce all experiments is publicly available at `https://github.com/krshay/MTD-2D-EM`.

3.1. Recovery error as a function of the SNR

Figure 2 presents recovery error as a function of the SNR. The measurements are of size $N = 2500$ pixels, and we use $K = 8$ possible rotations (8), and 5 random initial guesses for α. To save computation time (see Section 4), we initialize the approximate EM algorithm using the estimate achieved by autocorrelation analysis. We achieve a significant improvement in recovery accuracy using approximate EM, even though the search space of rotations is coarsely sampled, for all SNR regimes.

In an additional numerical experiment with SNR $= 2$ (low SNR, see Figure 1), $N = 10000$ pixels, and $K = 16$, the relative error of approximate EM was 0.017, whereas the error of autocorrelation analysis was 0.073, more than four times larger.

3.2. Recovery error as a function of the measurement size

Figure 3 presents recovery error and running time as a function of the measurement size N^2, with SNR $= 5$, $K = 16$ possible rotations, and 5 random initial guesses for α. Using approximate EM, the error decays as $1/\sqrt{N^2}$. The same trend is visible also for autocorrelation analysis for sufficiently large measurements. We achieve a significant improvement in recovery accuracy using approximate EM, although the search space of rotations is coarsely sampled. However, the computation time using our method is greater, and grows linearly with the measurement size. In particular, autocorrelation analysis is faster since it requires a single pass over the measurement, while the computational complexity of matching an image to the observed autocorrelations scale with L^2 (which is much smaller than N^2).

3.3. Recovery error as a function of discretization of rotations

Figure 4 presents recovery error and running time as a function of K, the size of the search space of rotations, for measurements with SNR $= 5$, $N = 1500$, and one random initial guess for α. Remarkably, even when the EM searches over only 4 rotations (recall that the rotations are drawn from a continuous distribution), the obtained estimation errors are similar to the estimation errors of autocorrelation analysis, which takes all possible rotations into account. As expected, the computation time grows linearly with the parameter K. This implies that one can save running time by coarsely sampling the rotations without severely degrading the estimation quality.

4. CONCLUSION

This paper is motivated by the effort of reconstructing small 3-D molecular structures using cryo-EM, below the current detection limit [7]. The main contribution of this paper is in introducing an approximate EM scheme for the 2-D MTD problem, and comparing it numerically to autocorrelation analysis. The numerical experiments show an improvement in estimation accuracy, but at the cost of computational time. As Figure 4 shows, the parameter K provides an accuracy-running time trade-off. A possible improvement is increasing the resolution of the search space as the iterations progress [2]; this is a standard procedure in current cryo-EM software packages [14, 15].

Our ultimate goal is developing an approximate EM scheme for recovering small molecular structures using cryo-EM [7]. In order to achieve a computationally efficient algorithm for the 3-D case of cryo-EM, parallel processing and randomized algorithms, such as stochastic or online EM [22, 23, 24, 25, 26], must be utilized. A further acceleration can be achieved by applying the EM algorithm on a lower dimensional representation of the data [27]. Moreover, adding a prior on the target image is expected to improve the robustness and accuracy of the scheme, at the cost of a possible model bias. Another research direction is replacing EM by more intricate techniques that aim to approximate the posterior distribution, such as variational inference [28] or variational auto-encoders [29].

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