Improvement of the Specificity of DCE-MRI Using a Dynamic Optical Imaging System

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Purpose: Dynamic contrast enhanced MRI (DCE-MRI) is an established approach for detection and diagnosis of breast lesions. DCE-MRI acquires a series of images before and after administration of contrast medium to measure contrast enhancement kinetics. Tumors can be characterized based on their morphology and enhancement kinetics for diagnosis. The currently available MR contrast agents for clinical use are low molecular weight extracellular agents that can diffuse freely from the vascular space into the interstitial space. Some benign lesions may also have vascularity and high interstitial volume, thus may show malignant type enhancement kinetics and give false positive results. Therefore, there is a great need to improve the specificity of DCE-MRI.

Frequency domain diffuse optical tomography (DOT) has a great clinical potential in breast imaging, especially in providing complementary information to improve breast cancer diagnostic specificity. It provides an effective separation of absorption and scattering properties of the tissue. In the NIR range the most widely used contrast agent is indocyanine green (ICG). ICG is indeed the only NIR optical agent approved by the FDA and has been used in the medical field since 1956. ICG is a blood pool agent that binds to plasma proteins; therefore, it is confined to the vascular compartment and behaves as a macromolecular contrast agent. Dynamic contrast enhanced diffuse optical tomography (DCE-DOT) can help to increase the specificity of DCE-MRI. Dual modality data acquisition (MRI and DOT) using one small agent Gd-DTPA for MRI and a blood-pool optical agent ICG for DOT can be performed without any residual signal overlapping problem or of an excessively long study time. DCE-DOT data are composed of a series of images acquired with high temporal resolution before and after the injection of ICG. Optical flux at the boundaries are converted to measurements of ICG concentration vs. time, C(t), that are then evaluated to extract hemodynamic parameters [1].

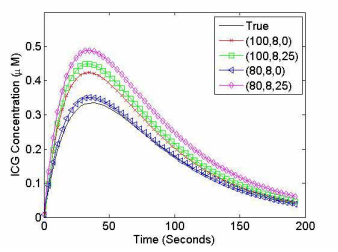
DOT imaging suffers from low spatial resolution, limited depth penetration, and nonlinear dependence of optical parameters on the imaging geometry. We performed several simulation studies to find the corresponding effects of these limitations on the analysis of the ICG kinetic curves.

Methods: ICG transport in tissue can be described using a two compartmental model [2]. The model consists of an intravascular (or plasma) compartment and an extravascular compartment (EES). EES compartment is the leakage space within the interstitial space of the tissue. The ICG pharmacokinetics can be approximated by a double exponential function, $C(t) = A \exp(-\alpha t) + B \exp(-\beta t)$, where α and β are the wash-in and wash-out rate respectively. (A+B) gives the initial ICG concentration. The change in the absorption coefficient can be related to injected ICG concentration as: $\delta\mu = 2.3\varepsilon\delta C$, where ε is the extinction coefficient of ICG.

We use the diffusion equation to model the propagation of light in tissue. It is well known that the diffusion equation can be solved accurately in breast-like geometries using finite element method (FEM). Based on this model, we formulate the forward and inverse problems in order to calculate the absorption coefficient changes in the tissue due to injected ICG concentration. Absorption coefficient at different time points can be calculated from the DOT measurements solving the inverse problem that is simply the data fitting very much like in the case of DCE-MRI data fitting. We use anatomical *a priori* information obtained by MRI to divide the domain of interest into two distinct regions, 1) region of interest (ROI), 2) background. This is a very efficient way to reduce the number of unknowns in the data fitting procedure. It is well known that malignant tumors exhibit a slower washout rate compared to benign tumors. To illustrate this difference, two different cases were studied: 1) Case I simulates ICG kinetics in a benign lesion, 2) Case II mimics ICG kinetics in a malignant lesion. Seven-second time-resolution in the simulations was chosen in accordance with our current frequency DOT system. This is currently the highest temporal resolution among the existing frequency domain systems. A high temporal resolution is vital to be able to follow the ICG uptake accurately considering that the peak contrast enhancement occurs in 60 to 90 seconds after the injection.

Results: Figure 1 and Figure 2 shows the ICG and normalized ICG kinetics curves calculated for Case II and I respectively. Four different situations using 80 mm and 100 mm breast sizes were simulated to study the effect of lesion size and location. 8-mm-diameter target was located at the center and 25 mm off-center. From these figures, it is clearly seen that the peak concentration that is most sensitive to vascular volume and permeability was dependent on the target size and location. In addition to this, the rising slope that is related to the permeability of the lesion was also dependent on the breast size and lesion location without proper normalization. When the curves were normalized with respected to their maximum values, they overlaid on top of each other. The normalized ICG kinetics curves were immune to breast size, lesion location and size. Therefore, we conclude that after normalizing each measurement to the maximum concentration, the ICG kinetics curves have the potential to characterize tumor metabolism and angionesis.

Tumor	α	β	A+B
Case I (Benign lesion)	2.1	1	0
Case II (Malignant lesion)	2.1	0.3	0



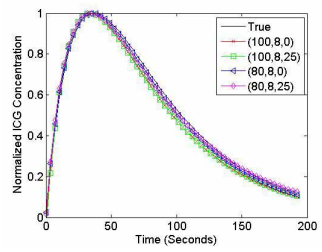
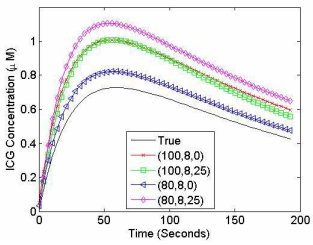


Figure 1. Comparison of ICG and normalized ICG curves for Case I. i.e. (100, 8, 25) denotes a 100-mm-diameter circular region with a 8-mm-diameter target located 25 mm away from the center.



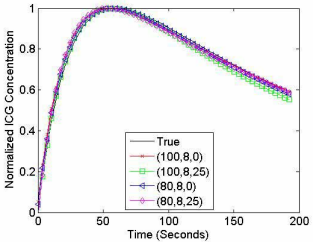


Figure 2. Comparison of ICG and normalized ICG curves for Case II. i.e. (100, 8, 25) denotes a 100-mm-diameter circular region with a 8-mm-diameter target located 25 mm away from the center.

Discussion: It has been shown that macromolecular agents can probe the vascular volume and permeability in a more sensitive manner [3]. The additional information obtained by the optical imaging system, the kinetics of ICG, is expected to increase the specificity of DCE-MRI. In this study, we investigated the use of a frequency domain DOT system to follow up ICG kinetics. We showed that the analysis of wash-in and wash-out rates in the ICG kinetics using normalized differential curves is immune to lesion size, location, and the breast size. Indeed, the use of a priori information obtained by MRI is vital in order to obtain ICG kinetics curves accurately in dynamic DOT. The optical imaging system described above is a low cost system and can be integrated with available MR systems with proper modifications. Such a hybrid system that can monitor the enhancement kinetics of an MR (Gd-DPTA) and an optical (ICG) contrast agent has a great potential for increasing specificity in breast cancer characterization.

References: [1] Intes X, et al, Med Phys. 30: 1039-47 (2003). [2] Cuccia DJ, et al, Appl Opt.42:2940-50 (2003) [3] Su MY, et al., J. Mag. Res. Img. 9; 177-86, (1999)

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