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В рамках программы Фонда Дмитрия Зимина «Династия»
«Краткосрочные визиты иностранных ученых в российские научные центры»
19 сентября 2015г. – 28 сентября 2015 г.

Основы взаимодействия света и биологических тканей

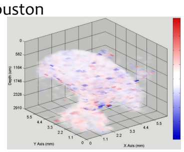
Bio Opt Lab
Biomedical Optics Laboratory

Optical coherence tomography: Noninvasive Sensing of Molecular Diffusion

Kirill V. Larin

Department of Biomedical Engineering
College of Optometry

University of Houston



Molecular Diffusion Studies

Monitoring and quantifying the diffusion of various molecular solutions and drugs in biological tissue

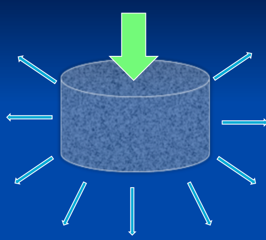
- Speed that drug permeates in tissues
- Effect of solutions' diffusion on tissues
- Distinguishing among normal and abnormal specimens by functional imaging

Ussing Chambers

Disadvantage:
Only *in vitro* studies

fOCT

Molecular Diffusion in Ocular Tissues

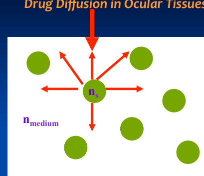


An important ability of a chemical compound (agent) to change the tissue scattering properties is based on a number of biophysical processes . The concept of two fluxes – agent into tissue and bulk tissue water out, which may be relatively independent or interacting fluxes defines the dynamic properties of tissue optical clearing and its efficiency

- refractive index matching/mismatching (generally for whole tissue matching an locally mismatching may take place),
- increase of tissue collagen fibers packing density (ordering of scatterers),
- and decrease of tissue thickness.

fOCT

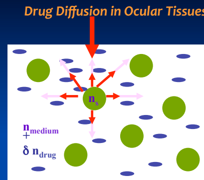
Drug Diffusion in Ocular Tissues



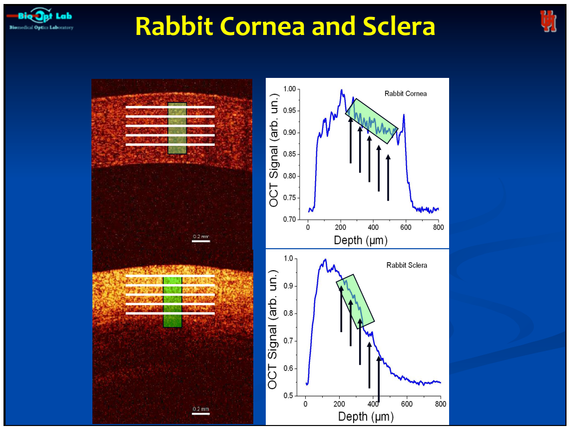
$$\mu_s' = 3.28\pi r^2 \rho_s \left(\frac{2\pi r}{\lambda}\right)^{0.37}\left(\frac{n_s}{n_{medium}}-1\right)^{2.09}$$

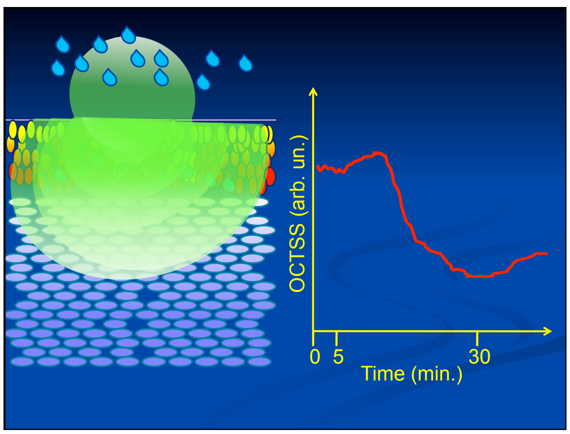
fOCT

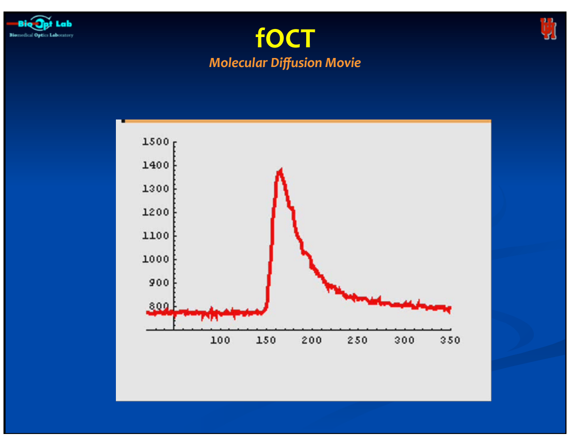
Drug Diffusion in Ocular Tissues

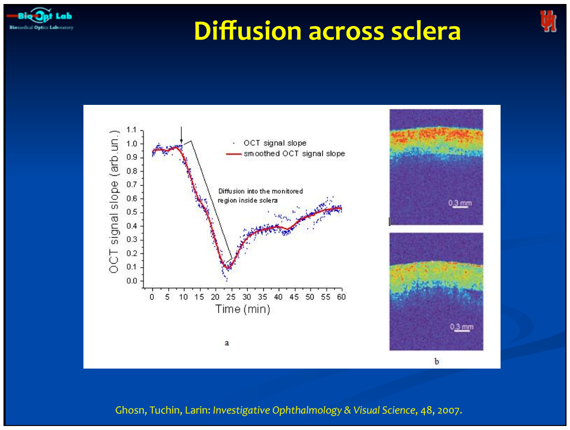


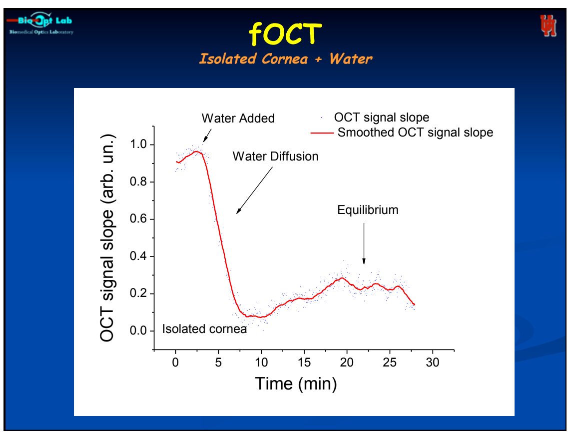
$$\mu_s' = 3.28\pi r^2 \rho_s \left(\frac{2\pi r}{\lambda}\right)^{0.37}\left(\frac{n_s}{n_{medium}+\delta n_{drug}}-1\right)^{2.09}$$

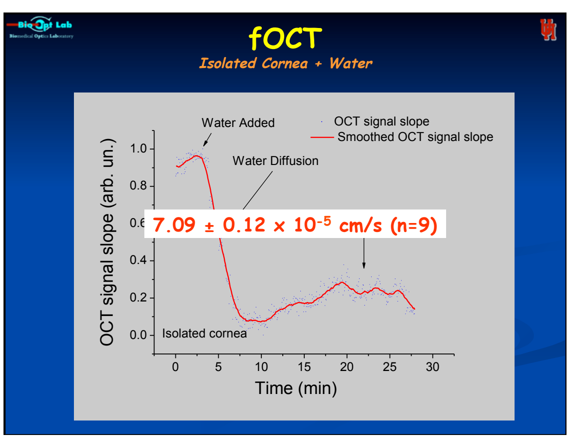

Rabbit Cornea and Sclera
Rabbit Cornea
OCT Signal (arb. un.)
Depth (µm)
Rabbit Sclera
OCT Signal (arb. un.)
Depth (µm)

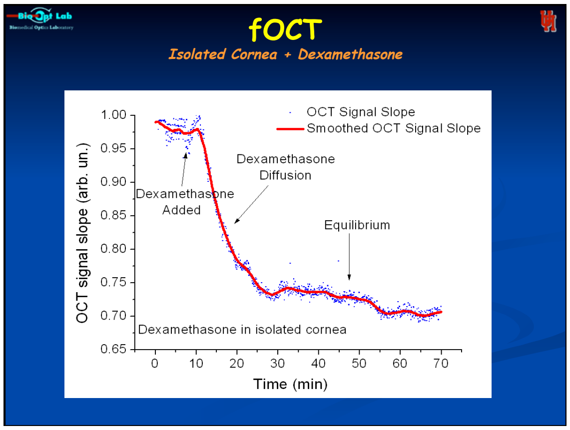

OCTSS (arb. un.)
0
5
30
Time (min.)

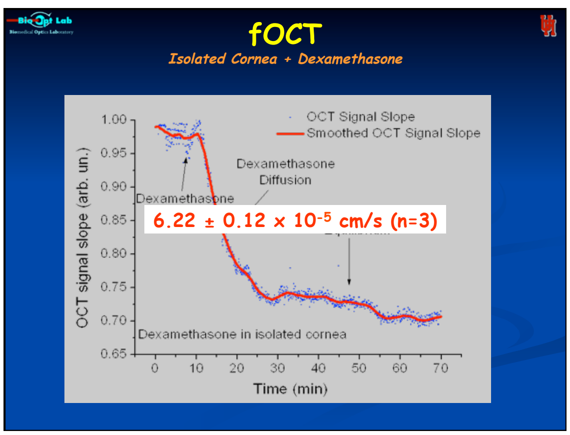

fOCT
Molecular Diffusion Movie

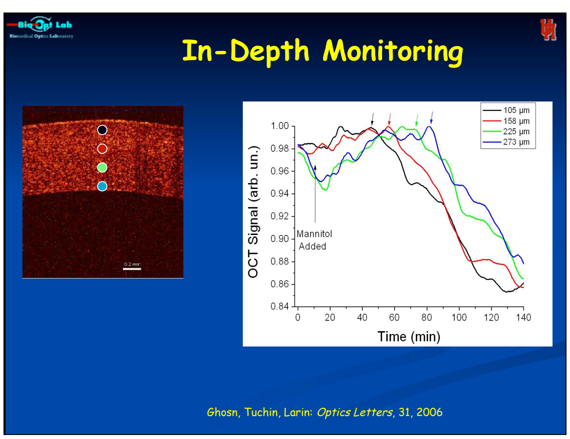

Diffusion across sclera
OCT signal slope
smoothed OCT signal slope
Diffusion into the monitored region inside sclera
OCT signal slope (arb. un.)
Time (min)
0.3 mm
a
b
Ghosn, Tuchin, Larin: Investigative Ophthalmology & Visual Science, 48, 2007.


fOCT
Isolated Cornea + Water
Water Added
OCT signal slope
Smoothed OCT signal slope
Water Diffusion
Equilibrium
Isolated cornea
OCT signal slope (arb. un.)
Time (min)

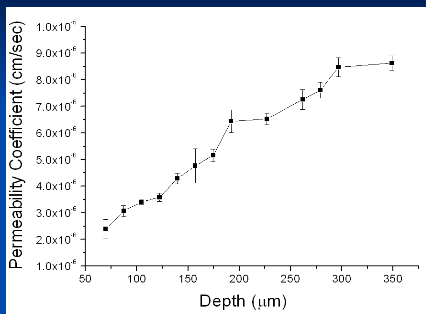

fOCT
Isolated Cornea + Water
Water Added
OCT signal slope
Smoothed OCT signal slope
Water Diffusion
7.09 ± 0.12 x 10^-5 cm/s (n=9)
Isolated cornea
OCT signal slope (arb. un.)
Time (min)


fOCT
Isolated Cornea + Dexamethasone
OCT Signal Slope
Smoothed OCT Signal Slope
Dexamethasone Added
Dexamethasone Diffusion
Equilibrium
Dexamethasone in isolated cornea
OCT signal slope (arb. un.)
Time (min)


fOCT
Isolated Cornea + Dexamethasone
OCT Signal Slope
Smoothed OCT Signal Slope
Dexamethasone Diffusion
6.22 ± 0.12 x 10-5 cm/s (n=3)
Dexamethasone in isolated cornea
OCT signal slope (arb. un.)
Time (min)

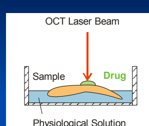

In-Depth Monitoring
105 µm
158 µm
225 µm
273 µm
Mannitol Added
OCT Signal (arb. un.)
Time (min)
Ghosn, Tuchin, Larin: Optics Letters, 31, 2006

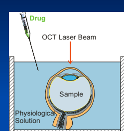
In-Depth Monitoring



Ghosn, Tuchin, Larin: *Optics Letters*, 31, 2006

Permeability Coefficients





Isolated sclera		Rabbit sclera in EYE	
Solution/Drug	PC ± SD (cm/sec)	Solution/ Drug	PC ± SD (cm/sec)
Water	$(1.33 \pm 0.28)\times10^{-5}$ (n=5)	Water	$(4.06 \pm 0.46)\times10^{-5}$ (n=4)
Glucose (20%)	$(8.64 \pm 1.12)\times10^{-6}$ (n=14)	Glucose (20%)	$(1.15 \pm 0.01)\times10^{-5}$ (n=10)
Ciprofloxacin	$(1.41 \pm 0.38)\times10^{-5}$ (n=3)	Ciprofloxacin	$(3.14 \pm 0.27)\times10^{-5}$ (n=2)

Larin, Ghosn: *Quantum Electronics*, 12, 2006

Permeability Coefficients

Rabbit Cornea in EYE		Rabbit sclera in EYE	
Solution/Drug	PC ± SD (cm/sec)	Solution/ Drug	PC ± SD (cm/sec)
Water	$(1.68 \pm 0.54)\times10^{-5}$ (n=8)	Water	$(1.33 \pm 0.28)\times10^{-5}$ (n=5)
Metronidazole	$(1.59 \pm 0.43)\times10^{-5}$ (n=5)	Metronidazole	$(1.31 \pm 0.29)\times10^{-5}$ (n=4)
Ciprofloxacin	$(1.85 \pm 0.27)\times10^{-5}$ (n=7)	Ciprofloxacin	$(1.41 \pm 0.38)\times10^{-5}$ (n=3)
Dexamethasone	$(2.42 \pm 1.03)\times10^{-5}$ (n=7)		
Mannitol 20%	$(8.99 \pm 0.72)\times10^{-6}$ (n=4)	Mannitol 20%	$(6.18 \pm 1.08)\times10^{-6}$ (n=5)
Mannitol 20%*	$(6.14 \pm 0.61)\times10^{-5}$ (n=4)		
Glucose 20%	$(1.78 \pm 0.23)\times10^{-5}$ (n=6)	Glucose 20%	$(8.64 \pm 1.12)\times10^{-6}$ (n=14)

Ghosn, Tuchin, Larin: *Investigative Ophthalmology & Visual Science*, 48, 2007.

Permeability Coefficients

Rabbit Cornea in EYE		Rabbit sclera in EYE	
Solution/Drug	PC ± SD (cm/sec)	Solution/ Drug	PC ± SD (cm/sec)
Water	$(1.68 \pm 0.54) \times 10^{-5}$ (n=8)	Water	$(1.33 \pm 0.28) \times 10^{-5}$ (n=5)
Metronidazole	$(1.59 \pm 0.43) \times 10^{-5}$ (n=5)	Metronidazole	$(1.31 \pm 0.29) \times 10^{-5}$ (n=4)
Ciprofloxacin	$(1.85 \pm 0.27) \times 10^{-5}$ (n=7)	Ciprofloxacin	$(1.41 \pm 0.38) \times 10^{-5}$ (n=3)
Dexamethasone	$(2.42 \pm 1.03) \times 10^{-5}$ (n=7)		
Mannitol 20%	$(8.99 \pm 0.72) \times 10^{-6}$ (n=4)	Mannitol 20%	$(6.18 \pm 1.08) \times 10^{-6}$ (n=5)
Mannitol 20%*	$(6.14 \pm 0.61) \times 10^{-5}$ (n=4)		
Glucose 20%	$(1.78 \pm 0.23) \times 10^{-5}$ (n=6)	Glucose 20%	$(8.64 \pm 1.12) \times 10^{-6}$ (n=14)

Ghosn, Tuchin, Larin: *Investigative Ophthalmology & Visual Science*, 48, 2007.

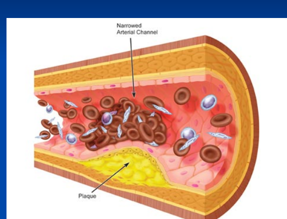
fOCT

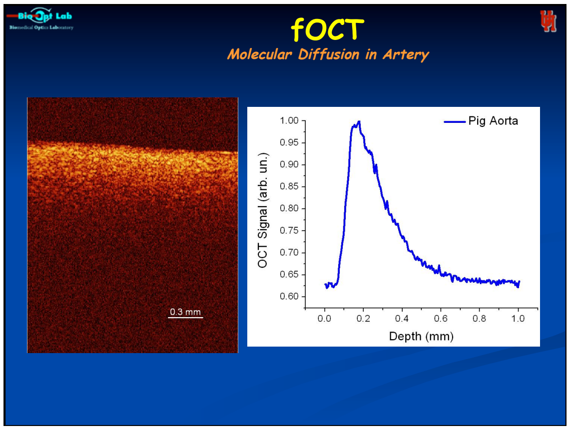
Molecular Diffusion in Vasculature

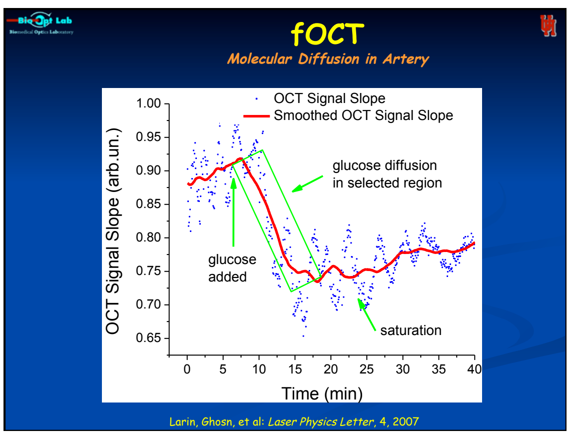
In collaboration with

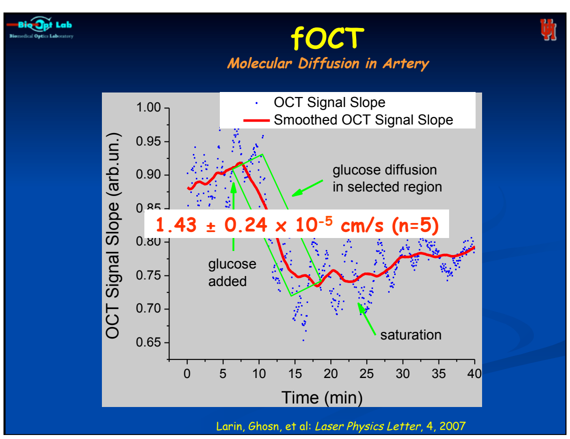
Joel Morrisett, Ph.D.
Professor
Medicine Athero & Lipo
Baylor College of Medicine

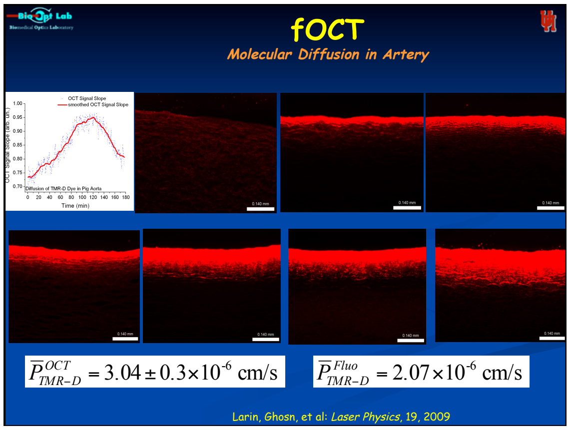
Atherosclerosis

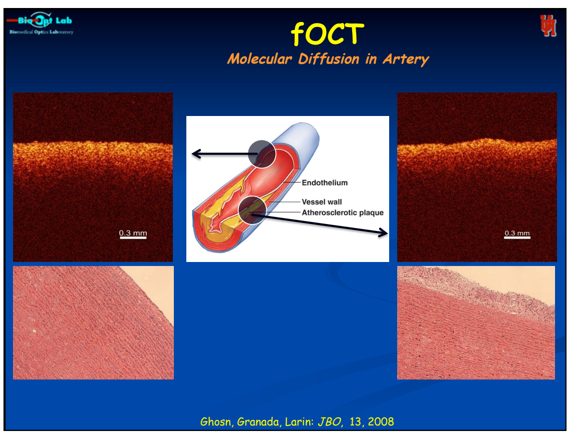


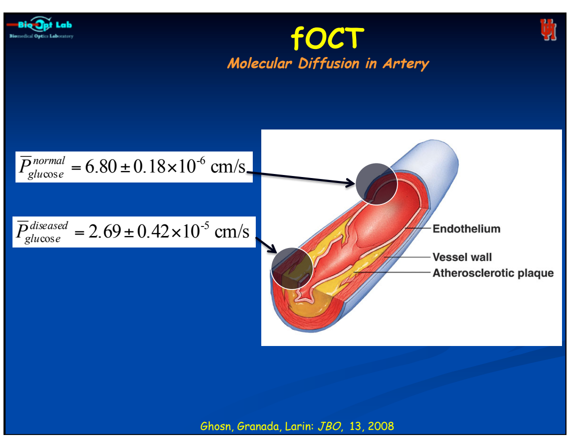

fOCT
Molecular Diffusion in Artery
0.3 mm
Pig Aorta
OCT Signal (arb. un.)
Depth (mm)


fOCT
Molecular Diffusion in Artery
OCT Signal Slope
Smoothed OCT Signal Slope
glucose diffusion
in selected region
glucose
added
saturation
OCT Signal Slope (arb.un.)
Time (min)
Larin, Ghosn, et al: Laser Physics Letter, 4, 2007


fOCT
Molecular Diffusion in Artery
OCT Signal Slope
Smoothed OCT Signal Slope
glucose diffusion
in selected region
1.43 ± 0.24 x 10-5 cm/s (n=5)
glucose
added
saturation
OCT Signal Slope (arb.un.)
Time (min)
Larin, Ghosn, et al: Laser Physics Letter, 4, 2007

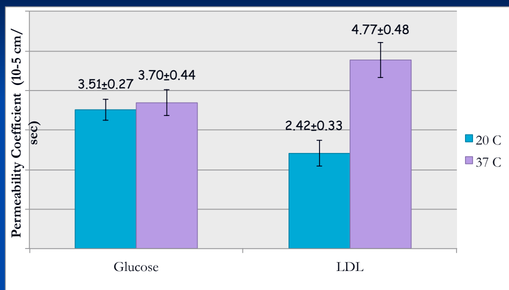

Bio Opt Lab
fOCT
Molecular Diffusion in Artery
$\bar{P}^{OCT}_{TMR-D} = 3.04 \pm 0.3 \times 10^{-6}$ cm/s
$\bar{P}^{Fluo}_{TMR-D} = 2.07 \times 10^{-6}$ cm/s
Larin, Ghosn, et al: Laser Physics, 19, 2009


Bio Opt Lab
fOCT
Molecular Diffusion in Artery
Endothelium
Vessel wall
Atherosclerotic plaque
0.3 mm
0.3 mm
Ghosn, Granada, Larin: JBO, 13, 2008


Bio Opt Lab
fOCT
Molecular Diffusion in Artery
$\bar{P}^{normal}_{glucose} = 6.80 \pm 0.18 \times 10^{-6}$ cm/s
$\bar{P}^{diseased}_{glucose} = 2.69 \pm 0.42 \times 10^{-5}$ cm/s
Endothelium
Vessel wall
Atherosclerotic plaque
Ghosn, Granada, Larin: JBO, 13, 2008

fOCT

Molecular Diffusion in human carotid artery

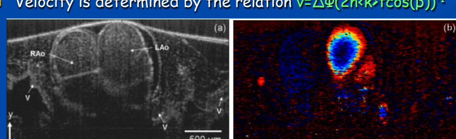


Ghosn, et al: *Journal of Biophotonics*, v. 10, 2009

Can OCT Sense Blood Flow?

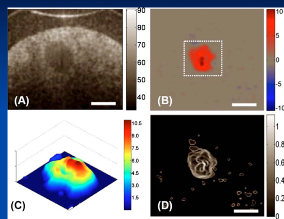
Doppler OCT (DOCT)

- Moving scatterers change the frequency/phase of the detected signal based on Doppler effect.
- The Doppler signal is obtained as phase difference between consecutive A-lines.
- Velocity is determined by the relation $v=\Delta\Phi(2n\langle k\rangle\tau\cos(\beta))^{-1}$



Vitkin et al. "Doppler optical cardiogram gated 2D color flow imaging at 1000 fps and 4D in vivo visualization of embryonic heart at 45 fps on a swept source OCT system"

Blood Flow Imaging



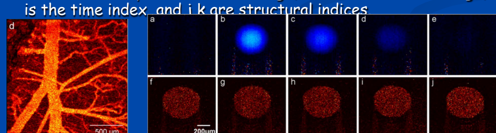
The flow characteristics for a chitosan scaffold with 250-m central microchannel measured by DOCT, where (a) the microstructural information and (b) the corresponding fluid flow can be visualized in situ. (c)The 3-D velocity plot of the region marked with the dashed box in b, where the flow is nonparabolic within the microchannel. (d)The corresponding local shear stress distribution within the cross section.

Jia, YL; Bagnaninchi, PO; Yang, Y; et al. "Doppler optical coherence tomography imaging of local fluid flow and shear stress within microporous Scaffolds" JOURNAL OF BIOMEDICAL OPTICS, 14 (3): Art. No. 034014 MAY-JUN 2009

Speckle Variation Imaging

- Speckle variance imaging uses the property that, speckle caused by dynamic scatterers changes in time, where as that of static scatterers do not.
- Speckle Image is generated by using the algorithm
- $SV_{ijk} = \frac{1}{N}\sum_{i=1}^{N}(I_{ijk} - I_{mean})^2$

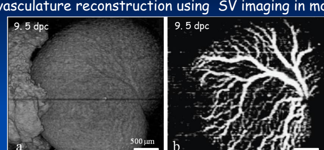
where, SV is the speckle variance image, I is the structural image, i is the time index, and j k are structural indices



Vitkin et al. "Speckle variance detection of microvasculature using swept-source optical coherence Tomography"

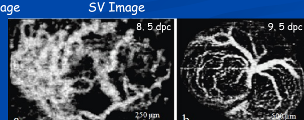
Speckle Variance

3D vasculature reconstruction using SV imaging in mouse embryo



Structural Image SV Image

• Embryos were placed on a translation stage and moved with a velocity of 20 µm /s
• Images acquired at 51 fps



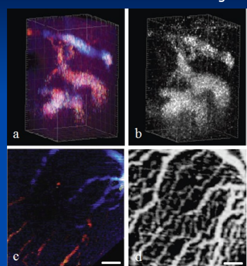
SV Image SV Image

• 3D SV image detects yolk sac vasculature
• Capable of monitoring development and remodeling of yolk sac vasculature

Sudheendran, et al: *Laser Phys Lett*, 8, 2011

Speckle Variance vs Doppler

3D vasculature reconstruction using SV imaging in mouse embryo



Embryonic brain vasculature at 8.5 dpc
a) Using DOCT
b) Using SV Imaging
Major ticks 50 µm

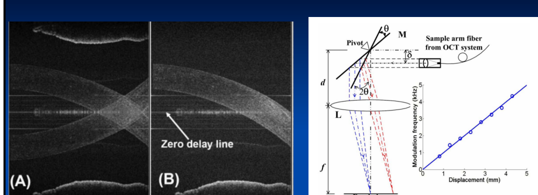
Yolk sac vasculature at 9.5 dpc
c) Using DOCT
d) Using SV Imaging
Scale bar 250 µm

- DOCT and SV imaging equally effective to image embryonic vessels where vessels are not perpendicular to beam
- SV imaging provided more information in yolk sac vasculature where vessels are perpendicular

Sudheendran, et al: *Laser Phys Lett*, 8, 2011

Full length Imaging by Doppler modulation of reference arm

- To resolve between positive and negative frequencies, a Doppler modulation frequency is introduced by moving the reference arm.
- Moving the reference arm with velocity of v_r produces a Doppler frequency of $f_d = 2\, v_0\, v_r/c$ where v_0 is the central frequency of source and c is the velocity of light in the medium.
- Now, the modulated signal detected is in the form of $\cos[2k(z_r-z_s)+2f_d t]$. Time t represents time between consecutive Alines.
- Full length imaging can now be performed be performing Hilbert transform across t with constant k (along row) and then performing FT across k with t constant (along column).

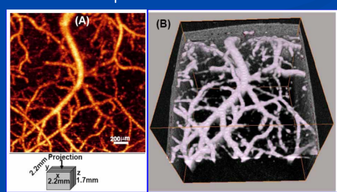


- Doppler frequency can also be introduced by offsetting the scanning mirror at the sample arm.
- $f_d=2k_0\delta\omega/\pi$, where ω is the angular frequency of the scanning mirror.

Wang et al, "Use of a scanner to modulate spatial interferograms for in vivo full-range Fourier-domain optical coherence tomography"

Optical Angiography (OAG)

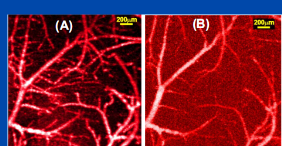
•Works on the same principle as that of full length imaging, except that the negative half FT is utilized for imaging velocities instead of structures.
•Let f_d be the modulation frequency introduced moving of reference arm with velocity of v_r. The modified interferogram can be represented by
$f(k)=\cos[2k(z_r-z_s)+2k_0(v_r+v_s)t]$
•When v_s has higher magnitude and opposite direction as that of v_r, then the velocity is reflected at the negative half of FT.
• Modulation frequency can also be introduced offsetting scanning mirrors at the sample arm.



Wang et al. "Three dimensional optical angiography "

Comparing OAG and DOCT

•OAG and DOCT are similar in the respect that, both detect axial velocity.
•DOCT is sensitive to very small velocities in orders of a few microns/sec, where as OAG is insensitive to low velocities including motion of animal being imaged.
•Disadvantage of DOCT is its high phase sensitivity.



OAG DOCT

Wang et al. "Three dimensional optical angiography "

THANK YOU!

http://bol.egr.uh.edu

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Department of Biomedical Engineering
University of Houston

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- Valery Tuchin – SSU
- Irina Larina – BCM
- Mary Dickinson – BCM
- Bruce Butler – UTHSC
- Michael Allon – HFC
- JamesMartin– BCM
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- Pradeep Sharma – UH
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- Marlowe Eldridge – UW, Madison
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NIH	R01-HL120140
NIH	U54-HG006348
DOD/NAVSEA	MSN129709