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Chapter 1

HIGH RESOLUTION RADIONUCLIDE IMAGING USING FOCUSING GAMMA-RAY OPTICS

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Abstract Significant effort is being devoted to the development of noninvasive imaging systems that allow *in vivo* assessment of biological and biomolecular interactions in mice and other small animals. Although single-photon emission tomography (SPECT) and positron emission tomography (PET) are well-matched to the study of physiological function in small animals, the spatial resolutions of $1-2$ mm currently achievable with these techniques limits the types of research possible. For this reason, we are developing a small animal radionuclide imaging system using grazing incidence optics to focus the low-energy gamma-rays emitted by ^{125}I, ^{95m}Tc, ^{96}Tc, and ^{99m}Tc. We compare this approach to the more traditional use of absorptive collimation.

Keywords: SPECT, small animal imaging, gamma-ray optics, X-ray optics

1. Introduction

Animal models, especially transgenic and knock-out mice, now affect research in every area of biomedical science and are available for a diverse range of human conditions [Bernstein and Breitman, 1989]. The emergence of transgenic animal technology as a key component along the entire research path, ranging from fundamental investigations to pharmacological development, requires high-resolution techniques suitable for noninvasive imaging of small animals. While magnetic resonance imaging (MRI), magnetic resonance spectroscopy and CT provide spatial resolution in the range $25-50$ μm, these techniques are best-suited for anatomical or metabolite concentration studies. Noninvasive metabolic and functional assessments are best performed using positron emission tomography (PET) and single-photon computed tomography (SPECT).

Although dedicated small-animal PET systems are being developed with spatial resolution of $1-2$ mm, it will be impossible to significantly improve the resolution beyond this due to the uncertainty in the position of the positron annihilation. (The mean positron range in water is 0.6 mm for ^{18}F, and much larger for other PET isotopes like ^{11}C, ^{13}N and ^{124}I [Bailey et al., 2003].) On the other hand, radionuclide imaging techniques using single-photon agents such as ^{125}I and ^{99m}Tc do not have a fundamental physics limit to their resolution.

2. Radionuclide Imaging

Traditional Approach

Current imaging methods for single-photon radionuclide studies rely on absorptive collimation, with either a converging parallel hole collimator or a pinhole collimator serving as the optical element. Figure 1.1 sketches the basic geometry of a pinhole collimator, which will serve to illustrate the basic properties of both types of systems. To first order, the resolution R of a pinhole imager scales with aperture diameter, while the efficiency η scales as the square of the aperture. Along with R and η, the third important parameter that determines the types of imaging studies that can be performed is the field of view (FOV). Accounting for all relevant effects, the complete on-axis system characteristics are defined by:

$$R = \sqrt{\left(d\left[\frac{b+l}{l}\right]\right)^2 + \left(\frac{p}{M}\right)^2} \tag{1.1}$$

$$\eta = \frac{d^2}{16b^2} \tag{1.2}$$

$$\mathrm{FOV} = 2b\tan\alpha, \tag{1.3}$$

where d is the pinhole diameter (assuming no septal penetration at the edges of the pinhole), l is the separation between the pinhole and the detector, p is the pixel size of the detector, b is the separation between the source and the pinhole, α is the half-angle of the collimator, and M is the magnification, $M \equiv l/b$.

In order to achieve sub-mm spatial resolution, either FOV or η must be reduced. This is easiest to see by rearranging Equations 1.1−1.3, eliminating d and solving for R as a function of FOV:

$$R = \sqrt{\frac{\eta \times \mathrm{FOV}^2 \left(1 + 1/M\right)^2}{\tan^2 \alpha} + \frac{p^2}{M^2}} \tag{1.4}$$

Figure 1.2 plots a family of curves for detector pixel sizes of 1 and 3 mm (representing current technology) and magnification $M = 20$. For efficiencies, we choose two values: $\eta = 1 \times 10^{-5}$ (or 0.4 cps/μCi), representing the lowest possible sensitivity allowed for practical measurements and $\eta = 1 \times 10^{-4}$ (or 4 cps/μCi). To understand the best possible resolution that can ever be achieved, we plot R vs FOV as $p \to 0$ (i.e., detector with infinitely good resolution) and $M \to \infty$. Finally, for context, Figure 1.2 shows R and FOV for three small animal SPECT systems; #1-[Choong et al., 2004], parallel hole collimator; #2-[Wu et al., 2002], #3-[Beekman et al., 2002], pinhole collimators.

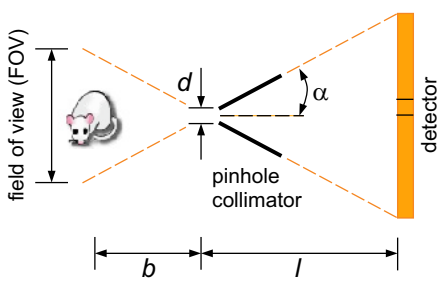

Figure 1.1. Schematic view of a pinhole collimator, indicating the relevant parameters that determine the system resolution, efficiency and FOV.

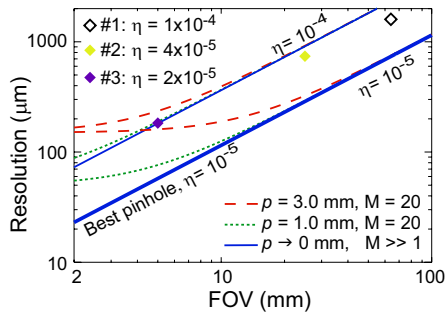

Figure 1.2. Resolution vs. FOV assuming different values of p and η. The diamonds indicate the performance of actual SPECT systems. Refer to the text for references.

Restricting attention to FOVs of at least 5 mm, the best spatial resolution possible with a pinhole collimator using modern detectors ($p \approx 2$ mm) and requiring a useful efficiency ($\eta > 10^{-5}$) is ∼100 μm. Even with an ideal detector or very high M, the theoretically best resolution only improves to 55 μm for a 5 mm FOV or 220 μm for a 20 mm FOV. Given this limit to absorptive collimation techniques, another approach is needed to perform radionuclide imaging at spatial resolution of 100 μm or better.

3. Radionuclide Imaging

Focusing γ-ray Optics

Reflective X-ray or γ-ray optics are one choice for high-spatial resolution radionuclide imaging. It is beyond the scope of this paper to discuss the underlying physics of these systems and the important design drivers for biomedical applications. Instead, we briefly summarize the salient points and refer the interested reader to [Pivovaroff et al., 2003] for a detailed discussion.

Figure 1.3 sketches the basic geometry of the γ-ray lens. In order to maximize sensitivity, the reflective surfaces are coated with multilayers. For systems designed to focus 17−20 keV photons (the low-energy lines emitted by ^{95m}Tc, ^{96}Tc or ^{99m}Tc) or 27.5 keV photons (the primary energy emitted by I^{125}), the efficiency is $\eta \approx (1-5) \times 10^{-5}$, and to first order, is determined solely by the multilayer reflectivity. The other design parameters have little or no influence on η. R and FOV are approximately given by:

$$R = \sqrt{\frac{8(b+l)^2}{(1+M)^2}\tan^2\alpha + \frac{p^2}{M^2}} \tag{1.5}$$

$$\mathrm{FOV} = 2b\tan\theta, \tag{1.6}$$

where α is the angular quality of the mirror surface, θ is the graze angle the photons reflect off the mirror, and the other parameters l, b, M, and p are the same as above.

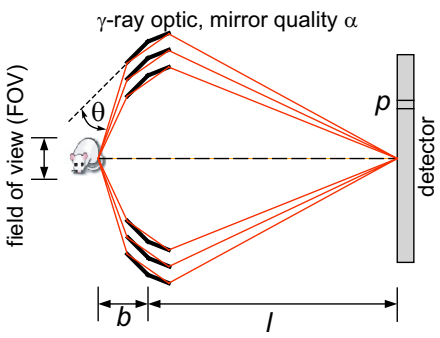

Figure 1.3. Schematic view of a γ-ray lens with three nested mirrors, indicating the relevant parameters that determine the system resolution and FOV.

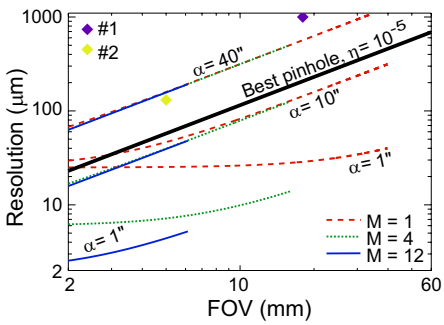

Figure 1.4. Resolution vs. FOV assuming different values of p and η. The diamonds indicate the performance of two prototype γ-ray lenses. Refer to the text for details.

It is also possible to re-arrange the system equations to solve for R as a function of FOV:

$$R = \sqrt{2 \times \mathrm{FOV}^2 \left[\frac{\tan\alpha}{\tan\theta}\right]^2 + \frac{p^2}{M^2}}. \tag{1.7}$$

Figure shows the resultant curves for a range of magnifications, $M = \{1, 4, 12\}$, pixel size $p = 25$ μm, and mirror performance $\alpha = \{40, 10, 1\}$ arc seconds. These values of α represent the quality of mirrors currently produced by a thermal forming process (40$''$:[Craig et al., 2000]), a replication process (10$''$:[Ramsey et al., 2002]), and a high-precision replication process under investigation (1$''$:[Nederbragt, 2003]). Optical designs are limited such that $b + l < 4.57$ m to minimize the amount of space needed for imaging experiments. The two diamonds indicate a prototype lens already tested (#1:[Pivovaroff et al., 2003]) and one under construction (#2). Figure 1.4 also plots the theoretical best $R-$FOV curve for a pinhole collimator with $\eta = 10^{-5}$, an efficiency comparable to what a γ-ray lens can achieve.

As seen in Figure 1.4, the use of X-ray focusing optics opens a large part of high spatial resolution parameter space unobtainable with traditional pinhole collimation techniques. For example, with modest 10$''$ mirrors, it is possible to achieve 125 μm resolution over a 16 mm FOV, using an optical design with $M = 4$ and a detector with pixels no larger than 80 μm. As mirror fabrication improves in the future [Nederbragt, 2003], it will be possible to build an radionuclide imaging system with better than 10μm resolution over a 5 mm FOV, using an optical design with $M = 12$ and a detector with 25 μm pixels.

Of course, the use of reflective γ-ray optics also has disadvantages, when compared to absorptive collimation techniques. First, the only way to improve the sensitivity of the system beyond a few times 10^{-5} ($\sim$1 cps/μCi) is to increase the number of lenses. The atomic physics sets up an upper limit on how well multilayer coatings can reflect high-energy photons. This is analogous to the hard limit PET suffers on spatial resolution due to the uncertainty in the location of the position annihilation. Second, a single lens will consist of several tens of nested mirror pairs, at a fabrication cost significantly more expensive than a single collimator element [Pivovaroff et al., 2003]. Finally, a complete focusing system will require more laboratory space than an absorptive collimation system, with separation distances between the small animal and detector equal to a few meters.

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