

## 2) 単一軌道データの不完全性

単一円軌道で得られる再構成画像の中央断面以外での画像歪みは、Fig. 3 に示すように、RI ディスク 1 と 2 の隙間がピンホールによって直接観察することができるのに対して、RI ディスク 3 と 4 の隙間は直接観察することはできないことに起因する。この状況を 3 次元周波数空間で説明すると、被写体の 3 次元周波数成分のうち Fig. 4 に示された円錐状の部分 (missing cone) が測定できずに欠落したものとなる [26, 27]。欠落の度合いは、再構成する点に依存し中央断面から離れるほど大きくなる。

厳密な 3 次元画像再構成のためには、3 次元周波数空間において、すべての周波数成分が測定されることが条件となる。この条件を満たした測定データが完全データと呼ばれる。

## 4. 完全データを利用したピンホール SPECT

### 1) 完全データ収集軌道

Tuy はコーンビーム CT において、厳密な 3 次元画像再構成のための完全データ収集軌道条件を幾何学的に明快に導いた (Tuy の条件) [28]。その条件とは「被写体 (再構成視野) と交わるすべての平面が X 線源の軌道と交わる」である。これはピンホール SPECT に対して「被写体と交

わるすべての平面がピンホール軌道と交わる」と置き換えることができる。Tuy の条件を満たす比較的实现が容易な 3 つの軌道として、Fig. 5 に示す「2 つの円」「らせん」「円と直線」などがある [29 ~ 32]。工藤と斉藤はこれらの軌道によって得られる円錐ビーム投影データから 3 次元 CT 画像が再構成できることを明らかにした [33]。Metzler らはらせん軌道 (ヘリカルスキャン方式) によって完全データ収集を実現した [34]。

### 2) 2 軌道完全データ収集システム

著者らは上記 3 つの代表的な軌道の中から、「2 つの円軌道」を採用した [35]。X 線 CT で採用されている「らせん」や「円と直線」の軌道は関心領域がガンマカメラの視野中心から外れるため感度低下をきたすのに対して、2 つの円軌道はピンホールの中心が常に関心領域の中心を向いているので、脳や心臓などの臓器の撮像に対して感度低下なく完全データが収集できると考えられる。また、ラットやマウスなどの被写体は縦長であるため、2 つの円軌道として、体軸に対して垂直な軌道と  $45^\circ$  傾いた軌道を採用した。この軌道は Fig. 6 に示すように Tuy の条件を満足しているため、単一軌道で欠落した周波数情報を補うことができる。

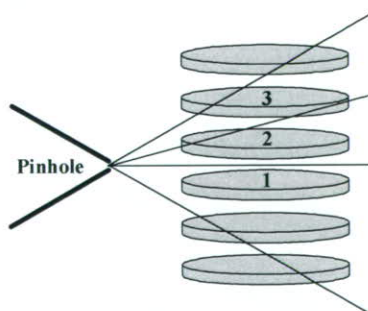


Fig. 3 Incompleteness of data in non-central slices, in case of pinhole SPECT with a circular orbit.

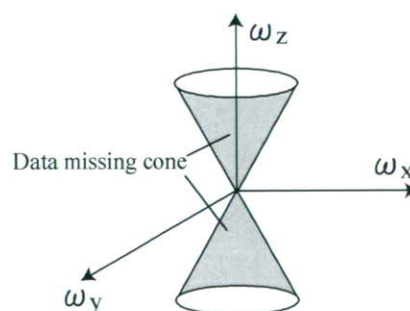


Fig. 4 Fourier spectrum obtained by single circular orbit.

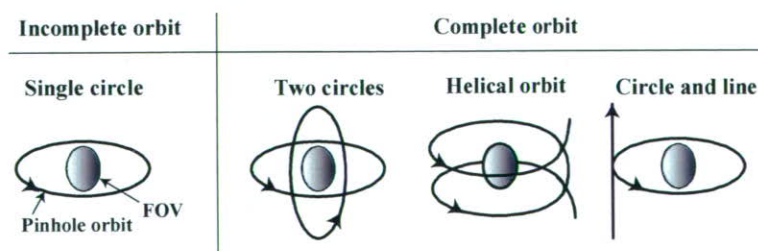


Fig. 5 Examples of the orbits satisfying Tuy's condition for complete data acquisition.

ピンホール SPECT システムを構築する場合、回転中心精度が問題となる。重いガンマカメラを回転させる臨床用 SPECT は、機構上回転中心のずれが生じるが、解像度 10 mm 程度の臨床撮像では問題にならない。しかし、高解像度のピンホール SPECT で、臨床用ガンマカメラを回転させた場合、微妙な中心のずれが再構成画像にアーチファクトや解像度低下をもたらす [11]。Habracken らはカメラを固定して小動物を回転させる方式で、回転中心のずれがほとんどないと報告している [36]。著者らも同様に被写体を回転させる方式で 2 軌道システムを構築した (Fig. 7)。Fig. 7(a) のように被写体を垂直に立てた状態

と、Fig. 7(b) のように被写体を 45° 傾けた状態でスキャンする。これによって、Fig. 6(b) に示した 2 軌道スキャンと等価なデータが得られる。

### 3) 2 軌道データからの画像再構成 (two-orbit 3D-OSEM)

Fig. 8 のように 2 軌道で収集されたデータからの MLEM 画像再構成は次式で表される。

$$\lambda_j^{k+1} = \frac{\lambda_j^k}{\sum_{l=1}^2 \sum_{i=1}^n C_{lij}} \sum_{l=1}^2 \sum_{i=1}^n \frac{y_{li} C_{lij}}{\sum_{j=1}^m C_{lij} \lambda_j^k} \quad (6)$$

ここで  $k$  は繰り返し回数、 $j$  は再構成マトリクスの座標で、1 から  $m$  までの通し番号で表される。また、 $i$  は検出器上の座標を表し、各軌道の回転角度方向のデータも含めて  $n$  個の一連のデータとする。 $\lambda_j$  は再構成マトリクス画素  $j$  の再構成値、 $y_{li}$  は軌道  $l$  での検出器上の画素  $i$  における測定投影データ、 $C_{lij}$  は軌道  $l$  での再構成画素  $j$  から出た光子 (ガンマ線) が検出器画素  $i$  に到達する割合 (検出確率) である。

このアルゴリズムは大まかに次の 4 つのステップからなる。(1) 再構成画像  $\lambda_j^k$  を検出器に投影する (順投影: forward-projection), (2) 測定投影データと順投影データの比を求める, (3) 2 つの軌道で得られた投影データの比 (2) の値) を再構成マトリクスに逆投影する (back-projection), (4) 逆投影した値を検出確率で規格化して、 $\lambda_j^k$  に掛け、更新画像  $\lambda_j^{k+1}$  を得る。

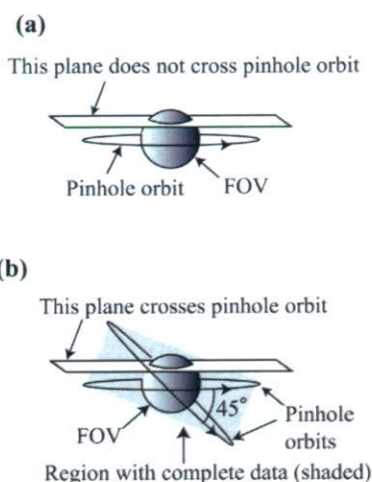


Fig. 6 Completeness of data acquired by each pinhole orbit. (a) A single circular orbit does not satisfy Tuy's condition. (b) Our employed two circular orbits, with one rotated by 45°, satisfy Tuy's condition. The two orbits can provide complete data for reconstruction in the shaded region, which encompasses the FOV as volume of interest.

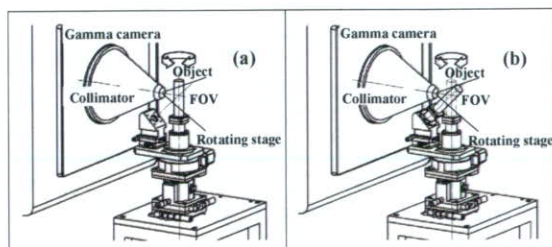


Fig. 7 Schematic diagram of our pinhole SPECT system with two circular orbits of pinhole. A pinhole collimator fitted to a conventional gamma camera is fixed. Two-orbit projection data are acquired by rotating stage, which holds an object at 0° (a: vertically) and 45° (b: obliquely) along the axis of rotation.

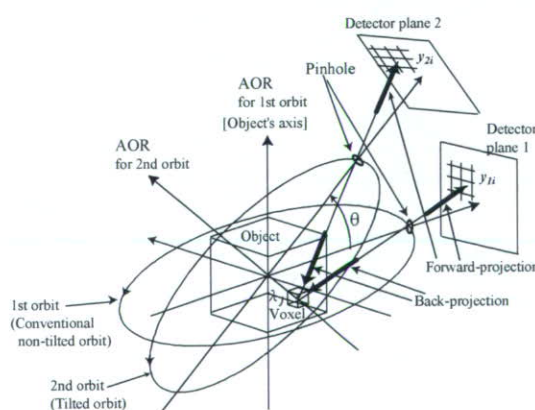


Fig. 8 Schematic diagram of the 3D-MLEM reconstruction from projection data by two circular orbits with our pinhole SPECT system.



著者らは、繰り返し回数を少なくして、収束を速くするために、OS アルゴリズムを 2 軌道投影データに適用した。2 つの投影データは均等にサブセット化された。たとえば、各軌道で 120 方向の投影データが収集され、2 軌道投影データを 8 サブセットに分けた場合、1 つのサブセットには 30 方向の投影データが割り当てられることになる (第 1 サブセットは 2 つの軌道の  $0^\circ, 24^\circ, 48^\circ, 72^\circ, \dots, 336^\circ$  の角度方向のデータで構成される)。本アルゴリズムでは、軌道の傾き角度  $\theta$  は任意に選択できる。

5. 評価実験

1) ディスクファントム実験

3 次元再構成画像における本システムの効果を確認するために、マルチディスクファントムを撮像し、体軸方向の解像度の均一性および統計ノイズ特性を評価した。ファントムは  $^{99m}\text{Tc}$  溶液が満たされた 1.5 mm 厚のディスク状領域が 10 mm 間隔で 8 つ配置されている。1 mm 径のピンホールを使用、ROR を 93 mm として、2 軌道を各 120 分間スキャンし、各軌道 120 の投影データを得た。

Fig. 9 が示すとおり、従来の単一軌道データを Feldkamp 法で再構成した結果では、視野の中心のみでディスクが認められるが、中心以外では画像が大きく歪み、ディスクを弁別することは

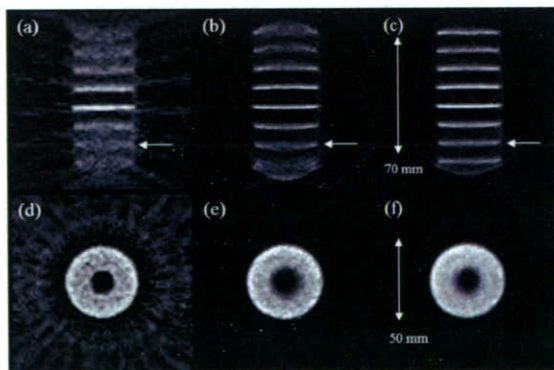


Fig. 9 Reconstructed images of the multiple disk phantom. (a)-(c) are coronal slices. (d)-(f) are transverse slices at the level indicated by arrows in coronal slices. (a) and (d) by Feldkamp method for single-orbit data. (b) and (e) by conventional 3D-OSEM method for single-orbit data. (c) and (f) by two-orbit 3D-OSEM method for two-orbit data.

困難であった (Fig. 9(a)). また、単一軌道データを 3D-OSEM で再構成した結果では、これまでの報告 [8, 25] のように画像歪みの改善は見られたが、周辺付近はまだ歪んでいる (Fig. 9(b)). 一方、2 軌道収集による完全データに 3D-OSEM を適用すると、視野全体ですべてのディスクが鮮明に描出され、画像歪みのない、ほぼ均一な解像度が得られた (Fig. 9(c)). また、中心から 30.7 mm 体軸方向に離れた位置 (Fig. 9(a)-(c) の矢印) のスライス画像の比較では、2 軌道データを用いた場合が、もともと統計ノイズが小さく、

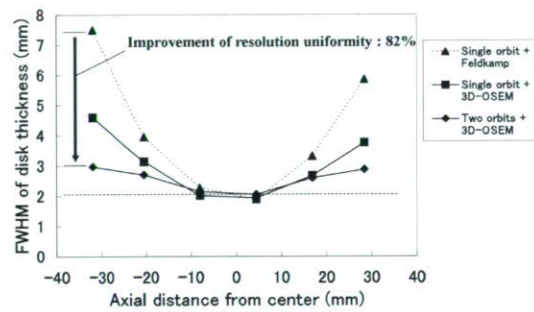


Fig. 10 The FWHMs of disk thickness on three reconstructed images.

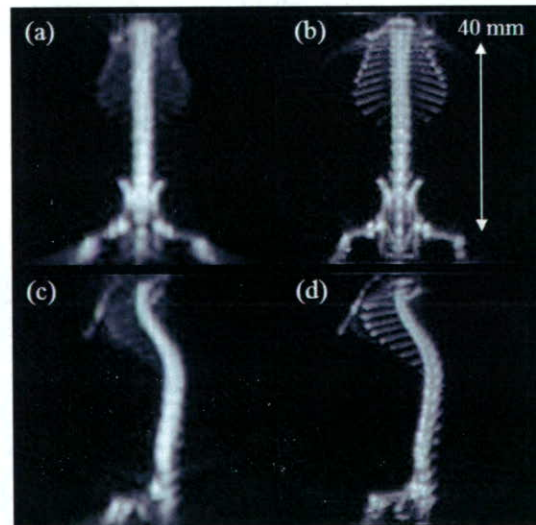


Fig. 11 MIP (maximum intensity projection) images of  $^{99m}\text{Tc}$ -HMDP accumulated in the bones of a mouse. (a) and (c) were reconstructed by Feldkamp method for single-orbit data. (b) and (d) were reconstructed by two-orbit 3D-OSEM method for two-orbit data. (a), (b) Anterior view; (c), (d) Lateral view. Scale bar is 40 mm.

濃度の均一性の高い画像が得られた (Fig. 9(d)-(f)).

Fig. 10 は, 2 軌道収集による解像度均一性の改善効果を定量的に評価するため, 再構成画像上の各ディスクの半値幅 (FWHM: full width at half maximum) を調べた結果である. 本手法によって体軸方向の解像度の均一性が 82% 改善していた.

## 2) マウス骨スキャン

小動物撮像における本システムの効果を評価するためにマウス骨スキャンを行った. 25 g のマウスに骨集積放射性薬剤  $^{99m}\text{Tc}$ -hydroxymethylene diphosphonate (HMDP) 1,184 MBq を尾静脈投与, 60 分後に sacrifice し, 93 分後に  $45^\circ$  および  $90^\circ$  の 2 軌道でデータ収集した. 各軌道 240 分間スキャンし, 各軌道 120 の投影データを得た. ピンホール径は 0.25 mm, ROR は 45.5 mm である.

Fig. 11 が示すとおり, 単一軌道データを Feldkamp 法で再構成した結果では認められなかった骨の詳細な構造が, 本完全データ収集法によって, 視野全体にわたって確認できた. また, 大腿骨や直径 0.5 mm の肋骨までも明瞭に観察できた.

## 6. まとめ

従来, ピンホール SPECT で問題となっていた画像の歪みは完全データ収集によって改善されることが明らかになった. これによって, ピンホール SPECT でも小動物 PET 同様に機能定量評価が可能になると考えられる. さらに, 高感度化, システムの小型化などが実現すれば, ピンホール SPECT は手軽に利用できるようになり, 創薬や新規治療法を評価するためのスタンダードなツールになると考えられる.

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PET 用  $^{15}\text{O}$  製造のための小型サイクロトロン開発計画

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## 概 要

$^{15}\text{O}$  標識ガスは脳梗塞などの脳血管疾患の適切な治療を行うために必要な Positron Emission Tomography (PET) 診断に利用されている。 $^{15}\text{O}$  のベータ崩壊半減期がおよそ 2 分であることから、この診断を行う PET 施設にはサイクロトロンの設置が必要不可欠で、 $^{15}\text{O}$  標識ガスを用いた PET 診断の普及には、サイクロトロンの簡単な操作性および小型化が望まれている。これまで PET による脳血流代謝診断方法および薬剤合成装置の改良が行われ、小型サイクロトロンの開発計画が進めており、本論文ではこの計画内容について述べる。

## 1. 序論

核医学的診断方法の一つである Positron Emission Tomography (PET) 診断はポジトロンを放出する放射性薬剤を投与し、その挙動を追跡することができることから解剖学的画像のみならず臓器や組織の機能画像を得ることができる[1]。特に半減期およそ 2 分のポジトロン放出核種である  $^{15}\text{O}$  を標識した薬剤を用いた PET 診断は、脳血流量や脳酸素代謝率という脳循環代謝を定量的に測定することができることから、脳梗塞の重症度を判定することができ、治療方針の決定に最も有効な診断方法である。我々の目的はこの  $^{15}\text{O}$  標識薬剤を用いた PET 診断の普及を図ることである。

脳梗塞は国内死亡率原因の第 3 位である脳血管疾患の中でも最も大きい割合を占める疾患であり[2]、高齢者医療費や後遺症による総介護費のうちの 1 位になっている原因疾患であることから[3, 4]、適切な治療の選択のできる  $^{15}\text{O}$  標識ガス( $\text{O}_2$ ,  $\text{CO}_2$ ,  $\text{CO}$ )を用いた PET 診断は医療経済的にも期待されている。この  $^{15}\text{O}$  は半減期が短いため、PET 診断施設内にサイクロトロンを設置する必要があり、 $^{15}\text{O}$  標識ガスの合成



に時間をかけることはできないが、繰り返し検査が可能であり、脳梗塞診断で行われているように複数の種類の放射性薬剤投与が比較的短時間でできるという特徴がある。

一方、 $^{15}\text{O}$  標識ガス PET がこれまでのところ普及が十分進んでいない。この理由として以下の3つが考えられている。1) 限られたサイクロトロン施設数。2)  $^{15}\text{O}$  標識薬剤合成が煩雑である。3) 検査が煩雑で時間がかかる。我々の研究ではこれらの諸問題を解決しつつある。1) に対する解決方法としてサイクロトロンの小型化を目指した。その方法は最大加速エネルギーがなるべく小さくサイクロトロン内で発生する放射線量をなるべく減らすためにビームが当たって放射線が発生するような場所には原子番号の大きい物質を使うという方法であり、実証試験機で詳細なデータを収集し、実用機に反映させる計画である[5]。2) については、常温での新規合成方法の開発に成功しており、高温にする部品が不要になったため迅速な  $^{15}\text{O}$  標識薬剤合成可能となった[6]。また、構造も単純になったため小型化に成功した[7]。3) については解析方法の工夫により、体内放射性物質の減衰を必要以上に待つことなく放射性薬剤の連続投与を行うことができた[8, 9]。この工夫をもとにした検査方法を健常者ボランティアに適用したり自家血血栓脳梗塞モデルに適用したりして脳の酸素摂取率などの PET による定量が成功していることを検証することができた[9]。

また、これらの成果以外にも本計画を進めるのに都合がよい背景がある。一つは FDG ( $^{18}\text{F}$ -2-fluoro-2-deoxy-D-glucose) というガン診断用薬剤の全国供給体制が整いつつあることから PET 施設が増加していることである。もう一つは、血栓溶解剤 t-PA が急性期脳梗塞の有効性が示されたことであり[10]、PET 診断が脳梗塞の重症度の判定、すなわち t-PA 投与の指針を決める上で重要であることが分かったことである。

## 2. サイクロトロンの小型化について

サイクロトロンの小型化および操作性の簡便化は放射性薬剤合成を行っている病院などでは特に期待されている。このため磁極半径が小さくなるように加速最大エネルギーは必要最小限に抑えている。また、サイクロトロンを設置する部屋は厚い遮蔽壁を持たなくても済むように自己遮蔽方式にしてコンパクトな構造にしている。

さらに高周波系の小型化がなされ、設置面積の小さい電源システムの導入がなされている。特に本計画では、キャビティをコイル状にすることにより、サイクロトロン本体からの突起物を減らし本体の小型化が実現する。

$^{15}\text{O}$  を生成するにあたって、窒素ガスを安価に購入できることから専ら  $^{14}\text{N}(d,n)^{15}\text{O}$  反応が利用されている。ターゲット上で 3.5 MeV 程度であれば PET 診断に必要な  $^{15}\text{O}$  標識ガスを生成することができるということが知られている[11, 12]。

磁極半径はビーム軌道面の平均磁束密度が2T程度であることやサイクロトロンとターゲットガスを隔てるフォイルなどによるエネルギー損失を考慮して決められた。フォイルにはエネルギー損失が小さくなるように薄くでき、丈夫で熱に強い材質が望ましい。かつてIBA社で製造された $^{18}\text{O}$ 生成専用重陽子加速サイクロトロンではチタン製フォイルが用いられ、その厚さは $4\mu\text{m}$ で、このフォイルにおける重陽子ビームのエネルギー損失は180keV程度と見積もられる[13, 14]。

なお、このような低エネルギー重陽子加速専用サイクロトロンによって $^{18}\text{F}$ を標識した薬剤も精製することも可能である。 $^{18}\text{F}$ の生成には反応のQ値が2.8MeVである $^{20}\text{Ne}(d, \alpha)^{18}\text{F}$ 反応を用いる[15]。

最近利用されている医療用サイクロトロンは自己遮蔽方式のものが一般的になっている。これは放射線発生源であるサイクロトロン本体とターゲット部分を放射線遮蔽材で覆うもので中性子などの漏洩線量が小さく設置施設の遮蔽壁を薄くすることができるため、建築費用の低減を図ることができるからである。

自己遮蔽もなるべく小型で軽量であるものが望ましい。自己遮蔽の小型化のために遮蔽計算において構造の最適化を行うが、発生放射線を抑制する工夫も重要となる。加速軌道においてビームを遮る構造物ができるだけ少なくすることが必要である。しかしながら、サイクロトロン内のディー電極や陽イオン加速の引き出しに使われるデフレクターなどによるビームロスやフォイルなどのビーム取り出し口付近におけるビームロスによる放射線の発生は避け難い。一方、この計画では重陽子の最大加速エネルギーが3.5 MeV程度であることからクーロン障壁の高い原子番号の大きい物質との核反応断面積が小さいことが予想され、その結果、発生する放射線は低減し、延いては自己遮蔽も減量できることが期待される。

中性子の遮蔽が特に問題となるため、サイクロトロンで使用する材料に重陽子ビームを照射し、発生する中性子の線量を計測する実験を行った。

### 3. 中性子線量当量率測定実験

実験は京都大学理学部タンデムバンデグラフ加速器施設で行った[16]。タンデム加速器で加速されたエネルギー3.5 MeVと10 MeV重陽子ビーム(+1価)をビームが完全に止まる厚さのターゲットに照射した。重陽子エネルギー3.5 MeVは計画している小型サイクロトロンのターゲット上の最大エネルギーで、10 MeVはPET用サイクロトロンで加速するときの典型的な最大加速エネルギーに対応している。実験のセットアップを図1に示す。

用いられたターゲットはAl, Ti, Fe, Cu, Nb, Mo, Gd, Ta, W, Pbで、それらの厚さは0.1 mmから0.5 mmであり、純度は99%以上であった。ビーム照射量は発生した2次電子が戻るように永久磁石を取り付けたターゲットラダーに接続されたカレントインテグレーターによって測定した。



発生した中性子は  
 ビームに対して  $0^\circ$  ,  $90^\circ$   
 あるいは  $135^\circ$  でターゲ  
 ットから 66 cm の距離に  
 設置された中性子線量計  
 (アロカ TPS-451C) によ  
 って測定した。この線量計  
 は高密度ポリエチレンに  
 よってヘリウム 3 比例計  
 数管が囲まれており、  
 0.025 eV から 15 MeV ま  
 での中性子の計測に適して  
 いるものである。

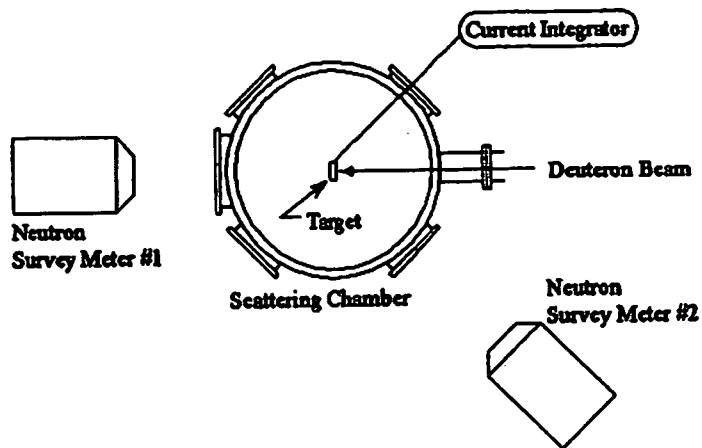


図 1. 実験セットアップ。ターゲットにビームを照射したときに発生した中性子の線量当量率を測定した。

#### 4. 実験結果と考察

図 2 は各ターゲット物質で得られた線量当量率を照射ビーム量と検出器の立体角によって規格化した値を計測した角度毎に示したものである。この結果に示されたように、ターゲットの原子番号が大きいほど、得られた線量当量率は小さくなる傾向が見られた。3.5 MeV における Ta や W という原子番号の大きいターゲットでの発生中性子線量当量は Al の 1/1000 程度になることが分かった。エネルギー依存性も特に大きな原子番号では大きく変化した。例えば、Ta や W では 3.5 MeV のときは 3 桁ないし 4 桁ほど小さい線量になることが分かった。これらの実験結果から、3.5 MeV 重陽子ビームが当たるような部品に Ta や W のような原子番号が大きく比較的熱に強い物質を使用したり 40  $\mu\text{m}$  程度の厚さのシートを貼り付けたりすることによって、出射エネルギーの高いサイクロトロンに比べて自己遮蔽の量を少なくすることが予想できる。

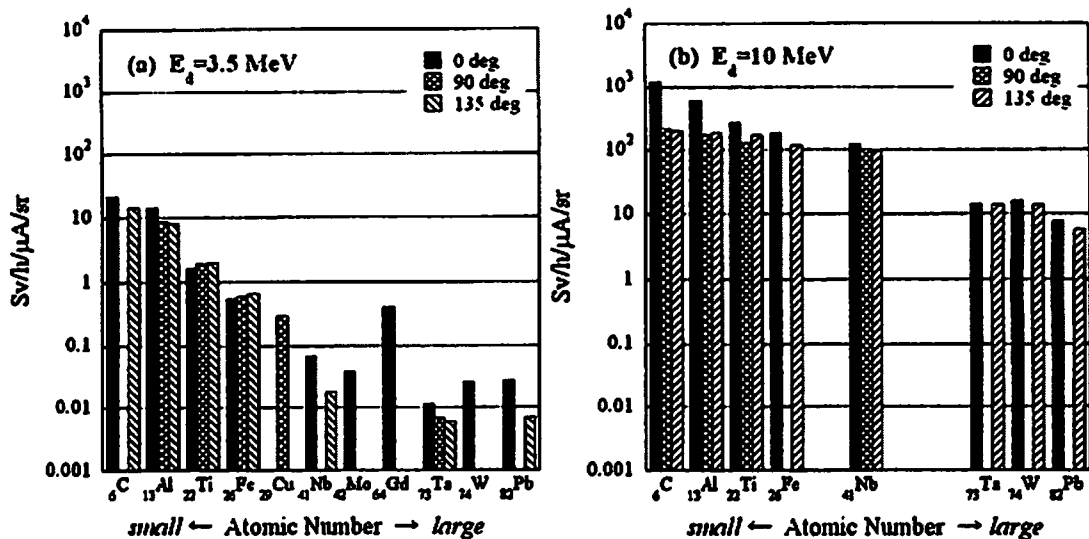


図 2. 中性子線量当量率。(a)  $E_d=3.5$  MeV. (b)  $E_d=10$  MeV.

## 5. 波及効果

<sup>15</sup>O 標識薬剤を用いた PET 診断は病院内で脳梗塞の循環代謝の評価のみならず、その他の診断にも利用することができる。一つは血管反応性が重要な疾患で、X線 CT による血管造影では観察できないような病変を PET による酸素代謝測定により早期発見できることが示唆されている。もう一つは、組織再生医療の客観的評価指針を提供することができることである。心臓組織の再生医療研究の評価に <sup>15</sup>O 標識薬剤 PET が利用されている。

また、薬剤開発費を抑えることができる。製薬を行う前の前臨床試験時にブタやサルなどのより大型の動物実験を行い PET によって薬剤評価をすることで薬剤開発費用の削減が可能になる。具体的には、ガン治療に利用が期待されている血管新生抑制物質の評価や、脳梗塞治療に用いられる組織保護剤の開発支援に有効である。将来的にはこれらの評価方法を確立することによりそれぞれの疾患の治療に役立つ可能性もある。

小型サイクロトロンは従来のサイクロトロンに比べ導入費や維持費の削減ならびに操作性が容易になることなどの理由から、脳梗塞診断以外の診断や薬剤開発の評価に対しても <sup>15</sup>O 標識薬剤を用いた PET の普及が見込まれるであろう。

## 5. まとめ

小型サイクロトロンを開発することにより<sup>15</sup>O標識薬剤を用いたPET診断の普及が見込まれる。この小型サイクロトロンは脳梗塞診断を行う病院のみならず薬剤開発を行う研究施設などでの利用も期待される。

これまでの成果として迅速な薬剤合成を可能にする小型合成装置の開発と、迅速な解析方法の開発により検査時間の短縮化に成功している。さらに、本計画ではサイクロトロンの本体の小型化するにあたって、キャビティをコイル状にして小型化すること、自己遮蔽を小型化するために発生する放射線を低減させるために原子番号の大きい材料をビームが当たる場所に使用することを提案するものである。特に原子番号の大きい材料に3.5 MeVの重陽子ビームを照射することによって発生した中性子が減少することは実験によって確かめることができた。今後は実証試験機を製作し発生する部位や漏洩線量を測定し最適な自己遮蔽の開発を進めたいと考えている。

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## System design and development of a pinhole SPECT system for quantitative functional imaging of small animals

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Recently, small animal imaging by pinhole SPECT has been widely investigated by several researchers. We developed a pinhole SPECT system specially designed for small animal imaging. The system consists of a rotation unit for a small animal and a SPECT camera attached with a pinhole collimator. In order to acquire complete data of the projections, the system has two orbits with angles of 90° and 45° with respect to the object. In this system, the position of the SPECT camera is kept fixed, and the animal is rotated in order to avoid misalignment of the center of rotation (COR). We implemented a three dimensional OSEM algorithm for the reconstruction of data acquired by the system from both the orbitals. A point source experiment revealed no significant COR misalignment using the proposed system. Experiments with a line phantom clearly indicated that our system succeeded in minimizing the misalignment of the COR. We performed a study with a rat and <sup>99m</sup>Tc-HMDP, an agent for bone scan, and demonstrated a dramatic improvement in the spatial resolution and uniformity achieved by our system in comparison with the conventional Feldkamp algorithm with one set of orbital data.

**Key words:** pinhole SPECT, complete data acquisition, small animal imaging

### INTRODUCTION

*IN VIVO* IMAGING of physiological functions (e.g., the tissue blood flow and receptor binding potentials) in small laboratory animals facilitates the objective assessment of pharmaceutical development and regenerative therapy in pre-clinical trials. Micro positron emission tomography (PET) has been extensively emphasized for achieving high spatial resolution in the imaging of small animals, which approaches 1.0 mm.<sup>1–3</sup> An alternative methodology for small animal imaging is micro single photon emission computed tomography (micro SPECT) in which a camera is fitted with a pinhole collimator.<sup>4–8</sup> Pinhole

SPECT has low sensitivity as compared with small animal PET; however, depending on the size of the pinhole, the spatial resolution achieved by pinhole SPECT can exceed that of PET. Unlike PET systems, the pinhole SPECT system does not require a cyclotron for producing radiopharmaceuticals, and it has an excellent cost/performance ratio. Moreover, the half life of radiopharmaceuticals used for pinhole SPECT is relatively longer than that used for PET, which is beneficial in investigating slow pharmacokinetics.

In addition to the lower sensitivity of pinhole SPECT, the existence of image distortion in the axial direction and non-uniform spatial resolution in the reconstructed image for the pinhole SPECT are also areas of concern. One explanation for this non-uniformity is due to incompleteness of data and use of Feldkamp filtered backprojection (FBP) algorithm as an approximate 3D FBP.<sup>9</sup> This non-uniformity can be suppressed by applying statistical reconstruction algorithms such as maximum likelihood expectation maximization (MLEM)<sup>10,11</sup> or ordered subsets expectation maximization (OSEM),<sup>12</sup> but in the periphering of FOV, the

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image is blurred.<sup>5,13</sup> This non-uniformity of the image resolution often hampers further quantitative analysis. Tuy showed that in order to obtain a strict three-dimensional (3D) tomogram in cone-beam CT, the following geometric condition should be fulfilled: "all the planes that cross an object cross the axis of the X-ray source."<sup>14,15</sup> Tuy's condition can be adapted to pinhole SPECT. The conventional pinhole SPECT with one circular orbit does not fulfill this condition. Kudo and Saito suggested examples of orbits that can satisfy Tuy's condition: use of two circular orbits, a spiral orbit, or a single circular orbit in conjunction with a straight line.<sup>16-18</sup> By satisfying Tuy's condition, Zeniya et al. demonstrated an improvement in the uniformity of the spatial resolution of pinhole SPECT by using two circular orbits with angles of 90° and 45° with respect to the object.<sup>19</sup> However, they did not present details of a system configuration including hardware and software. In this paper, we focused on the detailed descriptions of system (hardware as well as software) which is able to properly acquire data from two circular orbits.

## MATERIALS AND METHODS

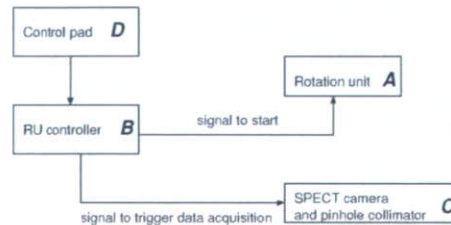
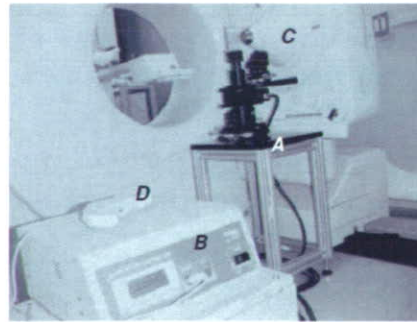
### System configuration

The misalignment of the center of rotation (COR) could be more critical for data acquisition with two orbits as compared with a single orbital system. Therefore, in the proposed system, the detector and collimator were fixed, and the small animal was rotated. The outline of the system and the data flowchart are shown in Figure 1. This system consists of a rotation unit (RU), rotation unit control board (RU controller), pinhole collimator, and SPECT camera.

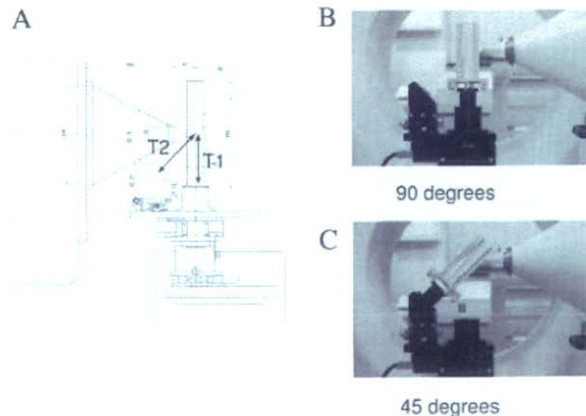
### Rotation unit (RU)

A small animal was rotated on the RU (Fig. 2), which consisted of a base-board and a rotating stage. The rotating stage was driven by a stepping motor (SGSP-120YAW- $\theta$ , Sigma Company, Tokyo, Japan) with a COR accuracy of 20  $\mu$ m. As shown in Figure 2, the small animal can be fixed in the direction of either 90° or 45°. The axes of the two directions intersect each other, and the distances between the intersection point and each base are equal ( $T1 = T2$ ). In order to perform data acquisition with two circular orbits, the intersection point must coincide with the COR of the pinhole detector, i.e., the line perpendicular to the detector center should cross the intersection point, as shown in Figure 2. An adjustment implement (Fig. 3) was utilized to achieve this. The implement was designed to position a radioactive point source at the COR. Then, the COR was adjusted by acquiring data with the point source for various angle directions.

The rat holder was prepared such that the femoral parts and tail of the rat would lie out of the holder (Fig. 4). It was fabricated from 0.5 mm-thick vinyl chloride.



**Fig. 1** Upper: Overview of the proposed pinhole SPECT system for small animals. Lower: Schematic diagram of the system. (A) rotation unit (RU), (B) RU controller, (C) SPECT camera and pinhole collimator, and (D) control pad.



**Fig. 2** Cross section of the rotation unit (A) and schematic views of the 90° orbit (B) and 45° orbit (C).

### RU controller

In order to control the RU, a general-purpose controller (Mark202, Sigma Company, Tokyo, Japan) was employed. The RU controller could control the starting point of the stepping motor, rotation direction, step angle, and speed of rotation using a control pad. The minimum amount of movements per pulse was 0.01° and the maximum speed of movement was 100°/s.

### Pinhole collimator

The pinhole collimator (NDCL709A, Toshiba, Tokyo, Japan) used had a tungsten knife-edge head, which was replaceable. The available hole sizes were 0.25 mm, 0.5

mm, 1 mm, 2 mm, and 4.8 mm. The pinhole had an open angle of 60°, and the distance between the pinhole center and the detector surface was 251 mm. The diameter of the bottom of the collimator was 288 mm.

### SPECT camera

A clinically used SPECT camera (GCA-7100A, Toshiba, Tokyo, Japan) with one detector was used. As shown in Figure 1, the camera stayed in one position during data acquisition. The acquired projection data had a matrix of size 128 × 128, and the pixel size 4.3 × 4.3 mm<sup>2</sup>.

In order to enable data acquisition with the proposed system, the software installed in GCA-7100A was modified to receive a signal from the RU controller. A signal was sent to the RU to begin rotation with a particular stepping angle. After that rotation, a trigger signal was sent to GCA-7100A to acquire the projection data (See Fig. 1). The above process was repeated until the RU completed 360° rotation.

### Image reconstruction

We developed a 3D OSEM algorithm for reconstructing the projection data-set acquired with two different circular orbits.<sup>19</sup> Figure 5 describes the coordinates for the 3D reconstruction with the proposed pinhole SPECT system based on two circular orbits, which are defined as (x, y, z), (x', y', z'), and (x'', y'', z''). The radioactivity concentration of the object is expressed within a fixed (x, y, z) system as f(x, y, z). The second coordinate system (x', y', z') represents the tilt of the (x, y, z) system about the y axis with an oblique angle of φ. The third coordinate system (x'', y'', z'') is a rotational coordinate system where (x', y', z') rotates around the z axis with an angle θ. The tilt of (x, y, z) by the angle φ produces the following transformations:

$$\begin{pmatrix} x' \\ y' \\ z' \end{pmatrix} = R_1 \begin{pmatrix} x \\ y \\ z \end{pmatrix}, R_1 = \begin{pmatrix} \cos \phi & 0 & \sin \phi \\ 0 & 1 & 0 \\ -\sin \phi & 0 & \cos \phi \end{pmatrix} \quad (1)$$

Similar to Eq. (1), which represents the transformation between the (x, y, z) and (x', y', z') coordinates, the following equation expresses that between the (x, y, z) and (x'', y'', z'') coordinates:

$$\begin{pmatrix} x'' \\ y'' \\ z'' \end{pmatrix} = R_2 \begin{pmatrix} x' \\ y' \\ z' \end{pmatrix} = R_2 R_1 \begin{pmatrix} x \\ y \\ z \end{pmatrix}, R_2 = \begin{pmatrix} \cos \theta & -\sin \theta & 0 \\ \sin \theta & \cos \theta & 0 \\ 0 & 0 & 1 \end{pmatrix} \quad (2)$$

In case of φ = 0, the geometry of the system equals that of conventional pinhole SPECT with one circular orbit.<sup>20,21</sup> Therefore, for reconstruction with an oblique orbit, a procedure similar to conventional pinhole SPECT can be applied using Eq. 2. The source voxel (x'', y'', z'') is projected toward the detector through the pinhole collimation of the oblique circular orbit, as shown in Figure 6. We denote the detector plane and a plane parallel to it that includes the source voxel as Plane 1 and Plane 2, respec-

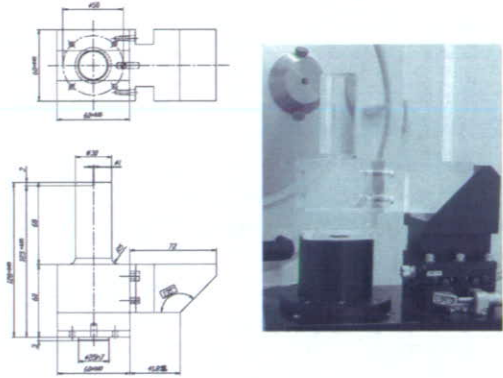


Fig. 3 Adjustment implement to position the point source at the COR of both orbits.

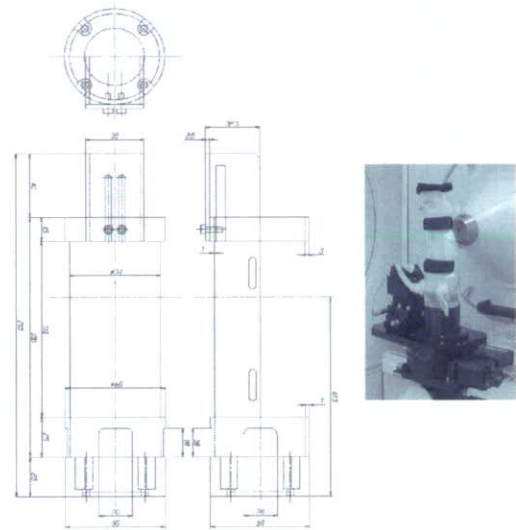


Fig. 4 Rat holder fabricated from 0.5 mm-thick vinyl chloride.

tively. The source point (t<sub>x</sub>, t<sub>z</sub>) = (x''<sub>1</sub>, z''<sub>1</sub>) on Plane 2 is the projected point (d<sub>x</sub>, d<sub>z</sub>) on Plane 1. This relationship can be expressed as

$$\begin{aligned} d_x &= -t_x f_i / a \\ d_z &= -t_z f_i / a \end{aligned} \quad (3)$$

where f<sub>i</sub> is the distance between the pinhole and the detector plane (focal length) and a is the distance between the pinhole and the plane parallel to the detector plane that includes the source point. The distance a can be expressed as

$$a = (h_x - x'_1) \sin \theta + (h_y - y'_1) \cos \theta \quad (4)$$

where (h<sub>x</sub>, h<sub>y</sub>, h<sub>z</sub>) = (r sin θ, r cos θ, 0) is the pinhole position translated by the rotation θ on the oblique circular orbit with radius of rotation r. We employed the MLEM<sup>10,11</sup> reconstruction algorithm for this pinhole geometry. The MLEM update for a two-orbit system can be expressed as



$$\lambda_j^{k+1} = \frac{\lambda_j^k}{\sum_{l=1}^2 \sum_{i=1}^n c_{lij}} \sum_{l=1}^2 \sum_{i=1}^n \frac{y_{li} c_{lij}}{\sum_{j=1}^m c_{lij} \lambda_j^k} \quad (5)$$

where, as shown in Figure 5,  $\lambda_{jk}$  is the value of the image voxel  $j$  for the  $k$ -th iteration,  $y_{li}$  is the measured value of the projection pixel  $i$  for the  $l$ -th orbit, and  $c_{lij}$  is the probability of detecting a photon originating from image voxel  $j$  at projection pixel  $i$  for the  $l$ -th orbit.

Here, we used an OS scheme<sup>12</sup> to reduce the number of iterations. Subsets were evenly divided from both orbits for the OS scheme. A 3D voxel-driven projector using bilinear interpolation on the detector plane was employed in both forward- and back-projections. While back-projecting, the projection data from different orbits were transformed into the same coordinate and combined in the reconstructed 3D matrix space. The software was implemented on a 2.4-GHz PC with Xeon CPU and 1 GB of physical memory, running on a Linux operating system (version 2.4.18).

#### Experiment with a point source

In order to validate whether the projection data from two orbits were correctly acquired, we performed an experiment using a radioactive point source. A point source of about 1.4 mCi/ml of  $^{99m}\text{TcO}_4^-$  was positioned at the COR using the adjustment implement (Fig. 3). A pinhole insert with a diameter of 4.8 mm was employed, and the distance between the pinhole center and point source was 39.5 mm. Projection data were acquired for 120 angular views in steps of  $3^\circ$ . The acquisition time for each step was 15 s. Three images were reconstructed from the projection data with the  $90^\circ$  orbit,  $45^\circ$  orbit, and both the orbits using the 3D OSEM algorithm (2 iterations and 8 subsets). The matrix size of the image was  $128 \times 128 \times 128$  and the voxel size was  $0.76 \times 0.76 \times 0.76 \text{ mm}^3$  (zooming factor of 6.35).

Since the point source was positioned at the center of both the  $90^\circ$  and  $45^\circ$  orbits, its positions in the three images should be identical. The 3D position of the point source in each image was estimated by calculating the image center of gravity, and the estimated positions in the three images were compared.

#### Experiment with a line source

As described above, the misalignment of the COR could be problematic especially for two orbit data acquisition. Thus, in our system, the camera was kept fixed while the target object was rotated. For evaluating the misalignment of the COR for our system as well as the conventional system, experiments were performed using a line source phantom with an inner diameter of 1.14 mm. The phantom was filled with about 4.0 mCi of  $^{99m}\text{TcO}_4^-$  solution. The phantom was carefully placed at the center in one projection view. First, the pinhole detector was rotated around the phantom with a rotation radius of 9 mm. Next, the phantom was rotated on the rotating stage. In both cases,

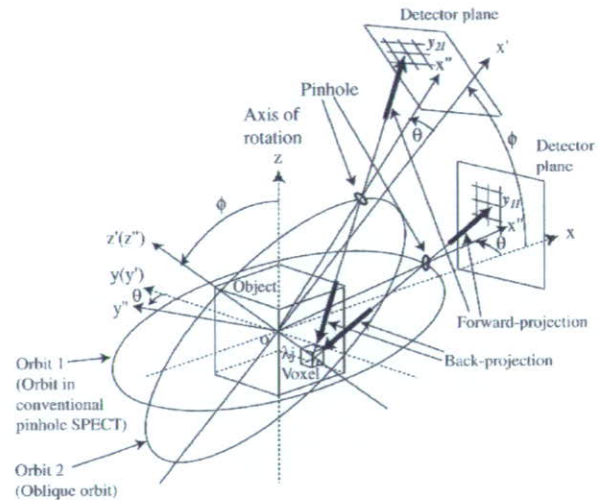


Fig. 5 Coordinate system of oblique circular orbits in pinhole SPECT with two circular orbits.

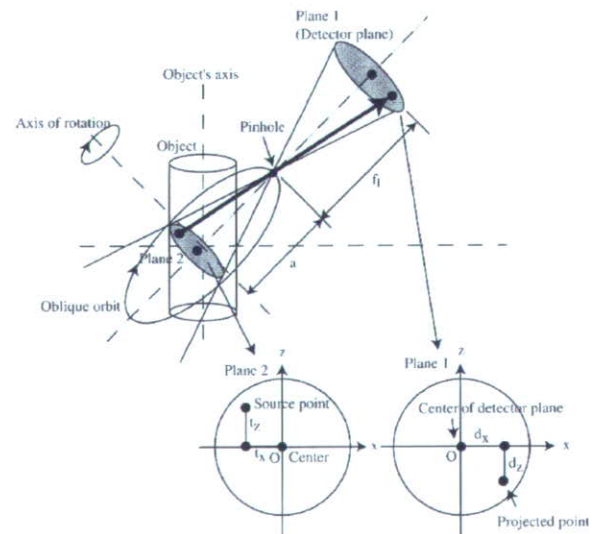


Fig. 6 Pinhole geometry for oblique orbit in pinhole SPECT with two circular orbits.

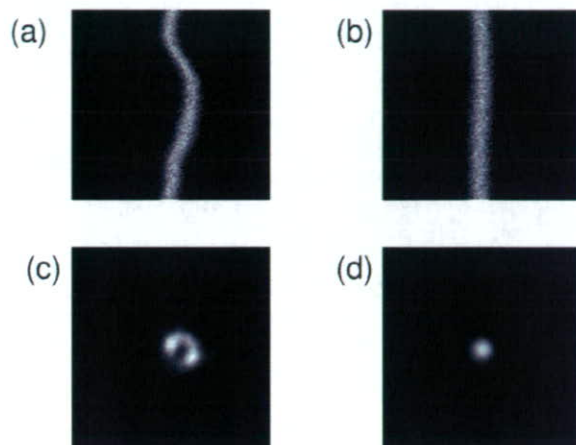
a pinhole with a diameter of 1 mm was used, and data were acquired from 120 angular views ( $3^\circ/\text{view}$ ). The data by both systems were reconstructed using the 3D OSEM algorithm.

#### Animal experiment

In order to demonstrate the reconstructed image by our system, a study was performed with a rat (SD rat; body weight: 150 g) and  $^{99m}\text{Tc}$ -HMDP, an agent for bone scanning.  $^{99m}\text{Tc}$ -HMDP was also accumulated in the bladder of the rat. Therefore, to eliminate the effect of radioactivity in the bladder, both kidneys of the rat were removed before  $^{99m}\text{Tc}$ -HMDP (185 MBq/ml) was intra-

**Table 1** Results of the experiment with a point source. Estimated position of the point source in the image

	$x$ (mm)	$y$ (mm)	$z$ (mm)
90° orbit	0.0505	0.0511	0.0137
45° orbit	0.0464	0.0426	0.0290
both orbits	0.0643	0.0504	0.0165



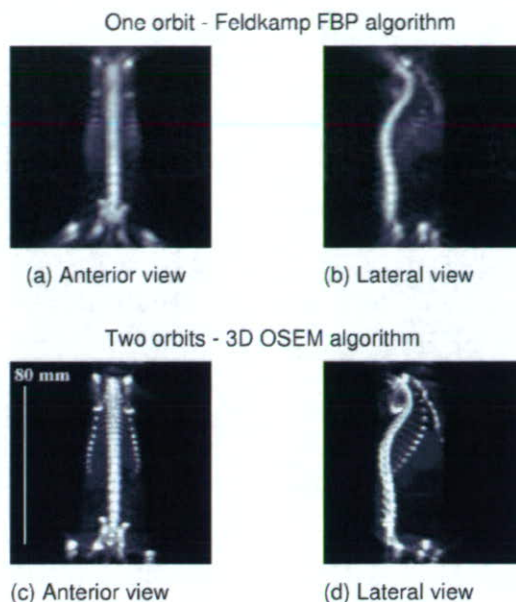
**Fig. 7** Results of the experiments with the line source phantom. (a) Sinogram data measured by the conventional system (rotating the camera), (c) image reconstructed by the conventional system, (b) sinogram data measured by the proposed system (rotating the object), and (d) image reconstructed by the proposed system.

venously injected. The rat was set on the rotation unit of 90° orbit and data acquisition using the proposed system was begun 1 h after the injection. The rotation radius was 85 mm, and data were acquired from 120 angular views (3°/view) for 40 min. Subsequently, the rat was set on the rotation unit of the 45° orbit and data were acquired for 40 min. The energy window was 140 keV  $\pm$  10%. The diameter of the pinhole insert was 1 mm. The acquired data were sent to the PC for reconstruction using the 3D OSEM algorithm with two iterations and eight subsets. For comparison, the conventional filtered backprojection algorithm (the Feldkamp FBP algorithm)<sup>9</sup> was employed to reconstruct the image using the data acquired from the 90° orbit. No correction for attenuation of photons or scattered rays was made in any of the processes.

## RESULTS

### Experiment with a point source

Table 1 lists the estimated positions of the point source in the three reconstructed images. These three point-source positions were almost at the center (the distance from the center was 0.083 mm at maximum) and were close in value. This indicates a sufficient accuracy of intersection of the two axes and the pinhole center.



**Fig. 8** Representative images of rat bone scintigrams by <sup>99m</sup>Tc-HMDP. The images of (a) and (b) were reconstructed using the Feldkamp FBP algorithm with data from the 90° orbit. The images of (c) and (d) were reconstructed using the 3D OSEM with two orbital data. All images were generated by the maximum intensity projection (MIP) method.

### Experiment with a line source

Figure 7 shows the results of the experiments with a line source phantom. Misalignment of the COR was clearly observed when the camera was rotated. This results in an artifact on the reconstructed image (Fig. 7 (c)). On the other hand, no obvious artifact was observed when our system was used.

### Animal experiment

Figure 8 shows the maximum intensity projection (MIP) images of the rat with <sup>99m</sup>Tc-HMDP obtained using the Feldkamp FBP algorithm with one set of orbital data and the 3D OSEM with two orbital data. The artifact of the image was significantly reduced, and a thin rib was clearly observed when data from two orbitals were used.

## DISCUSSION

In this paper, we present the pinhole SPECT system for imaging small animals using data from two orbits. In the proposed system, the position of the detector is kept fixed while the target object is rotated.<sup>22</sup> As compared with the conventional system with one orbit, our system requires a more accurate adjustment of the COR. The experiments with the point and line sources indicated that our system achieved sufficient accuracy in adjusting the COR of the two orbits. This result was apparent in the bone scan with a rat. Image distortion and axial blurring observed in the



one orbital system were greatly improved in the proposed system with two orbits.

Metzler et al. proposed the use of a helical scan system in order to acquire complete data by pinhole SPECT.<sup>23</sup> In the helical scan, sensitivity may be hampered when the pinhole moves across the target object. On the other hand, the sensitivity of our system is not affected since the object is positioned at the center of the field-of-view.

The system proposed in this paper is still in the prototype stage, and in order to acquire data from two orbits, the object must be moved from one orbit to the other. We plan to build a system with multiple pinhole detectors in order to increase the sensitivity.

Our final goal is to develop a system that achieves quantitative functional imaging of small animals. Although the image quality achieved by the proposed system has dramatically improved, several issues have yet to be considered for quantification. Penetrated photons at the collimator and photons scattered from the object as well as the collimator will degrade the image quality and quantity.<sup>24</sup> It is also important to consider the sensitivity compensation of the pinhole collimator when reconstructing an image.<sup>25</sup> In order to achieve a quantitative functional image using the proposed system, these issues should be rectified in the future.

## CONCLUSION

We developed a pinhole SPECT system for the imaging of small animals. The proposed system consists of two axes so that complete data are acquired. Image uniformity was dramatically improved by our system. This system will provide accurate quantitative information on the biological functions of small animals.

## ACKNOWLEDGMENT

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Technical note

# Comparison of multi-ray and point-spread function based resolution recovery methods in pinhole SPECT reconstruction

Antti Sohlberg<sup>a,b</sup>, Hiroshi Watabe<sup>a</sup>, Tsutomu Zeniya<sup>a</sup> and Hidehiro Iida<sup>a</sup>

**Background and objectives** Statistical reconstruction methods allow resolution recovery in tomographic reconstruction. Even though resolution recovery has the potential to improve overall image quality, pinhole SPECT images are still often reconstructed using simplified models of the acquisition geometry in order to reduce reconstruction time. This paper investigates the benefits of two resolution recovery methods, multi-ray and point-spread function based, in pinhole SPECT by comparing them to uncorrected reconstruction.

**Methods** Resolution recovery was incorporated into ordered subsets expectation maximization reconstruction algorithm. The first of the correction methods used a simple but very fast multiple projection ray approach, whereas the second, much slower, method modelled the acquisition geometry more accurately using the analytical point-spread function of the pinhole collimator. Line source, Jaszczak and contrast phantom studies were performed and used for comparison.

**Results** Resolution recovery improved resolution, contrast and visual quality of the images when compared to

reconstructions without it. The method based on the point-spread function performed slightly better, but was almost 50 times slower than the much simpler multi-ray approach.

**Conclusion** The multiple projection ray approach is a promising method for very fast and easy resolution recovery in pinhole SPECT. It has a profound effect on image quality and can markedly improve the resolution-sensitivity trade-off. *Nucl Med Commun* 27:823-827 © 2006 Lippincott Williams & Wilkins.

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**Keywords:** pinhole SPECT, resolution recovery, statistical reconstruction

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## Introduction

The use of pinhole single photon emission computed tomography (SPECT) in clinical practice has been limited to small and superficial targets such as the thyroid [1] and joints [2] due to the reduced field of view. Recently, there has been renewed interest in pinhole SPECT, because it enables small animal imaging, where a small field of view is not a serious problem [3-7]. The attractiveness of small animal pinhole SPECT arises from the fact that it can be performed without any dedicated hardware using only a conventional gamma camera, whereas small animal PET, for example, requires an imaging device suitable only for laboratory animals [8].

The quality of SPECT is degraded by three main factors: attenuation, scatter and collimator blurring of which attenuation and scatter are less pronounced in small animal pinhole SPECT [9]. The collimator blurring reduces spatial resolution and forces the use of small diameter pinhole apertures at the cost of severely reduced sensitivity, which is the most important drawback of small animal pinhole SPECT. The sensitivity of pinhole SPECT can be increased by using multi-pinhole

collimators [10], but this requires modifications to the standard clinical imaging equipment and is not widely applied. One solution to the poor sensitivity problem might be the use of statistical reconstruction methods such as the maximum likelihood expectation maximization (ML-EM) [11] or the ordered subsets expectation maximization (OS-EM) algorithms [12]. ML-EM and OS-EM can partly recover the loss in resolution caused by collimator blurring by incorporating a model of the acquisition geometry into the algorithm and might therefore allow the use of larger diameter pinhole apertures. Recovery of resolution has been shown to improve the quality of conventional SPECT imaging [13,14], but is not yet commonly used in small animal pinhole SPECT.

The biggest problem in incorporating resolution recovery in pinhole SPECT reconstruction is the large increase in computational burden. The calculation of point-spread function (PSF) look-up tables can take hours and might require several gigabytes of storage space. The fast resolution recovery methods such as the slice-to-slice blurring [15] often used in parallel-beam SPECT are not

very straightforward to extend for pinhole SPECT either due to converging nature of pinhole collimation. To overcome computational problems a relatively simple resolution recovery method for pinhole SPECT was recently presented [16]. This method is based on the use of multi-ray projections, where 7 or 21 projection rays, which intersect the pinhole aperture in a predetermined pattern, are used instead of a single ray going through the pinhole centre. The aim of this work is to compare the multi-ray projection approach to a method with a more accurate model of the acquisition geometry.

## Materials and methods

### Implementation of the algorithms

The ML-EM algorithm can be presented as

$$z^{k+1}(b) = \frac{z^k(b)}{\sum_d p(b,d)} \sum_d p(b,d) \frac{n^*(d)}{\sum_{b'} p(b',d) z^k(b')} \quad (1)$$

where  $z(b)$  is the number of counts emitted from image voxel  $b$ ,  $k$  is the number of iteration,  $p(b,d)$  is the probability that the emission in voxel  $b$  is detected in detector bin  $d$ , and  $n^*(d)$  is the measured projection count in detector bin  $d$ . The ML-EM algorithm updates the current image estimate using forward projection,

$$\sum_{b'} p(b',d) z^k(b'),$$

and back-projection,

$$\sum_d p(b,d) \frac{n^*(d)}{\sum_{b'} p(b',d) z^k(b')},$$

operations. In this study three different reconstruction algorithms based on ML-EM and accelerated using the ordered subsets approach were implemented. The first method (OS-EM<sub>noRR</sub>) used a simple ray-driven forward projector/voxel-driven back-projector pair assuming zero pinhole diameter. The second algorithm (OS-EM<sub>rayRR</sub>)

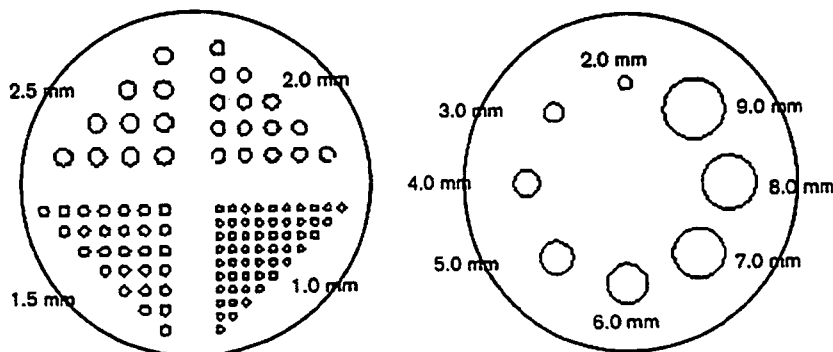
was implemented using ray-driven forward projection with seven projection rays and voxel-driven back-projector with a single ray. The seven projection rays intersected the pinhole aperture in a hexagonal pattern modelling the effect of the finite pinhole aperture diameter by inverse cone of rays [16]. The third method (OS-EM<sub>psfRR</sub>) incorporated analytical pinhole collimator point-spread functions into the reconstruction algorithm. The PSFs were calculated according to Metzler *et al.* [17] and stored into hard disk prior to reconstruction in contrast to approach used by the first and second method where the forward projection and back-projection were calculated on-the-fly during the reconstruction.

### Phantom studies

The phantom studies were performed using a Toshiba GCA-7200A (Toshiba, Japan) gamma camera equipped with a 251 mm focal length pinhole collimator (0.5, 1.0 and 2.0 mm pinhole apertures specially fabricated for small animal studies). Three phantoms were imaged. The line source phantom consisted of a line source holder and single line source filled with 5 MBq of <sup>99m</sup>Tc and placed accurately on the axis of rotation. The resolution was measured as full width at half maximum of horizontal profile taken at the central slice of the phantom. The Jaszczak phantom had four sectors with 1.0, 1.5, 2.0 and 2.5 mm diameter rods separated by a distance twice the rod diameter (Fig. 1). The Jaszczak phantom was filled with 52 MBq of <sup>99m</sup>Tc and used to assess the image quality visually. The contrast phantom consisted of eight rods (2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0 and 9.0 mm diameter) and a large background compartment (Fig. 1). The rods were filled with an approximately five times higher concentration of <sup>99m</sup>Tc than the background. The total activity in the phantom was 780 MBq. The contrast for each rod was calculated as

$$C = \frac{I_{rod} - I_{bg}}{I_{rod} + I_{bg}} \quad (2)$$

Fig. 1



One slice of the Jaszczak phantom (on the left) and contrast phantom (on the right). The phantoms had outer diameter and height of 50 mm. The diameters of the rods are marked on the phantoms.