Methods 48 (2009) 83–91

Contents lists available at ScienceDirect

Methods

journal homepage: www.elsevier.com/locate/ymeth

Review Article

Small animal imaging with multi-pinhole SPECT ☆

Johan Nuyts [a,*], Kathleen Vunckx [a], Michel Defrise [b], Christian Vanhove [b]

[a] Nuclear Medicine, Katholieke Universiteit Leuven, UZ Gasthuisberg, Herestraat 49, B3000 Leuven, Belgium
[b] Nuclear Medicine, Vrije Universiteit Brussel, Belgium

ARTICLE INFO

Article history:
Accepted 11 March 2009
Available online 26 March 2009

Keywords:
SPECT
Micro-SPECT
Pinhole
Tomography
Calibration
System matrix
Maximum-likelihood
Maximum-a-posteriori estimation

ABSTRACT

With Single Photon Emission Computed Tomography (SPECT), images of minute concentrations of tracer molecules can be acquired, allowing in vivo molecular imaging. For human imaging, the SPECT system has a modest spatial resolution of 5–15 mm, a large field of view and a high sensitivity. Using multi-pinhole SPECT, one can trade in field of view for resolution with preserved sensitivity, which enables the implementation of a small animal SPECT system with an improved resolution, currently ranging from 0.3 to 2 mm, in a much smaller field of view. The unconventional collimation and the more stringent resolution requirements pose problems that are not present in clinical SPECT imaging. This paper discusses how these problems can be solved to implement micro-SPECT imaging on a rotating gamma camera.

1. Introduction

In the last decade, small animal SPECT imaging has made considerable progress, driven by the demands from medical and biological research. Several approaches have been followed to implement small animal SPECT imaging. Some groups converted a clinical gamma camera into a micro-SPECT system using new collimators and software, others built a whole new system dedicated to high resolution imaging of a small object [1]. Most systems rely on pinhole collimation, although other collimators are being considered, including rotating slit–slat collimators [2], translating slit collimators acquiring linograms [3] and rotating slat collimators [4,5]. All these collimators scan along converging projection lines resulting in zoomed projections along one or two dimensions, which creates better usage of the available detectors.

In this paper, only multi-pinhole SPECT is considered. Many different system designs have been proposed, ranging from systems based on a rotating gamma camera [6–8], a stationary camera with rotating collimator [9] or a completely stationary camera [10–12]. We focus on multi-pinhole SPECT using a rotating gamma-camera, although part of what is presented here also holds for stationary systems.

For accurate reconstruction, the projector and backprojector must be based on an accurate model for the system geometry. This can be determined in several ways. The most straightforward one is to scan a small point source through the field-of-view, and directly measure the corresponding point spread function for each of the pinhole apertures [10–12]. This approach is slow and requires sophisticated positioning tools, but is highly accurate and directly measures the entire system matrix. It is probably best suited for stationary systems, because they are expected to have a more stable system matrix. In contrast, rotating systems, in particular those based on a clinical gamma camera, have many degrees of freedom and hence can use different system matrices for different scans. For those systems, an easier method to determine the system matrix is useful. In the next section, different approaches for modelling the system matrix are discussed. Finally, an approach to compare the effects of a particular choice of system design parameters on the resolution and noise characteristics of the reconstructed images is discussed.

2. System matrix model

Single or multi-pinhole SPECT projections using a rotating gamma camera provide incomplete tomographic information [13]. However, in practice, good reconstructions can be obtained with maximum-likelihood (ML) or maximum-a-posteriori (MAP) reconstruction. The algorithms use a discrete model to represent the unknown tracer distribution and the acquired projections; the relation between the two can be written as

$$Y = AX \quad \text{or} \quad y_i = \sum_j a_{ij} x_j, \tag{1}$$

☆ This work is supported by F.W.O. grant G.0569.08, by IAP-grant P6/38 and by MOSAIC, the K.U. Leuven Molecular Small Animal Imaging Center (KUL EF/05/08).
* Corresponding author. Fax: +32 16 34 37 59.
E-mail address: Johan.Nuyts@uz.kuleuven.be (J. Nuyts).

1046-2023/$ - see front matter © 2009 Elsevier Inc. All rights reserved.
doi:10.1016/j.ymeth.2009.03.015

where Y is a $I \times 1$ matrix containing the measured counts y_i in the detector elements $i = 1 \ldots I$, X is $J \times 1$ matrix with the reconstruction values x_j, and A is the $I \times J$ system matrix. Its element a_{ij} is the expected amount of photons contributed by a unit of activity at position j to the measurement at detector i. For reconstruction, the elements a_{ij} of the system matrix must be known with good accuracy; system modelling errors will cause reconstruction artifacts.

As discussed above, a first class of methods consists in directly measuring each element of the system matrix [10–12]; this *direct method* however requires long acquisitions to collect a sufficient number of counts in each detector i and for each position j of the source. This limitation can be alleviated by measuring the system response for a limited number of positions j of the source that sample the field-of-view; the response for other locations being estimated by interpolation [12]. Fitting a parametric model of the response to the point source measurement can also improve the stability of the estimated system matrix. For non-stationary micro-SPECT systems an additional difficulty with direct methods is the assumption of a perfect reproducibility of the scanner mechanical motion, required to ensure that the calibrated system matrix coincides with the actual matrix at the time of the measurement on the small animal. A potential solution to this problem would be to measure the system matrix A^0 for a single reference position ^{0} of the camera; during reconstruction the image matrix is premultiplied at each position $k = 1,\ldots,K$ of the scanner by a rigid body transformation matrix C^k determined using the geometric calibration described in Section 2.1. This amounts to writing

$$A = \begin{pmatrix} A^0C^0 \\ A^0C^1 \\ \cdots \\ A^0C^K \end{pmatrix} \tag{2}$$

where K is the number of positions of the camera. Care must be taken to use a robust interpolation when discretizing the geometric transformation to define C^k [14]. A similar decomposition of A has been applied to a micro-PET scanner based on rotating panel detectors [15], though in that case the reference system matrix A^0 was determined by means of a multi-ray method (see below). To our knowledge, this technique has not been applied in micro-SPECT.

A second class of methods estimates the system matrix elements using *Monte-Carlo simulation* [16–18]. Starting from an accurate description of all components of the detector, a simulated point source is placed in voxel j of the image matrix, the isotropic emission of a large number N_j of gamma rays is then simulated and the transport of each gamma ray towards the collimator, through the collimator, and finally through the gamma camera is simulated using for instance the Gate software simulation platform. The fraction of the simulated emission that is detected in detector i then yields an estimate $a_{ij} \simeq N_{ij}/N_j$, where N_{ij} is the number of simulated detections in detector i. If the Monte-Carlo simulation perfectly models the system, this method provides a bias-free estimate of a_{ij}, but affected by a relative standard deviation equal to $1/\sqrt{N_j}$. Reducing this standard deviation to an acceptable level while keeping the computation time—even if it is off-line—acceptable is the major challenge of the Monte-Carlo method. The use of variance reduction methods [19] and the ongoing development of a fast version of the Gate software (http://www.fgate.fr/) might in the near future make this approach practical for multiple pinhole SPECT. Note that Monte-Carlo simulation can already now be used to simulate parts of the system matrix, such as the penetration of the gamma rays through the edges of the pinhole aperture. The thus estimated quantities are then used to refine an approximate analytic model of the system matrix [20]. (A similar approach may be based on analytic models of the pinhole aperture [21–23]).

Two remarks are in order concerning the two classes of methods discussed so far, direct measurement and Monte-Carlo estimation. First, these methods yield a system matrix that does not model the attenuation and scattering of the gamma rays within the imaged body. This limitation is much less serious for small animal imaging than for clinical imaging, especially for mice. Attenuation correction, when nevertheless deemed necessary, needs to be incorporated separately by pre-multiplying the image by an attenuation matrix calculated e.g. from a micro-CT scan of the animal. Note that for multiple pinhole collimation, a separate attenuation matrix must be used for each camera position *and* for each pinhole aperture. Scatter correction can be estimated either from a separate, object dependent, Monte-Carlo simulation, or using dual or triple energy windows based methods. A second issue with direct measurement and Monte-Carlo estimation is that these methods are far too time consuming to be applied online. They therefore require storing the measured or calculated system matrix on disk, which is difficult in view of the huge size of the matrix: typically A might be a $10^6 \times 10^6$ matrix. Since object scatter is not included, this matrix is sparse, which reduces the number of non-zero elements to be stored to a more practical level. Additional storage gains may be obtained by considering a single scanner position A^0 as described above, by exploiting symmetries of the scanner, or other compression techniques similar to those proposed by Rehfeld et al. [24] for the PET application.

The system matrix measurement time and storage requirements can be further reduced by factorisation. A possible factorisation can be written as

$$A \simeq \sum_{m=1}^{M} A_1^m A_2^m \tag{3}$$

$$A_1^m[i,i] = S_1^m(\vec{i}) \tag{4}$$

$$A_2^m[i,j] = S_2^m(\vec{i}, j, G_D, \theta), \tag{5}$$

where A_1^m are $I \times I$ diagonal matrices and A_2^m are $I \times J$ matrices, $\vec{i} \in \mathbb{R}^2$ represents the 2D detector coordinates of element i and G_D is the set of parameters describing the pinhole geometry and θ is the acquisition angle. The summation is over all M apertures of the multi-pinhole system. $S_1^m(\vec{i})$ models the variation of the sensitivity with the angle of the projection line. For a particular aperture m, it depends on the detector position only, and can be measured using a uniform plane source. S_2^m models the blurring due to the aperture and the decrease of sensitivity with increasing distance to the aperture. The computation of S_2^m requires accurate determination of the position of the apertures with respect to the detector and to the object space. A method to determine these parameters is described in the next subsection. The second subsection briefly discusses the collimator sensitivity measurement, the last subsection presents some resolution modelling approaches.

2.1. Geometrical calibration

Mathematically, the calibration problem of a pinhole system is identical to that of a cone beam CT [25,26] or SPECT system [27,28]. Many authors have studied this problem and a series of different calibration procedures have been proposed. Many of those involve the acquisition of a calibration phantom consisting of point sources [29–33]. In these calibration methods, it is assumed that the projection of a point source through an aperture can be described with two coordinates, while in a real image, such a projection shows up as a small blob (Fig. 1). Typically, the mass center of the blob is computed as an estimate of the intersection of the detector plane and the line defined by the center of the point source and the center of the aperture.