MULTI-MODAL ACOUSTIC-PHOTO-ACOUSTIC IMAGING FOR SMALL ANIMAL IMAGING.

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INTRODUCTION

The study of neuronal function and disease in animal models and their understanding pose a great challenge to pre-clinical researchers. Electrophysiology can provide activity information of specific neuronal pools, but even with electrode arrays, this technique is difficult to use to measure plasticity changes of large neuronal populations. Magnetic Resonance Imaging (MRI) has been used to perform such measurements. It has been used in both small animals and humans but it carries large costs, is not very sensitive to molecular probes, and has time-resolution limits. Optical imaging techniques have emerged recently as an alternative in two different flavours: intrinsic optical imaging [1,2] providing high resolution images of neuronal activity and diffuse optical imaging [3] providing low resolution images of deep tissues (1-3 cm). The invasiveness of intrinsic optical imaging and its limitation to surface tissues as well as the poor resolution of DOI make those alternatives less appealing when one is interested in deeper neuronal structures and high resolution. Optical imaging however is very easily translated into a molecular imaging technique either by the use of transgenic animals (e.g. GFP, YFP) or injected compounds (e.g. Cyanine dyes, ICG).

When probing tissues at depths between 0-1cm, photo-acoustic imaging has recently been proposed as an appealing alternative combining the high spatial resolution of acoustics with the high contrast and molecular probe capabilities associated with optics [4-10]. Photo-acoustic tomography (PAT) is a method using a mix of optical propagation and ultrasound propagation. The physical process behind the technique is to first excite absorbers in animal or human tissue with light. The absorbers, which can be endogenous or exogenous, then dissipate that energy through heat. This method is referred to as thermo-acoustic or photo-acoustic imaging. By now, many applications of this technique have been explored in animals: brain tumours, functional activation, molecular imaging. Human applications are also emerging, e.g. skin cancer and breast cancer detection. Still much work remains to be done in the development of hardware as well as algorithms to bring the modality to the mainstream. This work aims to further this technology by integrating different modalities to PAT to complement the recovered images.

In the visible to near-infrared region, the dominant chromophore in tissues is hemoglobin (oxy or deoxy) and PAT can be used to generate fine images of the vasculature in vivo as well as study the vascular response to stimuli. The presence of an ultrasound transducer suggests that one could also use the same system to perform acoustic imaging in parallel. The motivation behind acoustic imaging is to add anatomical landmark to PAT imaging. In this work we show that it is possible to integrate a low voltage ultrasound pulser in the acquisition chain, in order to generate anatomical images at no cost in scanning time by interlacing laser and ultrasound pulses at rates reaching 10 KHz. We discuss potential applications to neuronal imaging and neuronavigation applied to small animal imaging.

MODEL

The photo-acoustic phenomenon can be modeled with the following inhomogeneous wave equation

$$\nabla^2 p(\vec{r},t) - \frac{1}{c^2}\frac{\partial p(\vec{r},t)}{\partial t} = -\frac{\beta}{C}\frac{A(\vec{r})\partial I(\vec{r},t)}{\partial t} \qquad (1)$$

where c is the sound velocity, p is the pressure, r is the position, t is the time, β is the isobaric volume expansion coefficient, and C is the heat capacity. The right hand side of the equation depends on the product of a spatial absorption coefficients A(r) and a temporal illumination function I(t). The objective here is to recover A(r) from the pressure measurements p(r,t) since the absorption contains information about the

underlying chromophores. One of the main difficulties towards quantification in PAT is to model light propagation in tissues and compute the 3D illumination function, I(r,t). Light propagation depends on the local absorption and diffusion in each tissue type and an a priori knowledge of anatomy is necessary to propagate a given illumination configuration into the 3D volume. This is one of the main motivations towards the inclusion of other modalities in parallel with PAT since no quantification can be obtained without a prior knowledge of anatomy. Here ultrasound is a potential candidate: it can provide delineated segments of the different organs and, with knowledge of optical properties of the different organs, could provide a solution to the quantification problem.

In the above model, the pressure can be isolated by using Green's functions, providing the forward problem

$$p(\vec{r},t) = \frac{\beta}{4\pi c}\int \frac{dr}{|\vec{r}-\vec{r}'|}\frac{\partial H(\vec{r}',t')}{\partial t'}\Big|_{t'=t-|\vec{r}-\vec{r}'|/c} \quad (2)$$

Here we will work in a dark field reflection mode and use a focused ultrasonic transducer. In this mode, the above equation appears as a linear problem that can be written as:

$$\vec{p} = GH \quad (3)$$

with G the discretized version of the integral operator in (2) and H(r) the sought heating function related to the sought absorption coefficients through the illumination function I(r,t). Image reconstruction amounts to inverting the above linear problem.

ACQUISITION

The system consists of a laser (Crystal laser, 532 nm) operating at repetition frequency of 1kHz. Fiber illumination is brought to the target and a large band focused transducer (3.5Mhz, Panametrics) then records echoes originating from the photo-acoustic phenomenon. The signal is then amplified and digitalized on a FPGA board (Altera Stratix II, DSP). The on board program averages the signal (1000 points) at the acquisition rate. A full diagram of the system is provided in figure 1.

One of the difficulties encountered here was to make sure the large signals generated by the ultrasound pulser would not interfere with the photo-acoustic detection. Given that photo-acoustic needs up to 1000 averages to generate a good signal with the laser used above, it was convenient to simply diminish the voltage of the ultrasound pulses to 5V and average the ultrasound signal the same number of time. This could be done here without any cost in scan time and, a posteriori, it is seen that the high voltage transistors used to pulse the transducer were not at all necessary and the system can be further simplified to operate with cheap off the shelf parts.

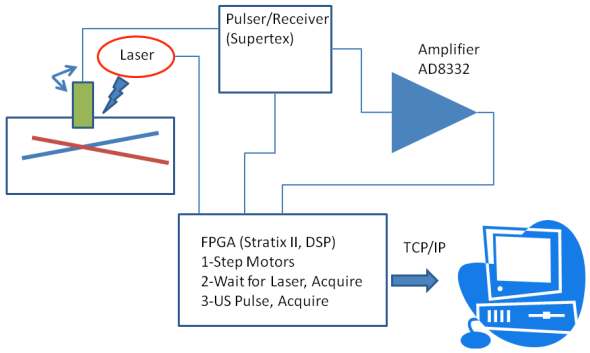

Figure 1: Overview of the system used for the validation below.

RESULTS

In order to validate the system, a phantom was constructed as follows: two transparent tygon tubes were fixed in a water container. The tubes have an internal diameter of 250um. As such the phantom is similar to vasculature that would be found in small animals. In order to get distinct contrasts in PAT and Ultrasound, one of the tubes was injected with india ink providing PAT contrast while the other was not.

The tubes were crossed and twisted together and a raster scan was performed over a region of 1.5 x 2.5 cm in 0.5 mm steps. At each step, the FPGA waits for a laser pulse to occur and triggers a PAT acquisition. Following this acquisition and prior to the next laser pulse, an ultrasound pulse is generated by a low voltage pulser (5V). This process is then repeated over time at no cost in acquisition time (i.e. the latency between the laser pulses is exploited).

Results are presented in Figures 2 and 3 where the sinograms over the whole scan and a maximum intensity projection image are presented. We clearly distinguish two tubes in the ultrasound scan (US) compared to a single tube in the PAT scan. Note that the time axis for each set of data is distinct here since the ultrasound image necessitates an echo and propagate twice as long where the PAT only necessitates one ultrasound propagation (light propagation is too fast to generate delays in here).

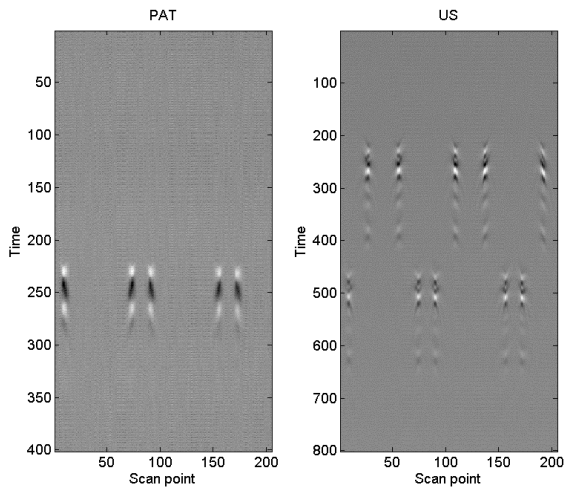

Figure 2: Simultaneous ultrasound and photo-acoustic scan of two 250um tygon tubes, one having ink, and the other empty. Only one tube is visible on the PAT scan.

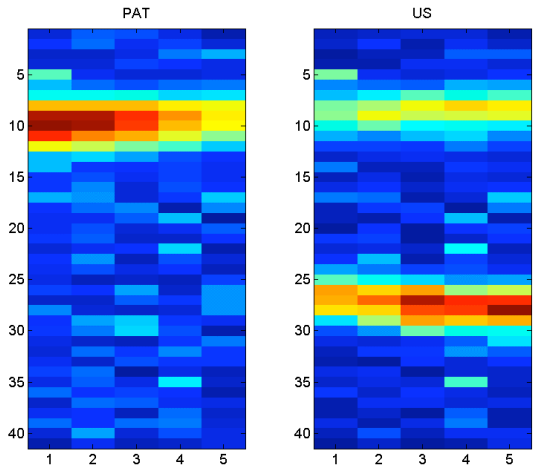

Figure 3: Maximum intensity projection of the PAT-US scan, a clear distinction between the different contrasts can be done.

DISCUSSION

Optical propagation in tissue is diffuse and there is an intrinsic limitation to the spatial resolution that can be obtained with this modality. Moreover, tissue heterogeneity leads to distinct optical properties in different organs and without a segmentation of the tissues and their optical properties, it is now generally accepted that no reconstruction algorithm will be able to provide accurate and quantitative measurement.

Photo-acoustics, for small distances, provides a high resolution alternative but is still hampered by quantification issues originating from the light propagation. Adding a separate modality to provide anatomical information is seen by the community as an alternative to generate quantifiable PAT images. In this work we integrated ultrasound to photo-acoustics towards that goal. We hope to move forward with both phantom studies as well as in vivo studies using the same system.

Molecular imaging using fluorescence can also be included in the current system by simply adding an optical detection channel. This in turn would provide a third modality aimed at molecular imaging that would be well complemented by ultrasound and PAT. We hope to come back to this in future work.

Acknowledgements

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