Interfering diffusive photon-density waves with an absorbing-fluorescent inhomogeneity

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Abstract: This work reports an investigation of the fluorescent field re-emitted by an object embedded in a highly scattering media illuminated by two-interfering sources. Simulations in the frequency domain with a finite difference method solving the diffusion equation were performed. The media considered had features typical of a soft-compressed breast. An absorbing-fluorescent inhomogeneity was embedded in the center of the slab. A qualitative study of the re-emitted field was achieved. The re-emitted field was found to possess unique features characteristic of the two-interfering sources excitation, *i.e.* null intensity when the object was between the two sources and a 180° transition crossing this position. Those features, when performing a scan of the two sources, permitted accurate localization of the inhomogeneity. Moreover, even when the detector was not placed on the mid-plane of the two sources, the re-emitted field still exhibited the interfering characteristic pattern, which was not seen at the excitation wavelength. Thus, for such configurations, the re-emitted field still possessed the specific sensitivity of phased array emission conversely to the excitation wavelength.

OCIS codes: (110.5100) Phased-array imaging systems; (170.5280) Photon migration; (170.3660) Light propagation in tissues; (170.5270) Photon density waves; (260.2510) Fluorescence.

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1. Introduction

The potential for Near Infrared (NIR) light to probe large organs has led to the use of diffuse light as a potential diagnostic tool. One of the most promising fields of application is the detection and characterization of tumors.

The most important challenge actually posed to NIR techniques is the ability to detect small subsurface cancers. Detection of small inhomogeneities is an important issue since the early detection of cancers, *i.e.*, the detection of small tumors, is strongly correlated with high survival rates[1]. To improve the ability of NIR techniques to detect small inhomogeneities, two promising approaches have been developed and will be discussed in this paper.

The first is based on the use of dual-interfering sources[2,3]. In this configuration, two rf-modulated out-of-phase sources with the same strength illuminate the media. The two scalar diffuse photon density waves propagate and add incoherently to create an interfering-like pattern[4]. The modulated amplitude is characterized by a null-plane at mid-distance for the two sources and the phase has a sharp 180° transition across this plane. These two features are specific to phased array systems. The presence of an absorptive inhomogeneity modifies this pattern, in effect pulling the null-line and the phase transition line towards the object. This configuration has been suggested to be more sensitive to the presence of an absorber than single-source configurations[5]. Experimental studies[6] and clinical trials using the configuration have proven valuable for detection of tumors[7] and physiological monitoring[8].

The second approach is based upon the use of contrast agents. Typically, the detection of tumors is based on the intrinsic contrast due to blood concentration (angionenesis) and deoxygenation (hypermetabolism). The sensitivity/specificity of the technique could be increased by using extrinsic contrast agents. The contrast agent indocyanine green (ICG) has demonstrated such enhancement clinically in breast tumors [9,10]. New contrast agents have been developed in the last few years that are very promising. These compounds are likely to improve specificity and sensitivity by specifically labeling the tumor and are retained therein after the adjacent normal tissue has becomes probe-free[11] or being delivered to the tumor and activated therein[12]. Moreover, these dyes excite and re-emit in the NIR spectral windows allowing the detection of the fluorescent field coming from deep within the tissue.

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Fluorescence spectroscopy may yield weaker detected signals, but it possesses high specificity and sensitivity. Furthermore, the monitoring of the fluorophore concentration and fluorescent lifetime promises to be a useful diagnostic tool[14-16].

In this study we investigate the coupling of the two techniques. More precisely, we have focused on the properties of the re-emitted field from an object excited by a phased-array system. We utilize a finite difference code to obtain the excitation field and the reemitted field in a case of an absorbing-fluorescent object to show that the use of dual-interfering-source configurations can lead to a specific detected fluorescent field. The detected field in several source-detector configurations possessed features of phased-array systems even when these features were lost at the excitation wavelength. The null amplitude and the phase transition of the fluorescent field occurred when the object was located exactly in the middle of the two sources. The null amplitude and the phase transition at the fluorescent wavelength can be used for an accurate localization of the inhomogeneity. The outline of the paper is as follows: in Section 2 we describe the methodology of the simulations, in Section 3 we present and discuss results obtained for the whole field and for several source-detector configurations, and in Section 4 we present conclusions and future research directions.

2. Methods

We have performed a study based on 2D simulations for computational efficiency. Cancellation techniques such as the phased-array method use the frequency domain. We adopt the diffusion equation as a model for light propagation in highly scattering media at low modulation frequencies (ω<1GHz). In this work, we solve with a finite difference method, the diffusion equation:

$$\nabla \cdot \left[D(\vec{r})\nabla U(\vec{r})\right] + \left(j\omega - c\mu_a(\vec{r})\right) \cdot U(\vec{r}) = -cS(\vec{r}) \qquad \textbf{(1)}$$

where $U(\vec{r})$ is the photon fluence [W.cm^{-2}], ω angular modulation frequency, c light speed in media, $D(\vec{r}) = c/3\mu_s'(\vec{r})$ the diffusion coefficient [cm^2.s^{-1}], $\mu_a(\vec{r})$ the absorption coefficient [cm^{-1}], $\mu_s'(\vec{r})$ the corrected transport scattering [cm^{-1}] and $S(\vec{r})$ the source term [W.m^{-3}].

The diffusion equation was solved with two out-of-phase sources of the same strength simultaneously illuminating the media ($S(\vec{r}) = \delta(\vec{r}_{s1}) + \delta(\vec{r}_{s2}) \times e^{i\pi}$). They were placed one mean free path inside the media to simulate a collimated beam source[17]. The two sources were separated by 2cm, modulated at a frequency of 200MHz, and were out of phase by 180°. The media considered had average optical properties of typical human breast[18]: $\mu_a^{background}$ =0.05cm^{-1}, $\mu_s'^{background}$ =10cm^{-1} and the geometry considered was the typical clinical situation of transmittance (cf. **Fig. 1** (a)). The geometrical size was chosen to be similar to the average breast size encountered in clinical trials[9]. The boundaries were air-tissue interfaces and modeled using the partial current boundary condition[19,20].

The inhomogeneity was a purely absorbing inclusion of 2×2mm^2 embedded in the center of the media. The object had an absorption contrast of 10:1 versus the background absorption coefficient (μ_a^{obj} =0.5cm^{-1}) to mimic contrast agent uptake by a tumor. We did not consider in this study a fluorescent background for simplicity. However, for a quantitative study, such background should be considered to more accurately model clinical situations.

The simulated diffuse photon density field at the excitation wavelength was obtained for two sources illuminating one side of the media shown in **Fig. 1** (a). The grid size used for the simulations was fixed to 0.5 mm. Thus 25 nodes sampled the object (*c.f.* Fig. 1 (b)). The results (amplitude and phase) of these first sets of simulations defined the values of the excitation field at each sampling node of the absorptive inclusion. Those values were then used as secondary sources for a second set of 'emission' simulations and in order to obtain the

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field re-emitted by the object, the diffusion equation was re-solved with these 25 sources to model a volume source.

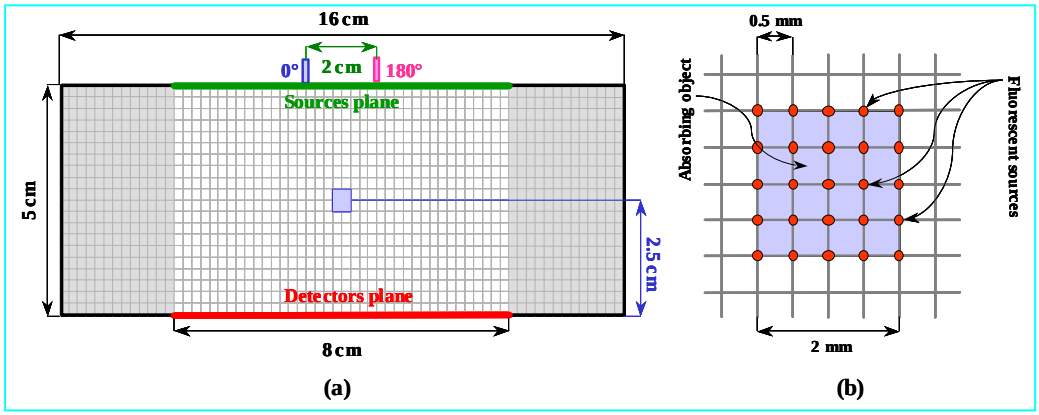

Fig. 1: (a) Simulated set-up map, (b) fluorescent object modeling.

Since we were not interested in a quantitative study, we did not modify optical properties of the media to account for differences at different wavelengths. Also, we did not model energy transformation modifications due to fluorophore quantum yield ($\eta = 1$) and fluorescent lifetime ($\tau = 0$ s) in this work. Amplitude discrepancy and phase shift are expected if those physical phenomenons are taken in account. Although, these effects do not modify the trend presented in this work[21].

The simulations methodology described above was used to mimic relevant clinical configurations. The considered experimental configurations are depicted in Fig. 2. The arrows denote a scanning of the specific part of the system in the simulations.

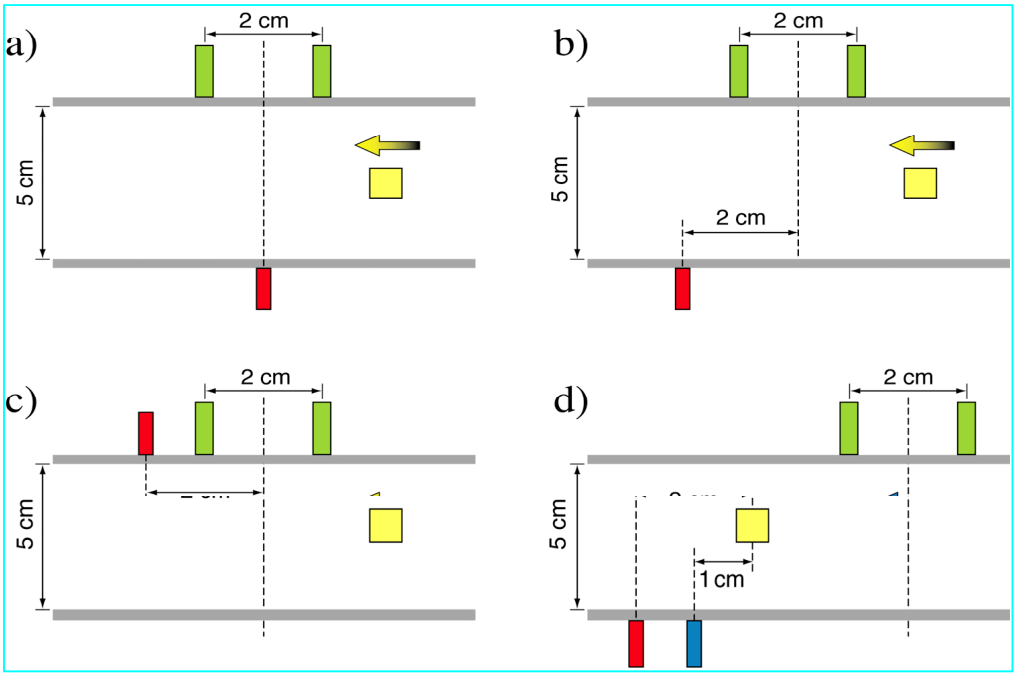

Fig. 2: Experimental situations investigated. Green bars represent the sources and red (blue) bars represent detectors. The fluorescent object is depicted in yellow. **(a)** scanning of the object in the classical phased-array configuration (equivalent to a scanning of the sources-detector system), **(b)** detector shifted from classical position, **(c)** reflectance case and **(d)** scanning of the sources for static object and detectors.

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The gray areas on Fig. 1 limited the scanning of the two sources to avoid the effects of the lateral boundaries. In this case, the media simulated was equivalent to an infinite slab geometry.

The detectors were considered point-detectors and the values of the field reaching them corresponded to the field value on the node at the corresponding location.

3. Results and discussion

In Fig. 3 we present the logarithm of the modulated amplitude and the phase for the excitation field and re-emitted field in the whole media. The two left pictures represent the values of the excitation field, and the two right pictures represent the values of the reemitted field. The X-axis corresponds to the dimension parallel to the sources and detector planes and the Y dimension correspond to the depth of the media.

The first position (first frame) corresponds to a position of X=5cm of the null line and each position (each frame) is 0.25cm away from this first position to finish at a position of X=11cm. Those two extreme positions correspond as explained previously to the demarcation of the gray areas in Fig. 1.

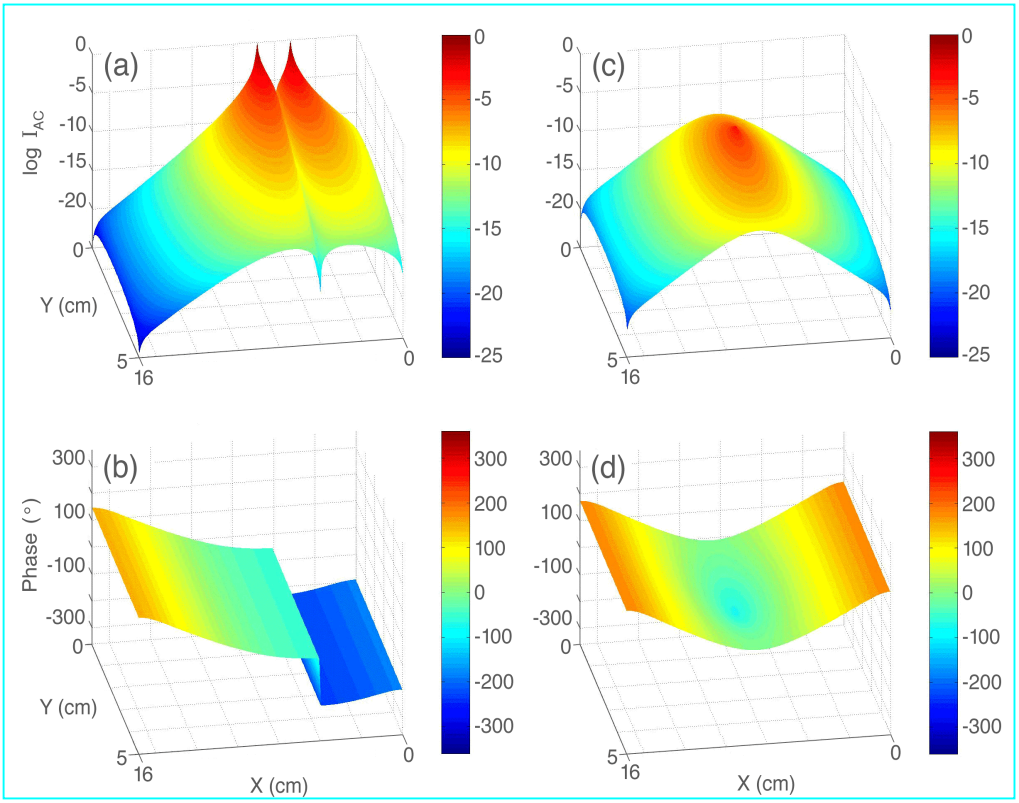

Fig. 3: (1.5 MB) Movie of (a) logarithm of the amplitude at the excitation wavelength – (b) phase at the excitation wavelength – (c) logarithm of the amplitude at the fluorescent wavelength and (d) phase at the fluorescent wavelength. The object is located in the center of the media (maximum of re-emitted amplitude). The sources plane correspond to the y=0 plane and the detectors plane correspond to y=5cm plane.

From the left column of **Fig. 3**, we can see the specific interfering pattern characteristic of the phased-array system. The amplitude valley and the phase transition are evident in the mid-plane separating the two sources. However, the intensity is not null in this plane and the value obtained is due to the perturbation created by the object. Only when the object is exactly located between the two sources does the mid-plane reach a null value in intensity. For this

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specific case, the excitation symmetry cancels out the perturbation. For other positions, the perturbation in amplitude is important especially when the object is close to a source.

The perturbation also affects the phase, however, the scale of the representation and the small shifts of the transition plane due to the small size of the inhomogeneity make the phenomenon difficult to follow on this movie. The effect will be presented below with other simulations.

The right column of **Fig. 3** gives the reemitted field for each scanning position of the two sources. The reemitted field behaves as an over damped spherical wave. This observation is true as long as the fluorescent object acts as a secondary volume source in a homogeneous medium[22]. More interestingly, the amplitude and the phase reemitted by the object are coded by the excitation pattern. The emission amplitude as a function of sources position follows the same trend as the minimum of the null-plane of the excitation amplitude (*c.f.* also simulations of **Fig. 4**). The amplitude increases until the object is in front of one of the two sources and decreases to a minimum when the object is located symmetrically with respect to the two sources. For this latter configuration, the object effectively acts as a new phased-array system inside the media at the emission wavelength. A 180° phase-shift field illuminates each side of the object. The reemitted field is the interference of the scalar waves reradiated by the out-of-phase sides of the object.

The reemitted phase exhibits the same specific features of a phased-array. The phase depends on the nearest source that illuminates the object. The phase transition is striking when the object is located in the exact middle plane. For this position, the two out of phase side of the object are well seen.

The pictures of the whole field show how the excitation field and the reemitted field behave in the media. Nonetheless, to have a better understanding of the features and the usefulness of the reemitted field we have to consider practical configurations.

Phased-array configuration

In **Fig. 4**, we display the modulated amplitude and the phase reaching a detector positioned in the typical situation of a phased array system, *i.e.* for a detector located on the middle plane and when the object is scanned in the media (*c.f.* Fig. 2(a)). The fluorescent amplitude displayed here has been arbitrarily normalized to permit a good presentation. The fluorescent field is almost 2 orders of magnitude smaller than the excitation field.

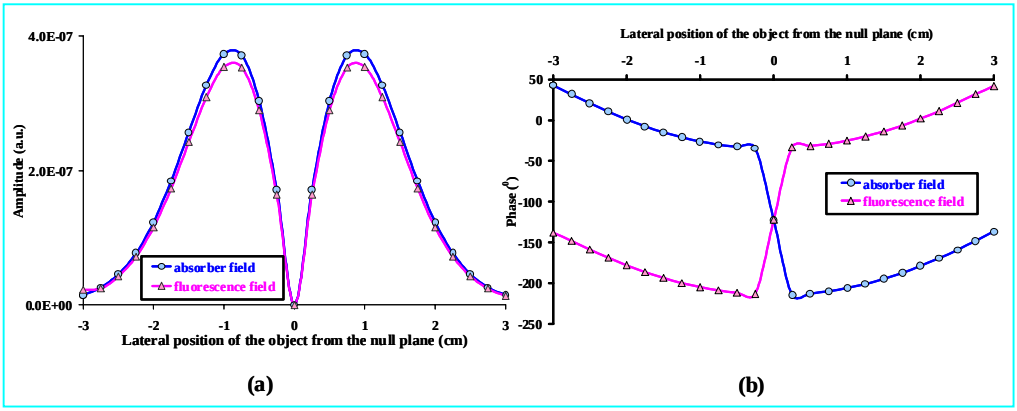

Fig. 4: Profile of the simulated field, (a) amplitude (b) phase for a scanning of the object and the middle detector (the amplitudes are processed for a better presentation).

As described above, the detected intensity at the excitation wavelength is only due to the presence of the absorbing inhomogeneity. The perturbation is more important when the object is close to a source and the reemitted intensity exhibits the same behavior. If one normalizes these two intensities, they will perfectly match. There is also a perfect symmetry between the two detected phases. The absorbing inhomogeneity creates a negative perturbation that is balanced by a positive perturbation at the fluorescent wavelength due to the transformation of

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the energy. In other words, when the object is an absorber, the object blocks the light coming from the nearest detector and so more light coming from the farther source is detected. When the object is a re-radiator, the object re-radiates more light derived from the closest source. This complementary effect is well depicted by the symmetry of the phases.

In this particular configuration, we see that the fluorescent field detected possessed some of the features of the phased-array excitation field. The null-plane and the phase transition are recovered when the object crosses the mid-plane between the two sources. The abilities of detection of phased-array system still exist at the fluorescent wavelength.

Detector off the null-plane

Other multi-sources-detector configurations could be envisaged. Especially in the case when several detectors are used in a parallel acquisition scheme, not all the detectors could be placed on the null-line.

In **Fig. 5**, we show a case where the detector was placed at 2cm off the null-plane and the object scanned (*c.f.* Fig. 2 (b)). In this case, the two fields do not exhibit the symmetrical effect described above.

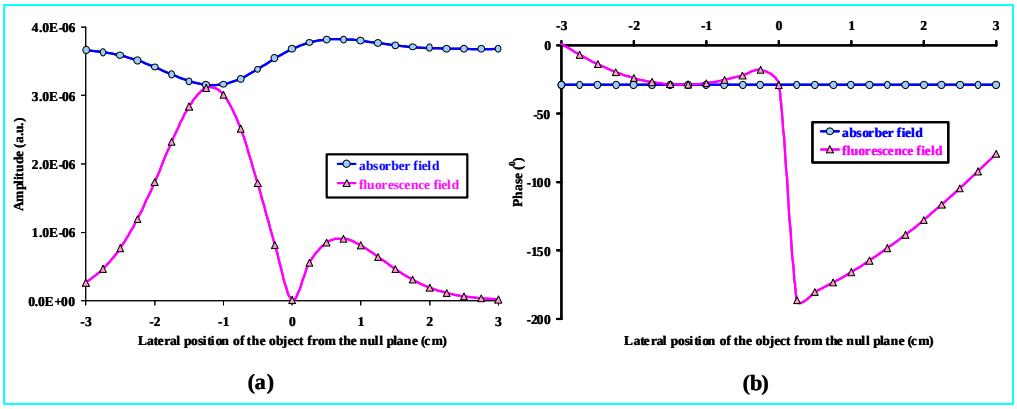

Fig. 5: Profile of the simulated field, (a) amplitude (b) phase for a scanning of the object and a detector at 2cm from the null-line.

In the case of the excitation field, we see that we do not detect the characteristic pattern of a phased array. In this case, the result is more like a one-source-detector system. The perturbation detected is important only when the object is in front of the nearest source to the detector position and quite insensitive to the other source. At the excitation wavelength, the phased-array system has lost its exquisite sensitivity to the inhomogeneity. In contrast, the reemitted field still possesses the characteristics of the phased array excitation. The amplitude, even if not symmetric, displays a null and the phase a 180° transition. These two features are still correlated to the cross of the null-plane by the object. Even in this configuration where at the excitation wavelength the ability of phased-array system to localize the inhomogeneity is deteriorated, the reemitted field is able to produce a valuable tool for the localization.

The same remarks could be drawn from **Fig. 6**. The same methodology is used in this case, but the detector is placed in reflectance geometry at 2cm from the null-line (*c.f.* **Fig. 2** (c)). The difference of sensitivity is more dramatic in this case.

As expected, the reemitted field is exactly the same as in **Fig. 5** provided the object is embedded in the center of a homogeneous media. Conversely, we see that the perturbation reaching the detector due to the presence of the object is far less important in reflectance than in transmittance. In transmittance, the perturbation at the excitation wavelength was estimated to $\Delta^{T}\theta = 1.5°$ and $\Delta^{T}I_{ac} = 10\%$ and only $\Delta^{R}\theta = 0.2°$ and $\Delta^{R}I_{ac} = 2\%$ in reflectance (maximum of the difference between the homogeneous case and the heterogeneous case). On the other hand, the fluorescence holds the same sensitivity between transmittance and reflectance. This is true as long as the object was placed exactly in the center of the media.

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Differences in sensitivity for reflectance and transmittance will result for other depth locations of the object. Nonetheless, the features of phased array will still exist at the fluorescent wavelength and an accurate localization of the object will still be possible in these configurations.

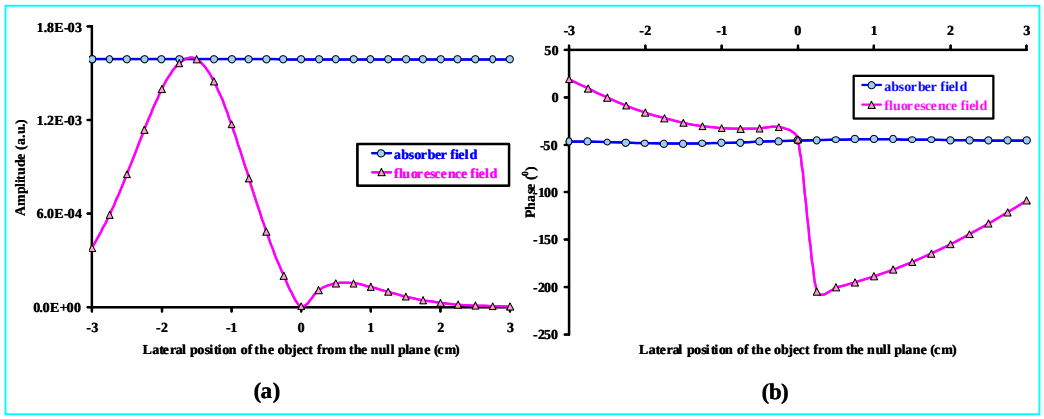

Fig. 6: Profile of the simulated field, (a) amplitude (b) phase for a scanning of the object and a detector at 2cm from the null-line in reflectance geometry.

Scanning of the sources

To underline the specificity of the reemitted field, we display in **Fig. 7** results obtained in another sources-detector configuration (*c.f.* Fig. 2 (d)). Here the detectors and the object were fixed and the two sources scanned. The detectors were placed at 1cm and 2cm respectively to the position of the object (transmission). The results were normalized in amplitude and processed in phase to achieve a better display quality.

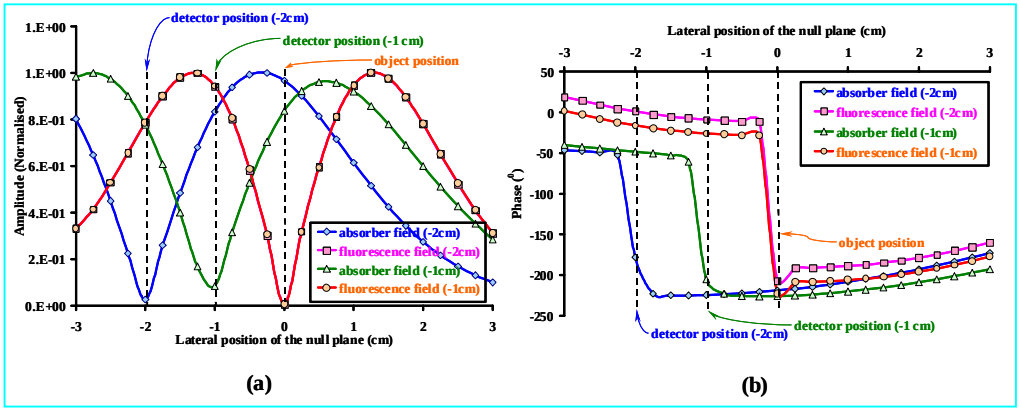

Fig. 7: Profile of the simulated field, (a) amplitude (b) phase for a scanning of the two sources and two positions of the detector. Due to the normalization, the two amplitudes of the fluorescence fields overlap.

This configuration is important as it is more clinically realizable than the absorption case, which requires scanning of both the source pair and the detector.

In both detector positions we see that there is a clear discrimination between the excitation and the fluorescent fields. The excitation field presents the features of a phased array system perturbed by the object. The minimum intensity and the 180º phase shift detected occurred when the null line was located on the detector position. Small modifications versus the homogeneous state were due to the absorbing object. On the other hand, in the case of the fluorescent field, the field had the exact pattern of a phased array system. Moreover, the intensity null, and the phase transition occurred when the object crossed the null line and not

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when the null line crossed the detector. This fact is striking and correlates perfectly the minimum intensity and fluorescent phase shift to the position of the object. The localization of the object is so easily performed by the detection of the phase transition or the null-amplitude at the fluorescent wavelength.

4. Conclusion

In this study we have carried out simulation as a first step to evaluate the usefulness of the re-emitted field from an object excited by dual interfering sources. We have seen that the fluorescent field possesses specific features when the excitation field is an interference pattern. These features are remarkable and permit accurate retrieval of the position of the fluorescent object. The specificity of the excitation pattern still holds even when the information is minimal at the excitation wavelength. The features described here, are also valid for the reflectance case, as long as the object acts as a secondary source inside the medium.

This paper described qualitatively the features of the fluorescent field. A quantitative study is however necessary to define the applicability of the technique in clinical setting. The determination of the smallest object detectable with widely used contrast agents is the next step that we will perform. The fluorescence of the non-tumor signals due to the background and typical experimental errors will be considered. Furthermore, the impact of a heterogeneous background and lateral boundaries should be considered to estimate the modification on the excitation null-plane. This quantitative study will be used as a basis for the rationale of modifications to the existing apparatus[8,23].

Also, these studies show the feasibility of performing 1D localization. Extension of this work to 2D localization with experimental configurations such as described in Chance *et al.*[6] and 3D localization with Diffuse Optical Tomography[24] will be considered.

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