The Use of Anatomical Information for Molecular Image Reconstruction Algorithms: Attenuation/Scatter Correction, Motion Compensation, and Noise Reduction

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Received: 1 September 2015 / Revised: 11 January 2016 / Accepted: 13 January 2016 / Published online: 11 February 2016
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Abstract PET and SPECT are important tools for providing valuable molecular information about patients to clinicians. Advances in nuclear medicine hardware technologies and statistical image reconstruction algorithms enabled significantly improved image quality. Sequentially or simultaneously acquired anatomical images such as CT and MRI from hybrid scanners are also important ingredients for improving the image quality of PET or SPECT further. High-quality anatomical information has been used and investigated for attenuation and scatter corrections, motion compensation, and noise reduction via post-reconstruction filtering and regularization in inverse problems. In this article, we will review works using anatomical information for molecular image reconstruction algorithms for better image quality by describing mathematical models, discussing sources of anatomical information for different cases, and showing some examples.

Keywords Iterative image reconstruction · Attenuation and scatter correction · Motion compensation · Regularization · Post-reconstruction filter · Anatomical side information

Introduction

Nuclear medicine imaging such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) is an important tool for providing valuable molecular information about patients to clinicians [1, 2]. However, it is challenging to obtain good-quality images of PET and SPECT due to highly noisy measurements and various artifacts. For the past few decades, hardware and software for nuclear medicine have been improved dramatically so that better image quality was able to be achieved and better utilization of molecular images became possible potentially for better diagnosis and therapeutic monitoring, sometimes with high-resolution anatomical information such as X-ray computed tomography (CT) or magnetic resonance imaging (MRI) from hybrid scanners such as PET-CT, SPECT-CT, and PET-MR [3–5].

Advances in nuclear medicine imaging hardware have enabled improved image quality of SPECT [6], time-of-flight (TOF) PET [7], and PET [8] through new scintillators, photodetectors, and fast electronics. The development of combined PET-CT or SPECT-CT made it possible to routinely obtain well-aligned CT with PET or SPECT in clinics, respectively [3, 9]. Recently, combined PET-MR has been actively researched so that MR images can be obtained simultaneously with PET [5, 10].

Novel software such as new iterative image reconstruction algorithms and various artifact correction methods are also key factors for improving the image quality of nuclear medicine [11, 12]. Using accurate statistical models for image reconstruction algorithms has brought significant improvement in image quality. A Poisson model for

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emission tomography was first used in [13] and then an expectation-maximization (EM) reconstruction algorithm was derived in [14, 15] based on [16]. An acceleration method called ordered subset EM (OS-EM) was proposed in [17]. OS-EM-based iterative image reconstruction software finally became available in clinical PET and SPECT scanners circa 1997. Iterative image reconstruction methods for emission tomography were comprehensively reviewed in [18]. Well-aligned anatomical information from hybrid scanners enabled advances of various correction methods such as attenuation corrections [19] and scatter corrections [20, 21] for better quantitative and qualitative imaging [12].

Advances of hybrid nuclear medicine scanners made it possible to obtain registered CT or simultaneously acquired MR along with PET or SPECT. Anatomical images such as high-resolution CT or MR can be used together with molecular images such as low-resolution PET or SPECT to take advantage of multi-modal imaging for diagnosis and therapeutic monitoring [3, 4, 10, 22]. Aligned anatomical images not only affect clinical decisions by providing fused images with molecular images but also play important roles in image reconstruction algorithms, which bring further advances of nuclear medicine software for improved image quality of PET or SPECT.

Even though molecular and anatomical images show different aspects about patients clinically, they also have a few things in common. Generating data of nuclear medicine involves interactions between molecular and anatomical information through medical physics models. Since anatomical structure contains activity distribution, they experience the same motion and have fairly good structural couplings or correlations. When gamma rays are emitted from injected activity in a patient, they go through part of the body so that attenuation and scatter occur. Using anatomical information, these effects can be compensated during image reconstruction. Attenuation correction methods have been investigated using CT [19, 23–26] or MR [27–29]. Scatter correction methods have also been studied in [30–34]. More recently, using the fact that molecular and anatomical images are affected by the same motion, motion correction for emission tomography has been investigated. Motion information from high-resolution anatomical information such as CT [35, 36] or MR [37–40] was incorporated into reconstruction for motion-corrected PET or SPECT. Ideas of using structural couplings between molecular and anatomical images for reconstruction have been studied a couple of decades ago [41–43]. Recently, interesting advances for noise reduction of molecular images using anatomical information have been introduced with state-of-the-art methods for post-reconstruction filtering [44–47] or regularization in inverse problems [48–53].

The development of nuclear medicine instrumentation has been well reviewed in many works [3–8] and the

advance of iterative image reconstruction algorithms have also been comprehensively reviewed in [18]. Attenuation correction methods using CT [54] or MR [55], and scatter correction methods [20, 21] have also been reviewed. However, to the best of the author's knowledge, algorithm-oriented research works for improving the image quality of nuclear medicine using anatomical information during or after image reconstruction in various ways have never been reviewed comprehensively. In this article, we attempt to review these works in terms of three sub-topics: attenuation/scatter correction methods, motion compensation, and noise reduction. We will elaborate on them in the mathematical framework of statistical image reconstruction.

Review of Iterative Image Reconstruction

We will briefly review iterative image reconstruction algorithms for emission tomography for the sake of self-contained discussion.

Measurement Model

A common mathematical model for a mean measurement $\bar{y}$ of emission tomography is

$$\bar{y} = \mathbf{P}f + s \quad (1)$$

where $\mathbf{P}$ is a system matrix that contains imaging geometry, attenuation, detector response (PET), or collimator-detector response (SPECT), f is an activity distribution, and s is an additional measurement such as random (PET) and/or scatter. Usually, $\mathbf{P}$ and s are assumed to be known and f is an unknown vector parameter (or image) that needs to be estimated.

Then, a statistical model for a measurement y of emission tomography (one realization) is [13]

$$y \sim \text{Poisson}(\mathbf{P}f + s). \quad (2)$$

In other words, the measurement y is a Poisson realization of the mean measurement $\bar{y}$. Thus, the image reconstruction problem becomes an inverse problem, such that the unknown f is estimated from the given y based on Eq. 2.

OS-EM Algorithm

Once a likelihood function with the given y and the unknown f is constructed from Eq. 2, the most proba-

ble f for the given y can be estimated by maximizing the likelihood function with respect to f :

$$\hat{f} = \arg \max_f L(f; y) \quad (3)$$

where

$$L(f; y) := \sum_{i \in \Omega} [y]_i \log([P]f + s)_i - ([P]f + s)_i$$

where Ω is an index set for measurement space. This is called maximum likelihood (ML) estimation. In Eq. 3, log of the likelihood is maximized instead of the likelihood itself, but the resulting estimate $\hat{f}$ is the same since log is a monotonically increasing function. As side notes, for the case of high count measurements, a weighted least square model can be a good approximation for Eq. 3 [56] and for the case of list mode data, a similar likelihood can be constructed [57] and optimization algorithms can be derived [58].

One of the most popular algorithms to solve (3) is the EM algorithm [14, 15]:

$$[f^{(n+1)}]_j = \frac{[f^{(n)}]_j}{\sum_{i \in \Omega} [P]_{ij}} \sum_{i \in \Omega} [P]_{ij} \frac{[y]_i}{[P]f^{(n)} + s}_i \quad (4)$$

where $[P]_{ij}$ is an element of the matrix P at the i th row and j th column and $f^{(n)}$ is an estimate of f at the n th iteration. This algorithm guarantees a positive estimate $f^{(n)}$ if $f^{(n-1)}$ is positive and also guarantees to converge. The EM algorithm (4) has to calculate one forward projection (Pf in the denominator) and one back projection (the summation for i in the numerator) at each iteration, which are time consuming.

An ordered-subset (OS) approximation enabled significant speed up for the EM algorithm [17]:

$$[f^{(n+k/M+1/M)}]_j = \frac{[f^{(n+k/M)}]_j}{\sum_{i \in \Omega_k} [P]_{ij}} \sum_{i \in \Omega_k} [P]_{ij} \frac{[y]_i}{[P]f^{(n+k/M)} + s}_i \quad (5)$$

where $k = 0, \dots, M-1$ and Ω_k 's are subsets of Ω such that $\bigcup_{k=0}^{M-1} \Omega_k = \Omega$ and Ω_k 's are disjoint. Even though part of the projection data y is used for each sub-iteration in Eq. 5, both one iteration of Eq. 4 and one sub-iteration of Eq. 5 yielded similar quality updates for estimating f at early iterations. Since this approximation reduced computation complexity of projections and back projections about M times, OS-EM achieved almost M times faster convergence speed for initial iterations. This algorithm has been used in many clinical scanners for PET and SPECT image reconstructions.

Penalized ML-EM Algorithm

More iterations of Eqs. 4 and 5 often lead to more noisy activity images $\hat{f}$ [59]. One simple and practical solution for this issue is to use an early stopping rule. Many clinical PET or SPECT images are obtained with a few to tens of outer iterations with tens of subsets. However, limiting the number of iterations not only reduces noise but also recovers less high-frequency information or details. As an alternative method, prior knowledge on f has been used to design filters that can be applied after reconstruction and regularizers in inverse problems. A regularizer can be incorporated into Eq. 3 as follows:

$$\hat{f} = \arg \max_f L(f; y) - \beta R(f) \quad (6)$$

where β is a regularization parameter and $R(f)$ is a function to encourage estimated images to satisfy prior knowledge. For example, if it is known that images are smooth, then $R(f) = \|Cf\|^2$ can encourage smooth images where C is a difference operator. If images are known to have many sharp edges, then $R(f) = \|Cf\|$ can help estimated images to contain sharp edges.

Once the regularizer is added to the objective function as shown in Eq. 6, one popular method to solve this penalized ML problem in the EM algorithm framework is the Green's one step late (OSL) algorithm [60]:

$$[f^{(n+1)}]_j = \frac{[f^{(n)}]_j}{\sum_{i \in \Omega} [P]_{ij} + \beta \dot{R}(f^{(n)})} \sum_{i \in \Omega} [P]_{ij} \frac{[y]_i}{[P]f^{(n)} + s}_i \quad (7)$$

where

$$\dot{R}(f^{(n)}) = \frac{\partial}{\partial [f]_j} R(f^{(n)}).$$

However, unlike the original EM algorithm, the OSL algorithm is not guaranteed to converge and is not even well defined for the case of

$$\sum_{i \in \Omega} [P]_{ij} + \beta \dot{R}(f^{(n)}) = 0.$$

Lange proposed a modification for the OSL algorithm (7) to ensure monotonicity and global convergence [61]. Other solutions for Eq. 6 can be obtained using advanced optimization algorithms such as generalized EM [62, 63] or optimization transfer methods such as De Pierro's algorithm [64]. More advanced iterative reconstruction algorithms are comprehensively reviewed in [18].

Anatomical Information for Attenuation/Scatter Correction

Mathematical Models for Attenuation/Scatter Correction

Attenuation and scatter corrections are important factors for determining the image quality of quantitative nuclear imaging. Once attenuation information is given, attenuation factors can be applied to projection data [19] or to reconstructed images [65]. However, one of the most common methods for attenuation correction is to incorporate it into iterative image reconstruction methods. It requires the matrix $\mathbf{P}$ of Eq. 2 to contain attenuation information.

In PET, a line of response (LOR) is constructed with two gamma rays from a single point through positron annihilation, so the same attenuation value should be assigned to the pairs between each LOR and all voxels in that LOR. Thus, the matrix $\mathbf{P}$ for PET can be decomposed into $\mathbf{P} = \mathbf{A}\mathbf{G}$ where $\mathbf{A}$ is a diagonal matrix with attenuation values for each LOR and $\mathbf{G}$ is a geometric system matrix. Implementation of the matrix $\mathbf{A}$ for PET can be easily done by a simple component-wise multiplication for the output of the operator $\mathbf{G}$.

In SPECT, unlike PET, different attenuation values should be assigned to the pairs between each LOR and all voxels in that LOR [66]. Thus, the decomposition of the matrix $\mathbf{P}$ can be done by a component-wise multiplication $\mathbf{P} = \mathbf{A} \odot \mathbf{G}$ where $\mathbf{A}$ is not a diagonal matrix anymore [67]. Implementation of the matrix $\mathbf{A}$ for SPECT is not as computationally efficient as that for PET. Usual implementation of the projection matrix for SPECT involves attenuation factor calculation for pairs of each LOR and all voxels in that LOR along with efficient depth-dependent collimator-detector response calculation [68].

Therefore, the ML-EM algorithm (4) with incorporated attenuation correction factor (PET case) is

$$[f^{(n+1)}]_j = \frac{[f^{(n)}]_j}{\sum_{i \in \Omega} [\hat{\mathbf{A}}\mathbf{G}]_{ij}} \sum_{i \in \Omega} [\hat{\mathbf{A}}\mathbf{G}]_{ij} \frac{[y]_i}{[\hat{\mathbf{A}}\mathbf{G}f^{(n)} + s]_i} \quad (8)$$

where $\hat{\mathbf{A}}$ is obtained from an attenuation image (μ -map). The accuracy of attenuation correction is dependent on the accuracy of attenuation images with correct attenuation values and with no misalignment between activity and attenuation images.

For scatter correction, once scatter information is given with or without the aid of anatomical information, then scatter correction can be performed by subtracting the scatter information from the projection data [30, 69] or by

incorporating it in the statistical model (2) so that the EM algorithm becomes as follows:

$$[f^{(n+1)}]_j = \frac{[f^{(n)}]_j}{\sum_{i \in \Omega} [\mathbf{P}]_{ij}} \sum_{i \in \Omega} [\mathbf{P}]_{ij} \frac{[y]_i}{[\mathbf{P}f^{(n)} + \hat{s}]_i} \quad (9)$$

where $\hat{s}$ is an estimated scatter image vector. Sometimes, $\hat{s}$ depends on the estimated activity image, so more accurate scatter correction may be possible by estimating scatter during image reconstruction or $\hat{s} = \hat{s}(f^{(n)})$. This can be implemented by using Monte Carlo (MC) simulations [70–72], model-based scatter estimation [32, 33], or dual matrix approach [73].

Sources of Attenuation/Scatter Information

There are three conventional sources to obtain attenuation images. The first method is to use a transmission scan using emission source to acquire an attenuation image [23, 24]. This approach can provide accurate attenuation values (from the same energy), but with low spatial resolution, high noise, and additional scanning time (2 to 20 minutes). The second method is to estimate both activity and attenuation only from emission data [25, 74, 75]. This method enables accurate attenuation value estimation without additional scans, but with low spatial resolution, high noise, and high computation complexity. The third method is to use a low-noise, high-spatial-resolution CT image and to transform it to an attenuation μ -map [76]. Using separately acquired CT information to derive attenuation image for emission tomography has been studied in the past [26]. However, CT-based attenuation correction for PET or SPECT became a popular technique in clinics after it became possible to obtain a well-aligned attenuation image from a CT image due to the advent of PET-CT and SPECT-CT [77]. PET-CT and SPECT-CT significantly improved the image quality of PET and SPECT using attenuation information from a very short scan (a few seconds) of an additional CT image [19, 22].

Recently, additional radiation dose from CT became one of the major concerns in clinics. There are three recent approaches to obtain accurate attenuation information without (or with minimal) additional radiation dose. One is to use a low-dose CT image to acquire the attenuation image [78–80]. Another is to perform simultaneous estimation of activity and attenuation from time-of-flight (TOF) PET [81, 82] based on the recent theoretical advance that TOF PET can reduce cross-talk between activity and attenuation images [83]. The last one is to extract attenuation information from MR images, especially for recently developed

simultaneous PET-MR scanners [84]. There are two ways of using MR images to generate μ -map. One is to segment a MR image into 3–5 classes (e.g., bone, air, soft tissue, lungs, etc.) and to assign a single value to each class. Using discretized attenuation values for μ -maps instead of a continuous attenuation image was evaluated in [28, 29] and the accuracy of reconstructed images is dependent on locations. It was claimed that it is feasible to use discretized μ -maps clinically. Segmentation is performed on T1-weighted or T2-weighted MR images [29, 85, 86] or on ultrashort echo time (UTE) sequence MR images for better imaging bones with very short T_2 values [87, 88]. The other is to use atlas-based methods with machine learning techniques [27, 89]. For more information about MR-based attenuation correction methods, see [55]. All methods reported that it is possible to obtain good-quality PET or SPECT images without regular-dose CT information. However, more investigation will be required for clinical applications.

For scatter corrections, some energy-resolved SPECT cases do not require explicitly given or implicitly estimated anatomical information to obtain accurate scatter information with methods such as triple energy window (TEW) technique [34]. However, in many cases, anatomical information is very important to accurately estimate scatter information along with an estimated activity image. There are many scatter estimation methods that use both anatomical image and activity image such as convolution-subtraction scatter estimation [30, 69], MC based scatter estimation [31, 34, 70–72], model-based scatter approximation [32], and single scatter simulation (SSS) [33].

Examples of Attenuation/Scatter Correction

Figure 1 demonstrates the importance of attenuation/scatter correction using an example of SPECT-CT in I-131 radioimmunotherapy for non-Hodgkin lymphoma. The original data was acquired under an institutional review board-approved protocol and this retrospective study was also performed under an institutional review board-approved process. The original SPECT data was obtained with a 20-min acquisition, body contouring, 60 views, and 128×128 bins (4.8×4.8 mm). Figure 1a shows a μ -map for attenuation correction that is transformed from a low-dose CT image with $128 \times 128 \times 81$ voxels ($4.8 \times 4.8 \times 4.8$ mm) using a bilinear fitting function. Scatter was estimated using TEW. The ML-OS-EM algorithm with 35 iterations, 6 subsets was performed to reconstruct all SPECT images. Collimator detector response was implemented in the system matrix of reconstruction algorithm [90].

Figure 1b shows a reconstructed SPECT image of a patient with both attenuation and scatter corrections. Figure 1c shows an estimated SPECT image using the ML-OS-EM algorithm with attenuation correction, but

Fig. 1 a μ -map image derived from a CT, b SPECT image with both attenuation and scatter corrections, c SPECT image with attenuation correction only, d SPECT image with scatter correction only. All SPECT image are in the same intensity scale

without scatter correction. Figure 1d shows a SPECT image without attenuation correction, but with scatter correction. Figure 1c, d show different activity levels and distributions as compared to Fig. 1b. This example shows how important it is to incorporate attenuation and scatter information for quantitative emission tomographic images.

Anatomical Information for Motion Compensation

Mathematical Models for Motion Compensation

Respiratory or cardiac motions of patients are inevitable in PET and SPECT imaging due to relatively long acquisition time (a few minutes to tens of minutes). In the past, motion artifact was ignored since the spatial resolution of PET and SPECT was poor. However, recent advances of PET and SPECT scanners have improved spatial resolution, so motion correction in PET and SPECT became one of the key factors to determine image quality.

When there is patient motion during scanning, Eq. 2 does not hold anymore since f is time-varying. Then, it is reasonable to assume that there are several f_k s (or gated images) corresponding to different motion phases (or gates), for pseudo-periodic respiratory or cardiac motions. A new count generation model is

$$y_k \sim \text{Poisson}(\mathbf{P}_k f_k + s_k), \quad k = 1, \dots, K \quad (10)$$

where $\mathbf{P}_k$'s contain different attenuation maps for different gates and y_k is a measurement at the k th gate (or frame). Note that the y in Eq. 2 and the sum of y_k 's in Eq. 10

should be the same since the y is time-binned into different y_k 's. Since gating methods use part of the data, resulting reconstructed images are noisier.

Many researchers have worked on motion compensated image reconstruction (MCIR) methods that use all the data while correcting for motion artifacts. There are three different motion correction models for MCIR. The first method is to sum motion-corrected gated images [91], called post-reconstruction motion correction (PMC) [92, 93]. Assume that motion information $T_{k,l}$'s between two gated images f_k and f_l are given such that

$$f_k = T_{k,l} f_l, \quad k, l = 1, \dots, K. \quad (11)$$

The gated images $\hat{f}_k$'s can be reconstructed from the gated measurements y_k 's by maximizing

$$\sum_{k=1}^K L_k(f_k; y_k) \quad (12)$$

with respect to all f_k 's using any reconstruction algorithm such as Eq. 5 where

$$L_k(f; y) := \sum_{i \in \Omega} [y]_i \log([\mathbf{P}_k f + s_k]_i) - ([\mathbf{P}_k f + s_k]_i).$$

Then, the final motion corrected image is

$$\hat{f}_{\text{PMC}} = \frac{1}{K} \sum_{i=1}^K T_{1,k} \hat{f}_k. \quad (13)$$

The second method is to design a temporal regularizer that encourages two motion-corrected gated images to be the same [94], called motion-compensated temporal regularizer (MTR) [92, 93]. This temporal regularizer can be incorporated into Eq. 12 as follows:

$$\sum_{k=1}^K L_k(f_k; y_k) - \eta \|f_{k+1} - T_{k+1,k} f_k\|^2 \quad (14)$$

where $T_{K+1,K} := T_{1,K}$.

The third method is to incorporate motion information into the measurement model [35, 36, 95–97], called parametric motion model (PMM) [92, 93]. The gated measurement model (10) can be combined with Eq. 11 to yield a measurement model at the k th gate with the activity image at the first gate:

$$y_k \sim \text{Poisson}(\mathbf{P}_k T_k f_1 + s_k), \quad k = 1, \dots, K \quad (15)$$

where $T_k := T_{k,1}$. Then, all the gated measurements y_k 's can be related to the activity image f_1 and the original objective function (12) becomes

$$\sum_{k=1}^K L_k(T_k f_1; y_k). \quad (16)$$

Maximizing (16) with respect to f_1 leads to algorithms such as the following motion-corrected EM algorithm:

$$[f_1^{(n+1)}]_j = \frac{[f_1^{(n)}]_j}{S_j} \sum_{k=1}^K \sum_{i \in \Omega} [\mathbf{P}_k \hat{T}_k]_{ij} \frac{[y_k]_i}{[\mathbf{P}_k \hat{T}_k f_1^{(n)} + s_k]_i}. \quad (17)$$

where $S_j = \sum_{k=1}^K \sum_{i \in \Omega} [\mathbf{P}_k \hat{T}_k]_{ij}$. Theoretically, PMM in Eq. 16 has lower variance than or equal variance to PMC in Eq. 13 when there are regularizers with carefully matched spatial resolution [92, 93]. MTR in Eq. 14 yields the same variance level as gated images in Eq. 12 if $\eta = 0$ and yields the same variance level as PMM in Eq. 16 if $\eta \rightarrow \infty$ [93].

Sources of Motion Information

When dividing the measurement into several gates corresponding to different motion phases, conventional methods are using surrogate signals of respiratory or cardiac motions. Examples of these signals are infrared sensors [98, 99], respiratory bellows [100], breathing temperature [101], list-mode data itself [102] for respiratory motion, and electrocardiogram (ECG) [100] for cardiac motion. For more detailed information on gating, see [103]. However, the recent development of combined PET-MR enabled measuring respiratory motion of diaphragm directly using MR navigator sequences [104] instead of using surrogate signals. For more information on motion correction options with PET-MR, see [105].

Motion information can be estimated without anatomical information such as simultaneous estimation of image and motion from emission data only [95–97]. However, joint estimation methods require high computation complexity. Motion estimation from gated 4D CT was considered in [35, 36], but radiation dose and motion mismatch due to sequential acquisition of CT and PET (or SPECT) were major concerns. Recent advances in simultaneous PET-MR showed potentials to estimate accurate motion from high-resolution MR images without additional radiation dose and achieved substantial quantitative improvements in PET imaging [37–40].

Examples of Motion Compensation

Figure 2 shows a motion-corrected image reconstruction example using simultaneous PET-MR. A balloon phantom with attached radioactive spheres was in the gel with background activity and the motion of the balloon mimics a cardiac motion with a 1-s period. PET-MR scanned this phantom for list-mode PET and GRE MR sequence with (or without) tagging simultaneously. Tagged MR sequence creates a temporary periodic magnetization patterns (tags) before MR acquisition. These patterns move with tissues

Fig. 2 **a** Simultaneously obtained 4D tagged MR images (two selected images are shown) and two estimated motion fields from non-tagged and tagged MR images with GRE sequence. **b** Reconstructed image using all the data without motion correction (uncorrected) yielded lower contrast in the sphere and lower noise in the background. Estimated image using part of the data corresponding to one motion

phase (gated) yielded higher contrast in the sphere and higher noise in the background. The image using all the data with MR-based motion correction (motion corrected) yielded higher contrast and lower noise. Reconstructed image using one motion phase corresponding data from 20 times more total measurements (ref gated) shows similar results with the MR-based motion correction

so that accurate tracking of the tissue motion becomes possible. Figure 2a shows results of 4D MR images (only two selected images were shown) and estimated motion fields with and without tagging information. These results show that tagged MR-based motion estimation can yield more realistic motion fields. This motion information from MR was incorporated in the image reconstruction (17) and Fig. 2b shows that the resulting image with MR-based motion correction (motion corrected, 6 min) yielded better contrast than that with no motion correction (uncorrected, 6 min) and lower noise than that with gating (gated, 6 min). Figure 2b also shows that MR-based motion correction yielded comparable results to our gold-standard reference motion correction method (ref gated, 120 mins), which is gating without motion estimation, but requiring 20 times longer acquisition time.

Anatomical Information for Noise Reduction

Mathematical Models for Noise Reduction

Noise reduction has been one of the fundamental topics in image processing. One of the most common models for denoising is a weighted sum of noisy image $\hat{f}$:

$$[\hat{z}]_i = \sum_{j \in \Theta_i} w_{ij} [\hat{f}]_j \quad (18)$$

where $\hat{z}$ is a denoised image and Θ_i is usually a set of local neighborhood voxels around the i th voxel. A popular weight function for w_{ij} is a Gaussian kernel. However, fixed weights not only reduce noise but also blur details of images. Image-dependent weights have been proposed:

$$[\hat{z}]_i = \sum_{j \in \Theta_i} w_{ij}(\hat{f}) [\hat{f}]_j. \quad (19)$$

For example, bilateral filter assigns higher weights for smaller distance between two voxels and smaller image intensity difference on the same two voxels for local neighborhood set Θ_i [106]. Non-local means (NLM) filter assigns higher weights for smaller intensity difference between two local patches around two voxels for non-local neighborhood set Θ_i [107]. Lastly, guided image filter determines weights based on statistical properties of a guide image (given noisy image or smoothed image with a Gaussian filter) for local neighborhood set Θ_i [108].

Even though anatomical information is different from functional (or molecular) information, it is believed that both have fairly good structural coupling or correlation. Since anatomical information usually has high spatial resolution (e.g., CT, MR) and functional information has low spatial resolution, there have been many attempts to improve functional image quality by using anatomical information (or side information) since the early 1990s. The basic idea is to use an anatomical image g in the post-reconstruction filter design or regularization design in inverse problems.

Anatomical information has been used to improve the accuracy of weights in Eq. 19 so that

$$[\hat{z}]_i = \sum_{j \in \Theta_i} w_{ij}(\hat{f}, g)[\hat{f}]_j \quad (20)$$

where anatomical image g was incorporated into filters. For example, in NLM type filters, weights can be determined based on the patch similarities from both PET (or SPECT) and the anatomical image or weights from the molecular image can be only used when the corresponding pixel pairs have high similarity for the anatomical image [44, 45]. In variants of guided image filters, the low-noise anatomical image can be used as a guide image to improve the quality of filtered image, especially when both molecular and anatomical images share the same edge structures [46, 47]. Note that guided image filter is much faster than NLM filter in computation.

Although post-reconstruction filters are computationally fast, using regularization in iterative image reconstruction is preferable over post-reconstruction filtering for better image quality [48]. There have been many attempts to incorporate the anatomical image g in the penalized ML framework:

$$\hat{f} = \arg \max_f L(f; y) - \beta R(f; g) \quad (21)$$

where a regularizer $R(f; g)$ can be designed based on prior information about molecular and anatomical images.

For example, regularizers can be designed to enforce less smoothing on edges [41, 50, 51]. Another regularizer can encourage similar intensity values of molecular image for similar regions of anatomical image such as Bowsher prior [42, 43, 109]. Information theoretic measure can be used to design $R(f; g)$ in Eq. 21 such as a negative mutual information or negative joint entropy [49, 53, 110]. A recent study showed that Bowsher prior-based image reconstruction [109] yielded the best image quality among edge information-based method, region-based method, and joint entropy-based method [52]. Iterative image reconstruction requires evaluating the gradient of regularizers at every (sub-)iterations, so computation complexity for using anatomical information-based regularizers is high. An advanced algorithm for computationally heavy regularizers was proposed and showed promising results of improved convergence speed [111].

Examples of Noise Reduction

Figure 3a, d show a filtered back-projection (FBP) C-11 ABP 688 dynamic brain PET image and a simultaneously acquired MR image, respectively. The original data was acquired under an institutional review board-approved protocol and this retrospective study was performed under an institutional review board-approved process. Figure 3b

Fig. 3 **a** FBP brain PET image, **b** Gaussian filtering image removes both noise and details, **c** NLM filtering without MR image removed noise more while preserves some edge information, **d** simultaneously

acquired MR image, **e** NLM filtering with MR image improved edge sharpness slightly compared to NLM, **f** Guided filtering with MR image improves edge sharpness the most

shows that Gaussian filtered image reduces noise and details such as sharp edges, but Fig. 3c shows that NLM filtering without MR image reduces noise more while preserves edge information. Figure 3e shows that NLM filtering with MR image improved edge sharpness compared to NLM on some areas with structural matching between PET and MR. Lastly, Fig. 3f shows that the guided filtering with MR image achieved the most sharp edges among all other methods. Even though using anatomical information can improve the image quality of molecular information in certain measures such as minimum mean square errors or recovery, the clinical impact of these improvements should be evaluated through more validations.

Conclusions

We reviewed the use of anatomical information in iterative image reconstruction methods in view of mathematical algorithms. Significant image quality improvements have been achieved through attenuation/scatter correction, motion compensation, and noise reduction using anatomical information from hybrid nuclear medicine imaging scanners. Attenuation and scatter corrections are used in many clinical procedures using PET or SPECT, but motion compensation and noise reduction with anatomical information are still at research level. Exploiting anatomical information for molecular image reconstruction may open new opportunities for better clinical outcomes, but more clinical validations will be required. Since the same anatomical information can be used for various correction methods multiple times, it will be more important to obtain well-aligned CT or MR images with molecular images to have more benefits for image quality improvement.

Acknowledgments This research was supported in part by the 2013 Research Fund (1.130006.01) of UNIST (Ulsan National Institute of Science and Technology) and in part by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (NRF-2014R1A1A1007928). The author would like to thank Prof. Jae Sung Lee, Seongho Seo at Seoul National University, Prof. Yuni Dewaraja at the University of Michigan Hospital, and Prof. Georges El Fakhri at Harvard Medical School for providing data.

Compliance with Ethical Standards For this type of study formal consent is not required. This article does not contain any studies with human participants or animals performed by any of the authors. This manuscript has not been published before or is not under consideration for publication anywhere else and has been approved by all co-authors.

Conflict of interests Se Young Chun declares that he has no conflict of interest.

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