Time-resolved Optical Imaging with Patterned Light for Pre-clinical Studies

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Abstract: We investigated the performance of the time-gated Diffuse Optical Tomography based on Monte Carlo model with patterned wide-field illumination on a mouse model. The reconstructions outperform classical punctual excitation schemes for similar data sizes.

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1. Introduction

Optical imaging of live animals is an essential tool in biomedical research thanks to developments in photonic technology and reporter strategies. To quantitatively image optical contrast at depths of several millimeters to centimeters, Diffuse Optical Tomography (DOT) techniques are required. DOT relies on mathematical models that describe photon propagation in tissues, combined with sophisticated illumination and detection schemes to perform volumetric imaging of thick samples, and has been explored broadly in clinical settings. However, application of DOT techniques to pre-clinical scenarios faces distinct challenges. Complex boundaries, small volumes probed, multiple organs imaged and, thus, optically heterogeneous volumes, require particular technological development.

Optical tomography performance is affected by numerous factors and herein data type selection plays a critical role in the DOT image accuracy. Acquisitions based on continuous wave data (CW) are the most wide-spread but they are unable to provide absolute estimates and/or resolve the tissue absorption and scattering properties [1]. Also, CW techniques cannot image intrinsic dynamic information such as fluorescence lifetime. These caveats can be overcome by employing Time Domain (TD) technology. TD methods illuminate tissue with femto-seconds photon pulses and resolve the arrival of the photons as a function of time at different locations around the tissue boundary. TD technology offers a rich data set that is unmatched by CW and frequency domain methods with additional data types improving quantitative accuracy, minimizing cross talk between chromophores, and improving resolution [2].

Recently, a new approach to perform 3D volumetric imaging of thick tissue based on structured illumination has been proposed [3]. The technique, termed modulated imaging, consists of illuminating the specimen with a wide-field, sinusoidal spatially modulated, continuous excitation light. Similarly, we investigate herein the feasibility to perform time-resolved optical tomography based on wide-field illumination for pre-clinical studies with complex boundaries.

2. Methods

We employ a massively parallel time-resolved Monte Carlo code that permits us to perform diffuse optical tomography based on time-gated data sets. The Monte Carlo (MC) method is easy to implement, flexible and proven to be accurate over a large span of optical properties, and accurate for small volumes. In the MC simulations, photon packets are uniformly injected into the tissue in the region of light illumination. Using multiple patterned light illuminations and detector readings, an estimate for the absorption perturbations is obtained applying the time-gated perturbation Monte Carlo method [4]. All reconstructions herein were performed with a Conjugate Gradient algorithm without regularization. The reconstruction program stops at 50 iterations or when the relative error is below 0.01.

The mouse model is generated from a 3D mouse atlas using CT and cryosection slices [5]. The synthetic murine phantom is discretized to 91 x 35 x 22 voxels with size of 1 mm³. The background optical values are $\mu_a = 0.04$ cm⁻¹, $\mu_s = 40$ cm⁻¹ with the anisotropy factor $g = 0.90$ and the refractive index 1.37. The lungs are considered as the absorptive inclusion having a contrast of 4 ($\delta\mu_a = 0.16$ cm⁻¹). Simulations were performed in transmittance geometry mimicking the configuration of a time-gated multi-spectral non-contact imaging small animal imager that is currently under development [6]. The temporal settings of the simulations were set to 200ps gate-width with 20ps time steps and 10⁶ photons were launched per source/pattern. A 12mm x 12mm area was considered for patterned excitation employing a simplistic pattern scheme based on a previous study [7]. The patterns and the illumination/detector setting are depicted in Fig1a and Fig 1c, respectively. The reconstructions were performed for
three gates that corresponded to the half-maximum rising, maximum and half-maximum decaying gates. For comparison, we simulated an array of 36 point impulse sources and 36 detectors on the mouse surface with a 1mm radius and 2.5mm separation evenly spanned in the pattern area as shown in Fig. 1b. As well, a 36 patterned illumination/detection configuration was simulated as shown in Fig. 1d.

![Image](https://via.placeholder.com/150)

**Fig. 1**: a) patterns simulated (red: mirror on; black: mirror off); b) simulated phantom with absorptive lungs and the classical punctual source-detector configuration; simulated c) phantom with absorptive lungs and the pattern illumination and punctual detector setting; d) simulated phantom with absorptive lungs and the pattern illumination/detection setting.

### 3. Results and discussion

Examples of typical detector readings for the homogeneous simulations are provided in Fig. 2. They correspond to the central excitation punctual/pattern source and the central punctual/pattern detector respectively. The Jacobians that are associated with these detector readings and for the three-gates considered are provided in the same figure. As observed in all cases presented, the detector readings display the marked temporal features of TPSFs. The use of patterned excitation and detection leads to a temporal broadening of the TPSFs (TPSF FWHM: (point/point = 300ns; pattern/point= 440ns; pattern/pattern = 420ns) but does not smear significantly the detected photons time of flight statistics. The broadening of the temporal information, associated to the larger volume probed by the detected photons in this configuration, is clearly depicted in the Jacobian spatial distribution.

![Image](https://via.placeholder.com/150)

**Fig. 2**: Detectors readings for the central source-pattern and associated Jacobians for the three gates selected. a) point source-point detector, b) patterned illumination-point detector; c) patterned illumination-patterned illumination.

Optical reconstructions based on these time-resolved data sets are provided in Fig. 3 as well as CW reconstruction for comparison. The maximum of the reconstructed images over the actual input image is provided in Fig. 3. The enhanced performance of TG data sets over CW data set is clearly demonstrated both in terms of resolution and quantification accuracy (cf Fig. 3a and Fig. 3b). For a similar time-resolved data set, pattern/point strategy outperforms point/point and pattern/pattern both in quantification and resolution.
Besides the DOT performances consideration, wide-field strategies offer numerous experimental advantages. First, wide-field excitation should lead to higher photon counts detected in transmittance. When both excitation and detection patterns are employed, the number of detected photons increases up to an order of magnitude (Fig. 2a). In experimental settings, we expect to have even higher photon counts as wide-field strategies are less restricted by the maximum permissible exposure limit. Thus, faster acquisition time can be achieved to reach appropriate statistics. Second, the spatial distribution of collected photons in transmittance is characterized by a smaller dynamic range compared to a point source excitation scheme. Especially when employing an ultra-fast CCD to generate time-gated data sets, this enables us to collect a higher number of point detectors with satisfactory statistics for stable reconstructions. Third, the strategies employing patterned light are less sensitive to the boundaries than discrete optodes as seen in the Jacobian spatial distribution of Fig. 3. Thus, structured patterned are potentially more appropriate to monitor deep tissue without interference from superficial layers.

4. Conclusion

This in-silico investigative work demonstrated that time-gated diffuse optical tomography based on patterned light strategies is feasible and can outperform classical punctual approaches for the same data set on a small animal model. We expect these new strategies to impact time-resolved preclinical study by providing dense spatial, temporal and potentially spectral data sets for quantitative high-resolution volumetric imaging at unmatched speed. We are currently developing the instrumentation to validate and optimize these schemes in vivo.

5. References