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Analytical radiography for planar radiographic images implemented with a multi-modal system

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ABSTRACT

A radiographic system is optimized for the contrast inherent to small animals and is developed for a multi-modal imaging system devised for in-vivo studies. The range of X-ray energies utilized (generally considered "soft X-rays") enables enhanced spatial resolution and superior contrast for detailed study of the mouse anatomy and smaller specimens. Despite the difficulties presented by the complicated energy spectrum of soft X-rays, relevant system calibrations for bone measures are described in detail and applied to the mouse. Further, long-bone symmetry modeling using a cylindrical projection is applied to the planar density image, providing convenient bone density estimates that are consistent with other methodologies.

1. Introduction

Experimental or preclinical radiology of small animals (particularly mice) has created a demand for more image resolution and more robust measures of material density. As discussed by Haidekker et al. [1], aspects of workflow and analysis have improved with digital methods, but traditional film radiography provides an indispensable resolution. The system requirements to enhance radiographic resolution can be optimized with a digital fluoroscopic method. Further, the fluoroscopic method provides a removable screen sensor where the same optical system is used for optical image methods (luminescence or fluorescence). The co-registration of the differing optical and radiographic images enables immense potential for experimental designs [2,3].

Optimizing the image resolution of a mouse radiograph involves considerable changes from the paradigms of human radiology. Optimizing the contrast of mouse constituents requires a much lower X-ray energy, and increasing the spatial resolution requires a much thinner sensor (fluorographic screen). Fortunately, these two constraints can be, and have been, simultaneously accommodated in a multi-modal digital imaging system (KODAK In-Vivo Imaging System FX, www.carestreamhealth.com/molecular-imaging). Thinning the screen phosphor enough to support the necessary resolution, but no more than necessary to maintain

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sufficient stopping power for the appropriate X-ray energy range, optimizes the system constraints. Other important factors of screen construction include light opacity, self-protection, minimal filtration and uniformity (both low and high spatial frequencies).

The system performance can exceed a spatial resolution of 30 LP/mm at 50% MTF and responds with an X-ray quantum efficiency approaching 100% in the range of energies from 10 to 15 keV (aluminum equivalent according to NIST mono-energetic X-ray attenuation). The radiographic performance assures the resolution of ∼30 μm anatomical features of small animals at a dose level that is far below a measurable biological response [4]. An alternative system configuration was recently reported that supports the concept of simultaneous radiography and optical imaging [5], but its performance capabilities have not been reported. A distinct advantage of most digital radiographic systems is the robust linear response to X-rays that readily enables quantitative analysis.

An important experimental advantage of combining optical and radiographic imaging modes is the associated minimally invasive applications—the opportunity to design and execute in-vivo experiments. Not only does in-vivo data offer the obvious advantage of relevance, it contributes the immense preclinical value of repeated measures on a valuable experimental subject. To this end, our analysis explores the extent to which radiological measures can be calibrated/validated for the live mouse and how these measures relate to the most relevant materials: bone and water.

2. Experimental methods and analyses

To more accurately estimate bone density in small animals, calibrated X-ray attenuation coefficients of the bone and water must be established in the relevant range of X-ray energy. A robust energy calibration is automatically performed by the system hardware using standard aluminum attenuation. Nominal aluminum thicknesses of 0.1, 0.2, 0.4, and 0.8 mm are utilized for calibration (precise surface density from Goodfellow Cambridge Limited). The complex soft X-ray energy distribution (a multi-modal spectrum, often referred to as "polychromatic", Fig. 1) complicates the determination of mean X-ray energy, but the automated routine assures a precise energy determination and may include whatever sample support material an experiment might demand. Further, the software processes the image with the appropriate illumination correction and, ultimately, provides the X-ray density image and image file ($\mu = -\mathrm{Ln}[I/I_0]$, where I_0 is the modal signal of unattenuated X-rays).

Model bone (hydroxyapatite (HA) or monobasic calcium phosphate ($CaPO_4$)) and water calibrations are successfully accomplished as a function of a calibrated energy. We apply the standard radiological model, where density $\mu = \mu(E)\rho t$, $\mu(E)$ is a function of X-ray energy, and ρt is the mass per area (the product of mass density and thickness). The product ρt is abbreviated simply with "d" for convenience, and the term $\mu(E)$, often designated as μ', is the X-ray attenuation coefficient for a particular material. By convention, all units are CGS.

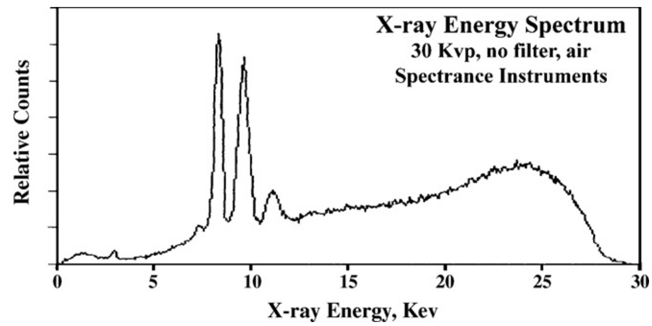

Fig. 1 – An X-ray energy spectrum for the tube used in this system is clearly dominated by the tungsten lines. The tube operation is continuous. The thin screen efficiency (stopping power) diminishes above 20 keV and the 50 cm air column of the system attenuates energy below 8 keV. The average detected energy is in the 10–15 keV range, depending upon the aluminum filter used.

2.1. *Attenuation calibration of materials*

For water calibration, $\mu/d = \mu(E)$ was measured for <11 mm depths of water (a relevant range for small animal depths) over the practical energy range of low-energy X-rays. The experimental design for this measure is simple, given that water can be weighed in thin plastic Petri dishes where the mass/area is accurately calculated. The graph in Fig. 2 shows the measured values of $\mu/d = \mu(E)$ in cm^2/g for water and the mean X-ray energy (as calibrated from standard aluminum). For water (density 1.0 g/cc), actual depth and ρt are numerically identical. The complexity of water attenuation is clearly apparent where the attenuation coefficient depends upon the water depth. This complexity is a departure from the simple interpretation of attenuation, and it is caused by the multi-modal nature of the X-ray spectrum—the very low energy X-rays are capable of penetrating the shallowest depths of water in the range of interest. To accurately model water, a continuous function of energy and depth is derived by interpolating the entire operational range, thereby calibrating $\mu'(E, d)$ for water. Note that since the density of water is unity, the column density (X-ray extinction) of water at depth d is numerically equivalent to $\langle \mu/t \rangle_{water} = \mu'(E, d)$.

Calibrating bone density relating to small animals is more challenging, since it requires a robust experimental design for small quantities. A diminishing amount of bone mass may be approximated by weighing very small amounts of HA or $CaPO_4$ on thin plastic for subsequent quantitative X-ray imaging over a relevant density range. After appropriate conversion to a density scale, the net density of a confined area of HA deposit is simply integrated, and the density equations are manipulated to calibrate the system: $\mu = \mu(E)\rho t$, $\mu(E) = (\text{pixel area, cm}^2) \times 1/\text{mass} \times \sum\mu$, as summarized in Eq. (1):

$$\mu = \mu'(E)\rho t; \quad \mu'(E) = \frac{\partial A \sum \mu}{g} \tag{1}$$

where $\mu'(E)$ is the attenuation coefficient in cm^2/g, ∂A is the pixel area in cm^2, $\sum\mu$ is the total net density within a defined region of an image and g is the total mass of material within