Simulating the light propagation in rodent brain tissues using ray tracing with a 3D microvasculature model

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INTRODUCTION

- Cortical neuronal activity, metabolism, and hemodynamics on the level of single cells and vessels can be measured by two-photon laser scanning microscopy (TPLSM) *in vivo.*
- Relatively large hemodynamic changes often accompany changes in neuronal activity and metabolism, distorting the signal of interest. One example is dynamic imaging of β-nicotinamide adenine dinucleotide (NADH) fluorescence reflecting metabolic activity.
- Prior work
  - Baraghis modeled hemodynamic distortion of TPLSM NADH fluorescence at specific points with realistic cortical microvasculature [1].
  - We modeled this distortion over cortical tissue of 0.3x0.3x0.3mm in rat and found that a single correction factor may be used to correct for the distortion in deeper tissue [2].
  - Our goal here is to test whether our results generalize across (1) individual vascular geometries and (2) different fluorophores ("dyes").

METHODS

We have to consider propagation of both excitation and fluorescence emission (Fig 1a) [1]

- **Excitation (only consider scattering due to blood vessels)**
  - Incident laser light (740 or 800nm): multiple rays uniformly distributed on the cortical surface within the excitation cone determined by NA (0.95) and n_{tissue} (1.36); initial intensity modeled as Gaussian distribution.
  - Each ray experiences a series of scattering events due to blood vessels in the path. The effect of all scattering events with vessels of the same diameter is lumped into a single scattering event at the averaged distance above the focal point. The ray is absorbed by the fluorophore at the focal volume (radius of 0.5 microns).
- **Fluorescence emission (only consider absorption due to blood vessels)**
  - Each ray emitted from the focal point within the same cone (determined by the NA) is considered; it experiences a series of absorption events due to blood vessels before exiting the tissue.

Tissue optical properties (Fig 1b depicts absorption and emission spectra)

- Non-vascular tissue: homogeneous and constant ⇒ ignore its effect
- Blood vessels:
  - heterogeneous ⇒ use microvasculature stack from TPLSM imaging:
    absorption: $\mu_a \propto Hematocrit[SO_2\varepsilon_{HbO}(\lambda) + (1-SO_2)\varepsilon_{Hb}(\lambda)]$
    oxygen saturation SO2: 0.75; hematocrit: determined by vessel diameter
    scattering [2]: $\mu_s \propto (1-Hematocrit)Hematocrit$
  - time-varying ⇒ simultaneously image and simulate a structural (time-invariant) fluorophore Sulforhodamine 101 (S101)

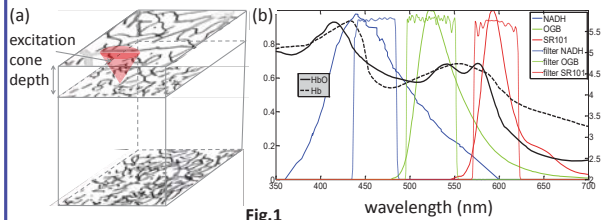


Fig.1

RESULTS

Fig.2 NADH and S101 fluorescence intensity profiles: comparison of simulation and measured results

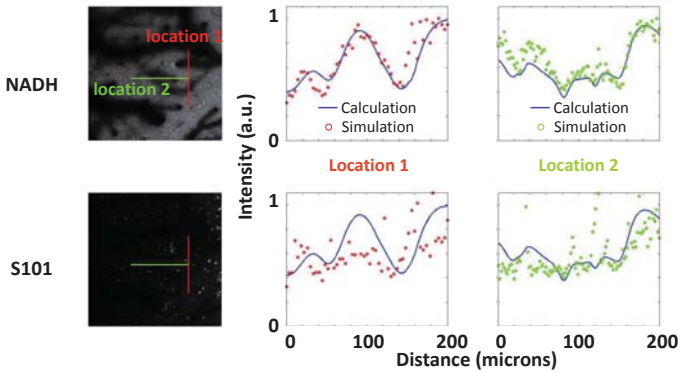
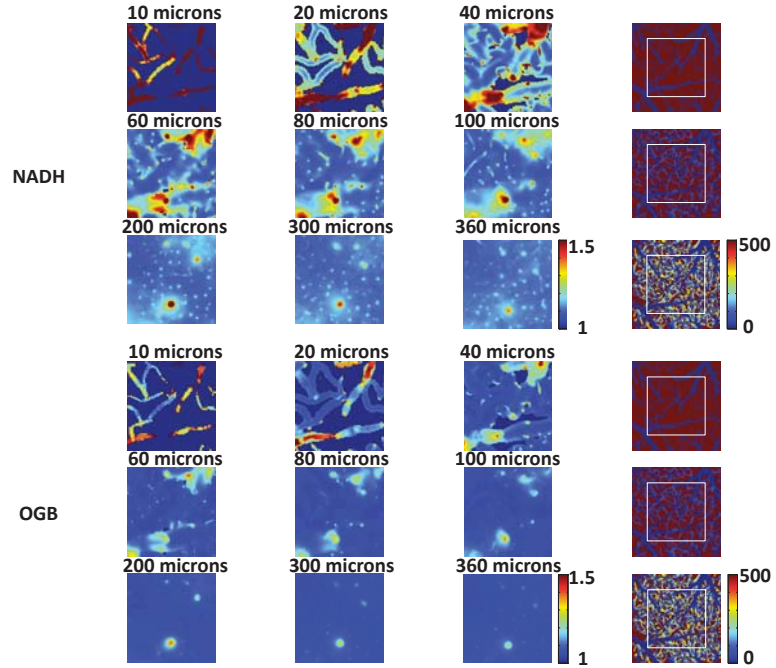


Fig.3 Map of correction factor K is sensitive to vascular geometry within the top 20-40 microns and becomes homogeneous deeper down.

K: ratio of relative change of the dye fluorescence over relative change of S101 fluorescence due to hemodynamic response

$$\frac{\Delta C_{dye}}{C_{dye}} = \frac{\Delta I_{dye}}{I_{dye}} - K\frac{\Delta I_{S101}}{I_{S101}} \quad \text{Eq (1)}$$

- $\frac{\Delta C_{dye}}{C_{dye}}$: true relative dye fluorescence change
- $\frac{\Delta I_{dye}}{I_{dye}}$: measured relative dye fluorescence change
- $\frac{\Delta I_{S101}}{I_{S101}}$: measured relative S101 fluorescence change



Left: Calculated K at various cortical depths. The area of each K graph is 0.4x0.4 mm. Right: Maximal intensity projection of vasculature in the cortical tissue within top 40, 100, and 360 microns.

CORRECTING HYMODYNAMIC DISTORTIONS

Fig.4 Averaged K (solid lines) reaches a plateau of ~ 1.1 deeper than ~ 100 microns (dashed lines: K for individual vascular geometries)

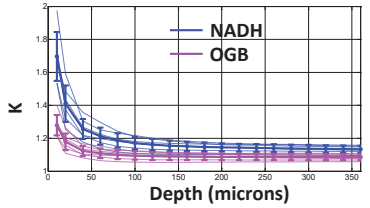


Fig.5 Left: Average distortion (solid lines), the difference between measured relative dye fluorescence change and true relative dye concentration change, is severe without correction (dashed lines: distortions for individual vascular geometries). Right: Distortions at 40 and 360 microns.

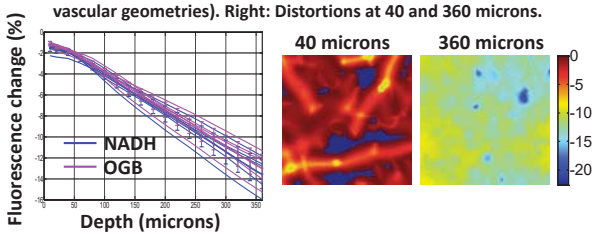
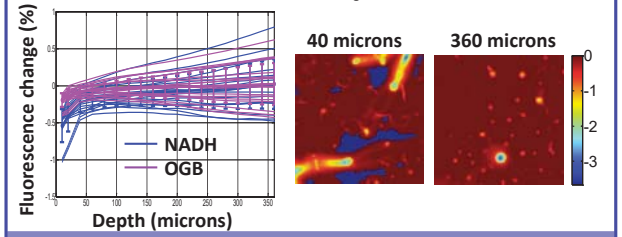


Fig.6 Average distortion (solid lines) with single value correction is 1/10 of the original (dashed lines: distortions for individual vasculature)

Left: From Fig.4, K reaches a plateau of 1.13±0.02 and 1.09±0.02 for NADH and OGB, respectively. Average distortions with correction using K = 1.11, 1.13, and 1.15 for NADH and K = 1.07, 1.09, and 1.11 for OGB are calculated for individual vasculatures. Right: Distortions at 40 and 360 microns.



SUMMARY

- K becomes homogeneous and reaches a plateau at depths ~100 microns, pointing to a single value correction scheme. While hemodynamic distortion is severe without correction, a single value K correction reduces it by 10 times. Without correction, the magnitude of distortion can be larger than the magnitude of the functional signal change.
- Correction factors obtained with 6 different realistic microvascular geometries and 2 dyes (NADH and OGB) indicate that our conclusions hold across the geometries and fluorophores.

REFERENCES

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