Monte Carlo simulation of spatial resolution and penetration depth of two dimensional optical imaging methods

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Introduction

Two dimensional (2D) optical imaging, based on either optical absorption (such as intrinsic optical imaging, IOI) or fluorescence (such as voltage sensitive dye imaging, VSDI) have been widely employed in functional brain imaging [1,2]. Hence, it is important to know the spatial resolution and penetration depth of the signals. The light scattering and absorption in biological tissues, however, make it difficult to estimate these characteristics. Currently, the spatial resolution is only reported for specific imaging configurations: the 240 μm spatial resolution of IOI, simulated by Polimeni et al was consistent with that (adjusted value of 280 μm) measured by Orbach and Cohen, but significantly different from 50 μm estimated by Grinvald et al [3-5].

Here, we employ Monte Carlo simulations to study systematically the spatial resolution and penetration depth of the 2D optical imaging based on both absorption and fluorescence and for a range of optical configurations typically encountered in functional brain imaging.

1. Grinvald, Annual Review of Neuroscience 8, 263 (1985)
2. Grinvald et al, Nature 324, 361 (1986)
3. Polimeni et al, Proceedings of the National Academy of Sciences102, 4158 (2005)
4. Orbach and Cohen, Journal of Neurosciences 3, 2251 (1983)
5. Grinvald et al, Modern Techniques in Neurosciences Research, 539 (1999) eds, Windhorst and Johansson (Springer, New York)

2D optical imaging system and brain tissue model

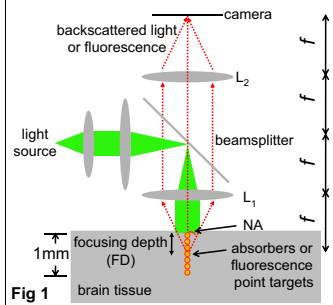


Fig 1

Excitation: collimated light illuminates the tissue

Detection: either backscattered light (in absorption imaging such as IOI) or fluorescence (fluorescent imaging such as VSDI) is collected and imaged by lenses L_1 and L_2 onto the camera.

L_1 and L_2 (focal length of *f*) are arranged in 4f configuration such that the object on the front focal plane of L_1 is imaged onto the back focal plane of L_2, typical of 2D optical imaging systems [6].

Optical imaging configurations

NA = 0.1, 0.2, 0.4

Focusing Depth (FD) = 20, 100, 200, 300, 400, 500, and 600 μm

Brain tissue model [3,7]

semi-infinite; refractive index = 1.4; anisotropic factor = 0.9; coefficient of scattering = 35/mm; coefficient of absorption = 0.27/mm.

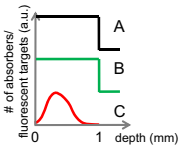


Fig 2

Distribution of absorbers and fluorescent point targets

Absorbers (Fig 2A) and fluorescent point targets (Fig 2B) are uniformly distributed along the optical axis from 0 -1 mm inside the tissue.

Some VSD imaging observed non uniform staining of the fluorescent dyes, so we also simulate for this case (Fig 2C) [8].

6. Ratzlaff and Grinvald, Journal of Neuroscience Methods 36, 127 (1991)
7. Cheong, Prahl, and Welch, IEEE Journal of Quantum Electronics 26, 2166 (1990)
8. Ferezou, Bolea, and Petersen, Neuron 50, 617 (2006)

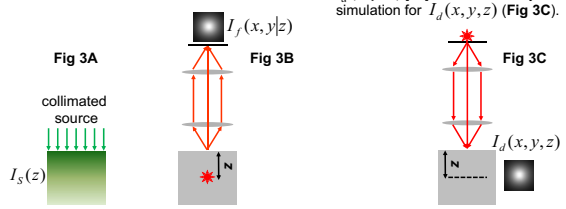
Calculate images induced by individual point targets using Monte Carlo [9-11]

Image simulation

We calculate the fluorescence /absorption images induced by individual point targets under the illumination of collimated light on the brain tissue as follows. Step I: simulate the photon distribution of collimated light source inside the tissue, $I_s(z)$(z = the depth inside the tissue) **(Fig 3A)**. Step II: obtain the photon distribution on the camera plane caused by a point target located at depth z, $I_f(x,y|z)$. The resultant image is$I_s(z)$x $I_f(x,y|z)$**(Fig 3B)**.

Improve simulation efficiency

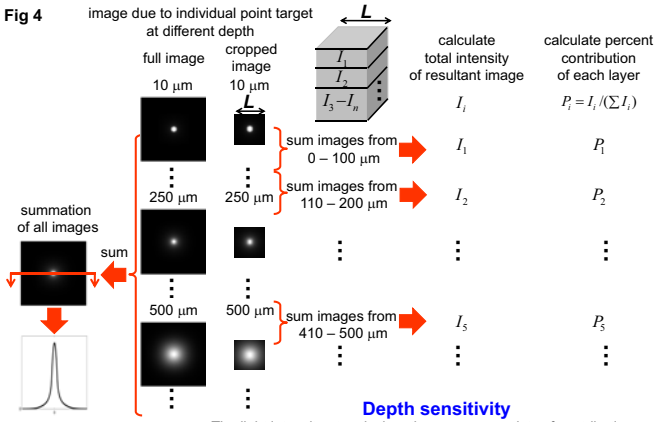
Step II requires the calculation of many (100 here) point sources, thus, many Monte Carlo simulations. Since Monte Carlo is time consuming, it is important to reduce this number. Due to the principle of reciprocity, the shift invariance of tissue, and the 4f configuration of the image system, the photon distribution calculated in Step II, i.e. $I_f(x,y|z)$is the same as the photon distribution on the plane at depth z inside the tissue if we have the point source located at the center on the camera plane $I_d(x,y,z)$ [12]. Hence, we only need one simulation for $I_d(x,y,z)$ **(Fig 3C)**.



9. Wilson and Adam, Medical Physics 10, 824 (1983)
10. Wang, Jacques, and Zheng, Computer Methods and Programs in Biomedicine 47, 131 (1995)
11. Boas et al, Optics Express 10,159 (2002)
12. Dunn and Boas, Optics Letters 25, 1777 (2000)

Quantify spatial resolution and depth sensitivity

Fig 4



Spatial resolution

Full width at half maximal amplitude of the profile is the spatial resolution.

Depth sensitivity

The light intensity at a pixel on the camera consists of contributions from different depth slabs ($I_1 \ldots I_n$ in the gray cube in Fig 4). From the intensity contribution of each layer I_i (such as I_1 from 0 – 100 μm), we obtain the percent contribution of every layer $P_i = I_i/(\sum I_i)$, which is the depth sensitivity that reflects the penetration depth. I_i can be obtained from the images due to point targets as illustrated here.

Spatial resolution worsens with the increase of NA and focusing depth

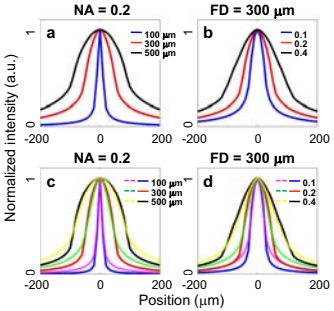


Fig 5 Profile of the absorption (a, b) and fluorescence images (c, d) for different NA and focusing depth. c, d: and uniform and non-uniform distributions of fluorescent targets.

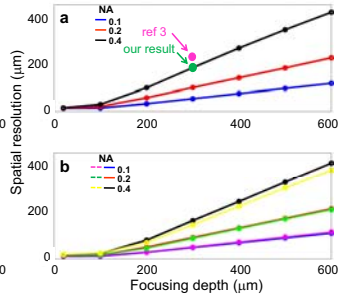


Fig 6 Spatial resolution of the absorption (a) and fluorescence (b) images versus focusing depth. b: and uniform and non-uniform distributions of fluorescent targets.

1. Our spatial resolution of 200 μm is consistent with 240 μm from ref [3] under similar optical configuration (NA ~ 0.4, FD = 300 μm).
2. Spatial resolution (20 to 400 μm) is sufficient to resolve most functional columns.

Changing NA and focusing depth does not affect the depth sensitivity for large activation area (≥ 200x200 μm²)

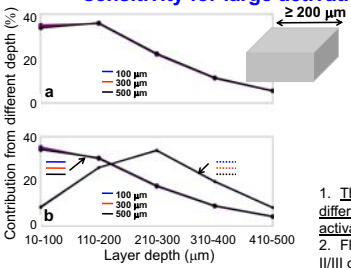


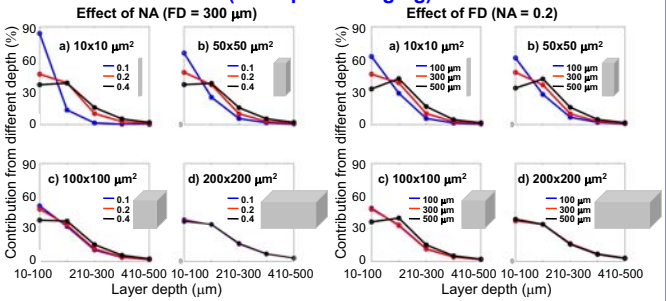
Fig 7 Depth sensitivity of the absorption (a) and fluorescence images (b) for different focusing depth at NA = 0.2 (data for NA = 0.1 and 0.4 are similar). b: and uniform and non-uniform distributions of fluorescent targets.

Table 1 Depth sensitivity may vary with imaging modality and animal models

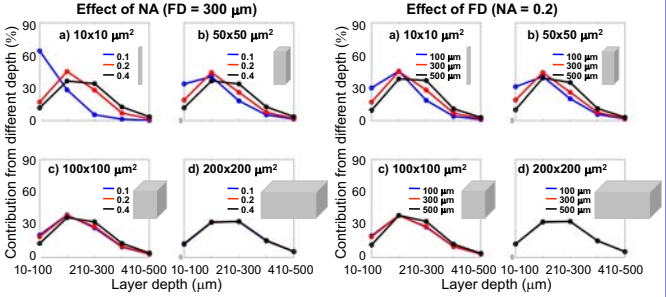
	uniform absorbers/ fluorescent targets		Non-uniform fluorescent targets	
	Layer I	Layer II/III	Layer I	Layer II/III
Mouse		Dominant		Dominant
Rat	Dominant			Dominant
Cat	Dominant		Similar	Similar
Monkey	Dominant			Dominant

1. There is little difference in the depth sensitivity with different NA and focusing depth (Fig 7) when activated area is large.
2. Fluorescent imaging with more dyes staining layer II/III of the brain tissue (Fig 2C) sees deeper than 2D imaging with uniform distributions of absorbers or fluorescent dyes.
3. This result offers guidance in data interpretation and cross modality comparisons of functional brain imaging.

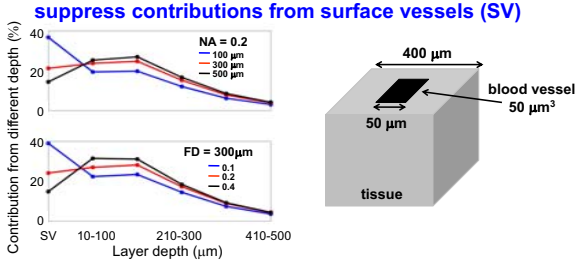
Larger NA and FD help see deeper for small area of activation (absorption imaging)



Larger NA and FD help see deeper for small area of activation (fluorescence imaging with non-uniform staining shown in Fig 2C)



For absorption imaging, larger NA and FD suppress contributions from surface vessels (SV)



Summary

1. We have simulated spatial resolution and estimate the percent contribution to the 2D optical imaging from different depth of the brain tissue for a wide range of optical configurations (NA = 0.1, 0.2, and 0.4 and focusing depth = 20, 100, 200, 300, 400, 500, 600 μm).
2. We have found that
   - Spatial resolution worsens with the increase of NA and focusing depth; It (20 to 400 μm) is sufficient to resolve most functional columns.
   - For functional imaging applications with large activation area (≥200x200 μm²) and devoid of large surface vessels, increasing NA and FD does not improve the depth sensitivity, but reduce the spatial resolution.
   - Increasing NA and FD improves the depth sensitivity for functional imaging applications with small activation area (≤100x100 μm²), which may be useful in imaging optically activated neuronal circuits (ChR2 etc.).
   - For functional imaging applications with large surface vessels in the field of view, increasing NA and FD does suppress the contribution from these vessels, thus reflecting more contribution from the brain tissue.
3. Our results are consistent with those from ref [3-4] at the corresponding optical configuration. They offer guidance in the optimization of optical imaging protocols for different applications, in particular with regards to NA and the focusing depth, staining profile and cortical thickness. Modeling of photon migration in the context of 2D optical imaging is important for data interpretation and cross modality comparisons of functional brain imaging.

Acknowledgements

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