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Technical notes

Design of a multimodal fibers optic system for small animal optical imaging

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ABSTRACT

Small animals optical imaging systems are widely used in pre-clinical research to image *in vivo* the bio-distribution of light emitting probes using fluorescence or bioluminescence modalities. In this work we presented a set of simulated results of a novel small animal optical imaging module based on a fibers optics matrix, coupled with a position sensitive detector, devoted to acquire bioluminescence and Cerenkov images. Simulations were performed using GEANT 4 code with the GAMOS architecture using the tissue optics plugin. Results showed that it is possible to image a 30 × 30 mm region of interest using a fiber optics array containing 100 optical fibers without compromising the quality of the reconstruction. The number of fibers necessary to cover an adequate portion of a small animal is thus quite modest. This design allows integrating the module with magnetic resonance (MR) in order to acquire optical and MR images at the same time. A detailed model of the mouse anatomy, obtained by segmentation of 3D MRI images, will improve the quality of optical 3D reconstruction.

Introduction

Small animals optical imaging systems are widely used in pre-clinical research to image *in vivo* the bio-distribution of light emitting probes using bioluminescence [1,2], fluorescence [3] or Cerenkov luminescence [4–7], modalities. The basic setup of a non-contact optical imaging device for small animals is rather standard and consists of a camera, usually a charge coupled device (CCD) detector plus a set of lens and filters, enclosed in a light tight black box. In this work we presented a set of Monte Carlo (MC) simulated results of a novel small animal optical imaging system based on a fibers optics matrix coupled with position sensitive detectors like, for example, pixelated photomultiplier tube, avalanche photodiodes, etc. Although the complexity of the proposed system is high due to its multimodal nature, the optical components have been proven to be compatible with MRI for diffuse optical tomography [8]. However in the past little attention has been paid on spacing optical fibers for the detection of bioluminescence sources to avoid loss of spatial resolution with respect to continuous approaches. More precisely our approach is aimed to skip the burdensome projection of non-contact optical measurements on the surface of the animal by demonstrating that an optimal contact sampling is feasible with a relatively small array of fibers. The main goal of this paper is to investigate these aspects for preclinical *in vivo* small animal imaging.

Methods

As mentioned in the introduction the main goal of this paper was to propose and to evaluate the potentials of a system characterized by discrete and spatially separated sampling in order to obtain the fluence at the animal surface. Fig. 1 shows a schematic representation of the system: the fibers are uniformly distributed over the entire animal surface, the emitted light is transported to a light position sensitive detector and each channel gives a signal proportional to the light collected by the corresponding fiber. The precise position (x, y, z) of each fiber can be determined by MR imaging itself by attaching to the end of the fiber a tiny ring of an MR compatible marker like glycerin. In the scheme presented in Fig. 1 we included an optional laser excitation source in order to point out the possibility of acquiring not just bio-luminescence but also fluorescence imaging. However, for the sake of clarity, we would like to underline here that in the rest of this manuscript we focused on investigating the bioluminescence acquisition mode only.

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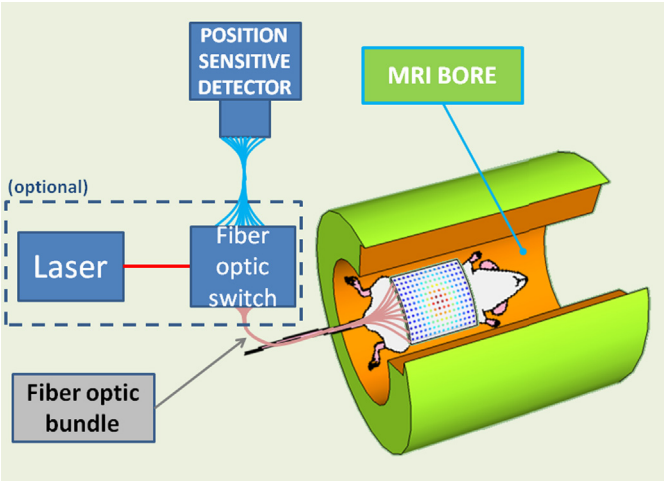

Figure 1. Schematic representation of the system. A set of optical fibers are uniformly distributed over the entire animal surface, the emitted light is then transported to a position sensitive detector. The fiber optics bunch can be inserted into an MR bore in order to acquire optical and MR data at the same time.

In order to obtain a continuous distribution of light fluence from the mouse surface, the signal collected by the fiber can be interpolated using different interpolation algorithms like for example: linear, bilinear, and cubic spline. The latter was used in this work.

The broad distribution of scattered light at the animal surface hints that an interpolation of a coarse sampling could obtain results comparable with almost continuous sampling detector like CCD. We present here a criterion for determining an optimal compromise between spatial sampling, so the number of fiber used, and surface fluence reconstruction in some realistic simulated scenarios. At the best of our knowledge it was never done for bioluminescence sources and to simulate a system coupled with a position sensitive detector. This design allows direct acquisition of 3D map of fluence at the surface of the animal body, system compactness and, more importantly, the possibility of inserting the system inside a magnetic resonance (MR) bore, allowing joint optical and MR images acquisitions.

The model fiber spacing is closely related to the spatial resolution and has been determined by simulating the scattering and absorption of a light point source at different depths as described below. The simulations were performed using GEANT 4 [9] code with the GAMOS architecture [10] and tissue optics plugin [11] and were carried out using Mie scattering in the Henyey-Greenstein approximation of the phase function. We adopted a cylindrical digital phantom of 15 mm radius and 30 mm height [12]. We used reduced absorption coefficient of mouse muscle for the simulation of light transport, values of absorption ranged between 0.20 and 0.05 cm^{-1} in the range of wavelength of interest (600–800 nm) [13]. Reduced scattering coefficient was computed by assuming a constant anisotropy on all the wavelength of 0.9 and ranged between 9 and 8.4 cm^{-1}. A refractive index of 1.4, constant on all simulated wavelength range, was assumed as the average refractive index of soft tissue.

A point source with a flat spectrum between 600 and 800 nm was simulated at several depths respect to the surface of the cylinder (r coordinate) ranging between 8 and 1 mm depth. Along the z coordinate, the source was placed in the middle of the cylinder. The optical photon source was approximated as pointlike, therefore smaller than the typical optical mean free path of photons in tissues. In the computation, its dimension was 0.02 mm in diameter. The number of simulated photons emitted by the source varied between 2.5×10^6 photons at 1 mm to 11×10^6 photons at 8 mm depth, to balance the greater tissue absorption. Directional distribution was assumed isotropic over the solid angle.

The other materials used in the simulations were air and PMMA of the fiber cores. Optical properties of these two were not considered, as air was assumed perfectly transparent and light transport through the fiber was not simulated; we therefore imposed $g = 0$ and μ_a, $\mu_s' = 10^{-7}$ for all the wavelength in the simulated range. Refractive index of PMMA is well known to be 1.49 for various kind of optical grade PMMA. Optical fibers were simulated with a numerical aperture of 0.55; every photon hitting on the section of the fiber at an angle that would allow transmission was selected and recorded.

It is quite difficult to provide a meaningful quantitative comparison in terms of detecting efficiency since it will be heavily dependent on the choice of CCD detector (e.g. quantum efficiency at different wavelength) and of the lens characteristics (e.g. f number). We thus decided to focus on investigating the effects of discrete sampling on the shape of the resulting surface fluence.

The spatial Fourier power spectrum of the light fluence at the phantom surface was then calculated in order to determine the spatial cutoff frequency (1/10 of the Fourier power spectrum maximum) of light emission at different source depths. The value of the spatial cutoff frequency f_{cut} (1/mm) can be used to determine the Nyquist spatial sampling frequency, and, thus, the corresponding fibers spacing f_s (mm). The effects of spatial sampling on the measurements of the surface light fluence were further investigated by simulating a set of 0.5 mm diameter multimode optical fibers equally spaced with a grid of: 1, 2, 3, 4, and 5 (mm).

Realistic MC mouse simulations [14] were performed considering a phantom composed of 6 tissues: skin, muscle, liver and spleen, hearth, lung and bone. This phantom was obtained by using Micro-CT Mouse Data [15].

Results

Figure 2 shows the value of the cutoff frequency f_{cut} for different source depths inside the cylindrical phantom. Frequencies differ between the two axes because of the phantom cylindrical geometry. Interestingly, the cutoff frequency range is quite small for a source located below more than 2 mm. This allows justifying a rather coarse spatial sampling of the surface light fluence. In order to define a criterion of optimal spacing of the sampling fibers an

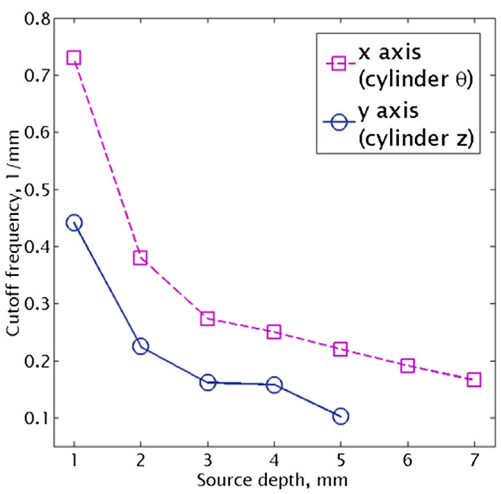

Figure 2. Plot of f_{cut} (1/mm) along the x (long axis of the cylinder shown in Figure 1) and y axis for a simulated pointlike source placed at different depths inside a cylindrical phantom.

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