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Convex Accelerated Maximum Entropy Reconstruction

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Abstract

Maximum entropy (MaxEnt) spectral reconstruction methods provide a powerful framework for spectral estimation of nonuniformly sampled datasets. Many methods exist within this framework, usually defined based on the magnitude of a Lagrange multiplier in the MaxEnt objective function. An algorithm is presented here that utilizes accelerated first-order convex optimization techniques to rapidly and reliably reconstruct nonuniformly sampled NMR datasets using the principle of maximum entropy. This algorithm – called CAMERA for Convex Accelerated Maximum Entropy Reconstruction Algorithm – is a new approach to spectral reconstruction that exhibits fast, tunable convergence in both constant-aim and constant-lambda modes. A high-performance, open source NMR data processing tool is described that implements CAMERA, and brief comparisons to existing reconstruction methods are made on several example spectra.

Keywords

Multidimensional NMR; Nonuniform sampling; MaxEnt; NESTA; CAMERA

1. Introduction

Multidimensional (nD) NMR experiments play an essential role in studies of biomolecular structure, function and dynamics, as they report many useful time-averaged properties of nuclear spin systems. By utilizing atomic connectivities to spread this molecular information into multiple dimensions, nD NMR methods have the potential to resolve many more unique signals than simpler one- or two-dimensional methods. In practice, the potential resolution enhancements of conventional (*i.e.* uniformly sampled) nD NMR are squelched by the amount of time required to collect high-resolution multidimensional data [1]. For experiments having three or more dimensions, spectroscopists are often forced to uniformly sample at a digital resolution far less than the natural line width of the sample, resulting in suboptimal data. Nonuniform sampling (NUS) of a small subset of the original uniform data is one means of overcoming this “sampling-limited” regime, and provides several

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opportunities for improving spectral resolution [2, 3] and sensitivity [3-6], while reducing total acquisition time [1, 7, 8].

While NUS is a powerful framework for accelerated or enhanced data collection in nD NMR, it requires additional data processing steps in order to yield a final spectrum [7, 9]. Direct application of the discrete Fourier transform (DFT) to zero-augmented NUS data will produce strong aliasing artifacts. These artifacts, or intra-band aliases [10], are a result of multiplying the complete uniform data by the nonuniform sampling function in the time domain. This multiplication is equivalent to a convolution of the true spectrum with the point-spread function (PSF) of the sampling schedule in the frequency domain. In order to deconvolve the PSF from the true spectrum, non-Fourier reconstruction methods must be employed. *Footnote 1: It is worthy of mention that other reconstruction methods, such as CLEAN and SCRUB [11], attempt to directly deconvolve the PSF from the true spectrum without the use of an explicitly defined regularization functional.* Contemporary reconstruction methods include multidimensional decomposition (MDD; [12, 13]), iterative soft thresholding (IST; [14-16]), iteratively reweighted least-squares (IRLS; [17]), and maximum entropy (MaxEnt; [18]). In fact, *all* these methods may be interpreted as involving the optimization (*i.e.* minimization or maximization) of a regularization functional, subject to a data consistency constraint. *Footnote 2: The (S)MFT method [19] is not technically a reconstruction method, as it effectively involves the direct application of the DFT to the data.* The employed regularization functional typically takes the form of an ℓ_p norm (IST/IRLS), an entropy measure (MaxEnt), or a sum of component amplitudes (MDD), and is used to penalize non-baseline spectral features. Thus, spectral reconstruction methods generally attempt to identify a maximally sparse model spectrum that is consistent with the measured NUS data. In IST, IRLS and MDD, the data consistency constraint is expressed as an equality to zero, resulting in a complete preservation of the measured data. In contrast, traditional MaxEnt expresses its data consistency constraint as an inequality, allowing its reconstructed data points to vary from the measurement within a specified tolerance. A more comprehensive enumeration of existing NUS reconstruction methods may be found in Hyberts *et al.* [7].

Of the aforementioned reconstruction methods, MaxEnt holds the longest and richest history within the NMR field [20, 21]. In truth, MaxEnt embodies an entire class of reconstruction methods that are based on the statistical principle of maximum entropy [22]. MaxEnt yields the spectrum that has minimal statistical information content, while still maintaining agreement with the measured time-domain data. As a further testament to the statistical roots of MaxEnt, data consistency is typically quantified by a χ^2 statistic. Original applications of MaxEnt to radio astronomy and NMR maximized the Shannon entropy of a real spectral image, subject to the constraint that the inverse (Fourier) transform of the image agreed with the measurement [22, 23]. Eventually, hypercomplex entropy functionals were derived specifically for use in NMR spectral reconstruction [20, 23]. As MaxEnt matured in the NMR field, it was modified to support the deconvolution of exponential decays and J -coupling multiplets [21, 24]. Most recently, special cases of MaxEnt that enforce absolute consistency with the measured time-domain data (*e.g.*, MINT, FM and FFM) have been described [25-27]. These “linearized” MaxEnt implementations highlight the inherent nonlinearity of MaxEnt, a feature not observed in other reconstruction algorithms. This

capacity for nonlinearity is not unique to MaxEnt, *per se*. Indeed, any regularization functional that penalizes nonzero-intensity spectral features will exhibit nonlinearity under inequality constraints. Therefore, the linearity of ℓ_1 -norm minimization algorithms like IST and IRLS is a direct consequence of their strict preservation of the measured data. This linearity comes at a cost, however, as it increases the likelihood of producing artefactual, statistically insignificant spectral features [28]. Thus, even though the nonlinearity of MaxEnt can complicate the task of reconstruction, it remains a powerful and useful feature of the method. Excepting the very recently described *mllr* algorithm [28], MaxEnt remains the only method capable of tolerating a discrepancy between the measured data and their reconstruction.

Recently, accelerated first-order optimization techniques [29-31] were applied to the ℓ_1 -norm minimization problem of compressed sensing (CS) recovery [32]. The resulting method, called NESTA as a shortening of “Nesterov’s algorithm,” exhibited rapid convergence properties far beyond the capabilities of standard gradient or conjugate gradient methods. The NESTA-NMR software tool, which implements NESTA specifically for NUS reconstruction, was subsequently described. By employing Nesterov’s method to minimize a smoothed ℓ_1 -norm regularization functional subject to exact data constraints, NESTA-NMR achieves IST-S spectral reconstructions in nearly an order of magnitude fewer iterations than IST-S [33]. Briefly stated, Nesterov’s method is a strategy for rapidly minimizing smooth convex functions under convex constraints using only local gradient information. The Hoch-Hore entropy functional [20, 23], which is smooth and convex, is therefore an ideal candidate for NESTA-like implementation. This work describes the Convex Accelerated Maximum Entropy Reconstruction Algorithm (CAMERA), which uses Nesterov’s accelerated first-order method to rapidly compute MaxEnt reconstructions. The performance and convergence properties of CAMERA are investigated in-depth, and several use cases are described to highlight its flexibility. It is shown that CAMERA achieves dramatic speed improvements over FFM, in analogy to NESTA’s improvements relative to IST-S. The differences in convergence between CAMERA and “Cambridge” MaxEnt are also examined.

2. Theory

2.1. Canonical MaxEnt

Given a nonuniformly subsampled time domain dataset, maximum entropy (MaxEnt) reconstruction aims to identify the spectrum having maximum entropy (*i.e.* minimal information content) whose inverse discrete Fourier transform is statistically consistent with the original measured data [34]. The MaxEnt reconstruction problem may be formally expressed as the following constrained optimization:

$$\begin{aligned} & \text{maximize} && f(\mathbf{X}) \\ & \text{subject to} && \|\mathbf{b} - \mathbf{K}\mathbf{W}\mathbf{F}\mathbf{X}\|_2 \leq \varepsilon \end{aligned} \quad (1)$$

where $f(\mathbf{X})$ is the entropy regularization functional computed over all data points in the reconstructed spectrum $\mathbf{X} \in \mathbb{H}^N$. The inverse discrete Fourier transform $\mathbf{F} \in \mathbb{H}^{N \times N}$ and

subsampling matrix $\mathbf{K} \in \{0,1\}^{n \times N}$ relate the spectral estimate to the measured data $\mathbf{b} \in \mathbb{H}^n$, where $n \leq N$. The optional diagonal matrix $\mathbf{W} \in \mathbb{R}^{N \times N}$ of convolution coefficients may be introduced to deconvolve a known line shape from the spectral reconstruction [24, 34, 35]. The parameter ε reflects the estimated uncertainty, and is related to the measurement noise standard deviation σ through the following equation:

$$\varepsilon = \sigma \cdot \sqrt{2Dn} \quad (2)$$

where D is the number of hypercomplex bases in $\mathbb{H}$. In practice, this inequality-constrained maximization problem is solved by converting it into an unconstrained maximization of the Lagrangian,

$$\mathcal{L}(\mathbf{X}, \lambda) = f(\mathbf{X}) - \lambda \|\mathbf{b} - \mathbf{K}\mathbf{W}\mathbf{F}\mathbf{X}\|_2 \quad (3)$$

where λ is a Lagrange multiplier, which is either dynamically adjusted to achieve $\|\mathbf{b} - \mathbf{K}\mathbf{W}\mathbf{F}\mathbf{X}\|_2 = \varepsilon$ or held fixed during iterative optimization. The terms “constant-aim” and “constant- λ ” are used for optimizations in which λ is allowed to float or is fixed, respectively [36]. Constant-aim optimization adjusts λ to maintain the feasibility of its solution, resulting in a nonlinear scaling based on signal intensity. However, constant-aim optimization across multiple sub-spectra is known to complicate the use of MaxEnt reconstructions in applications requiring quantitation of relative signal intensities. The use of constant- λ optimization is one strategy to overcome differential nonlinearities between reconstructed sub-spectra. A second strategy, embodied by the MaxEnt interpolation (MINT) and forward MaxEnt (FM) methods, is to optimize equation (3) in the large- λ (*i.e.* small ε) limit [2, 25-27]. While MINT and FM yield highly linear reconstructions, they increase the likelihood of obtaining artefactual signals and do not produce statistically significant results [28].

Several algorithms have been proposed for locating the global maximum of equation (3). The most efficient methods are the “Cambridge” algorithm of Skilling and Bryan [22] and the “Rowland” algorithm of Stern and Hoch [37]. The Cambridge algorithm, which uses a modified nonlinear conjugate gradient algorithm, requires six fast Fourier transforms (FFTs) per iteration. The Rowland algorithm requires slightly less memory than the Cambridge algorithm, and only computes four FFTs per iteration. However, because of additional computations performed per iteration, the Rowland algorithm converges to a solution in a time comparable to that of the Cambridge algorithm.

2.2. The Entropy Functional

The algorithm presented here uses the Hoch-Hore entropy functional, as it exhibits several ideal mathematical properties [20, 23]. Most importantly, the Hoch-Hore entropy is concave, smooth, and monotonically decreasing, and was intentionally developed to handle hypercomplex vector spaces. The functional takes the following form:

$$f(\mathbf{X}) = - \sum_{i=1}^N S(\mathbf{X}[i]) \quad (4)$$

where $S: \mathbb{H} \rightarrow \mathbb{R}$ is a nonlinear map from the hypercomplex scalars into the real scalars:

$$S(z) = |z| \log \left(\frac{|z|}{2\delta} + \sqrt{1 + \left(\frac{|z|}{2\delta} \right)^2} \right) - \sqrt{|z|^2 + 4\delta^2} \quad (5)$$

where δ is a default background parameter, also referred to as *def*, and the hypercomplex modulus $|z|$ has been defined as follows:

$$|z| \equiv \sqrt{\sum_{\phi \in \mathcal{P}_D} z\{\phi\}^2} \quad (6)$$

The recently published formalism for hypercomplex algebra has been adopted to simplify notation [38]. The first derivative of S , used to compute the gradient of f , is therefore:

$$\frac{\partial S}{\partial z} = \frac{z}{|z|} \log \left(\frac{|z|}{2\delta} + \sqrt{1 + \left(\frac{|z|}{2\delta} \right)^2} \right) \quad (7)$$

and the second derivative is,

$$\frac{\partial^2 S}{\partial^2 z} = (|z|^2 + 4\delta^2)^{-1/2} \quad (8)$$

It follows from equations (7) and (8) that f is a smooth functional whose gradient ∇f is Lipschitz continuous with a Lipschitz constant L_f equal to,

$$L_f = (2\delta)^{-1} \quad (9)$$

which implies that the background parameter δ may be used to tune the degree of curvature that the regularization functional exhibits. It is important to note that this Lipschitz constant is a global bound on the curvature of f . The local curvature may be substantially lower at larger spectral intensities $|z|$.

2.3. CAMERA

The presented algorithm is an application of Nesterov's accelerated first-order convex optimization method [29, 30] to the maximum entropy problem in equation (1). Because the negative of the Hoch-Hore entropy regularization functional is a smooth, Lipschitz-continuous convex function, it is particularly well suited for Nesterov's method without any need for smoothing techniques that are required by NESTA [32]. As in NESTA, a change of

variables is made in CAMERA that allows for efficient computation of each iteration by only two fast Fourier transforms, resulting in the following optimization:

$$\begin{aligned} & \text{minimize} && -f(\mathbf{F} * \mathbf{x}) \\ & \text{subject to} && \|\mathbf{b} - \mathbf{K}\mathbf{W}\mathbf{x}\|_2 \leq \varepsilon \end{aligned} \quad (10)$$

where the asterisk denotes complex transposition. Simply put, CAMERA computes the time-domain model signal $\mathbf{x} \in \mathbb{H}^N$ whose discrete Fourier transform $\mathbf{F}^*\mathbf{x}$ has maximum entropy, such that the nonuniformly subsampled weighted model signal $\mathbf{K}\mathbf{W}\mathbf{x}$ is consistent with the measured data in $\mathbf{b}$. Initially, a trial model signal $\mathbf{x}_0$ is constructed by zero-augmenting the measured data:

$$\mathbf{x}_0 = \mathbf{K}^T \mathbf{b} \quad (11)$$

An additional vector $\mathbf{y}_0$ is also initialized to the same value as $\mathbf{x}_0$. At iteration t , the time-domain gradient $\nabla \hat{f}$ of the model signal is computed,

$$\nabla \hat{f}(\mathbf{x}_{t-1}) = -\mathbf{F} \nabla f(\mathbf{F} * \mathbf{x}_{t-1}) \quad (12)$$

and is used to calculate a proximal gradient mapping step [31], $\mathbf{y}_t$. Each $\mathbf{y}$ iterate is computed as follows:

$$\mathbf{y}_t = (\mathbf{I} + \lambda L^{-1} \mathbf{W}^T \mathbf{K}^T \mathbf{K} \mathbf{W})^{-1} \left(\mathbf{x}_{t-1} + \lambda L^{-1} \mathbf{W}^T \mathbf{x}_0 - L^{-1} \nabla \hat{f}(\mathbf{x}_{t-1}) \right) \quad (13)$$

where the Lagrange multiplier λ equals,

$$\lambda = \max \left(0, L\varepsilon^{-1} \|\mathbf{b} - \mathbf{K}\mathbf{W}\mathbf{x}_{t-1} + L^{-1} \mathbf{K}\mathbf{W} \nabla \hat{f}(\mathbf{x}_{t-1})\|_2 - L \right) \quad (14)$$

The $\mathbf{y}$ -update is effectively an inequality-constrained (projected) proximal gradient step, with step size equal to $L^{-1} - L_f^{-1}$. From $\mathbf{y}_t$, a new $\mathbf{x}$ iterate is computed as follows:

$$\mathbf{x}_t = \mathbf{y}_t + \left(\frac{t-1}{t+2} \right) (\mathbf{y}_t - \mathbf{y}_{t-1}) \quad (15)$$

If $L = L_f$ or the resulting iterate $\mathbf{x}_t$ produces a decrease in the objective function, *i.e.* if,

$$f(\mathbf{F} * \mathbf{x}_t) > f(\mathbf{F} * \mathbf{x}_{t-1}) \quad (16)$$

then the iteration counter t is incremented and the algorithm proceeds. Otherwise, the local Lipschitz constant L is updated,

$$L \leftarrow \min\{2L, L_f\} \quad (17)$$

and the algorithm recalculates $\mathbf{y}_t$ using the updated step size. By introducing contributions from previous gradient steps into each $\mathbf{x}$ iterate in the form of a “momentum” term, Nesterov's method converges to the global (feasible) optimum of $\hat{f}$ in an order of magnitude fewer iterations than required by standard gradient descent [31, 32, 39]. In fact, the convergence rate enjoyed by CAMERA is theoretically optimal for algorithms using only gradient information [31]. The left-hand matrix in equation (13) is diagonal and thus trivially invertible, so equations (13-15) may be computed in linear time, making the effective computational cost of each iteration that of equation (12): two fast Fourier transforms. One additional fast Fourier transform is required every time equation (17) is evaluated, but this is an infrequent event. Because CAMERA is a first-order method, its storage requirements are also linear: six N -element hypercomplex arrays must be maintained for a single reconstruction. A more precise description of CAMERA is provided in Supplementary Code Listing S-1.

2.4. Constant- λ CAMERA

Under constant-aim control, CAMERA updates its Lagrange multiplier λ at each iteration, according to equation (14). At the constrained MaxEnt solution, this results in an optimal Lagrange multiplier, λ^* . In constant- λ CAMERA, the Lagrange multiplier is held fixed to a user-specified value, typically such that $\lambda = \lambda^*$. In such situations, CAMERA converges rapidly to the unconstrained solution of equation (3).

3. Materials and Methods

3.1. Software implementation

A reconstruction utility that implements CAMERA was written in ANSI C99-compliant C source code. To fully exploit the rapid convergence properties of the algorithm, several optimization strategies were employed, including multi-scope parallelism. At the level of individual hypercomplex scalars, single-instruction multiple-data (SIMD) programming constructs were used to accelerate functional, gradient and modulus computations. In addition, the OpenMP application programming interface was utilized to incorporate support for executing multiple reconstructions in parallel [40]. Using OpenMP, parallel reconstructions are supported at all dimensionalities, and require no external scripts to function. Fast approximate natural logarithms were implemented to further improve performance of functional and gradient computations [41]. Finally, a radix-2 multidimensional hypercomplex FFT algorithm was implemented by adapting the GNU Scientific Library (GSL) complex radix-2 FFT [42] to the hypercomplex algebra of NMR [38]. Instead of performing multiple complex FFTs per dimension of a multidimensional array, CAMERA performs a single hypercomplex FFT that minimizes the number of expensive memory transfer operations required during computation.

The CAMERA utility reads and writes NMRPipe-format data, and integrates seamlessly with NMRPipe processing scripts [43]. Minor script modifications are required to incorporate CAMERA into a standard processing workflow. Conversion into NMRPipe

format and direct-dimension processing are accomplished in a manner similar to that employed by hmsIST [14] and NESTA-NMR [33]. Then, the data are transposed and the indirect dimensions are reconstructed using CAMERA. Finally, all reconstructed indirect dimensions are processed as if they were collected using standard uniform sampling. Minimal example NMRPipe scripts are provided in the Supporting Information, and complete scripts for all datasets discussed in this work are available online in the CAMERA source code repository.

3.2. Software benchmarking

In order to compare the novel convergence of CAMERA to that of existing MaxEnt algorithms, a representative trace of a ^1H - ^{15}N HSQC dataset (*vide infra*) was reconstructed using RNMRTK [34], gradient descent (GD) FFM, and conjugate gradient (CG) FFM [25]. Parameters were set within the MSA routine of RNMRTK v3.2 to yield a similar result to CAMERA within 500 constant-aim iterations. Both FFM implementations were run for 10,000 iterations in order to reach convergence to a stationary point of the Hoch-Hore entropy functional. To ensure fair comparison to CAMERA, each FFM step was scaled by a step size of $L_f^{-1} = 2$. Figures 1 and 2 illustrate the convergence properties of CAMERA relative to FFM and RNMRTK v3.2, respectively.

3.3. Datasets

In order to fully evaluate the performance of CAMERA, datasets having dimensionalities ranging from 2D to 4D were reconstructed using a range of parameters. All datasets were collected on a Bruker Avance III HD 700.213 MHz spectrometer equipped with a 5.0 mm inverse quadruple-resonance (^1H , ^{13}C , ^{15}N , ^{31}P) probe with cryogenically cooled ^1H and ^{13}C channels and a z-axis gradient. All data were acquired at 298.0 K on a 7 mM sample of uniformly [^{15}N , ^{13}C]-labeled ubiquitin in aqueous phosphate buffer at pH 6.5.

A 2D gradient-enhanced ^1H - ^{15}N HSQC (*hsqcetf3gpsi*, [44]) was collected with 16 scans and 32 dummy scans over a grid of 2,048 and 1,024 hypercomplex points along ^1H and ^{15}N , respectively. Spectral widths were set to $3,293 \pm 4,209$ Hz along ^1H and $8,514 \pm 1,419$ along ^{15}N . Points were nonuniformly sampled along ^{15}N at 5% sparsity using a sine-gap sampling schedule [45]. Direct dimension traces were multiplied by a squared-cosine window, Fourier transformed and phase corrected prior to reconstruction of indirect traces. Data reconstruction was performed using 200 iterations of CAMERA in both constant-aim and constant- λ modes with $\sigma = 10^5$ and $\lambda = 0.02$, respectively. For constant- λ mode, the value of λ was chosen from an examination of the Lagrange multipliers that were produced in constant-aim mode. Results of CAMERA reconstruction of the ^1H - ^{15}N HSQC data are illustrated in Supplementary Figure S-1.

A 2D gradient-enhanced band-selective ^1H - $^{13}\text{C}\alpha$ HSQC (*shsqcetgpsisp2.2*, [46]) with additional ^{15}N decoupling was collected with 4 scans and 32 dummy scans over a grid of 2,048 and 2,048 hypercomplex points along ^1H and ^{13}C , respectively. Spectral widths were set to $3,287 \pm 4,209$ Hz along ^1H and $3,521 \pm 5,285$ Hz along ^{13}C . Points were nonuniformly sampled along the ^{13}C dimension at 5% sparsity using a sine-gap schedule. Direct dimension traces were multiplied by a squared-cosine window, Fourier transformed

and phase corrected using NMRPipe, and reconstruction was achieved using 800 iterations of CAMERA in constant-aim mode, with $\sigma = 7 \times 10^5$. Doublets arising from the $^{13}\text{C}\alpha$ - $^{13}\text{C}\beta$ J -coupling were deconvolved within CAMERA using a coupling constant equal to 36 Hz. Results of CAMERA reconstruction of the band-selective ^1H - $^{13}\text{C}\alpha$ HSQC with and without J -coupling deconvolution are shown in Supplementary Figure S-2.

A 3D gradient-enhanced HNCO (*hncogp3d*, [47]) was collected with 8 scans and 32 dummy scans over a grid having 2,048, 48 and 128 hypercomplex points along ^1H , ^{15}N and ^{13}C , respectively. Spectral widths were set to $3,293 \pm 4,209$ Hz along ^1H , $8,350 \pm 1,300$ Hz along ^{15}N , and $30,988 \pm 1,936$ Hz along ^{13}C . Points were nonuniformly sampled within each ^{15}N - ^{13}C plane at 5% sparsity using a sine-burst sampling schedule [45]. Direct dimension processing was achieved using squared-cosine apodization, Fourier transformation and manual phase correction. The indirect dimensions were reconstructed using 100 iterations of CAMERA in the MINT (small σ) regime, upon an extended grid of 128 by 256 hypercomplex points. A ^{13}C - ^{15}N projection of the reconstructed HNCO data is shown in Supplementary Figure S-3.

A 4D HSQC-NOESY-HSQC (*hsqcnoesyhsqcccgp4d*, [48, 49]) was collected 8 scans, 32 dummy scans and a 1.0 s relaxation delay on a grid having 1,024, 64, 64 and 64 hypercomplex points along $^1\text{H}_i$, $^{13}\text{C}_i$, $^1\text{H}_j$ and $^{13}\text{C}_j$, respectively. Spectral widths were set to $3,291 \pm 4,223$ Hz along $^1\text{H}_i$, $6,162 \pm 6,596$ Hz along $^{13}\text{C}_i$ and $^{13}\text{C}_j$, and $3,291 \pm 3,501$ Hz along $^1\text{H}_j$. Points were nonuniformly sampled within each indirect cube at 0.8% sparsity using a subrandom exponentially weighted sampling schedule [50]. The subrandom schedule in use was constructed by drawing 2,614 points from an exponential weighting function using subrandom (Halton) number sequences in lieu of pseudorandom number sequences. Direct dimension processing was achieved using squared-cosine apodization, Fourier transformation and manual phase correction. Indirect cubes were reconstructed using 200 iterations of constant-aim CAMERA in the MINT regime.

4. Results and Discussion

Like NESTA, CAMERA highlights the generality of Nesterov's method for rapidly solving problems in the form of equations (1) and (10). In short, NESTA and CAMERA are accelerated modifications of the traditional gradient-descent IST-S and FFM methods. Thus, exactly as NESTA converges more rapidly than IST-S, CAMERA exhibits enhanced convergence relative to FFM (Figure 1). While both gradient descent and conjugate gradient FFM required nearly 10,000 iterations to reconstruct a representative indirect-dimension trace, CAMERA needed only a few hundred iterations to reach the same result. Because the costs per iteration of CAMERA and FFM are essentially equivalent to two FFTs [25], the accelerated convergence of CAMERA directly results in dramatic time-savings for whole-spectral reconstructions. By enabling backtracking line searches within CAMERA, an even greater acceleration is observed (Figure 1, bold trace). When the convergence of CAMERA is compared to that of RNMRTK, the non-canonical optimization behavior of the Cambridge algorithm is made apparent [22]. Normalized entropy functional values were plotted as a function of the number of executed FFTs for each method in Figure 2, in order to more directly compare the two methods. As expected for a minimization routine, CAMERA

begins to immediately reduce its functional and smoothly “levels out” at the final solution. In contrast, RNMRTK builds more slowly to a rapid descent, overshoots below the optimal objective value, and eventually converges to the result. The “underdamped” behavior of the Cambridge algorithm is partially a result of the weighted average it performs between iterations to achieve a stable descent trajectory [22, 37]. Moreover, it is a consequence of the radically different starting points of the two algorithms. By initializing its model signal to the zero-augmented measurement, CAMERA can ensure that its intermediate $\mathbf{x}$ iterates are feasible according to problem (10). On the other hand, RNMRTK begins with a zero-intensity model signal, initially minimizes its data constraint, and finally maximizes its entropy functional. As a result, intermediate iterates (*e.g.*, prior to 200 transforms in Figure 2) from RNMRTK are not feasible from a constrained minimization perspective [51, 52].

The tunable curvature of the Hoch-Hore entropy functional was investigated during convergence analyses of CAMERA. As δ was increased, the resulting decreased curvature of the entropy functional was directly utilized in CAMERA, in the form of an increased gradient step factor. Thus, increasing δ within a CAMERA reconstruction is a simple means of accelerating its convergence (Figure 3). This use of δ -acceleration should be used in moderation, however, as larger values of δ yield more nonlinear reconstructions having lower signal-to-noise ratios (SNR; Figure 4). The appearance of broadband spectral noise as δ is increased is a direct consequence of the decreased functional curvature. As curvature around zero spectral intensity tends towards zero (*i.e.* as δ increases), the intensity range of baseline signals having acceptable entropy values is widened, resulting in a noise-like effect.

One feature of NESTA not present in CAMERA is continuation [32]. While the non-smooth IST-S functional requires a series of approximate solutions of increasing accuracy, the smooth Hoch-Hore entropy requires no such approximation techniques. However, the connection between δ and entropy functional curvature in CAMERA is analogous to that of the smoothing parameter (μ) in NESTA. In short, δ and μ are both inversely related to the Lipschitz constants of their respective functionals. Continuation – or stepped- μ operation – in NESTA is achieved by performing a sequence of minimizations by Nesterov’s method, each having a smaller value of μ than the previous minimization, and using the last $\mathbf{x}$ iterate of the prior minimization to seed the next. Using continuation, earlier iterations are allowed to converge quickly, resulting in more rapid progress towards the final solution. In CAMERA, backtracking line searches are used instead of continuation. Line search acceleration is achieved in CAMERA by choosing a small initial Lipschitz constant $L \ll L_f$ and allowing the algorithm to adjust L as needed. Therefore, all $\mathbf{x}$ iterates in CAMERA are computed using the exact entropy functional instead of a smoothed approximation. As demonstrated in Figures 1 and 2, line-search CAMERA produces a “stepped” convergence curve that is similar in appearance to curves produced by μ -continuation in NESTA.

Constant- λ operation, an important feature of other MaxEnt algorithms [27, 28, 36], is also supported within CAMERA. Figure 5 shows an example of how maintaining a constant Lagrange multiplier affects convergence. From constant-aim reconstruction of the same data, the Lagrange multiplier at the solution, λ^* , was determined to be slightly less than 2.2. When the constant value of λ is near λ^* , the convergence of CAMERA remains unchanged. However, when $\lambda \ll \lambda^*$, CAMERA converges to a different, more nonlinear solution. In

practical constant- λ reconstruction procedures, it is common to set $\lambda = \lambda^*$ where λ^* was obtained from the strongest signal(s) in the dataset [53]. Another potential use of constant- λ mode is when $\lambda \ll \lambda^*$, which effectively places the algorithm into the MINT regime [27]. Constant- λ reconstructions in CAMERA under both of the aforementioned conditions will converge within the same number of iterations required by constant-aim reconstructions of the same input data. Thus, it may be safely concluded that CAMERA supports all practical cases of constant- λ operation.

Because CAMERA is a complete MaxEnt solver, it necessarily exhibits nonlinearity under the same circumstances as existing MaxEnt algorithms. To demonstrate this nonlinearity, a set of synthetic NUS measurements was created and reconstructed using several values of σ , the estimated noise standard deviation. The experimental details followed closely with those of previous analyses [36]. In short, measurements having a range of signal intensities were reconstructed using constant-aim CAMERA under multiple values of σ , and the resulting reconstructed spectral intensities were computed. Figure 6 illustrates the relationship between input and output signal intensity – and therefore overall linearity – in CAMERA as a function of estimated noise tolerance. Thankfully, the beneficial aspects of nonlinear MaxEnt reconstruction are also retained in CAMERA. To highlight the nonlinearity of CAMERA, a recently published synthetic analysis [28] was recapitulated, as summarized in Figure 7. Measurements containing an intense, sharp signal nearby a broad signal of tenfold less intensity were nonuniformly subsampled and reconstructed using IST-S, MINT-regime CAMERA, and Bayesian-regime CAMERA. In all reconstructions, both the real and imaginary components of each data point were included during functional and gradient evaluations. While CAMERA operating in the highly linear MINT regime produced a similarly artifact-prone reconstruction to IST-S, CAMERA in the Bayesian regime tended to yield smoother, more artifact-free reconstructions. This tradeoff between nonlinearity and spectral quality of reconstructions is an expected feature of maximum entropy methods.

Deconvolution of a known line shape, including exponential decay deconvolution and J -coupling deconvolution, is fully supported in CAMERA. As an example, the ^1H - $^{13}\text{C}\alpha$ dataset described above, which contains a known $^{13}\text{C}\alpha$ - $^{13}\text{C}\beta$ coupling, was reconstructed with J -coupling deconvolution at several fixed values of coupling constant (*cf.* Supplementary Figure S-2). Figure 8 illustrates the results of deconvolving a 36 Hz J -modulation during reconstruction. Like RNMRTK MaxEnt [24], CAMERA yields nearly fully deconvolved spectral reconstructions when provided with J -coupling constants that are within a few Hertz of the true coupling. Therefore, any NUS dataset that contains a relatively constant, known coupling along one or more dimensions may be deconvolved using CAMERA. Once again like RNMRTK MaxEnt, CAMERA requires more iterations to converge to a final solution when deconvolution is in use. In general, enabling deconvolution in CAMERA necessitates a two- to four-fold increase in the number of reconstruction iterations.

The execution times of CAMERA were recorded for all datasets described in the Materials and Methods. Ranging from standard 2D HSQCs to 4D NOESYs, these experiment types represent a varied cross-section of computational requirements. To compare the time requirements of CAMERA on different hardware setups, two personal computers running

Debian GNU/Linux were used to perform the same battery of reconstructions. The first computer used an Intel Core i7 quad-core processor clocked at 3.4 GHz, with 24 GB RAM. The second system used two Intel Xeon E5-2620 six-core processors clocked at 2.4 GHz, with 128 GB RAM. Both computer systems supported hyper-threading and contained enough memory to afford running CAMERA with the maximum number of threads. Only the Intel Xeon system provided processor support for Advanced Vector Extensions (AVX). Table 1 summarizes all execution time results on both systems. By and large, these results demonstrate that CAMERA reconstructions require a comparable amount of time to equivalent reconstructions in NESTA-NMR [33]. Furthermore, CAMERA appears to reconstruct 4D data slightly faster than RNMRTK, based on previously reported uses of 4D MaxEnt [54]. Finally, the large disparity in NOESY reconstruction times in Table 1 highlights a key difference between the two hardware setups, namely support for the AVX instruction set on the Xeon computer. For reconstructions of 4D NUS data, support for AVX instructions dramatically reduces CAMERA execution time.

5. Conclusions

The Convex Accelerated Maximum Entropy Reconstruction Algorithm (CAMERA) is an application of Nesterov's accelerated first-order methods to the Hoch-Hore entropy regularization functional. As such, CAMERA is a novel algorithm for maximum entropy spectral reconstruction. Because CAMERA maximizes the convex Hoch-Hore entropy, it produces identical results to any other algorithm that solves either problem (1) or problem (10) above. As opposed to the Cambridge and Rowland algorithms, which require 4 and 6 FFTs per iteration, respectively, CAMERA performs only 2 FFTs per iteration. Furthermore, the memory requirements of CAMERA are highly similar to the Cambridge algorithm when applied to NUS reconstruction. As a consequence, CAMERA may be used to reconstruct data having three indirect dimensions in a few hours on mid-range workstations. Finally, CAMERA is a fully general MaxEnt solver, and supports both constant-aim and constant- λ modes, MINT-like interpolation and extrapolation, exponential decay deconvolution and J -coupling deconvolution.

Software implementing CAMERA for 2D, 3D and 4D NUS datasets was described, characterized and tested using real data. Because it interleaves with standard NMRPipe processing scripts, CAMERA facilitates rapid, simple incorporation of MaxEnt reconstruction into existing workflows. The CAMERA implementation presented herein is free and open source, distributed under version 3.0 of the GNU General Public License. All source code and example NMRPipe processing and reconstruction scripts and datasets are available for download from <http://github.com/geekysuavo/camera>. A modern C compiler is highly recommended for building CAMERA from its source code. Alternatively, precompiled executable versions of CAMERA are available upon request from the author.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- Highly efficient maximum entropy spectral reconstruction technique
- General, powerful method supporting all existing MaxEnt features
- High-performance software tools for CAMERA spectral reconstruction

Figure 1.

Comparison of convergence rates of FFM and CAMERA in the MINT regime. Using either gradient descent (G.D.) or conjugate gradient (C.G.) FFM, convergence is reached in approximately 10,000 iterations. For the same input data, constant-step (C.S.) CAMERA reaches convergence to the same global minimum after only 400 iterations, and line-search (L.S.) CAMERA converges within 100 iterations. All three reconstructions optimized the Hoch-Hore entropy with $\delta = 1$, and reconstruction with CAMERA used $\sigma = 10^3$.

Figure 2.

Comparison of convergence rates of RNMRTK MaxEnt and CAMERA, as a function of the number of fast Fourier transforms performed by each method. Vertical axis values are scaled to place the initial and final objective values of each method at 1 and 0, respectively.

Objective values from CAMERA represent the negative entropy, while values from RNMRTK represent the entropy. Both reconstructions optimized the Hoch-Hore entropy with $\delta = 2$. Reconstruction with CAMERA used $\sigma = 10^3$ and reconstruction with RNMRTK used $\chi_0 = 10$.

Figure 3. Convergence of constant-aim CAMERA under several constant values of δ . Reconstruction was performed using the same ^1H - ^{15}N HSQC trace from Figure 1. As expected, increasing values of δ yield increasingly rapid convergence to the global optimum due to the inverse relation between δ and entropy functional curvature.

Figure 4. Spectra from constant-aim CAMERA under several constant values of δ . As δ is increased, the resulting decreased curvature of the entropy functional results in near-equivalence of multiple near-baseline intensities, producing a broadband noise effect in the reconstructed spectrum.

Figure 5.

Comparison of convergence of constant- λ CAMERA under several values of λ .

Reconstruction was performed using the same ^1H - ^{15}N HSQC trace from Figure 1. From these convergence traces, it can be seen that constant- λ CAMERA converges normally when λ is within an order of magnitude of the constant-aim value ($\lambda^* = 2.2$), retaining the fast convergence expected of Nesterov's method.

Figure 6.

Nonlinearity analysis of constant-aim CAMERA under several values of σ . Like existing MaxEnt implementations, CAMERA exhibits an increasingly nonlinear scaling of reconstructed signals with increasing values of estimated noise (σ). A noise standard deviation value of $\sigma = 0.05$ was used to generate the synthetic input data.

Figure 7.

Reconstructions from IST-S and CAMERA, at two different levels of sampling sparsity, illustrating the effects of moving from the MINT regime ($\sigma = 10^{-6}$) to the Bayesian regime ($\sigma = 0.8$) on a broad, low-intensity signal. While IST-S and MINT produce more linear results, they introduce spikes into peaks that could be misinterpreted as signal splitting. When the tolerance is relaxed to 0.8 in CAMERA, broad signals become smoother, especially when reconstructing with less missing data.

Figure 8.
Constant-aim CAMERA reconstructions of a ^1H - $^{13}\text{C}\alpha$ indirect trace, with **(B-H)** and without **(A)** deconvolution enabled, under several J -coupling constants.

Table 1

Execution times of various CAMERA reconstructions on a Core i7 workstation and a Xeon E5 server node. A more detailed description of the two execution environments may be found in the Results and Discussion. The execution time of each dataset is representative of all reconstructions of equal dimensionality, grid size and iteration count.

	Core i7 8 threads	Xeon E5 24 threads
2D, ^1H - ^{15}N HSQC 1,024 pts 200 iterations	13 s	4 s
2D, ^1H - $^{13}\text{C}\alpha$ HSQC 2,048 pts 800 iterations	1.2 m	24 s
3D, HNCO 64×128 pts 100 iterations	8.2 m	1.3 m
3D, HNCO 128×256 pts 100 iterations	38 m	6 m
4D, NOESY 64×64×64 pts 200 iterations	10.5 h	1.5 h