A Hybrid Inversion Technique for Extremely Rapid Fluorescence Molecular Tomography Reconstructions

Joshua Kempner[1], Jorge Ripoll[2], and Wael Yared[1]
[1]Life Sciences and Technology, PerkinElmer, Hopkinton, MA
[2]Dept. of Bioengineering, Universidad Carlos III of Madrid, Spain

1 Introduction

Fluorescence Molecular Tomography (FMT) is commonly used in small animals, most commonly mice. A significant challenge in imaging larger anatomies is the computation time required to perform both the forward model for light propagation and the matrix inversion for computing the distribution of fluorophores in the animal. We present a technique for reducing the size of the problem through the use of hybrid computations in real space and in Fourier space, which results in a speed-up in computation time by several orders of magnitude.

2 Forward Model

FMT reconstructions use a forward model for light propagation through tissue based on the commonly used diffusion approximation. This approximation uses Green's functions to model the propagation of light between a grid of excitation light source locations, the voxels within the reconstruction, and the camera detectors. Accounting for reflection and refraction at the tissue-air interface as part of this model is computationally very intensive. The "Boundary Removal" technique description by Ripoll & Nztiachristos (2006) simplifies this computation by in effect transforming the measurement data to how it would appear in an infinite homogeneous medium instead of a diffusive medium with a defined 3D surface. However, the weight matrix produced by this forward model is still very large (on the order of 10^8 elements), so the inversion of this matrix with the data to produce the fluorophore distribution, e.g. by the Algebraic Reconstruction Technique (ART), is very time consuming.

For the technique described here, we transform the image data into the Fourier domain with a relatively low frequency cutoff. This enables us to represent the data with many fewer "detectors" than if the data were represented in real space. By using on the order of 25 frequency components, compared to 10^3 detectors in real space, we reduce the size of the problem by 2 orders of magnitude. The computation time of the forward model's weight matrix scales non-linearly with the size of this matrix, so the resulting speed improvement is much greater than 100-fold.

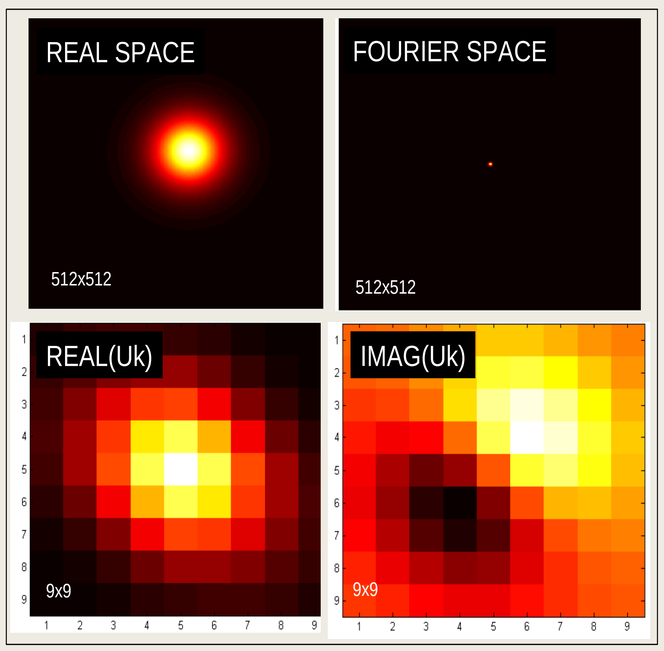

Fig. 1: The top row shows the real space intensity for a point source and the absolute value of its Fourier transform. The bottom row shows the real and imaginary cropped Fourier data. Note the difference in size (512x512 versus 9x9) while still maintaining all the information.

The forward model uses the standard normalized Born approximation, within which the fluorescence intensity due to a collection of fluorophores with concentration $F(r)$ distributed within a volume V in an otherwise infinite space is

$$U_{fl}(r_s, r_d) = \int_V U^{(inc)}(r_s, r) F(r) g(r, r_d)\, dr$$

Transforming this in the detector plane z_d along with the similar expression for the excitation light, the normalized fluorescence expression for a given source position z_s becomes

$$\frac{\tilde{U}_{fl}(R_s, K_d; z_s, z_d)}{\tilde{U}_0(R_s, K_d; z_s, z_d)} = \int_V \frac{g(R_s, R; z_s, z)\tilde{g}(R, K_d; z, z_d)}{\tilde{g}(R_s, K_d; z_s, z_d)} F(R, z) dR\, dz$$

We then discretize this to produce the normalized hybrid equation for the weight matrix:

$$\tilde{U}_n(R_s, K_d; z_s, z_d) = \sum_{i=1}^{N} \tilde{W}(R_s, R_i, K_d; z_s, z_i, z_d) F(R_i, z_i)$$

We refer to this as a "hybrid" technique because the source and voxel components of the weight matrix are kept in real space. This approach also has the advantage of avoiding the reconstruction artifacts and non-quantitative results that are obtained from a pure Fourier approach such as back-projection or direct inversion techniques. Furthermore, the direct inversion approach requires O(10^3) source locations (Markel & Schotland, 2001), which is not practical for in vivo imaging, whereas the hybrid approach requires only O(10^2) or fewer.

3 Optimized Frequency Components

A critical step in the development of this technique is optimizing the number of frequency components to strike an appropriate balance between the resolution of the final reconstruction and the computation time. The optimal resolution can be determined directly from the FWHM of a point source at the source-detector separation L, as translated into Fourier space. Given the diffusion length, $L_d = \sqrt{D/\mu_a}$, the FWHM in real space is

$$\Delta d = \frac{1}{2}\left(\left(\frac{1}{2\pi L_d} + \frac{\log(2)}{2\pi L}\right)^2 - \frac{1}{(2\pi L_d)^2}\right)^{-1/2}$$

From this we use the relationship between the FWHM of a function and that of its Fourier Transform to derive a cut-off frequency in the range $K_{max} \le K_{cut} \le 3K_{max}$, where

$$K_{max} = 4\pi\left(\left(\frac{1}{2\pi L_d} + \frac{\log(2)}{2\pi L}\right)^2 - \frac{1}{(2\pi L_d)^2}\right)^{1/2}$$

This limits the size of the weight matrix discussed above to $N_s \times N_K \times N_M$ elements, where M stands for the positions of the voxels being reconstructed.

4 Validation

Critically, this technique maintains the quantitative nature of real-space FMT reconstructions and accurate depth recovery, both in phantoms and *in vivo*. Sample *in vivo* results are shown below. These reconstructions showed good agreement both quantitatively and qualitatively with pure real space reconstructions of the same data. Increasing the value of K_{cut} in these reconstructions had a significant effect on the apparent resolution of the reconstruction.

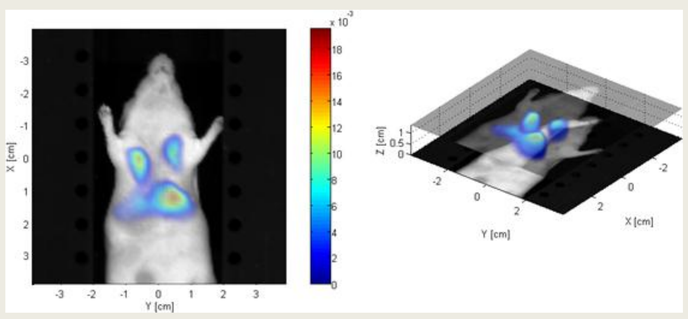

Fig. 2: Volume renderings from two different angles of a hybrid reconstruction of a mouse with primary tumors in the upper mammary fat pads, imaged with ProSense® 750. The liver signal is also clearly visible.

We imaged solid phantoms with dye inclusions at a range of depths and examined both the quantitation and depth accuracy. The linearity of concentration recovery was excellent (see Fig. 4). The depth recovery was also very good, only showing small departures from the expected depth near the surface where the diffusion approximation starts to break down (see Fig. 3).

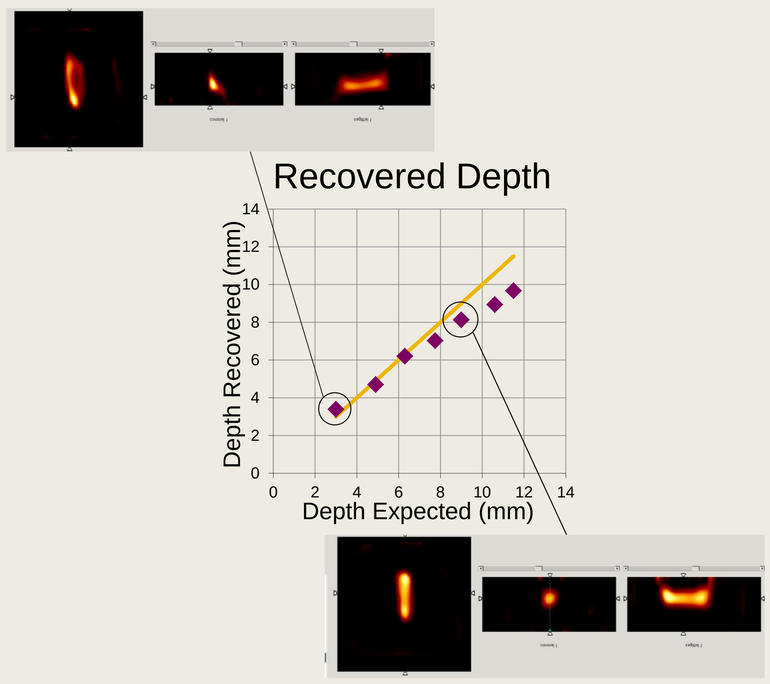

Fig. 3: A series of 1.5cm thick phantoms were imaged, each with a 100 µL fluorescent inclusion at a different depth. The line indicates 1-to-1 correspondence between the known depth and recovered depth. Sample images of two reconstructions are included for reference.

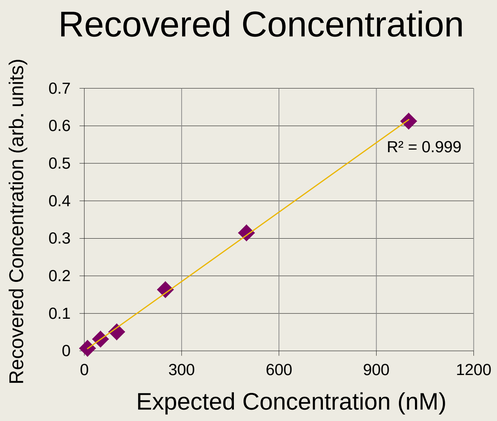

Fig. 4: Linearity of recovered concentration using a titration series in six successive scans of a phantom with a fluorescent inclusion at full depth.

6 Summary

We have demonstrated a novel approach to reconstruction of fluorescence signal in a turbid medium using a hybrid forward model that transforms the detector data into Fourier space. By using a small number of frequency components, we reduce the size of the weight matrix by roughly 100-fold as compared to a purely real space approach. This improves computation times by well more than 100x. Maintaining the voxels in real space, as opposed to a pure Fourier approach, enables the method to avoid the reconstruction artifacts and non-quantitative results inherent in such techniques.

References

- Ripoll & Nztiachristos, 2006, PRL 96, 173903
- Markel & Schotland, 2001, PRE 64, 035601