Di-chromatic interpolation of magnetic resonance metabolic images

Nicholas Dwork1 · Jeremy W. Gordon1 · Shuyu Tang1 · Daniel O’Connor2 · Esben Søvsø Szocska Hansen3 · Christoffer Laustsen3 · Peder E. Z. Larson1

Received: 4 June 2020 / Revised: 10 December 2020 / Accepted: 15 December 2020 / Published online: 27 January 2021
© European Society for Magnetic Resonance in Medicine and Biology (ESMRMB) 2021

Abstract
Objective Magnetic resonance imaging with hyperpolarized contrast agents can provide unprecedented in vivo measurements of metabolism, but yields images that are lower resolution than that achieved with proton anatomical imaging. In order to spatially localize the metabolic activity, the metabolic image must be interpolated to the size of the proton image. The most common methods for choosing the unknown values rely exclusively on values of the original uninterpolated image.

Methods In this work, we present an alternative method that uses the higher-resolution proton image to provide additional spatial structure. The interpolated image is the result of a convex optimization algorithm which is solved with the fast iterative shrinkage threshold algorithm (FISTA).

Results Results are shown with images of hyperpolarized pyruvate, lactate, and bicarbonate using data of the heart and brain from healthy human volunteers, a healthy porcine heart, and a human with prostate cancer.

Keywords Interpolation · Image processing · MRI · Spectroscopy

Introduction

Magnetic resonance imaging (MRI) following injection of hyperpolarized compounds has permitted the investigation of metabolism in a noninvasive way without ionizing radiation [1, 19, 40]. Imaging of hyperpolarized Carbon-13 (13C) has been shown to be valuable for cancer staging and treatment evaluation purposes [24, 26, 35], and cardiac evaluation [9]. As the carbon atoms move between compounds via metabolism, the relative amounts of each metabolite are observed based on their spectral chemical shift. For example, with a hyperpolarized [1,13C] pyruvate imaging study, one can image pyruvate, lactate, and bicarbonate to assess the cellular metabolism of carbohydrates [18, 27].

Unlike conventional MRI of protons, where the signal returns to an equilibrium state that can be repeatedly measured, the hyperpolarized nuclei have a finite amount of longitudinal magnetization that can be used for imaging. Due to the limiting signal decay rate of the hyperpolarized nuclei and the low signal-to-noise ratio of the metabolic by-products, the resolution of the metabolic images is typically lower by approximately a factor of 5–10.

A metabolic imaging study typically consists of at least two sets of images: a high-resolution proton image (necessarily weighted by proton density and possibly additionally weighted by other physical characteristics, e.g., T1 and/or T2) and a set of low-resolution images, one for each metabolite containing the hyperpolarized atom. Interpolation is used to enlarge the metabolic images to the size of the proton image which permits the localization of the metabolic activity. Additionally, the enlarged metabolic image is often made into a false color image and fused with the proton image for improved localization [43]. The most common interpolation algorithms used include nearest-neighbor, linear, and sinc (which can be accomplished by zero-filling in the Fourier domain). These methods rely exclusively on the values of the

---

ND would like to thank the Quantitative Biosciences Institute at UCSF and the American Heart Association as funding sources for this work.

Nicholas Dwork
nicholas.dwork@ucsf.edu
http://www.nicholasdwork.com

1 Department of Radiology and Biomedical Imaging, University of California in San Francisco, San Francisco, USA
2 Department of Mathematics and Statistics, University of San Francisco, San Francisco, USA
3 Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
uninterpolated metabolic image and do not take advantage of the high-resolution proton image. In this manuscript, we present an algorithm that does.

Other problems where an image of one modality is used to improve the resolution of another include MR and positron emission tomography (PET) [25], computed tomography (CT) and PET [7], and MR and CT [13]. Existing techniques aim to simultaneously reconstruct both images from the raw data: the sinogram of CT, the Fourier samples of MR, and the projection data of PET. We accept, as input, magnitude images, while prior work accepts raw complex data. The problems differ fundamentally: Prior work is attempting to reconstruct both images from raw data with high fidelity, while we are trying to interpolate one image using the information of another.

Interpolating directly from the magnitude images has several advantages. Doing so eliminates the need to model the physics of the MRI system. For a gradient-based optimization solution, this eliminates two multiplications by sensitivity maps, and a Fourier transform and an inverse Fourier transform for each coil in each iteration of the optimization algorithm [16]. By avoiding these operations, the proposed method is computationally efficient. The resulting image in all cases is a magnitude image; thus, it is sensible to regularize the interpolated magnitude image. If one were to include data consistency of the raw complex data in the objective function, the interpolated image would be non-convex which could yield a sub-optimal solution. By working directly with the magnitude images, we are able to regularize accordingly while presenting a convex optimization problem which maintains theoretical guarantees of optimality [3]. Finally, we were able to regularize the interpolated magnitude image, the resulting optimization problem would be non-convex which could yield a sub-optimal solution. By working directly with the magnitude images, we are able to regularize accordingly while presenting a convex optimization problem which maintains theoretical guarantees of optimality [3]. Finally, we were able to regularize the interpolated magnitude image, the resulting optimization problem would be non-convex which could yield a sub-optimal solution.

In this work, we present a new interpolation scheme for the metabolic images where the higher-resolution image is used to inform the interpolation values. By doing so, the spatial localization of the metabolic activity is made more apparent. The interpolated image is the solution of a constrained convex optimization algorithm, which is efficiently solved with the fast iterative shrinkage threshold algorithm (FISTA). Matlab routines for this project are available at the author’s website: http://www.nicholasdwork.com.

**Methods**

Consider the sample data shown in Fig. 1; the high-resolution anatomical image is shown on the left, and the low-resolution metabolic image is shown on the right. The high-resolution anatomical image is necessarily weighted by proton density; therefore, there is only signal where there is tissue. However, there may be additional contrast imposed on the image as well (e.g., $T_2$ or $T_1$ contrast); we will address this phenomenon in “Accounting for additional contrast.”

We desire an image of the resolution of the proton image that presents the intensity of the metabolic image. We know that if we average and downsample the interpolated image, the resulting intensity should be close to the intensities of the low-resolution image. That is, we will assume the following degradation model (commonly used with optical interpolation in pan-sharpening algorithms [17, 30, 44]):

$$M = DBI_M + n,$$

where \( M \in \mathbb{R}^{M \times N} \) is the low-resolution metabolic image, \( I_M \) is the interpolated metabolic image, \( B \) is a circulant matrix that represents convolution with the blur kernel, \( D \) represents the downsampling operator, and \( n \) is additive Gaussian noise. This is an underdetermined linear system.

If we imagine that each square block of color in the low-resolution image were a square piece of putty or dough and we were asked to mold it so that it would look like the anatomy, intuitively, we would shape it to have the same contours, hills, and valleys as the high-resolution proton image. This intuition suggests that we should incorporate the gradient vectors of the anatomical image into the interpolation. While constraining the solution with the physical equation of (1), we will encourage the gradients of the interpolated magnitude image to be similar to those of the high-resolution anatomical image. This idea is commonly used with Bayer-patterned demosaicing in optical imaging [32].

In order to make the gradient vectors meaningful for the low-resolution image, though, we will first have to accommodate differences in the dynamic ranges of the images,
which may be different due to different coil geometries, excitation, or receiver gain. Both images are scaled so that their values lie in the [0, 1] interval: \( A = \hat{A} \max(\hat{A}) \) and \( M = \hat{M} \max(\hat{M}) \), where \( \hat{A} \in \mathbb{R}^{M_a \times N_a} \) and \( \hat{M} \in \mathbb{R}^{M_M \times N_M} \) are the original anatomical and metabolic images, respectively. The values \( M_a \) and \( N_a \) are the number of rows and columns of the metabolic image, respectively, and \( \times \) represents the Cartesian cross-product. Similarly, \( M_M \) and \( N_M \) are the number of rows and columns in the anatomical image. The gradient vectors of the scaled images can be used to inform the interpolation.

**Constructing the optimization problem**

We employ two separate methods for controlling how much the gradient vectors of the anatomical image and the interpolated image should match: a global user specified parameter \( \lambda \), and a pixel-based weighting. To determine the interpolated image, one solves the following convex optimization problem:

\[
\min_{I_M} \quad \frac{1}{2N_F} ||DBI_M - M||^2_{F} + \frac{\lambda}{2N_H} \|\nabla I_M - \nabla A\|_{w,2}^2
\]

subject to \( 0 \leq I_M \leq 1 \)

where \( \lambda > 0 \) is a regularization parameter, \( A \in \mathbb{R}^{M_a \times N_a} \) is the high-resolution anatomical image, and \( || \cdot ||_F \) represents the Frobenius norm (the square root of the sum of the matrix’s elements squared). The scalars \( N_A = M_a \cdot N_a \) and \( N_M = M_M \cdot N_M \) represent the number of pixels in \( A \) and \( M \), respectively. The \((1/(2N_M))||DBI_M - M||^2_{F} \) term in the objective function is a data consistency term that accounts for the model of (1). The symbol \( \nabla : \mathbb{R}^{M_a \times N_a} \to \mathbb{R}^{M_a \times N_a \times 2} \) represents the discrete gradient. Recall that \( \mathbb{R}^{M_a \times N_a \times 2} \) is a vector space comprised of a three-dimensional array. Each pixel of a two-dimensional array yields a gradient vector with two elements in it: the horizontal component and the vertical component; the third dimension of the array to represent the different components: the first/second slice of this array is the horizontal/vertical component, respectively. The \( || \cdot ||_{w,2} \) symbol represents a weighted \( L_2 \) norm, defined as

\[
||x||_{w,2} = (w_1 \cdot x_1^2 + w_2 \cdot x_2^2 + \cdots + w_N \cdot x_N^2)^{1/2}.
\]

Each term in the objective function was divided by the relevant number of elements in the corresponding norm (\( N_a \) or \( N_M \)) to make the regularization parameter robust to changing image sizes. The data consistency term was multiplied by \( 1/2 \) as a convenience so that the factor cancels when multiplied by 2 during the computation of its derivative. Note that one could simply multiply the entire objective function by 2 and yield an equivalent problem. Problem (2) is a constrained least-squares problem. The value of each pixel is constrained to be greater than 0 (since the value represents a magnitude) and less than 1 (a normalized maximum value).

Note that the gradient of the interpolated image and the proton image should not be related everywhere across the image. As an extreme example, consider a region of the metabolic image without any hyperpolarized metabolite (which would appear dark in the metabolic image). In this region, we want the values of the interpolated image to remain small (and not fluctuate with the gradient of the proton image). More generally, we want the gradient to be similar for pixels where the values of the metabolic images are high, but unrelated for pixels where the values of the metabolic images are low. To address this, we make use of the weighted norm in (2). Similar to the morphology enabled dipole inversion (MEDI) algorithm of [31], the weights are set to the values of the metabolic image linearly interpolated to be the size of the proton image.

If the user parameter \( \lambda \) is very small, then the underdetermined linear system of (1) dictates the output. As \( \lambda \) is increased, the regularization term \( R(I_M) = \frac{\lambda}{2N_H} \|\nabla I_M - \nabla A\|_{w,2}^2 \) encourages the solution to have gradient vectors of \( A \), especially so where the values of \( w \) are high.

**Solving the optimization problem**

The problem presented in (2) is a convex optimization problem; thus, a solution can be determined with known algorithms and existing software solutions [11, 22, 23]. However, by forming an equivalent optimization problem, the interpolated image can be determined with the more efficient fast iterative shrinkage threshold algorithm (FISTA). This algorithm exhibits convergence of \( O(1/k^2) \), where \( k \) is the iteration number, requiring fewer iterations than other methods for a given error.

FISTA solves problems of the form:

\[
\min_{I_M} \quad F(I_M) + G(I_M).
\]

Let \( F \) and \( G \) be defined as follows:
\[ F(I_M) = \frac{1}{2N_m} \| DBI_M - M \|_{F}^2 + \frac{\lambda}{2N_H} \| \nabla I_M - \nabla A \|_{W,2}^2 \] and 
\[ G(I_M) = \mathbb{I}_{[0,1]}(I_M). \]

Here, \( \mathbb{I}_{[0,1]} \) is the indicator function of the \([0, 1]\) interval applied to each element of the input individually. It equals 0 if every element is within the interval and infinity otherwise. Then, problems (2) and (3) are equivalent (i.e., they are solved by the same solution set).

To improve the rate of convergence, we chose to use FISTA with line search [38]. A general description of this algorithm is presented in Appendix. The proximal operator of \( G \), required by the algorithm, is a Euclidean projection onto the \([0, 1]^W\) set: \( \text{prox}_G(\cdot) = \min(\max(\cdot, 0), 1) \) for any \( t > 0 \), where the max and min operations are performed on each component of the input.

### Accounting for additional contrast

As we stated in “Introduction,” the contrast of the high-resolution image is necessarily weighted by proton density; this is unavoidable with standard MRI. Therefore, there is only signal where there is tissue. However, there may be additional contrasts imposed on the anatomical images such as \( T_2 \) or \( T_1 \) contrast. If this contrast is the same as the contrast of the metabolite, then there is not an issue. However, the contrast in the tissue of the anatomical image may be the negative of the contrast of the metabolic images, implying that the gradients of the anatomical image are opposite the desired gradients of the interpolated image.

It may be known, a priori, how the contrast of the anatomical image relates to the metabolic image. If that is the case, then the user should choose to either use \( I_A \) or \( -I_A \) as the anatomical reference if the contrast is the same as or opposite to the metabolic contrast, respectively. If the relationship of the contrast (and the gradient directions) is not known a priori, a simple metric can be used to determine whether to interpolate the metabolic images with \( I_A \) or \( -I_A \). We chose to use both to interpolate the metabolic image, yielding \( I_M^{(+)} \) and \( I_M^{(-)} \), respectively. Then, the result with contrast most similar to the contrast of the input metabolic image is selected as the final output.

### Di-chromatic interpolation

Algorithm 1 is the complete di-chromatic algorithm for interpolating MR data from a multi-slice acquisition. The multiple slices may be acquisitions of adjacent slices in space, or it may be acquisitions of the same slice at different times. It is assumed that the slices of the anatomical and metabolic volumes \( \hat{V}_A \) and \( \hat{V}_M \) are well registered.

#### Algorithm 1: Di-chromatic Interpolation

**Inputs:** \( \hat{V}_A, \hat{V}_M, B, D, \lambda \)

**For** each slice of \( V_A \) and \( V_M \) {
- Set \( \hat{A} \) and \( \hat{M} \) to the current slice of \( \hat{V}_A \) and \( \hat{V}_M \), respectively.
- Set \( A = \hat{A} / \max(\hat{A}) \) and \( M = \hat{M} / \max(\hat{M}) \).
- Linearly interpolate \( M \) to the size of \( A \) to determine \( w \).
- Solve problem (2) with inputs \( M \) and \( A \) to determine \( I_M^{(+)} \).
- Solve problem (2) with inputs \( M \) and \( (1 - A) \) to determine \( I_M^{(-)} \).
- Set the current slice of \( \hat{V}_I^{(+)} \) and \( \hat{V}_I^{(-)} \) to \( I_M^{(+)} \cdot \max(\hat{M}) \) and \( I_M^{(-)} \cdot \max(\hat{M}) \), respectively.
- Store the value of \( w \cdot \max(\hat{M}) \) as a slice in a new volume \( \hat{V}_w \).
}

**If** \( \| \hat{V}_w - \hat{V}_I^{(+)} \|_{w,2} < \| \hat{V}_w - \hat{V}_I^{(-)} \|_{w,2} \) {
- \( \hat{V}_I = \hat{V}_I^{(+)} \)
} **Else** {
- \( \hat{V}_I = \hat{V}_I^{(-)} \)
}

**Output:** \( \hat{V}_I \)
Comparing to an existing algorithm

An underlying idea for several of the existing algorithms is a regularization term that encourages edges of both images to be in the same location. This is done with parallel level sets [14, 39] or joint total variation (JTV) regularization [5, 33]. (Recall that the \( y \)-level set of a function \( f \) is the subset of its domain where the function equals \( y \).) For comparison purposes, we have altered the method of [33], which uses JTV, for reconstructed magnitude images as follows:

\[
\text{minimize } I_A, I_M \quad \frac{1}{2N_A} \| I_A - A \|_{F}^2 + \frac{1}{2N_M} \| DB I_M - M \|_{F}^2 + \lambda \| (\nabla I_A, \nabla I_M) \|_{\text{JTV}}.
\]

The \((\cdot, \cdot)\) notation represents array concatenation along the last dimension of the input arrays; therefore, \((\nabla I_A, \nabla I_M) \in \mathbb{R}^{M_A \times N_A \times 4}\). The JTV norm is a group sparsity metric that computes the sum of the magnitudes of the 4 element concatenated gradient vectors.

Problem (4) can be solved with the primal dual hybrid gradient method [4, 15, 36]. The resulting \( I_A \in \mathbb{R}^{M_A \times N_A} \) is a denoised version of the anatomical image [37], and the resulting \( I_M \in \mathbb{R}^{M_M \times N_M} \) is the interpolated metabolic image. We will compare the method presented in this paper, detailed in “Methods,” to the JTV interpolation of solving (4).

Experiments

In addition to a numerical phantom, MR images of an experimental phantom, humans, and a pig were processed for this paper. Images were collected with a 3 T General Electric MR750 clinical scanner (GE Healthcare, Waukesha, WI). For all studies, hyperpolarized \([1-^{13}C]\) pyruvate was generated in a 5 T SPINlab polarizer operating at 0.8 K. Samples were polarized for at least 2.5 h and then rapidly dissolved and neutralized. All data processed in this manuscript were originally acquired for other purposes.

Numerical phantom

To demonstrate the utility of this technique, we created a set of phantom tumors (homogeneous and heterogeneous) in a metabolic image, shown in Fig. 2a. We used the Shepp–Logan phantom to represent the anatomy (Fig. 2b). The tumors were super-imposed on the Shepp–Logan phantom in Fig. 2c. Tumor 1 is homogeneous, and one side corresponds to an edge in the anatomical image, tumor 2 is heterogeneous and is mismatched with the edge in the underlying anatomy, tumor 3 is heterogeneous and in a homogeneous region of anatomy, and tumor 4 is homogeneous with edges that match the underlying anatomy. We performed linear and di-chromatic interpolation and compare the results in Fig. 2g.

Fig. 2  a A high-resolution metabolic numerical phantom made of two homogeneous tumors (labeled ‘1’ and ‘4’) and two heterogeneous tumors (labeled ‘2’ and ‘3’). b The Shepp–Logan phantom will serve as the high-resolution numerical anatomical phantom. c The tumors super-imposed on the anatomical phantom. d The metabolic phantom reduced in resolution to 25% of its original size. e The reduced resolution phantom of d interpolated to the size of the phantom with nearest neighbor interpolation. f The result of di-chromatic interpolation on the low-resolution metabolic phantom. g Sub-images of the tumors resulting from linear interpolation (top) and di-chromatic interpolation (bottom). The red arrow indicates the portion of the tumor that was aligned with an anatomical edge.
Experimental phantom

Three solution-filled bottles were used for an experimental phantom. A 5 mL 13C-urea (1 mol) and a 5 mL 13C-acetate (1 mol) phantom were placed along with a 5-mL saline phantom. All cylinder phantoms were simultaneously imaged in an axial plane with three separate acquisitions. For the proton imaging, a stock CINE SSFP sequence was used. For the carbon imaging, a spectral-spatial (SPSP) acquisition and single-shot spiral read-out were used. Imaging specifics were: 80 Hz single band excitation, flip angles for lactate/pyruvate were 90°/8°, the field of view was 30 × 30 cm², recon matrix = 128 × 128, real pixels size = 10 mm, and slice thickness = 20 mm.

Human acquisitions

Prior to injection of the hyperpolarized solution, the pH, pyruvate and residual paramagnetic agent concentration, polarization, and temperature were measured. After release by the pharmacist, a 0.43 mL/kg dose of approximately 250 mM pyruvate was injected at a rate of 5 mL/s, followed by a 20-mL saline flush.

Porcine cardiac acquisitions

Metabolic images were acquired of a Danish domestic feed pig weighing 40 kg with a clamp shell transmit coil and a 16-channel array receive coil (Rapid Biomedical, Rimpar, Germany). A 25 mL of approximately 180 mM pyruvate solution was injected 20 s after dissolution into central venous access over 10 s with a 15-mL saline flush. The pig received intravenous propofol (12 mg initial dose; thereafter 0.4 mg/kg/h for maintenance anesthesia), intravenous fentanyl (8 μg/kg/h), and was mechanically ventilated. Catheterization was performed through the femoral vein for the administration of hyperpolarized [1-13C] pyruvate. Imaging was done in the supine position.

Proton CINE cardiac short-axis images were acquired with a stock GE Healthcare provided FIESTA sequence with cardiac gating and breath-hold. Imaging specifics were: flip angle = 55°, field of view = 400 × 400, recon matrix = 512 × 512, real pixels size = 2.2 mm, and slice thickness = 10 mm. Pyruvate cardiac short-axis images were obtained using a spectral-spatial excitation and a single-shot spiral read out with cardiac gating. Imaging specifics were: 80 Hz single band excitation, flip angles for lactate/pyruvate were 90°/8°, the field of view was 30 × 30 cm², recon matrix = 128 × 128, real pixels size = 10 mm, and slice thickness = 20 mm.

Human cardiac images

Proton density weighted images of a healthy volunteer were acquired using a multi-slice free-breathing gradient echo sequence with a 3 × 3 mm² in-plane resolution, an echo time of 2.8 ms, and a repetition time of 12.8 ms with the system’s body coil. These data were collected using a commercial software package (RTHawk, HeartVista, Los Altos, CA). The pyruvate, lactate, and bicarbonate images were acquired alternately using a multi-slice free-breathing cardiac-gated sequence with a 12.5 × 12.5 mm² in-plane resolution and a field-of-view of 75 × 75 cm². For the metabolic images, a Helmholtz clamshell transmit coil and an 8-channel paddle receive array were used. A single band spectral-spatial excitation scheme was used with a single-shot spiral readout trajectory [8]; the flip angles for pyruvate, lactate, and bicarbonate were 20°, 30°, and 30°, respectively [29, 41]. Bolus tracking was used to trigger the acquisition with real-time frequency and power calibration [41].

Human brain

One hyperpolarized brain dataset was acquired in a healthy volunteer with a variable-resolution single-shot echoplanar imaging acquisition [20] using a birdcage coil for transmit with an integrated 24 element receiver (Rapid Biomedical, Würzburg, Germany). Scan parameters were 125 ms TR, 30.7 ms TE, 32 × 32 matrix size, eight 1.5 cm slices with an axial orientation. Pyruvate was excited with a 20° flip angle and acquired at 7.5 × 7.5 mm² resolution, while lactate and bicarbonate received a 30° flip angle and were acquired at 15 × 15 mm² in-plane resolution [29]. Data acquisition started 5 s after the end of saline injection. Twenty frames were acquired with a 3 s temporal resolution, yielding a total scan time of 1 min. For anatomic reference, a 3D inversion recovery spoiled gradient echo sequence dataset was acquired with a birdcage transmit coil and an integrated 8 channel receive coil [21]. Scan parameters were 6.7 ms TR, 2.5 ms TE, 450 ms IR time, 25.6 × 25.6 × 18.6 cm² field of view, 256 × 256 × 124 matrix (1 × 1 × 1.5 mm³ resolution).
**Human prostate**

Data of a prostate with cancer were acquired with a three-dimensional undersampled spectroscopic imaging sequence with compressed sensing reconstruction [6, 28]. Whole organ coverage was achieved with a resolution of $8 \times 8 \times 8$ mm$^3$ and a spectral bandwidth of 540 Hz. Metabolite volumes were acquired every 2 s using varying flip angles to improve the signal-to-noise ratio [45].

For anatomic reference, $T_2$ weighted proton images were acquired with a repetition time of 6 s, an echo time of 102 ms, a field of view of $18 \times 18$ cm$^2$, an image size of $384 \times 384$, and a slice thickness of 3 mm.

**Results**

In this section, we present results from a healthy porcine heart, a human heart of a healthy volunteer, a human brain from a healthy volunteer, and a human prostate with cancer. Finally, we present results showing the effect of changing the regularization parameter.

**Numerical phantom**

The result of di-chromatic interpolation applied to the numerical phantom is shown in Fig. 2. The relative errors of the linear interpolation and the di-chromatic interpolation results are 0.33 and 0.31, which quantifies an improvement with the di-chromatic interpolation. Note that relative error is defined as $\frac{\|\text{estimate} - \text{true}\|_{\text{Frobenius}}}{\|\text{true}\|_{\text{Frobenius}}}$, where $\|\cdot\|_{\text{Frobenius}}$ denotes the Frobenius norm.

In the di-chromatic interpolated image, tumor 1 becomes sharper on the side that corresponds to the anatomical edge (as indicated by the red arrow) and the other sides do not significantly change quality. In tumor 2, the mismatched images have been eliminated and the JTV interpolation result appears smoother. (Column 4/column 5) $I_M^{(+)}$ and $I_M^{(-)}$ from Algorithm 1, respectively, with a regularization parameter $\lambda = 10$. The cyan arrows indicate a location where the contrast of $I_M^{(+)}$ is opposite that of $I_M^{(-)}$. The green boxes show the contrast selected by the di-chromatic interpolation algorithm for final output; note that $I_M^{(+)}$ was selected as the output for pyruvate, but $I_M^{(-)}$ was selected as the output for lactate.
anatomical edge is incorporated into the interpolated image, but the overall contrast and presence of the tumor are not significantly affected. The incorporated edge empowers the observer to localize the tumor in the anatomy well. Tumor 3 does not significantly change in the di-chromatic interpolated result; its contrast is maintained. Tumor 4 becomes sharper by incorporating anatomical edges. Both heterogeneous phantoms retain their structure and contrast, even though they are not present in the underlying anatomic image used for interpolation. In all cases, di-chromatic interpolation offers a benefit.

**Experimental phantom**

Figure 3 shows the original images of the experimental phantom along with the di-chromatic interpolated metabolic images. Note the clear separation of the different metabolites; and note that the saline phantom without a carbon substrate does not have significant signal in either of the interpolated metabolic images. The flat top of the acetate phantom is likely due to a susceptibility-induced artifact resulting from the spiral acquisition. As a result, the di-chromatic interpolation generates strong edges on the left,
right, and bottom of the carbon phantoms and reflects the lack of a distinct edge near the tops of the bottles. This is similar to the results shown with tumor 1 in the numerical phantom of Fig. 2.

**Porcine cardiac images**

Figure 4 shows results of imaging protons, pyruvate, and lactate in the porcine heart. In this case, the contrast of the lactate is opposite to that of the proton image. Note the high intensity of the lactate in the myocardium and the low local contrast of the same region in the proton image. The green

![Fig. 7](image-url) Interpolated metabolic image of the cardiac study with $\lambda = 1$ fused with the proton image using the CLS fusion algorithm. The first, second, and third row shows pyruvate, lactate, and bicarbonate, respectively. There are five different slices of the heart shown in the five different columns.

![Fig. 8](image-url) (Row 1) A high-resolution proton image. (Row 2/row 3/row 4) The metabolic images of pyruvate, lactate, and bicarbonate, respectively. (Columns 1–6) Individual slices of the brain. Note that the native resolution of the pyruvate is twice that of the lactate and bicarbonate. The cyan arrows point to a urea phantom used for power calibration.
boxes show the interpolated image selected by Algorithm 1, which presents the contrast most similar to the non-interpolated image.

The interpolated images show the pyruvate primarily localized to the blood pools and lactate primarily localized to the myocardium, which matches with our expectation since pyruvate is the injected substrate and lactate would be produced in the muscle. In this example, the papillary muscle is also delineated in the proton image, and the interpolation shows relatively little pyruvate and high lactate in this structure, as expected.

Figure 4 also compares the di-chromatic interpolation algorithm to linear interpolation and JTV interpolation. JTV interpolation eliminates some amount of the artifacts that remain with linear interpolation, but the results are very similar. Since JTV interpolation is much more computationally intensive, it is not necessarily the case that the improvement in quality is worth the cost. The di-chromatic interpolation results incorporate the anatomical information much more.

**Human cardiac images**

Figure 5 shows five slices of a heart at a single point in time where much of the pyruvate has been converted to lactate and bicarbonate through metabolism at its native resolution; Fig. 6 shows the interpolated image. Note the additional detail in the interpolated image. The bicarbonate image retains a markedly different spatial distribution compared to the pyruvate and lactate images. In particular, the bicarbonate is accurately localized to the myocardium.

An alternative method of presenting the metabolic image is to fuse it with the proton image. Figure 7 shows the interpolated image of Fig. 6 made into a false color image with Matlab’s hot colormap and fused with the proton image using the CLS fusion algorithm [12]. The CLS fusion algorithm was designed to present the anatomical information while retaining the information in the color image.

**Human brain**

Figure 8 shows the high-resolution proton images and the lower-resolution pyruvate, lactate, and bicarbonate images for 6 slices of the brain. In order to improve the signal-to-noise ratio of the metabolites with lower abundance, lactate and bicarbonate, the resolution of those images was reduced by a factor of 2 from that of pyruvate [20].

Figure 9 shows the di-chromatic interpolated images of the brain for pyruvate, lactate, and bicarbonate. The interpolation puts the majority of metabolite signals within the brain as expected. However, some of the fine structure contrast observed (e.g., metabolite signals outside the brain or in the CSF) do not reflect metabolic activity. With the enhanced details in the interpolated metabolite images, it is easier for the observer to determine the regions of the brain where the activity is taking place based on the metabolic images alone.

**Human prostate**

Figure 10 shows pyruvate and lactate images of a slice of a prostate taken approximately 2 s apart in their native resolution. The di-chromatic Interpolation Algorithm 1 with a regularization parameter of $\lambda = 10$ was applied with the anatomical reference image presented in Fig. 1 (left). The

---

**Fig. 9** Di-chromatic interpolated image with $\lambda = 10$ of (row 1/row 2/row 3) pyruvate, lactate, and bicarbonate, respectively. (Columns 1–6) Individual slices of the brain. Note that the native resolution of the pyruvate is twice that of the lactate and bicarbonate.
Fig. 10  Dynamic images from a single slice of a pyruvate and b lactate in the prostate at native (8 × 8 mm²) resolution, ordered temporally from left to right and then top to bottom. Each image shows the pyruvate content at a different time; images are separated by approximately 2 s.

Fig. 11  Interpolated images of a pyruvate and b lactate in the prostate with λ = 10, ordered temporally from left to right and then top to bottom. Each image shows the pyruvate content at a different time; images are separated by approximately 2 s.
results are shown in Fig. 11. Note that one is able to better comprehend, where in the prostate, the metabolic activity is taking place by only looking at the interpolated metabolic image.

Although the image is more detailed, Fig. 11 shows a limitation of the di-chromatic interpolation algorithm. The pyruvate largely arrives at this slice of the prostate through a blood vessel and diffuses into the surrounding tissue. We would not expect the regions of fat to have a large pyruvate uptake. The di-chromatic interpolation algorithm does not take this physiology into account. So, though the interpolation better localizes the metabolic energy to regions of tissue, the fat region encompassed with the red circle in Fig. 1 is bright.

**The regularization parameter**

The regularization variable $\lambda$ is a user-selected parameter. Figure 12 shows how the details of the interpolated image are altered by changes to the regularization parameter of (2). The first, second, and third rows of Fig. 12 show results for data from the human heart, prostate, and porcine heart, respectively. Generally, as the regularization parameter increases, the interpolated image appears more similar to the proton image. This can be seen in the pyruvate image of the porcine heart with $\lambda = 100$; the image appears extremely similar to the corresponding proton image (seen in Fig. 11) and the metabolic information has almost entirely been lost.

As the regularization parameter is reduced, the interpolated image appears less natural, becoming artificially detailed to better solve the data-consistency term in the objective function of (2). The data consistency attempts to de-blur the image, which gathers energy in the images. This effect can be seen dramatically in the prostate with $\lambda = 10^{-2}$ and $\lambda = 10^{-1}$.

**Discussion**

The di-chromatic interpolation algorithm improves the observer’s comprehension of the location of metabolic activity attained from an injection of a hyperpolarized solution. This has great potential for improved localization of tumors and malfunctions of cardiac tissue. Additionally, the method performs a deblurring operation which gathers the energy of the hyperpolarized metabolite according to the blur kernel. This reduces the apparent spread of the activity, possibly reducing the possibility of falsely mischaracterizing tissue as metabolically hyperactive.

Note that the interpolation algorithm does not generate the same results that would be achieved with a high-resolution image (where it is possible to create one). The
interpolated image is a better reflection of the metabolic activity in the anatomy, but not necessarily a completely physical one. Our results suggest that this method is well suited for cardiac imaging because the high-resolution anatomical structures match the expected compartmentalization of the hyperpolarized metabolites. The proton images clearly define the blood and myocardium, and these are surrounded by lung tissue, while the hyperpolarized metabolites typically are distributed in the blood and/or myocardium, but not in the lungs.

However, in the brain and prostate we observed that the high-resolution anatomical contrast was likely too complex and detailed compared to the expected hyperpolarized metabolite distributions. While we observed some apparent improvements in localization of metabolites to the prostate and brain, the algorithm also places metabolite signals in other structures such as intra-abdominal and subcutaneous fat where it is very unlikely that the metabolites resides. The results for some applications may be improved by selecting the contrast of the high-resolution anatomical image acquired with the metabolic images to better match the expected distribution of hyperpolarized metabolites.

The regularization parameter determines the quality of the output to a significant degree. If it is too low, then the output is largely determined by the noise in the input. If it is too high, then the output becomes too similar to the anatomical image. In our experience, though, we have found that a single regularization parameter works well for all slices of the same volume. Our hope is that future collections can depend on quality results from the same regularization parameter determined for data of the same resolution. We have not demonstrated this yet. Future investigations could identify a heuristic that automatically selects the regularization parameter, perhaps by finding the parameter at the knee of the pareto-optimal curve [10].

With dynamic data (images of metabolic processing through time), the temporal results are correlated. This has been taken into account in MR image reconstruction with total-variation regularization imposed in the temporal dimension [42]. In a similar vein, total-variation regularization can be added to problem (2) for dynamic data.

Gordon et al. have shown that the low signal-to-noise ratio of some hyperpolarized compounds (e.g., bicarbonate) can be compensated with a lower spatial resolution [20]. For data collected in this way, it may be beneficial to use the pyruvate image as the reference high-resolution image to interpolate the lower-resolution bicarbonate image.

Though we presented this technique in the context of hyperpolarized MRI, this technique may be applicable to other imaging systems. For example, it may be used to combine data from an MR/positron emission tomography (PET) machine. Or, in another MR application, it may be used to interpolate xenon pulmonary images [34]. When inhaled, the xenon gas perfuses into regions where tissue is absent. Since the di-chromatic interpolation may select the negative of the proton MR image, the result could be informative. We leave the investigation of these possibilities for future work.

Conclusion

In this work, we present the di-chromatic interpolation algorithm for MRI that informs the interpolation of a low-resolution image of hyperpolarized compounds using the gradients of a high-resolution image. The algorithm is based on known physics, and the solution space is further limited with a heuristic method incorporating information from a high-resolution anatomical image. We show results using data of the human prostate, the human heart, and a porcine heart. We demonstrate the interpolation algorithm for data that vary spatially and data that vary temporally. This algorithm accepts, as input, reconstructed images. Since it does not require raw data collected by the scanner, it is feasible to deploy this algorithm for use on clinical patient data (for data that will be collected in the future or that has been collected in the past).

Appendix: Fast iterative shrinkage threshold algorithm

The fast iterative shrinkage threshold algorithm (FISTA) solves problems of the form:

\[
\min_{x \in \mathbb{R}^N} F(x) + G(x),
\]

where \( F \) is differentiable and \( G \) has a simple proximal operator [2, 38]. The FISTA algorithm with line search is described in Algorithm 2. Note that \( \langle \cdot, \cdot \rangle \) represents an inner product. To initialize the algorithm, set \( v^{(0)} = x^{(0)} \), where \( x^{(0)} \) is the initial guess and can be any value. Select a \( t_0 > 0 \), and select a maximum number of iterations \( K \). Select a backtracking line search parameter \( r \in (0, 1) \) (a common choice of \( r \) is 0.9) and select a step size scaling parameter \( s > 1 \) (a common choice of \( s \) is 1.25).
Algorithm 2: FISTA with line search

For $k = 1, 2, \ldots, K$
\[ t_k = \sigma t_{k-1} \]
While true
  If $k == 1$
    \[ \theta_1 = 1 \]
  Else
    \[ \theta_k = \text{positive root of } t_{k-1} \theta^2 = t_k \theta_{k-1}^2 (1 - \theta) \]
  End If
  \[ y^{(k)} = (1 - \theta_k)x^{(k-1)} + \theta_k v^{(k-1)} \]
  \[ x^{(k)} = \text{prox}_{t_k G} (y^{(k)} - t_k \nabla F(y^{(k)})) \]
  If $F(x^{(k)}) \leq F(y^{(k)}) + \langle \nabla F(y^{(k)}), x^{(k)} - y^{(k)} \rangle + \frac{1}{2} \| x^{(k)} - y^{(k)} \|_2^2$
    break
  End If
  \[ t_k := \tau t_k \]
End While
\[ v^{(k)} = x^{(k-1)} + \frac{1}{\theta_k} (x^{(k)} - x^{(k-1)}) \]
End For

Acknowledgements The authors would like to thank Roselle Abraham, Rahul Aggarwal, Robert Bok, Hsin-Yu Chen, John Kurhanewicz, James Slater, and Daniel Vigneron for their assistance in the imaging of human subjects. The authors would like to thank Gennifer T. Smith for her helpful suggestions regarding the editing of this document. ND would like to thank the Quantitative Biosciences Institute at UCSF and the American Heart Association as funding sources for this work.

Funding ND has received post-doctoral training funding from the American Heart Association (Grant number 20POST135200152). ND has received funding from the Quantitative Biosciences Institute at UCSF (no grant number). JG has received funding from the National Institute of Health/National Institute of Biomedical Imaging and Bioengineering (Grant number U01EB026412). PL has received funding from the National Institute of Health (Grant number NIH R01 HL136965).

Compliance with ethical standards

Conflict of interest No conflicts of interest, financial or otherwise, are declared by the authors.

Human and animal participants All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. MR data of humans were gathered with institutional review board (IRB) approval and Health Insurance Portability and Accountability Act (HIPAA) compliance. Informed consent was obtained from all individual participants included in the study. All applicable international, national, and/or institutional guidelines for the care and use of animals were followed. Animal experiments were done in accordance with relevant laws and ethics under permission from the Animal Experiments Inspectorate of Denmark.

References

1. Ardenkjær-Larsen JH, Fridlund B, Gram A, Hansson G, Hansson L, Lerce MH, Servin R, Thaning M, Golman K (2003) Increase in signal-to-noise ratio of >100,000 times in liquid-state NMR. Proceedings of the National Academy of Sciences 100(18):10158–10163
2. Beck A, Teboulle M (2009) A fast iterative shrinkage-thresholding algorithm for linear inverse problems. SIAM journal on imaging sciences 2(1):183–202
3. Boyd S, Boyd SP, Vandenberghe L (2004) Convex optimization. Cambridge University Press, Cambridge
4. Chambolle A, Pock T (2011) A first-order primal-dual algorithm for convex problems with applications to imaging. Journal of mathematical imaging and vision 40(1):120–145
5. Chen C, Li Y, Huang J (2013) Calibrationless parallel MRI with joint total variation regularization. In: International Conference on Medical Image Computing and Computer-Assisted Intervention, pp. 106–114. Springer
6. Chen HY, Larson PE, Gordon JW, Bok RA, Ferrone M, van Criekeging M, Carvajal L, Cao P, Pauly JM, Kerr AB et al (2018) Technique development of 3D dynamic CS-EPSI for hyperpolarized 13C pyruvate MR molecular imaging of human prostate cancer. Magnetic resonance in medicine 80(5):2062–2072
7. Cui X, Mili L, Wang G, Yu H (2018) Wavelet-based joint CT-MRI reconstruction. Journal of X-ray science and technology 26(3):379–393
8. Cunningham CH, Chen AP, Lustig M, Hargreaves BA, Lupo J, Xu D, Kurhanewicz J, Hurd RE, Pauly JM, Nelson SJ et al (2008) Pulse sequence for dynamic volumetric imaging of hyperpolarized metabolic products. Journal of magnetic resonance 193(1):139–146
9. Cunningham CH, Lau JY, Chen AP, Geraghty BJ, Perks WJ, Roifman I, Wright GA, Connelly KA (2016) Hyperpolarized 13C metabolic MRI of the human heart: initial experience. Circulation research 119(11):1177–1182
10. Das I (1999) On characterizing the “knee” of the pareto curve based on normal-boundary intersection. Structural optimization 18(2–3):107–115

11. Diamond S, Boyd S (2016) CVXPY: A python-embedded modeling language for convex optimization. The Journal of Machine Learning Research 17(1):2909–2913

12. Dwork N, Lasry EM, Pauly JM, Balbás J (2017) Formulation of image fusion as a constrained least squares optimization problem. Journal of Medical Imaging 4(1):014003

13. Ehman EC, Johnson GB, Villanueva-Meyer JE, Cha S, Leynes AP, Larson PEZ, Hope TA (2017) Pet/mri: where might it replace pet/ct? Journal of Magnetic Resonance Imaging 46(5):1247–1262

14. Ehrhardt MJ, Markiewicz P, Liljeroth M, Barnes A, Kolehmainen V, Duncan JS, Pizarro L, Atkinson D, Hutton BF, Ourselin S et al (2016) PET reconstruction with an anatomical MRI prior using parallel level sets. IEEE transactions on medical imaging 35(9):2189–2199

15. Esser E, Zhang X, Chan TF (2010) A general framework for a class of first order primal-dual algorithms for convex optimization in imaging science. SIAM Journal on Imaging Sciences 3(4):1015–1046

16. Fessler JA (2010) Model-based image reconstruction for MRI. IEEE signal processing magazine 27(4):81–89

17. Garzelli A (2016) A review of image fusion algorithms based on the super-resolution paradigm. Remote Sensing 8(10):797

18. Golman K, Petersson JS, Magnusson P, Johansson E, Åkeson P, Chai CM, Hansson G, Månsson S (2008) Cardiac metabolism measured noninvasively by hyperpolarized 13C MRI. Magnetic Resonance in Medicine: An Official Journal of the International Society for Magnetic Resonance in Medicine 59(5):1005–1013

19. Golman K, Thaning M et al (2006) Real-time metabolic imaging. Proceedings of the National Academy of Sciences 103(30):11270–11275

20. Gordon JW, Autry AW, Tang S, Graham JY, Bok RA, Zhu X, Villanueva-Meyer JE, Li Y, Ohliger MA, Abraham MR et al (2020) A variable resolution approach for improved acquisition of hyperpolarized 13C metabolic MRI. Magnetic Resonance in Medicine

21. Gordon JW, Vigneron DB, Larson PE (2017) Development of a symmetric echo planar imaging framework for clinical translation of rapid dynamic hyperpolarized 13C imaging. Magnetic resonance in medicine 77(2):826–832

22. Grant M, Boyd S (2008) Graph implementations for nonsmooth convex programs. In: Blondel V, Boyd S, Kimura H (eds.), Recent advances in learning and control. Lecture Notes in Control and Information Sciences, pp. 95–110. Springer-Verlag Limited.

23. Grant M, Boyd S (2014) CVX: Matlab software for disciplined convex programming, version 2.1. http://cvxr.com/cvx. Accessed 6 Feb 2019

24. Grinst JT, McLean MA, Riemer F, Schulte RF, Deen SS, Zaccagna K, Bowsher’s method as segmentation-free anatomical priors for bowsher’s method. IEEE transactions on medical imaging 36(1):1–16

25. Guo H, Tian L, Tang S, Criekinge M, Carvajal L, Mammoli D et al (2018) Investigation of analysis methods for hyperpolarized 13C-pyruvate metabolic MRI in prostate cancer patients. NMR in Biomedicine 31(11):e3997

26. Larsson PE, Hu S, Lustig M, Kerr AB, Nelson SJ, Kurhanewicz J, Pauly JM, Vigneron DB (2011) Fast dynamic 3D MR spectroscopic imaging with compressed sensing and multiband excitation pulses for hyperpolarized 13C studies. Magnetic resonance in medicine 65(3):610–619

27. Larsson PE, Chen AP, Hurd RE, Cunningham CH (2011) Spectral-spatial excitation for rapid imaging of DNP compounds. NMR in Biomedicine 24(8):988–996

28. Luo AZ, Chen AP, Hurd RE, Cunningham CH (2011) Spectral-spatial excitation for rapid imaging of DNP compounds. NMR in Biomedicine 24(8):988–996

29. Li Z, Leung H (2009) Fusion of multispectral and pansharmonic images using a restoration-based method. IEEE transactions on geoscience and remote sensing 47(5):1482–1491

30. Liu J, Liu T, de Rochefort L, Ledoux J, Khalidov I, Chen W, Tsioiris AJ, Wisnieff C, Spinicaelle P, Prince MR et al (2012) Morphology enabled dipole inversion for quantitative susceptibility mapping using structural consistency between the magnitude image and the susceptibility map. Neuroimage 59(3):2560–2568

31. Lukin A, Kubasov D (2004) High-quality algorithm for bayer pattern interpolation. Programming and Computer Software 30(6):347–358

32. Mehranian A, Belzunce MA, Prieto C, Hammers A, Reader AJ (2017) Synergistic PET and SENSE MR image reconstruction using joint sparsity regularization. IEEE transactions on medical imaging 37(1):20–34

33. Mugler JP III, Driehuys B, Brookeman JR, Cates GD, Berr SS, Bryant RG, Daniel TM, De Lange EE, Downs JH, Erickson CJ et al (1997) MR imaging and spectroscopy using hyperpolarized 129 Xe gas: preliminary human results. Magnetic resonance in medicine 37(6):809–815

34. Nelson SJ, Kurhanewicz J, Vigneron DB, Larson PE, Harzstark AL, Ferrone M, van Kurkinke M, Chang JW, Bok R, Park I et al (2013) Metabolic imaging of patients with prostate cancer using hyperpolarized [1-13C] pyruvate. Science translational medicine 5(198):198ra108

35. Pock T, Cremers D, Bischof H, Chambolle A (2009) An algorithm for minimizing the mumford-shah functional. In: 2009 IEEE 12th International Conference on Computer Vision, pp. 1133–1140. IEEE

36. Radin LI, Osher S, Fatemi E (1992) Nonlinear total variation based noise removal algorithms. Physica D: nonlinear phenomena 60(1–4):259–268

37. Scheinberg K, Goldfarb D, Bai X (2014) Fast first-order methods for composite convex optimization with backtracking. Foundations of Computational Mathematics 14(3):389–417

38. Schramm G, Holler M, Rezaei A, Vunckx K, Knoll F, Bredies K, Boada F, Nuyts J (2017) Evaluation of parallel level sets and pattern interpolation. Programming and Computer Software 43(198):198ra108

39. Schroeder MA, Clarke K, Neubauer S, Tyler DJ (2011) Hyperpolarized magnetic resonance: a novel technique for investigating normal human brain metabolism using hyperpolarized [1-13C] pyruvate and magnetic resonance imaging. NeuroImage 59(3):2560–2568

40. Tsiouris AJ, Wisnieff C, Spincemaille P, Prince MR et al (2012) Morphology enabled dipole inversion for quantitative susceptibil-ity mapping using structural consistency between the magnitude image and the susceptibility map. Neuroimage 59(3):2560–2568

41. Wang Y, Cao N, Liu Z, Zhang Y (2017) Real-time dynamic MRI spatial excitation for rapid imaging of DNP compounds. NMR in Biomedicine 24(8):988–996

42. Zhang ZJ, Ohliger MA, Larson PE, Gordon JW, Bok RA, Slater J, Villanueva-Meyer JE, Hess CP, Kurhanewicz J, Vigneron DB
(2019) Hyperpolarized 13c mri: State of the art and future directions. Radiology 291(2):273–284
44. Wu H, Zhao S, Zhang J, Lu C (2019) Remote sensing image sharpening by integrating multispectral image super-resolution and convolutional sparse representation fusion. IEEE Access 7:46562–46574
45. Xing Y, Reed GD, Pauly JM, Kerr AB, Larson PE (2013) Optimal variable flip angle schemes for dynamic acquisition of exchanging hyperpolarized substrates. Journal of magnetic resonance 234:75–81

Publisher’s Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.