Medical adventures in the near-infrared

Andrew Berger

Abbe lecture #1: Research

17 Dezember 2013

Welcome to the near-infrared

Measuring mouse bone quality

Sensing organelle size distributions

Sensing blood activity in the brain

The Institute of Optics, Rochester NY

Massachusetts Institute of Technology

BECKMAN LASER INSTITUTE & MEDICAL CLINIC
UNIVERSITY of CALIFORNIA - IRVINE

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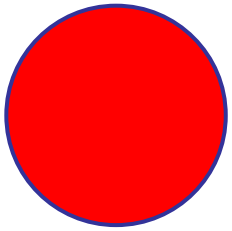
Near infrared photons

phineasandferb.wikia.com/wiki/Where%27s_My_Perry



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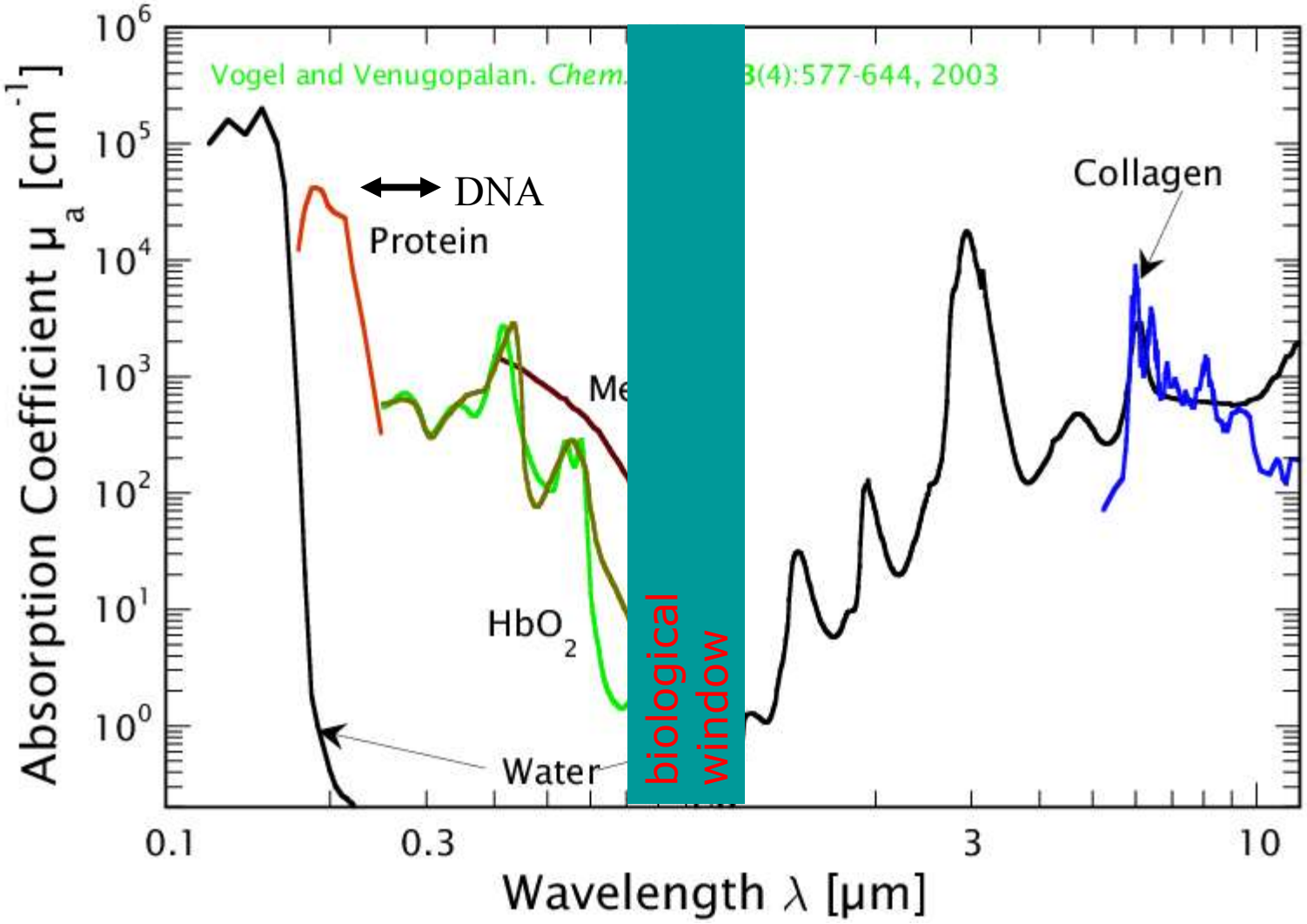
NIR photon

biomedical spy

The near-infrared “window”



Optical Penetration Depth vs. Wavelength

Wavelength (nm)

Penetration depth (μm)

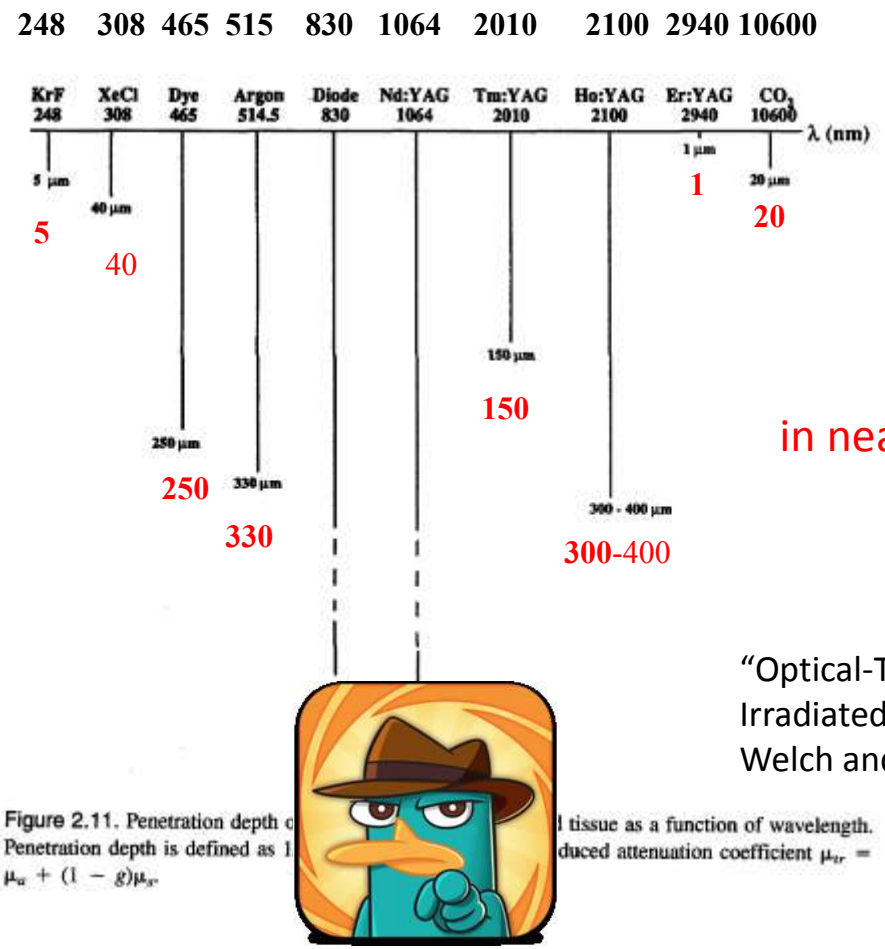
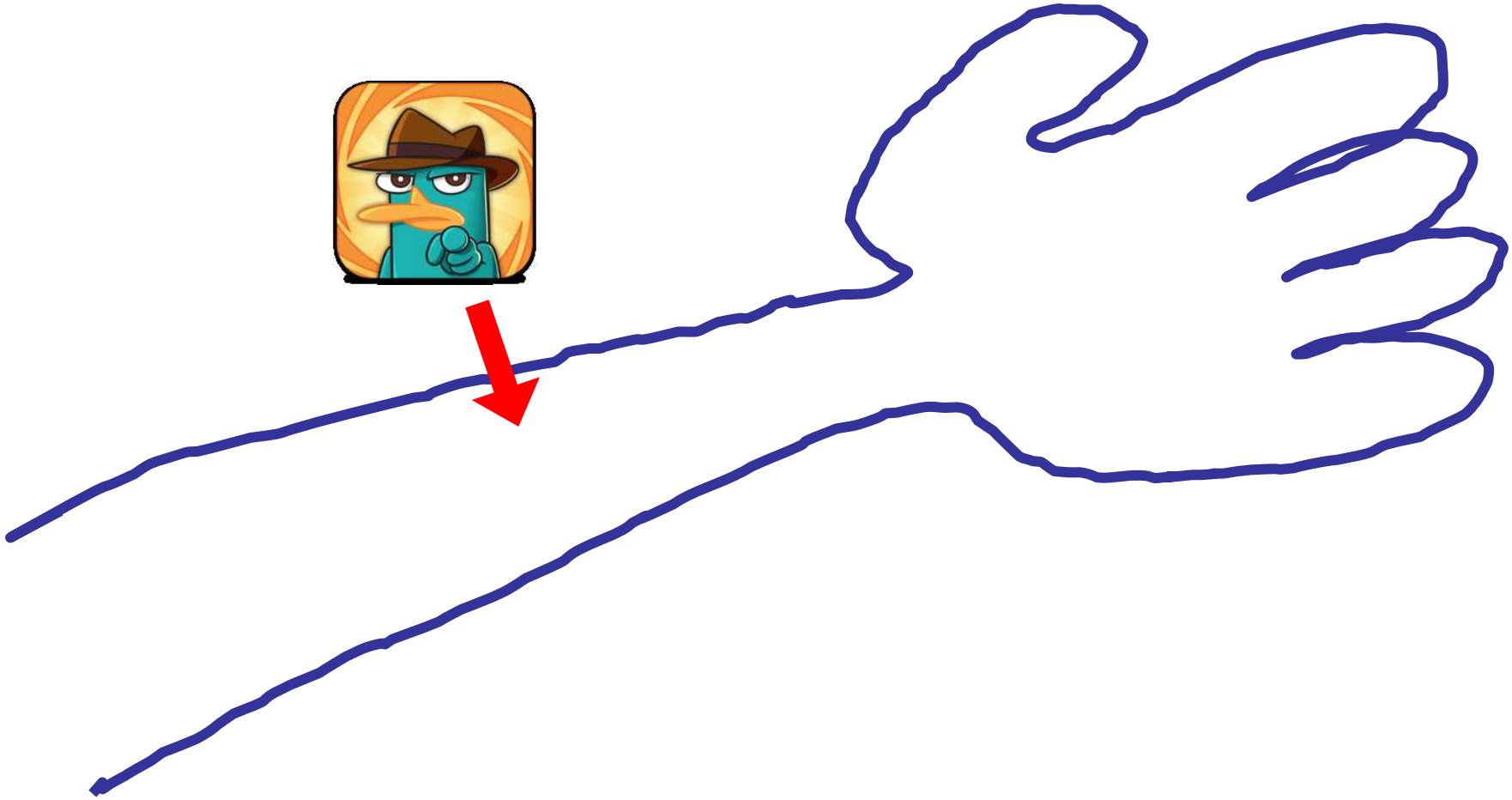


Figure 2.11. Penetration depth c l tissue as a function of wavelength. Penetration depth is defined as 1 duced attenuation coefficient μ_{tr} = $\mu_a + (1 - g)\mu_s$.

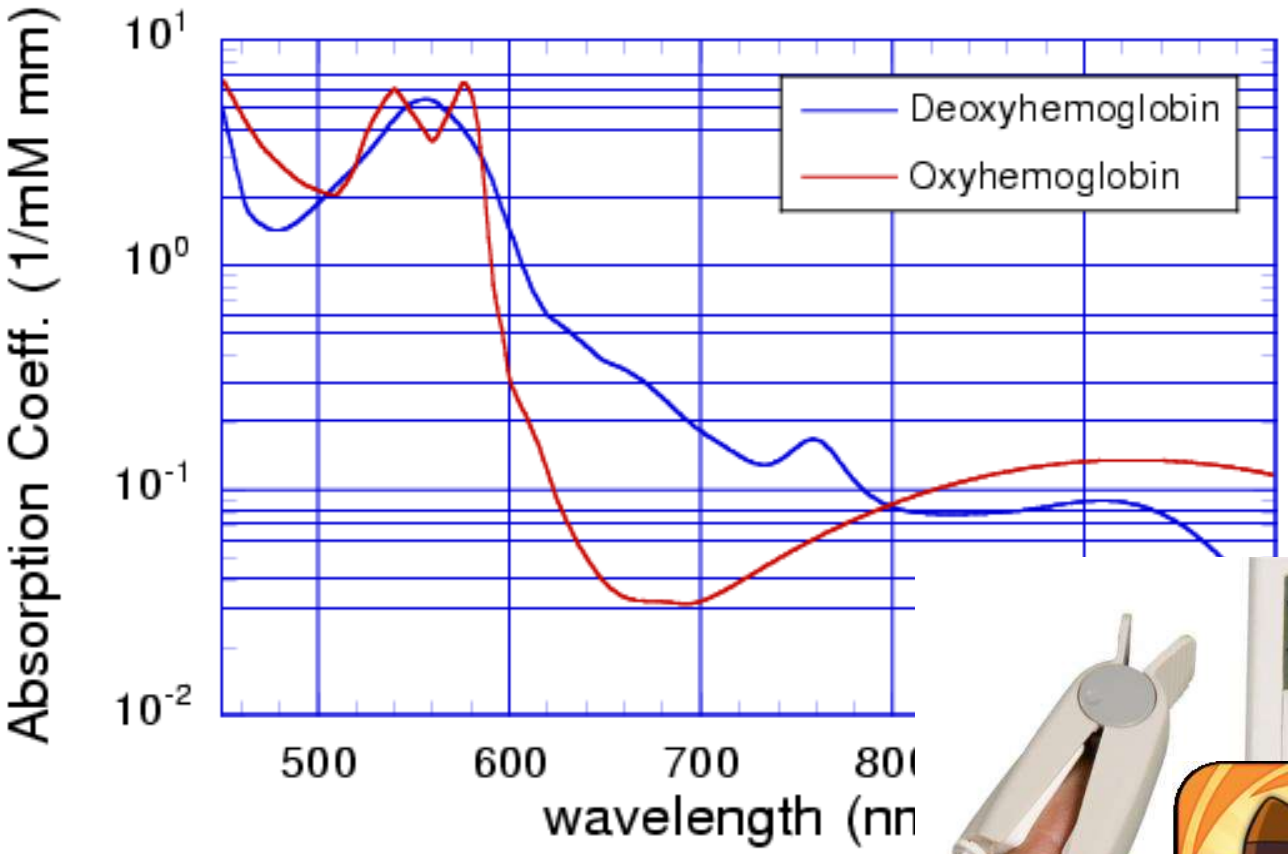
in near-IR, d ~ 1 mm

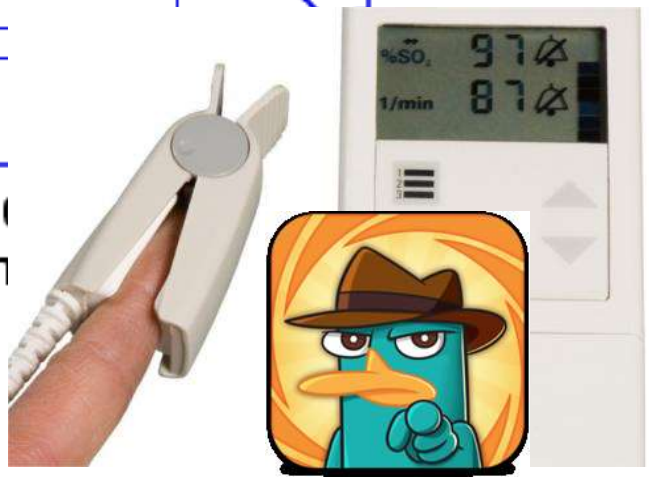
"Optical-Thermal Response of Laser-Irradiated Tissue" (1995), Welch and van Gemert (eds)

Going below the surface



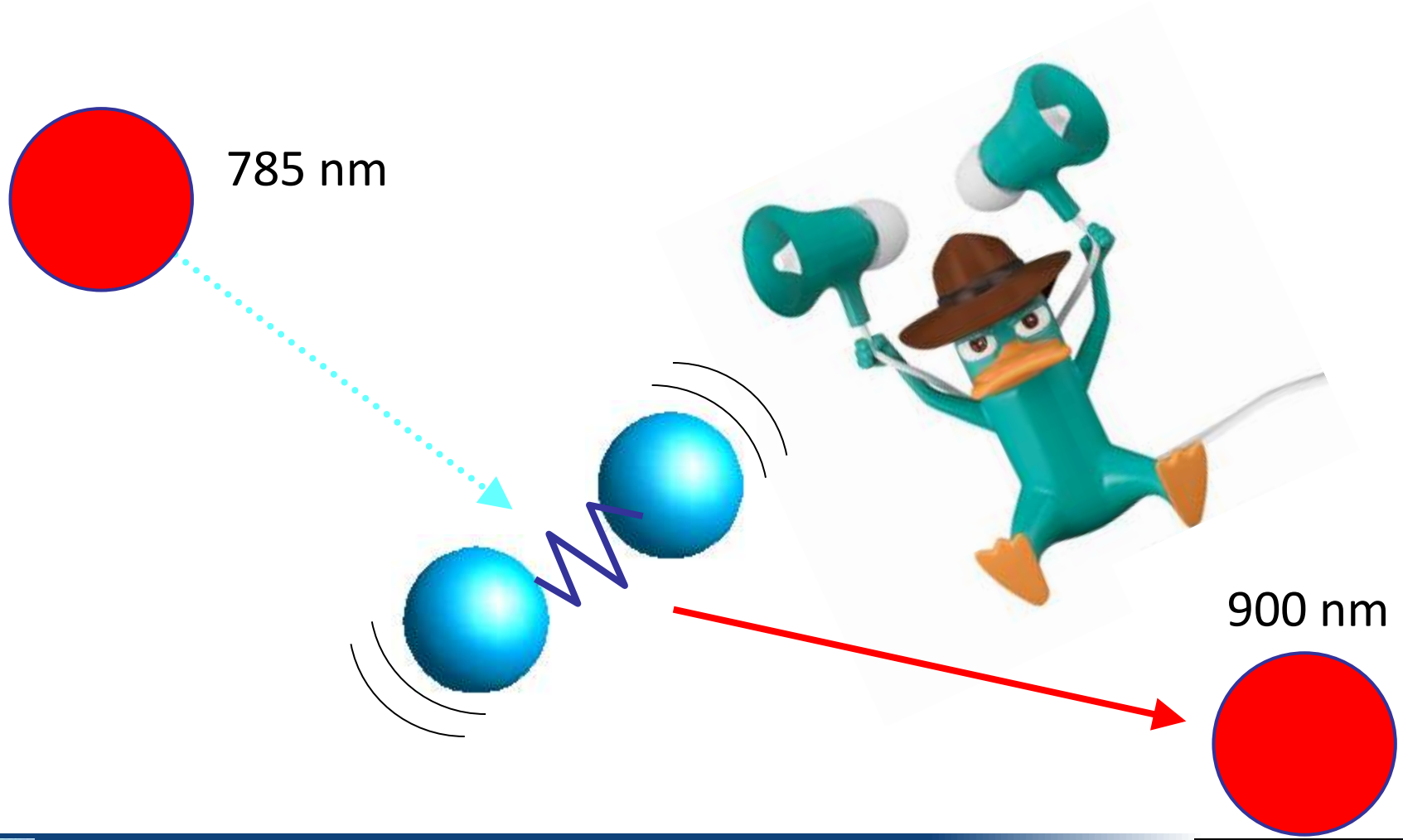
Hemoglobin



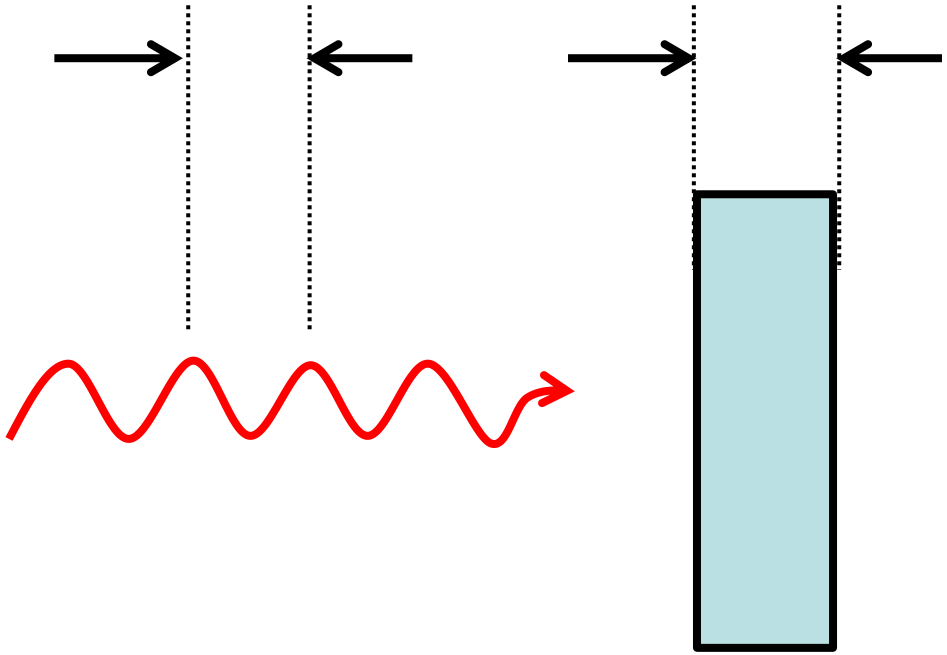


www.istockphoto.com

Chemical sensing: Raman scattering

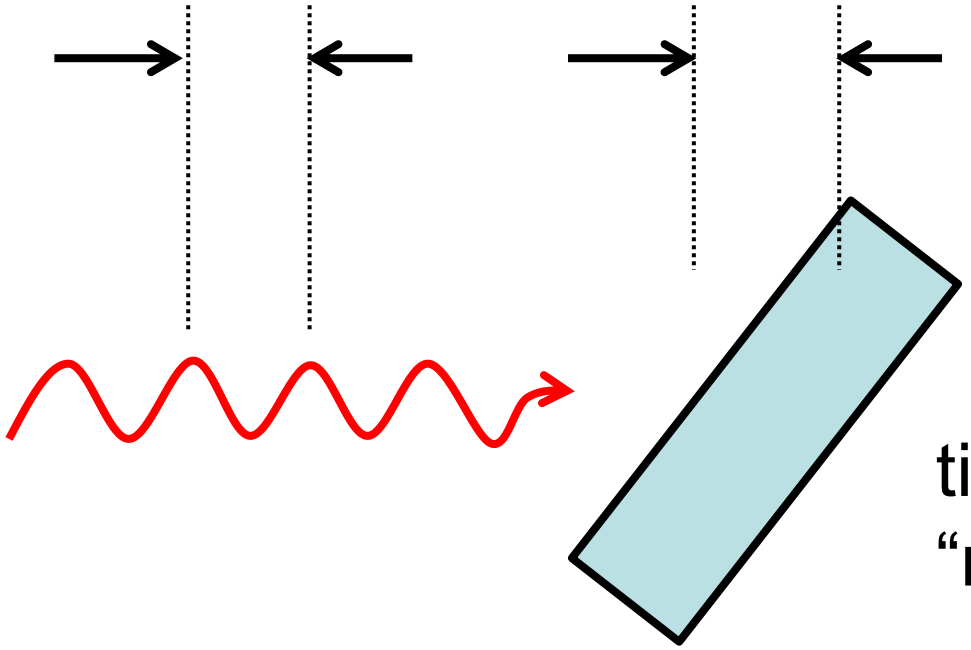


Size-dependent elastic scattering



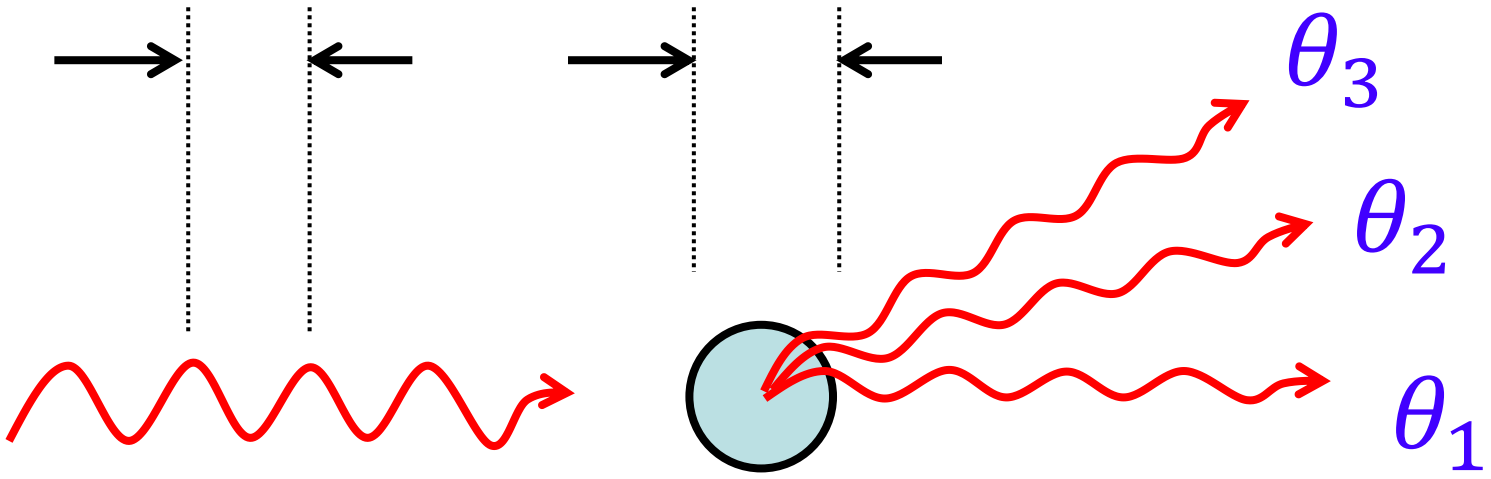
resonant wavelengths "tunnel through"

Size-dependent elastic scattering



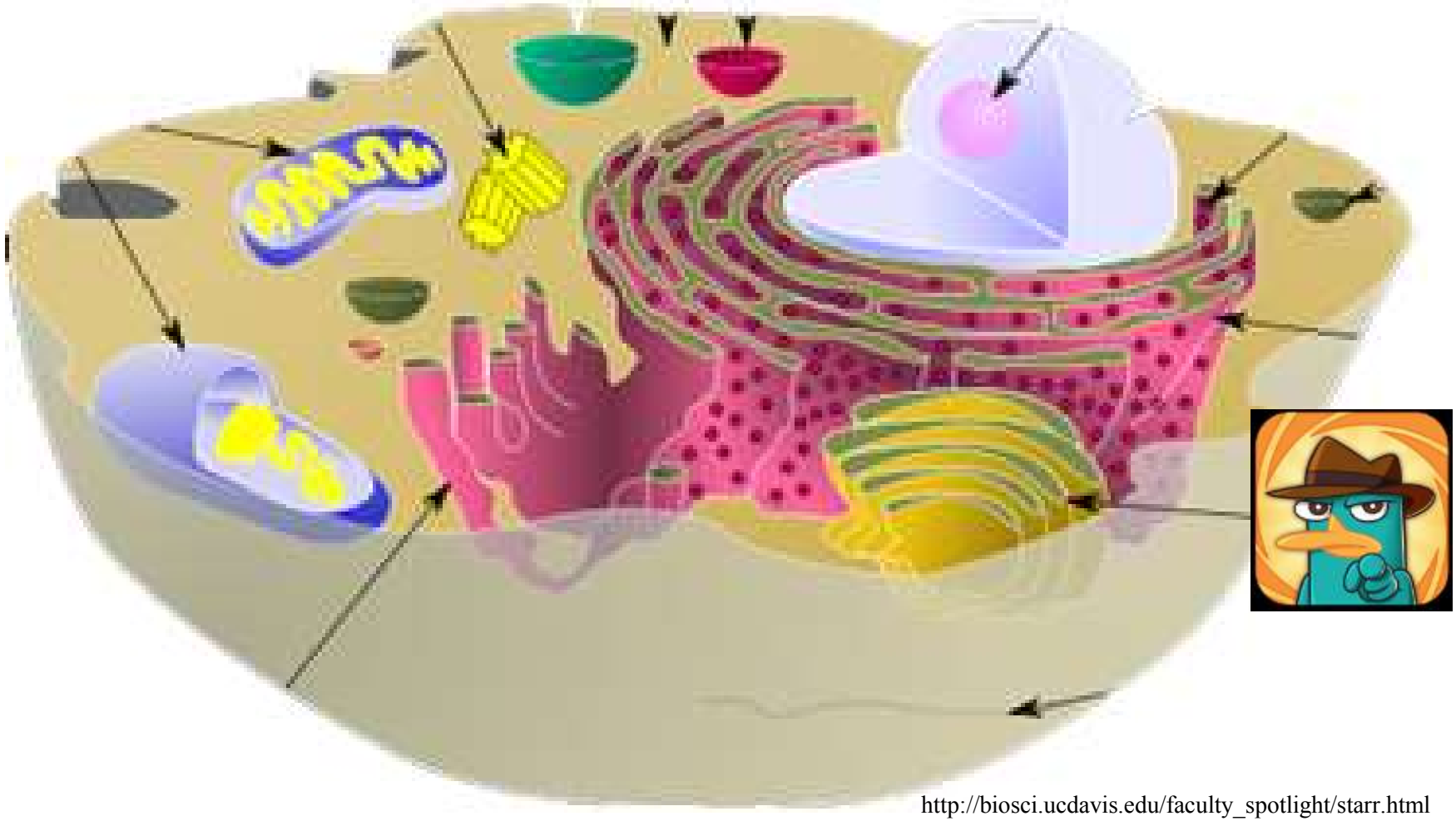
tilting changes the
“resonant wavelength”

Size-dependent elastic scattering



sphere: angle-dependent resonance

Sensitivity to organelle size



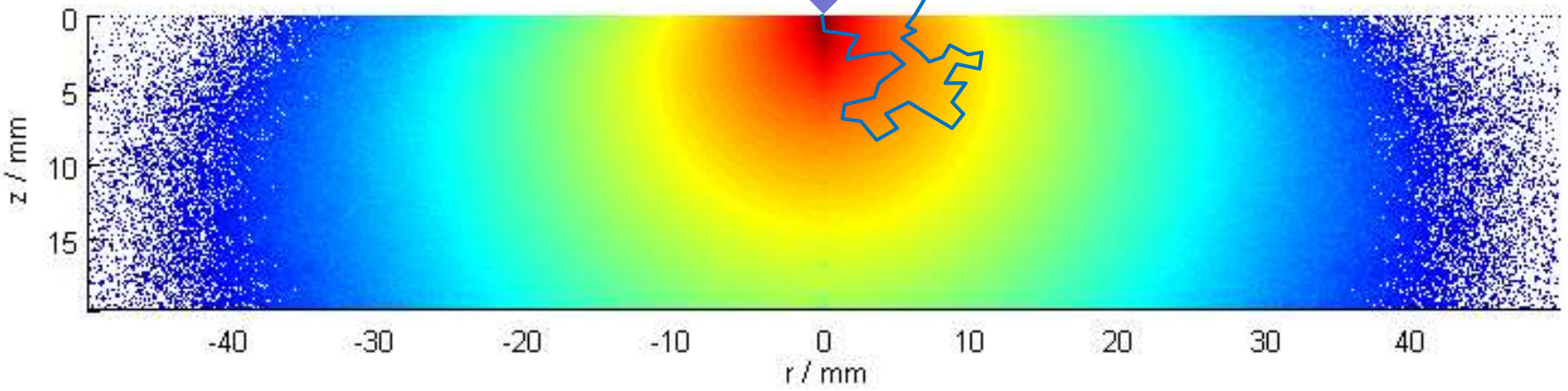
http://biosci.ucdavis.edu/faculty_spotlight/starr.html

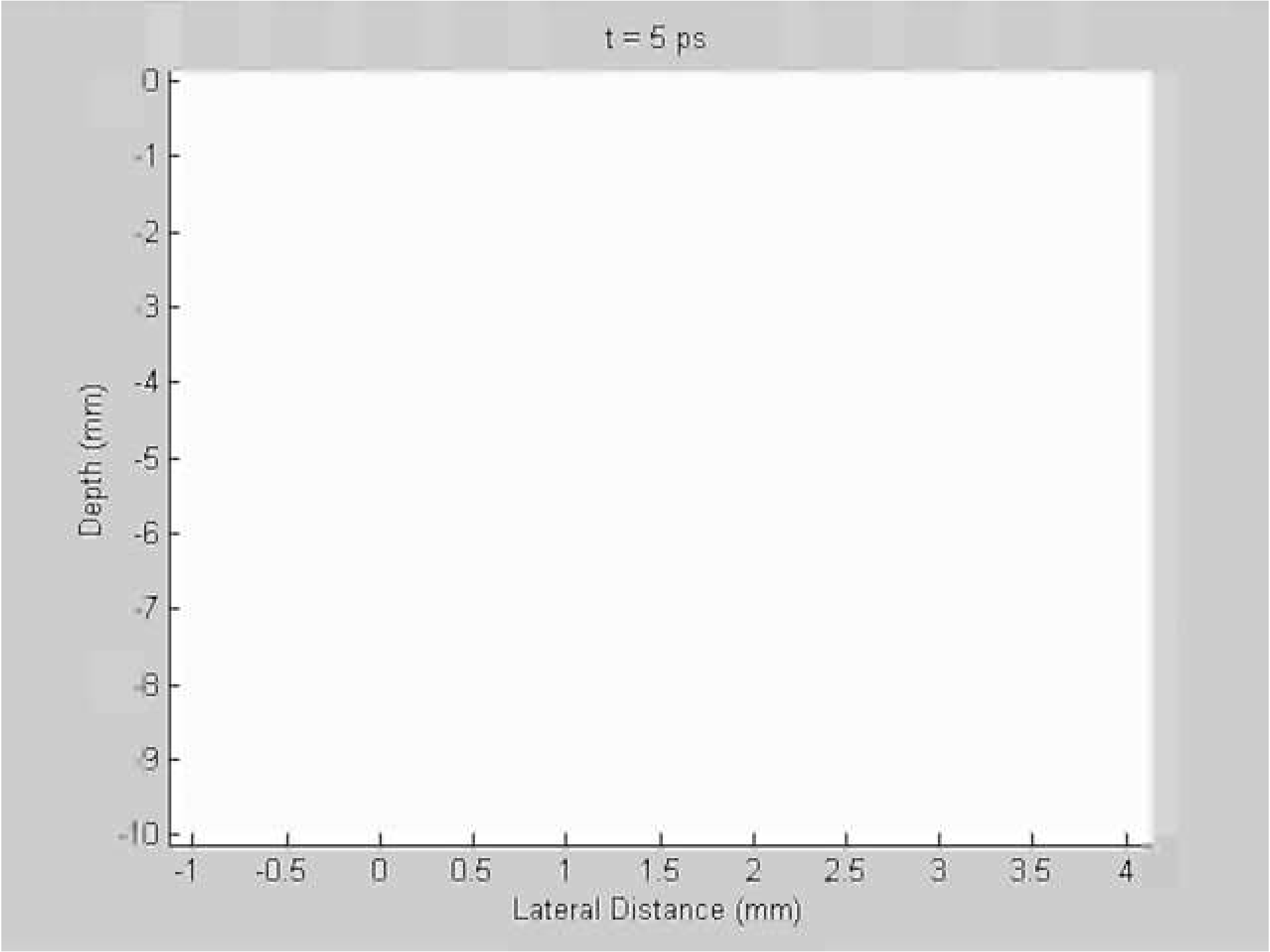
Photon diffusion

photons in

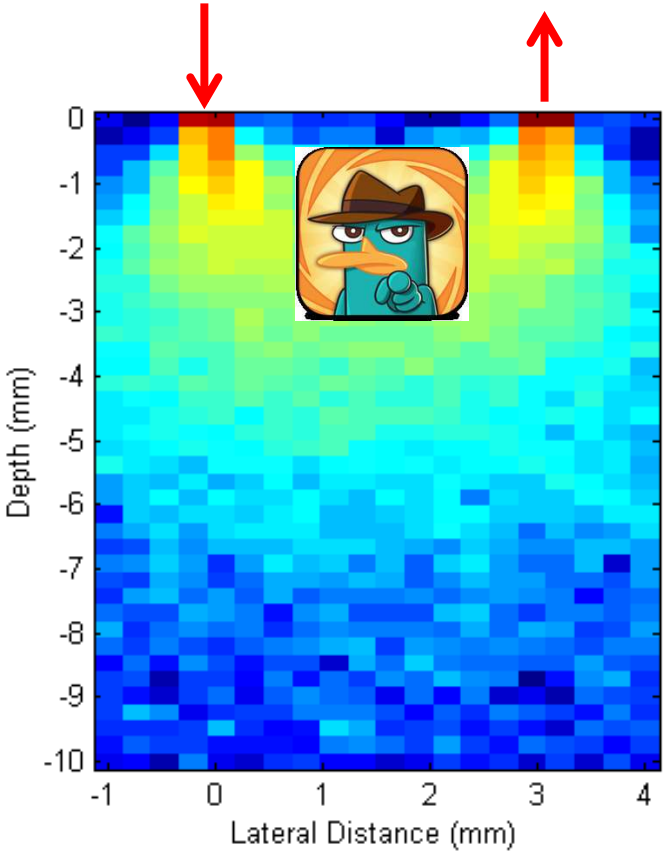
- *mean free path*

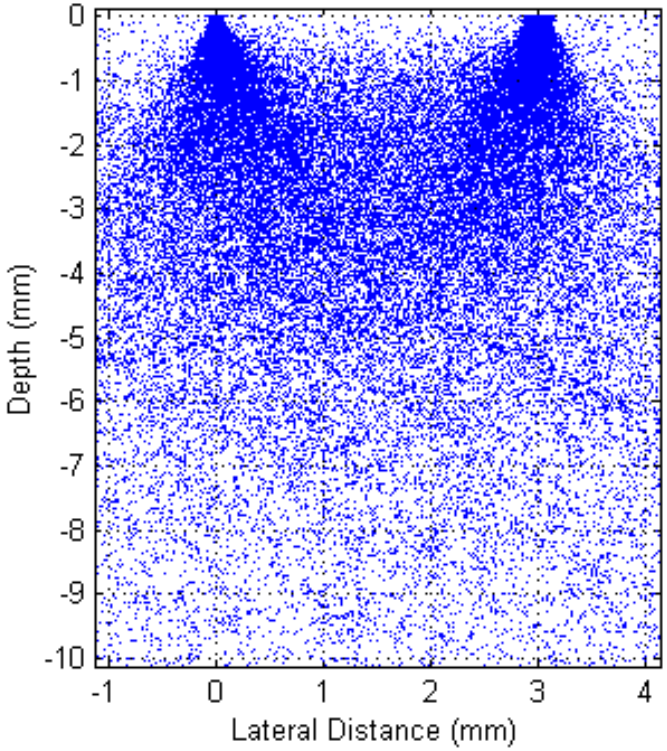
photon out




t = 5 ps
Depth (mm)
0
-1
-2
-3
-4
-5
-6
-7
-8
-9
-10
-1
-0.5
0
0.5
1
1.5
2
2.5
3
3.5
4
Lateral Distance (mm)

The biomedical optics “banana”!

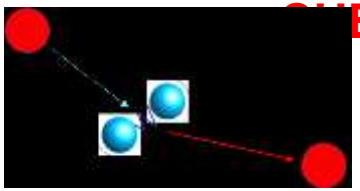




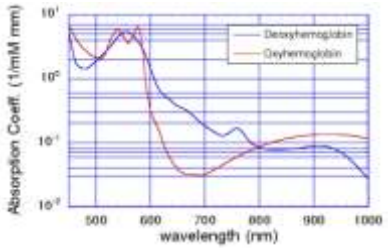
Summary of NIR interactions

biological sample

inelastic scattering:
CHEMISTRY

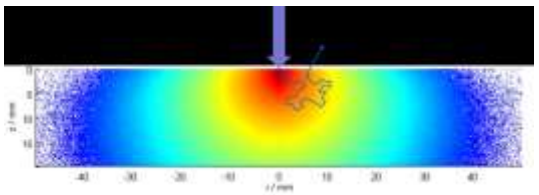


angle-dependent elastic scattering:
SIZE



wavelength-dependent absorption:
BLOOD

diffusive propagation:
DEPTH



Welcome to the near-infrared

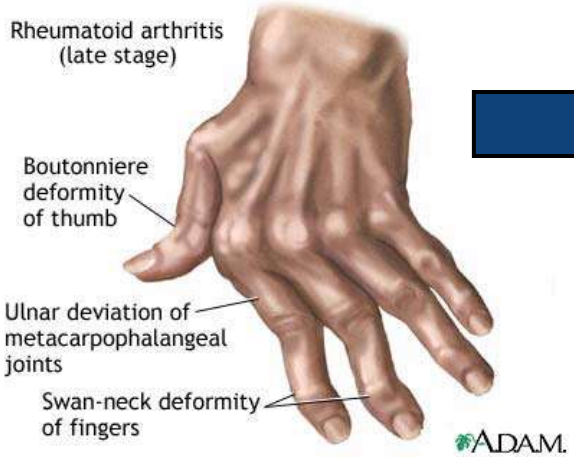
Measuring mouse bone quality

Sensing organelle size distributions

Sensing blood activity in the brain

Jason Maher

Motivation

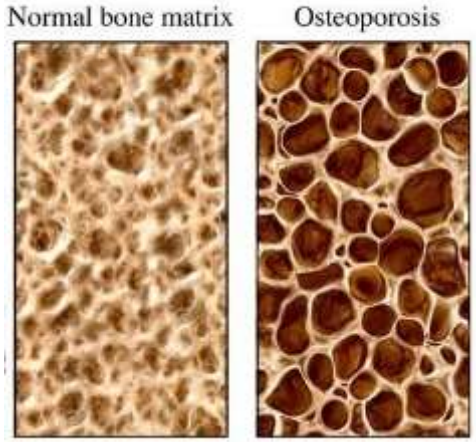


http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/17130.jpg

glucocorticoid treatment

control inflammation

extended exposure



http://www.southwestfloridaspineinstitute.com/clientuploads/osteoporosis3.jpg

osteoporosis treatment

http://www.carrollarthritis.com/dxa.html

Bone mineral density (BMD)

- Prior to pathologic fracture, BMD test to diagnose osteoporosis
  - **Dual energy X-ray absorptiometry (DXA)**
    - most widely used, validated to predict fracture risk
  - **Quantitative computed tomography**
    - more expensive, higher radiation dose, but provides

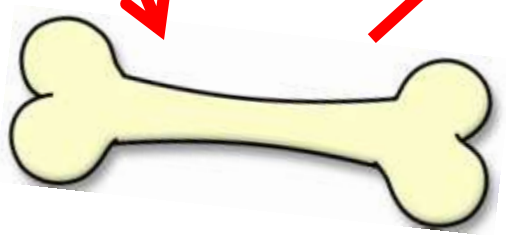
BMD alone is a poor predictor of fracture risk

http://www.carrollarthritis.com/dxa.html

Need better "bone quality" assessment:
both ***structure*** and ***chemical composition***

Did somebody say “chemical”??

laser irradiation

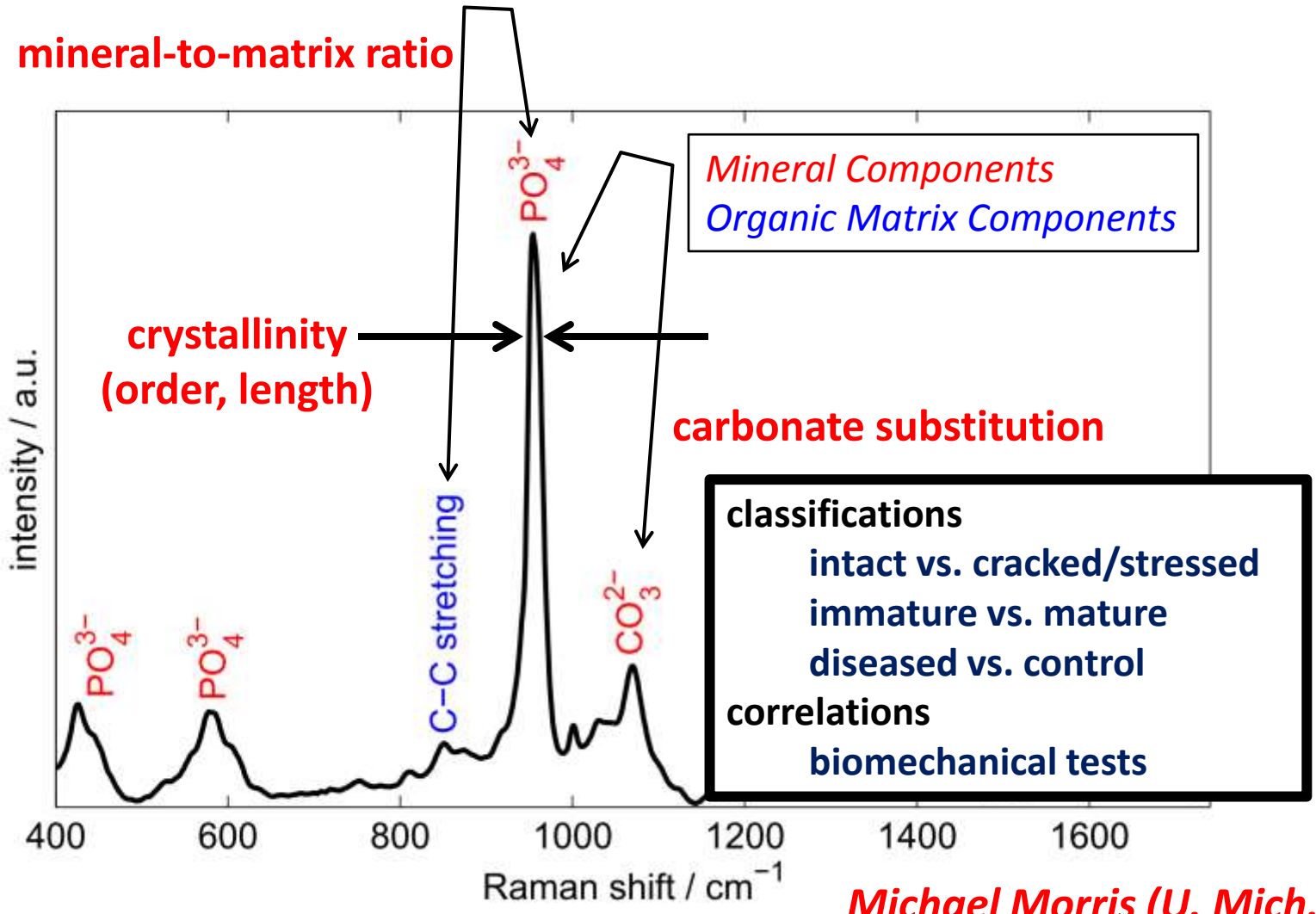


Raman spectrum

bone specimen

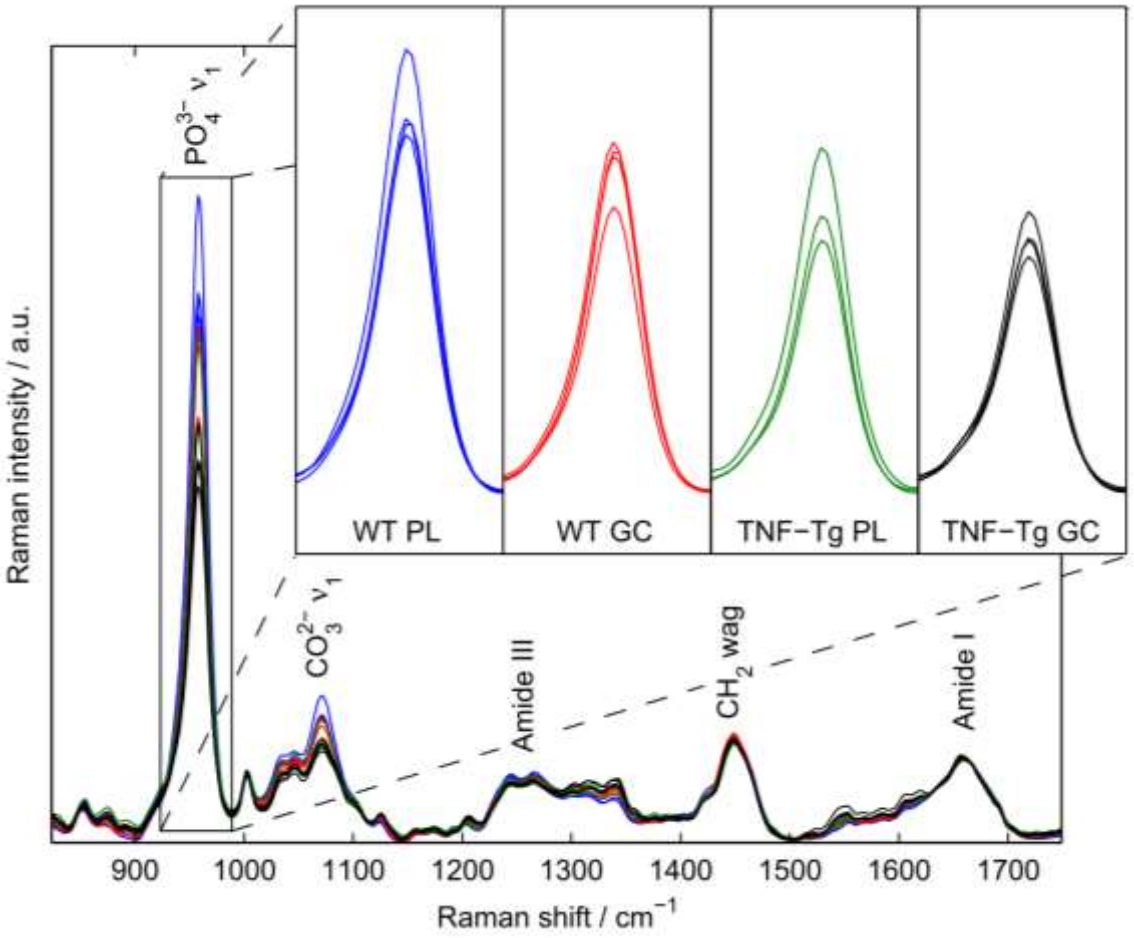
“bone quality” estimate

Raman spectrum of bone



Michael Morris (U. Mich.)

Trends in the Raman spectra



more mineral

WILD TYPE + PLACEBO

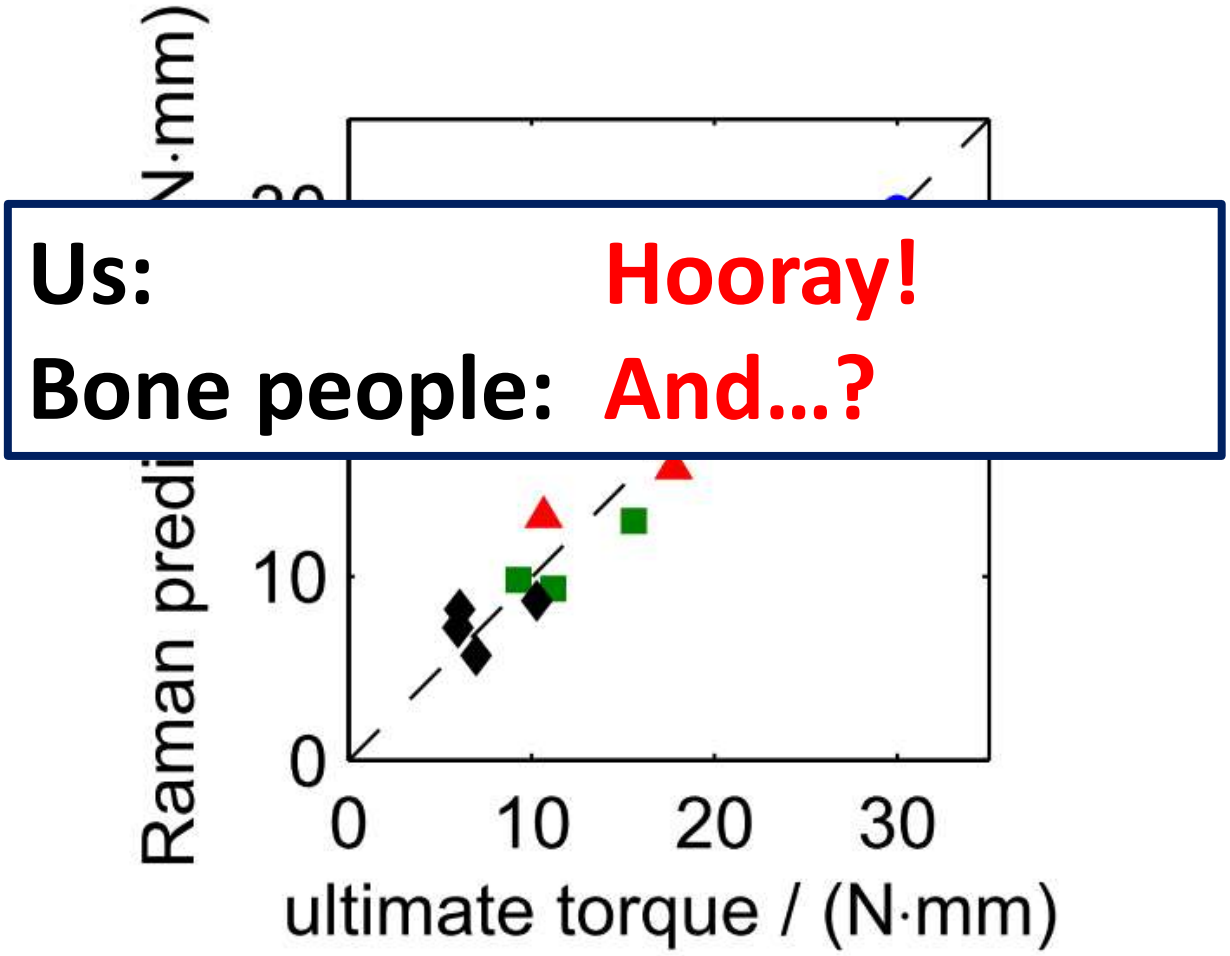
WILD TYPE + STEROID

RHEUMATOID + PLACEBO

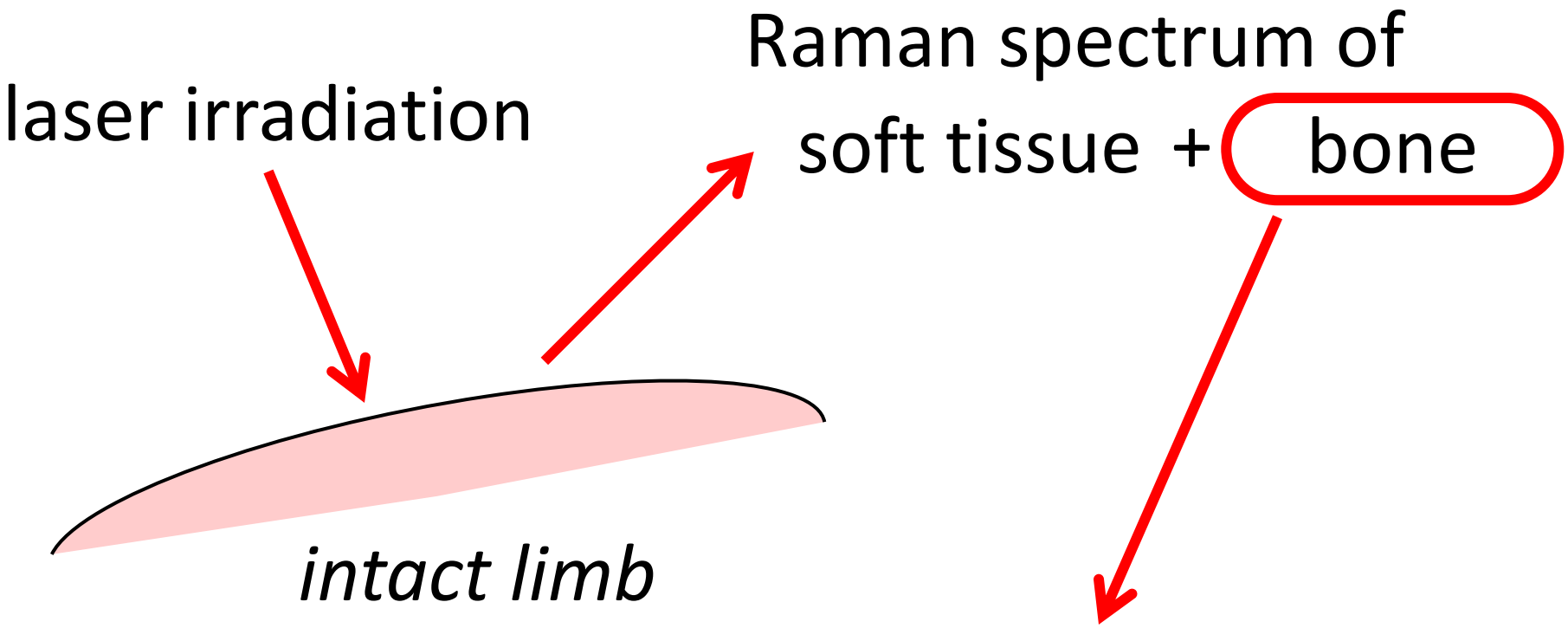
RHEUMATOID + STEROID

less mineral

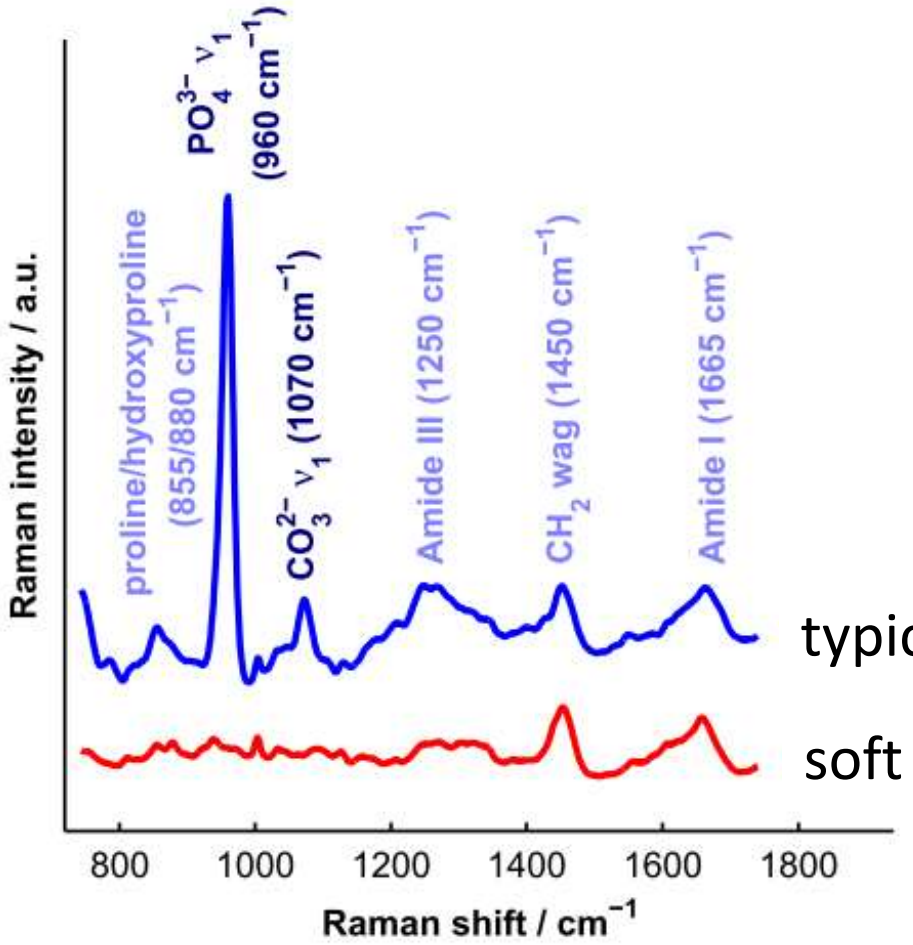
Bone-by-bone: Raman predicts bone strength



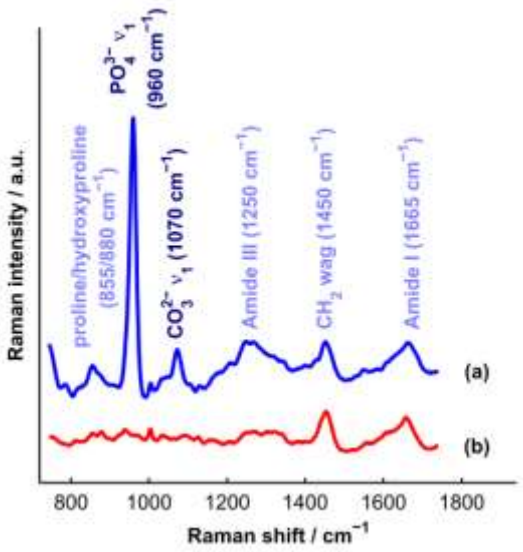
But how about this….



Spectral similarity of bone and soft tissue

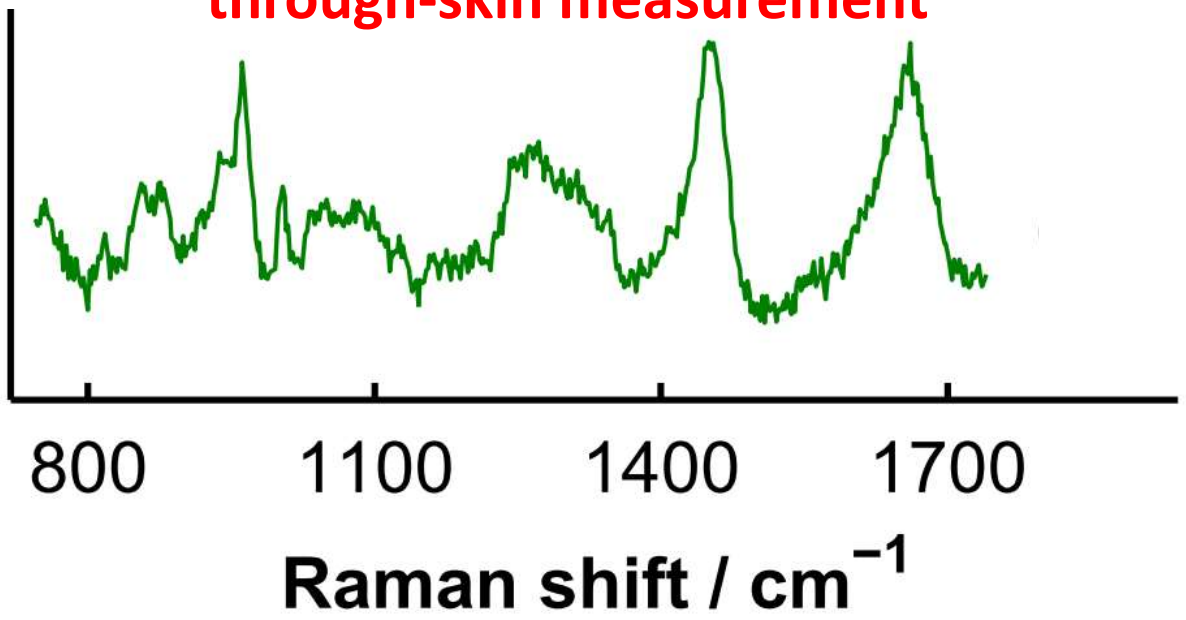


Transcutaneous spectrum: ambiguous

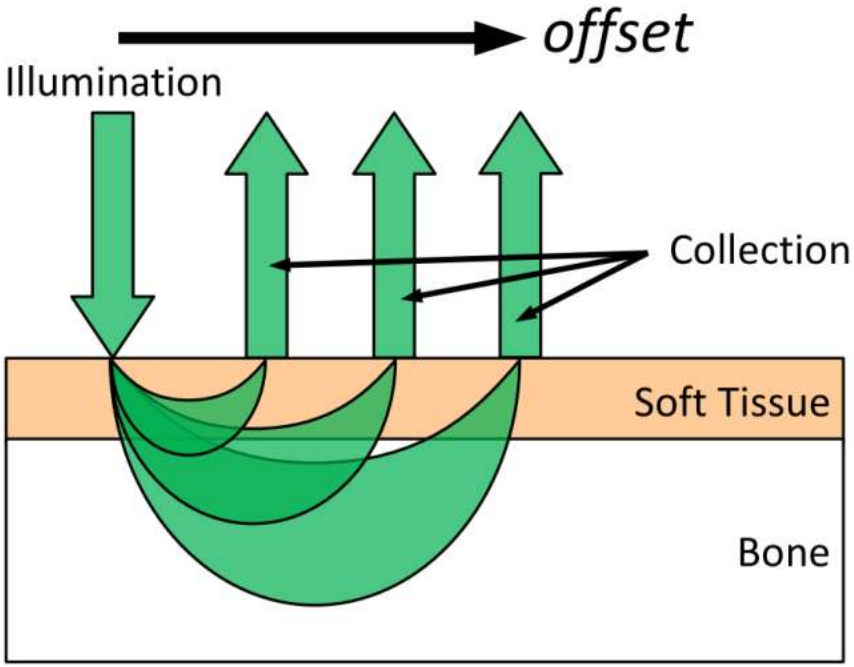


??

through-skin measurement



Vary distance to vary depth sensing



Summary of NIR interactions

biological sample

inelastic scattering:
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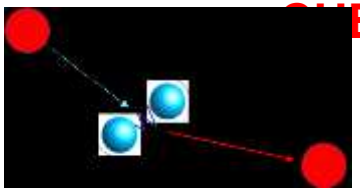
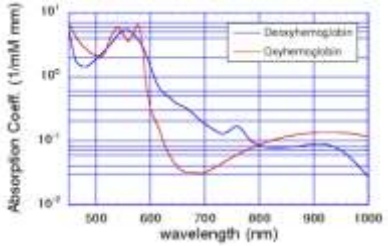
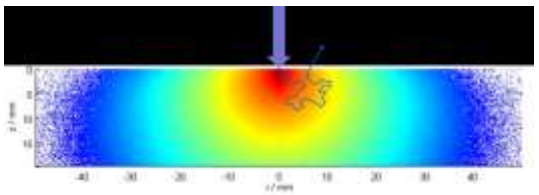


angle-dependent elastic scattering:
SIZE

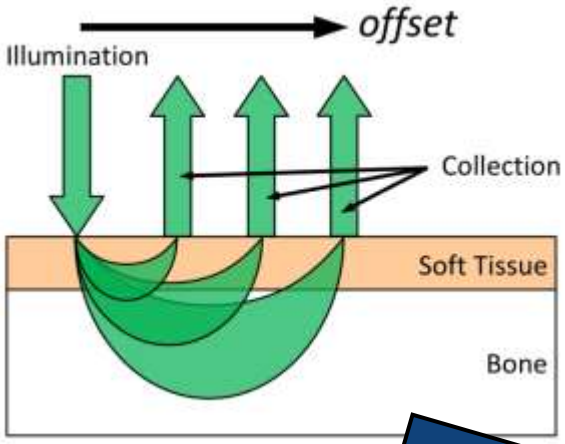


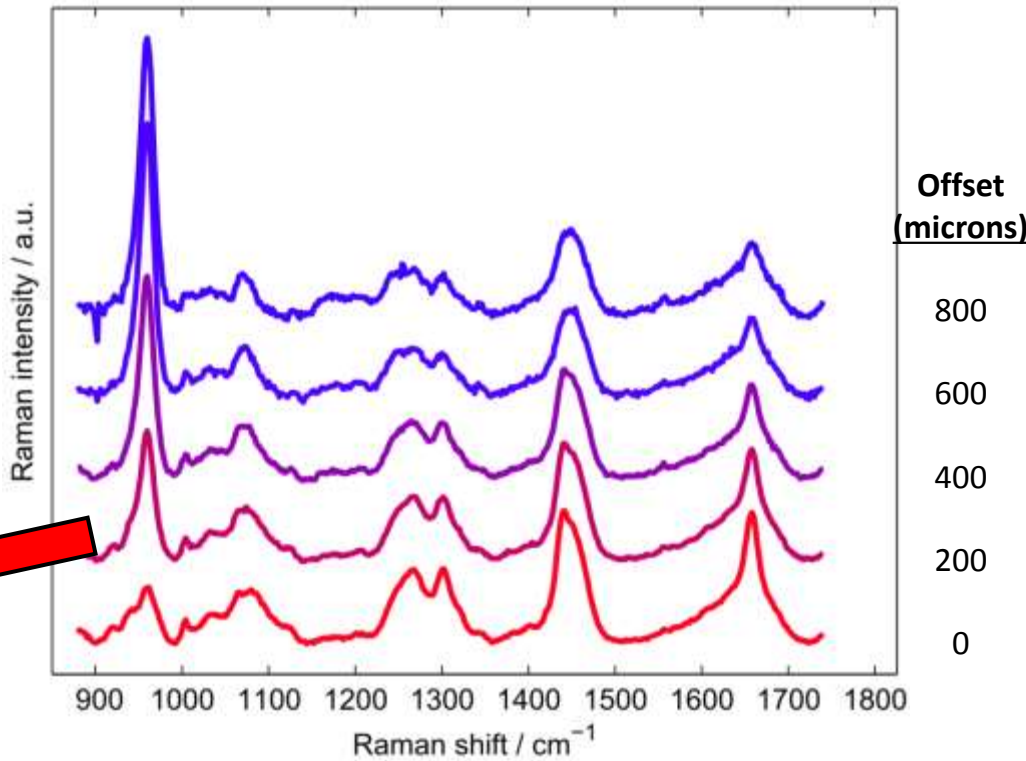
wavelength-dependent absorption:
BLOOD

diffusive propagation:
DEPTH



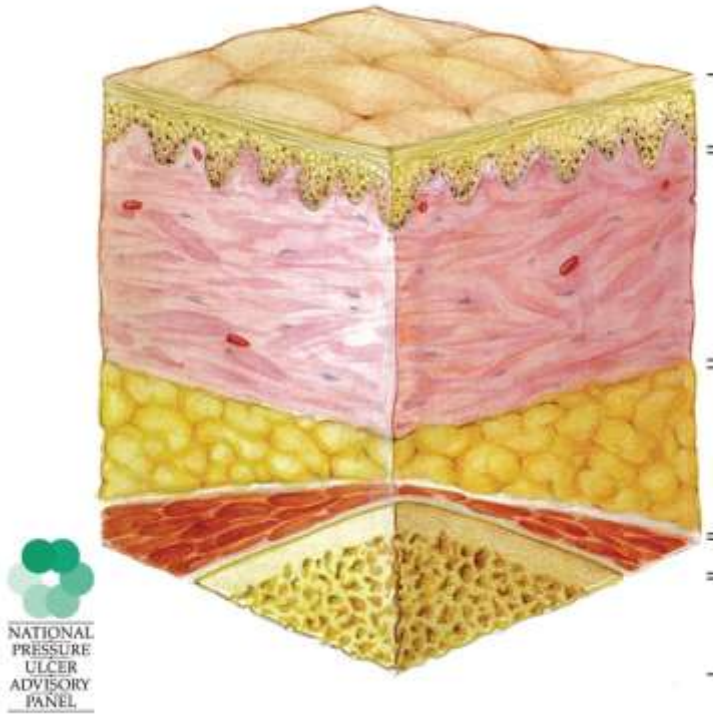
Putting diffusion to work!



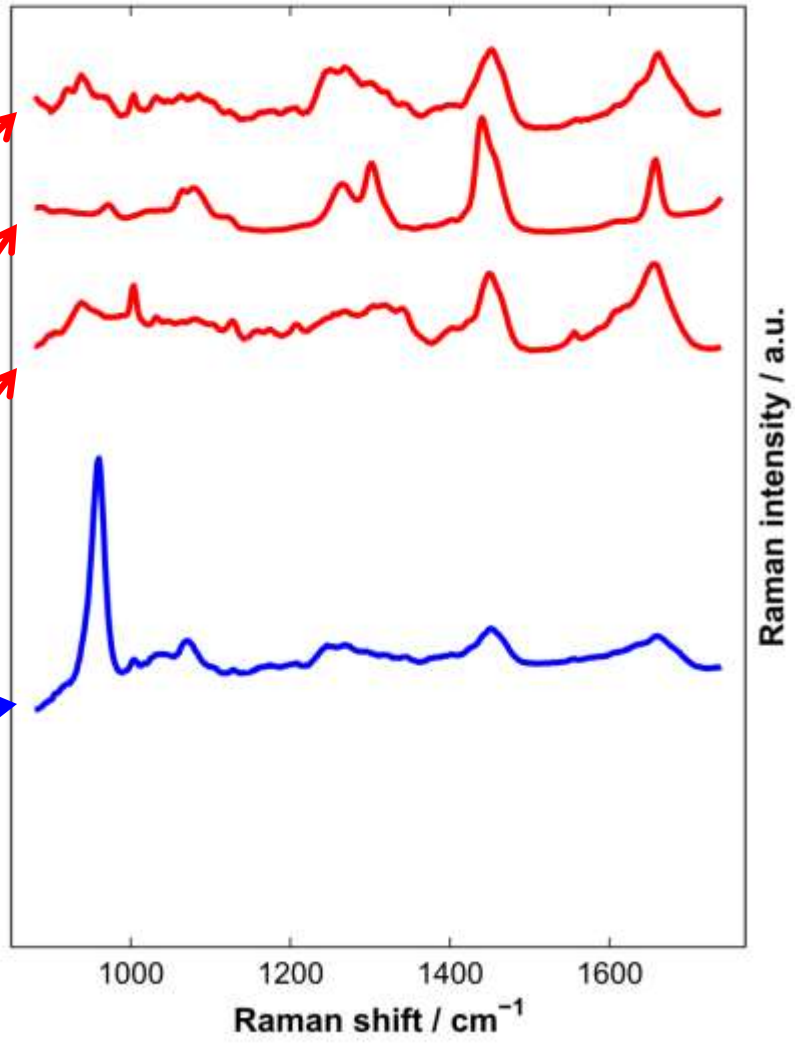


determine bone spectrum?

Layered model of soft tissue and bone

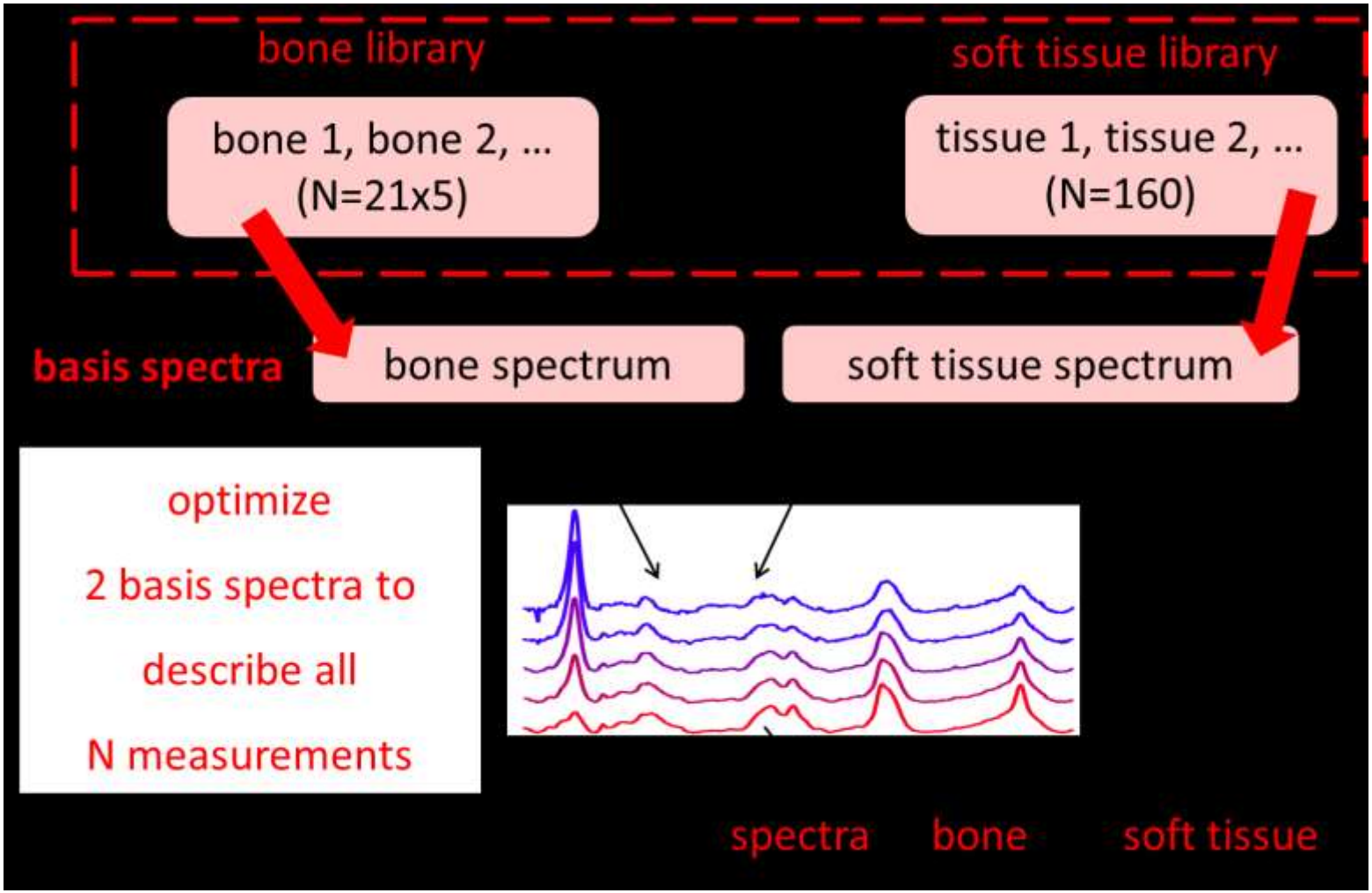


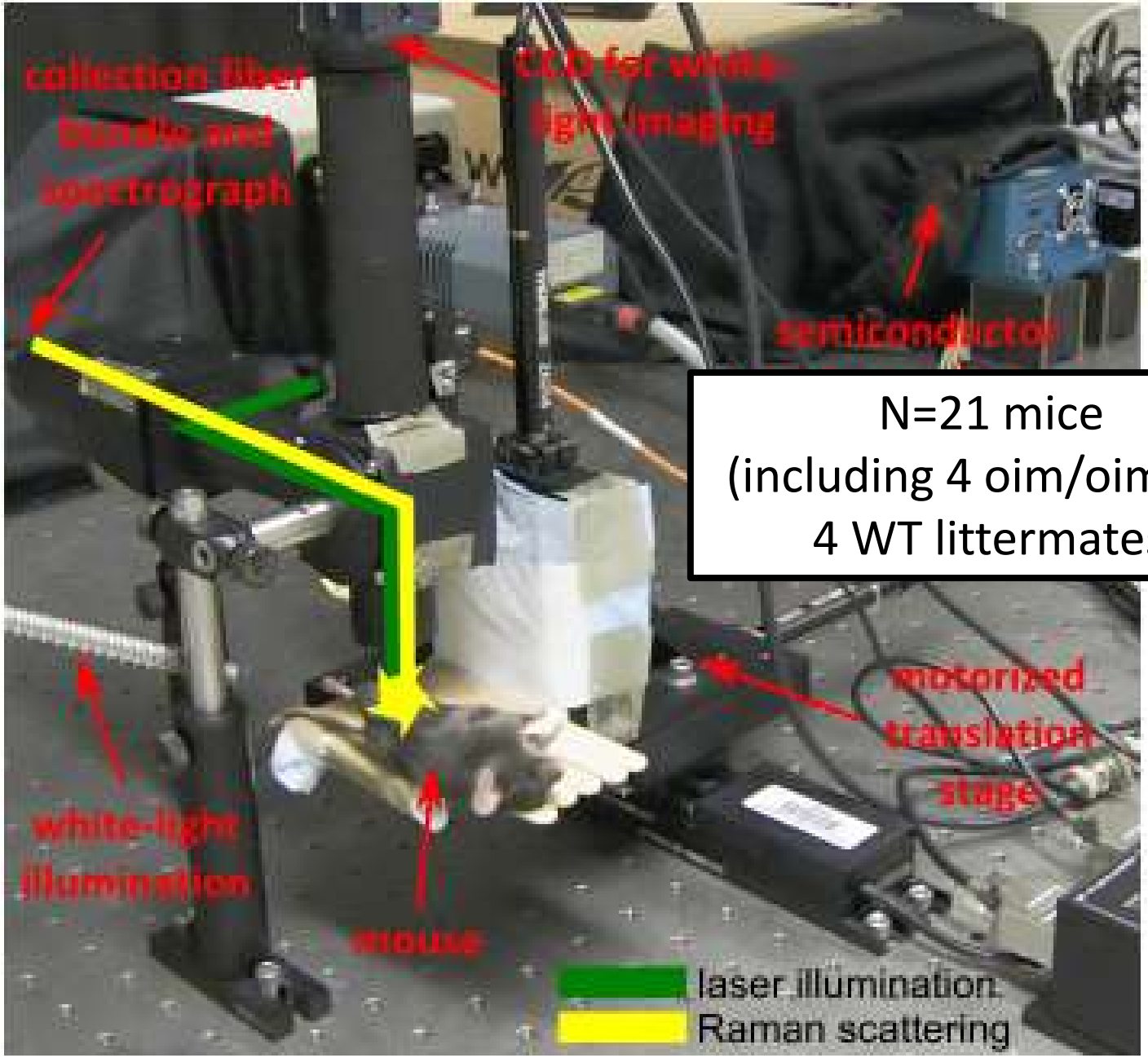
http://www.npuap.org/NPUAP-Normal.jpg



Type I collagen is main component of both dermal tissue and organic bone matrix!

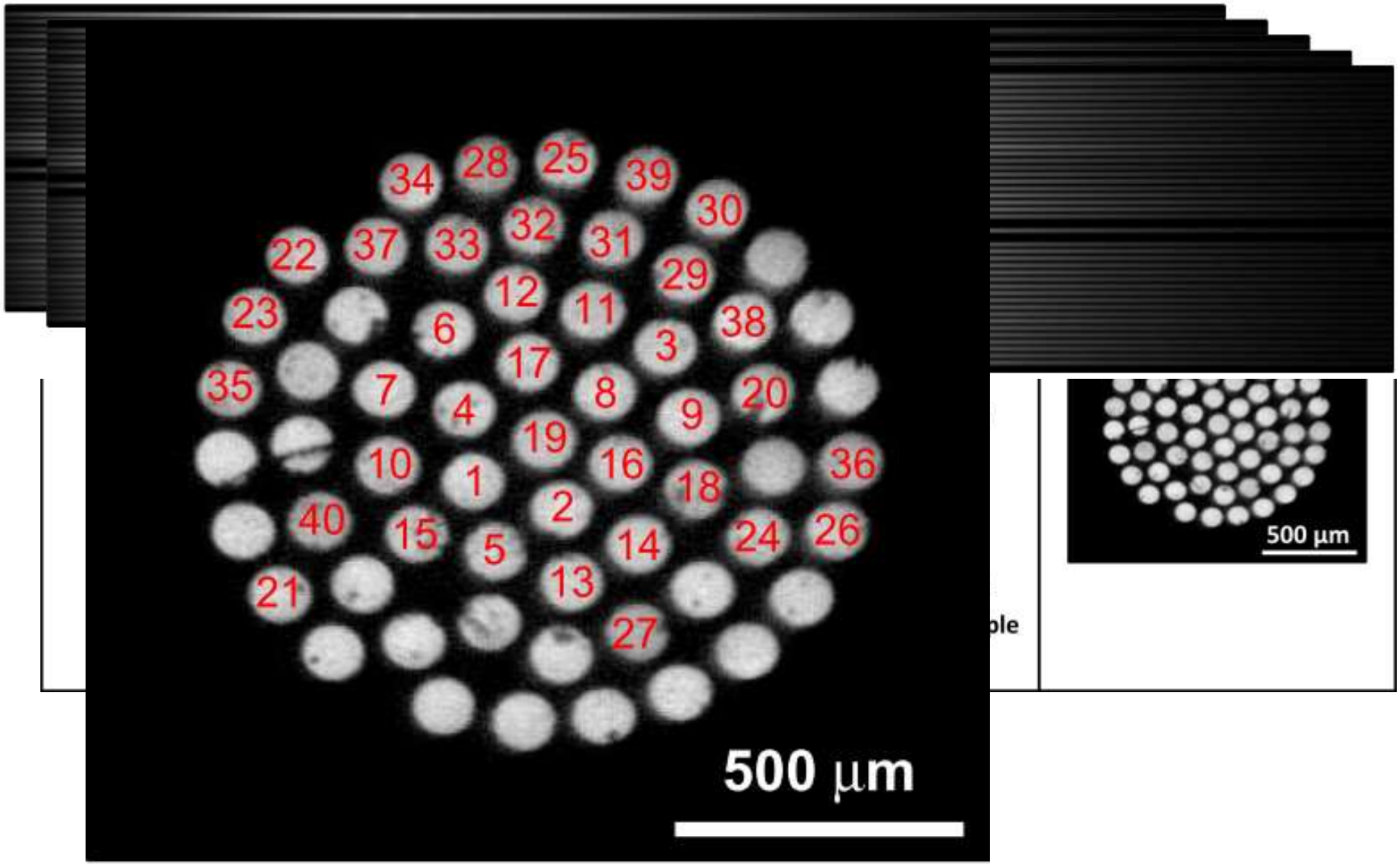
Simultaneous, overconstrained, library-based decomposition (SOLD)





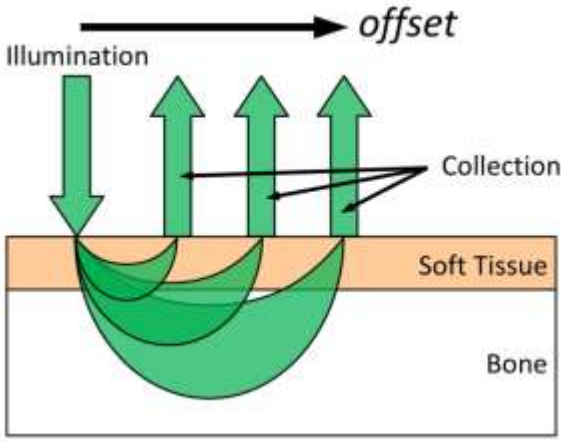
N=21 mice
(including 4 oim/oim and 4 WT littermates)

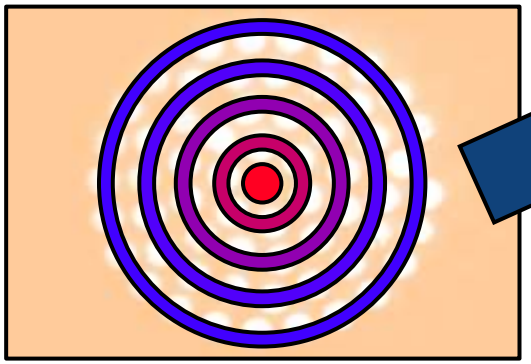
Raman spectroscopy system



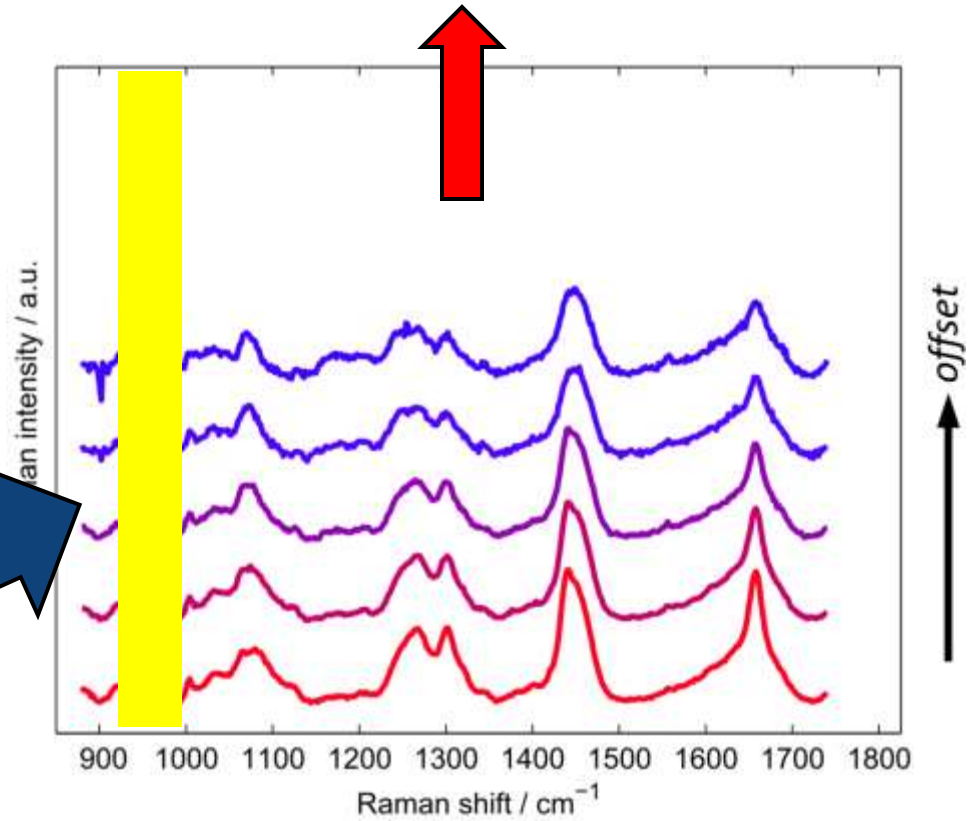
Spatially offset Raman spectroscopy (SORS)

deduce bone spectrum
via SOLD

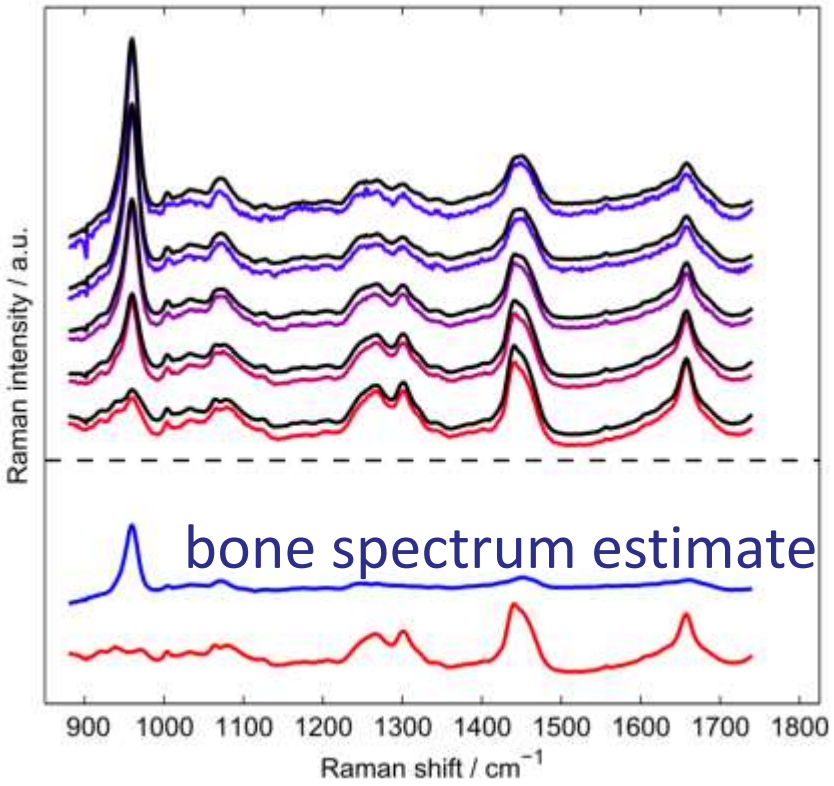




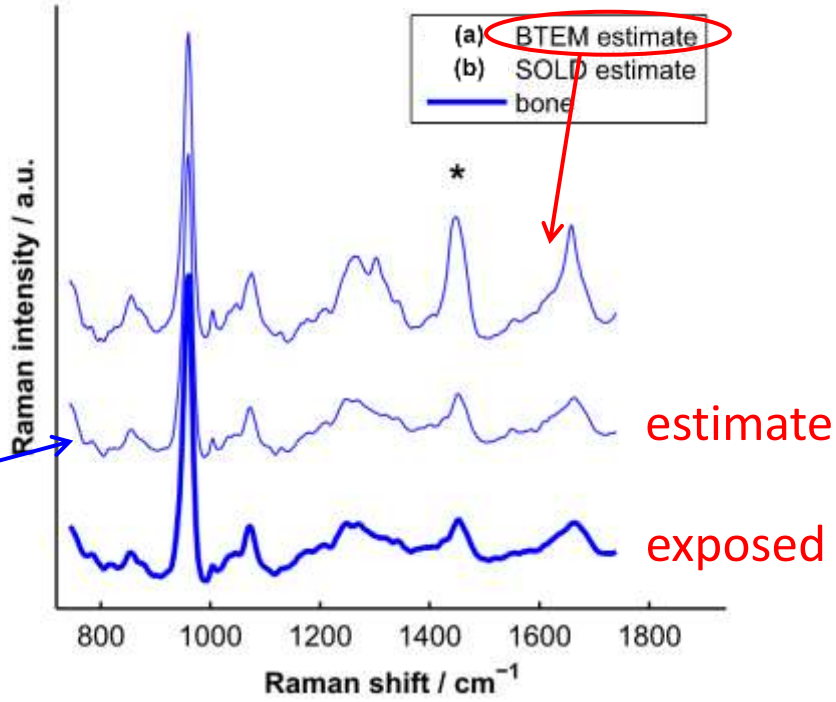
● : illumination spot



Estimating the correct bone spectrum

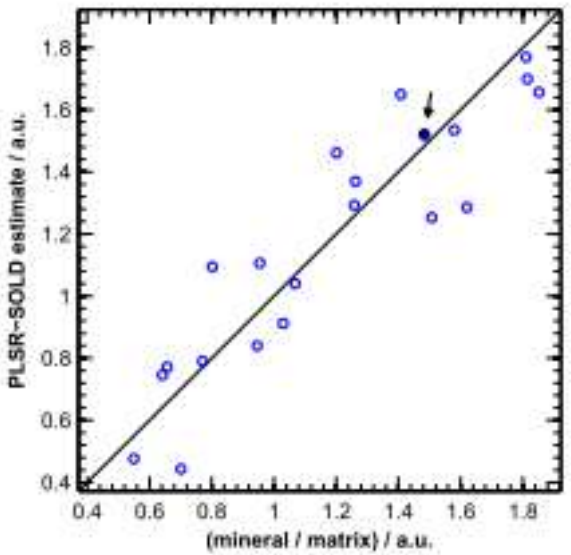


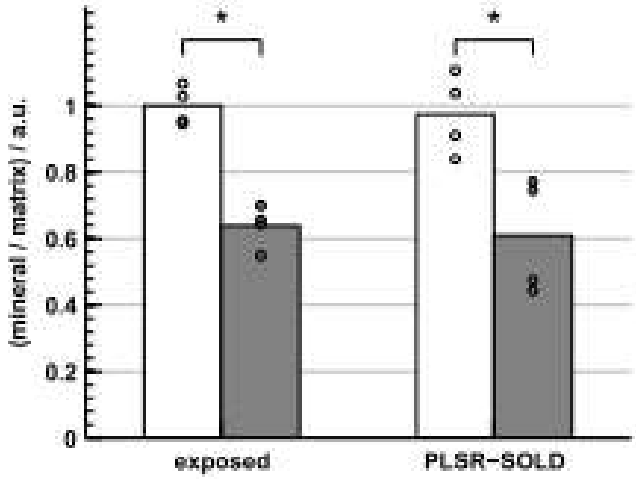
less complete method



Diagnostically-sensitive transcutaneous measurements

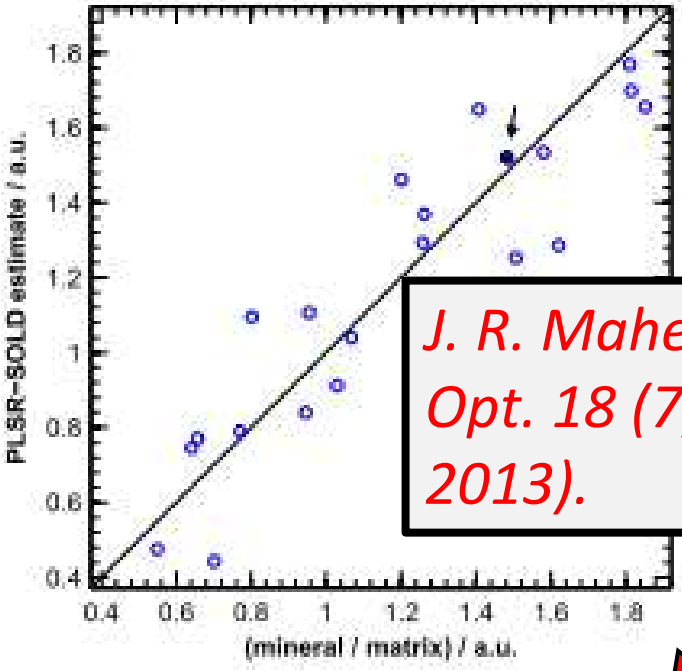
- Intact mice measured at mid-shaft of tibia
- Wild-type (WT) mice and mouse models of osteogenesis imperfecta (OI) and rheumatoid arthritis (N = 21 total mice)
- Mineral/matrix ratio estimated by SOLD completely separates WT and OI mice



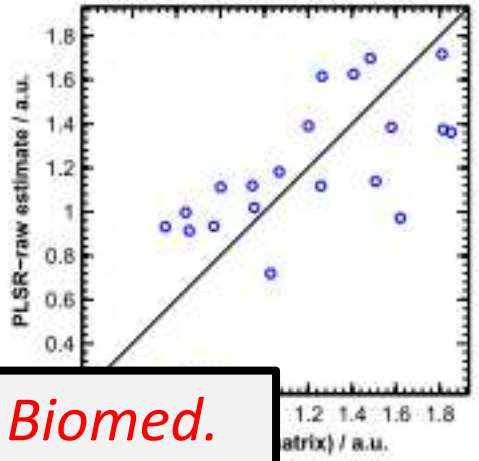


Most robust measurement of mineral to matrix ratio

SOLD processing

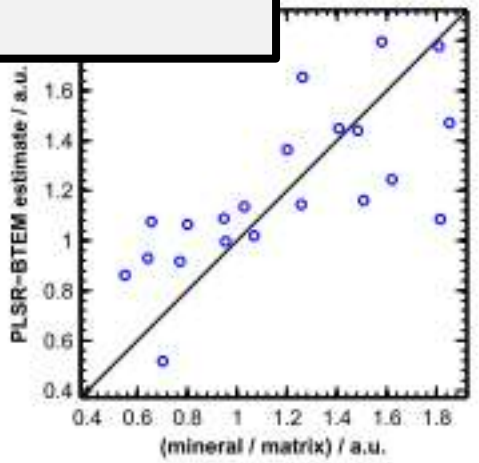


unprocessed spectra



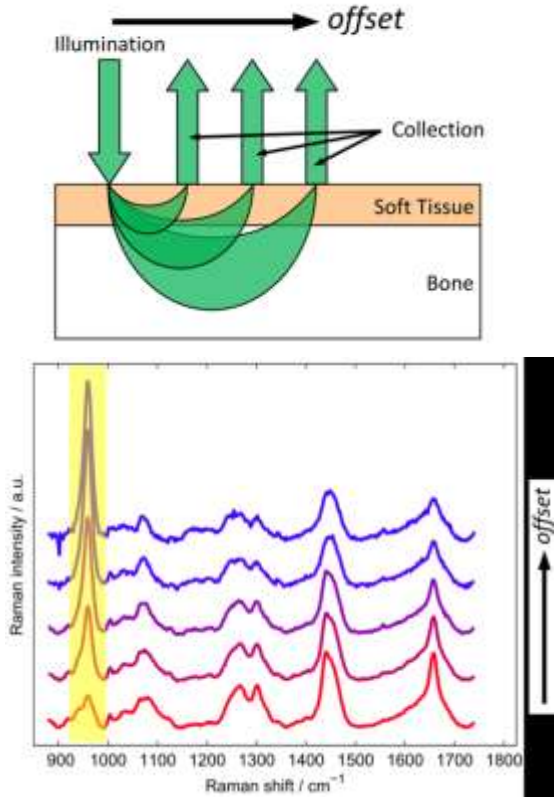
J. R. Maher et al., J. Biomed. Opt. 18 (7), 077001 (July 01, 2013).

e constraint

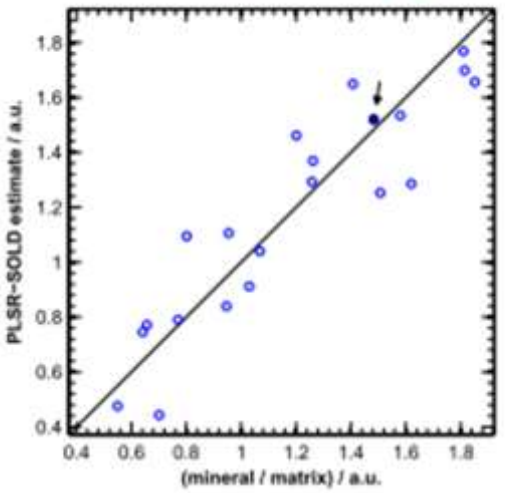


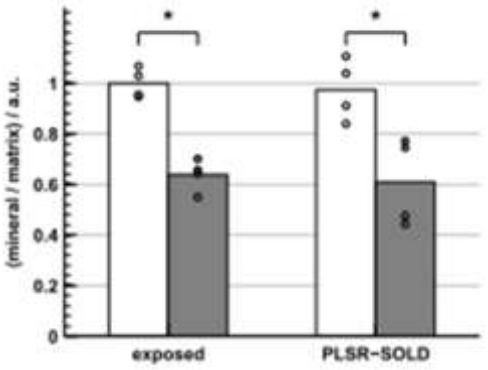
other methods also fail to separate OI from WT mice

Summary: bone work



SOLD processing





Multiple source-detector separations: essential for determining mineral-to-matrix ratio of bone transcutaneously

Dustin Shipp

Welcome to the near-infrared

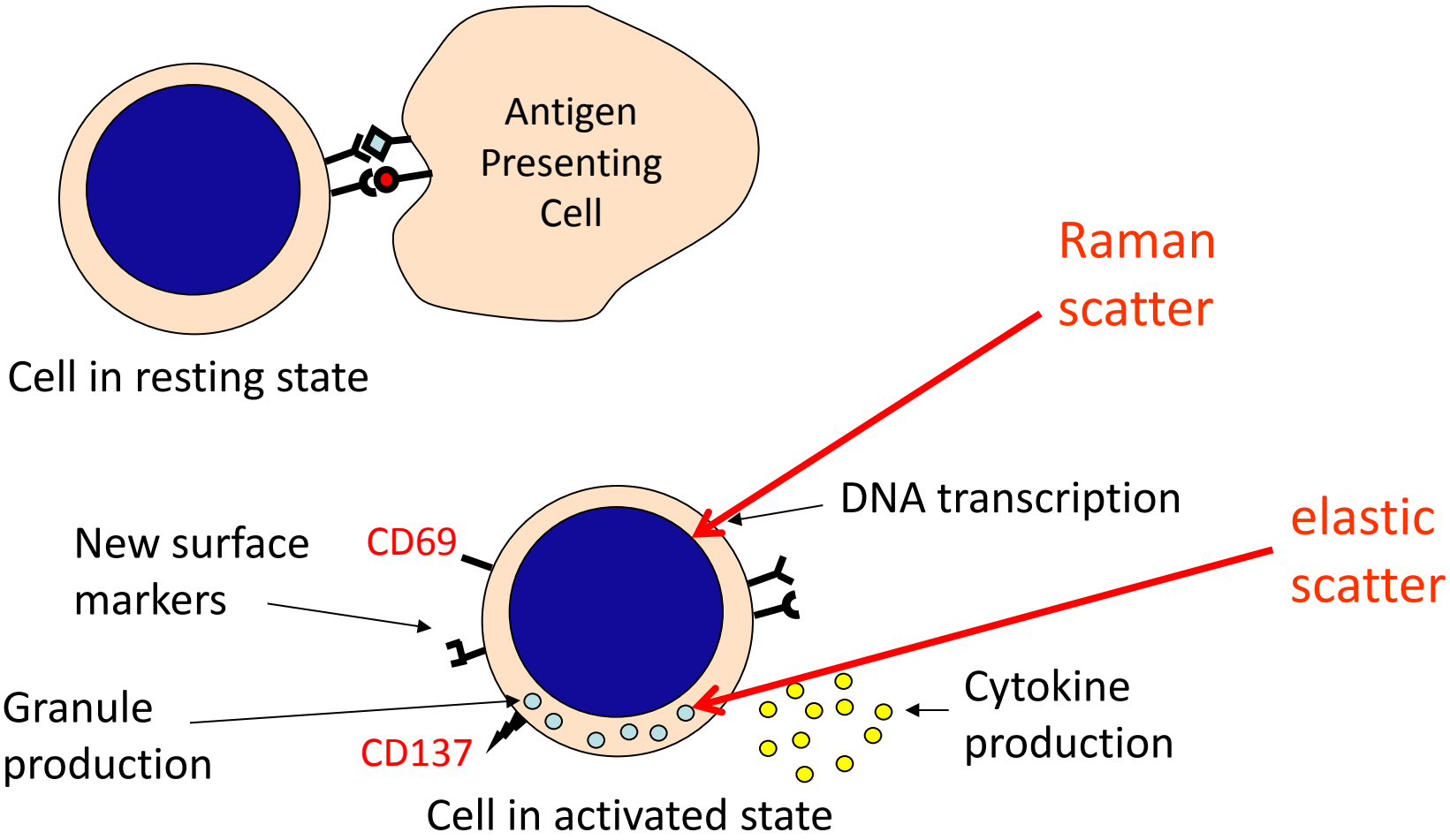
Measuring mouse bone quality

Sensing organelle size distributions

Sensing blood activity in the brain

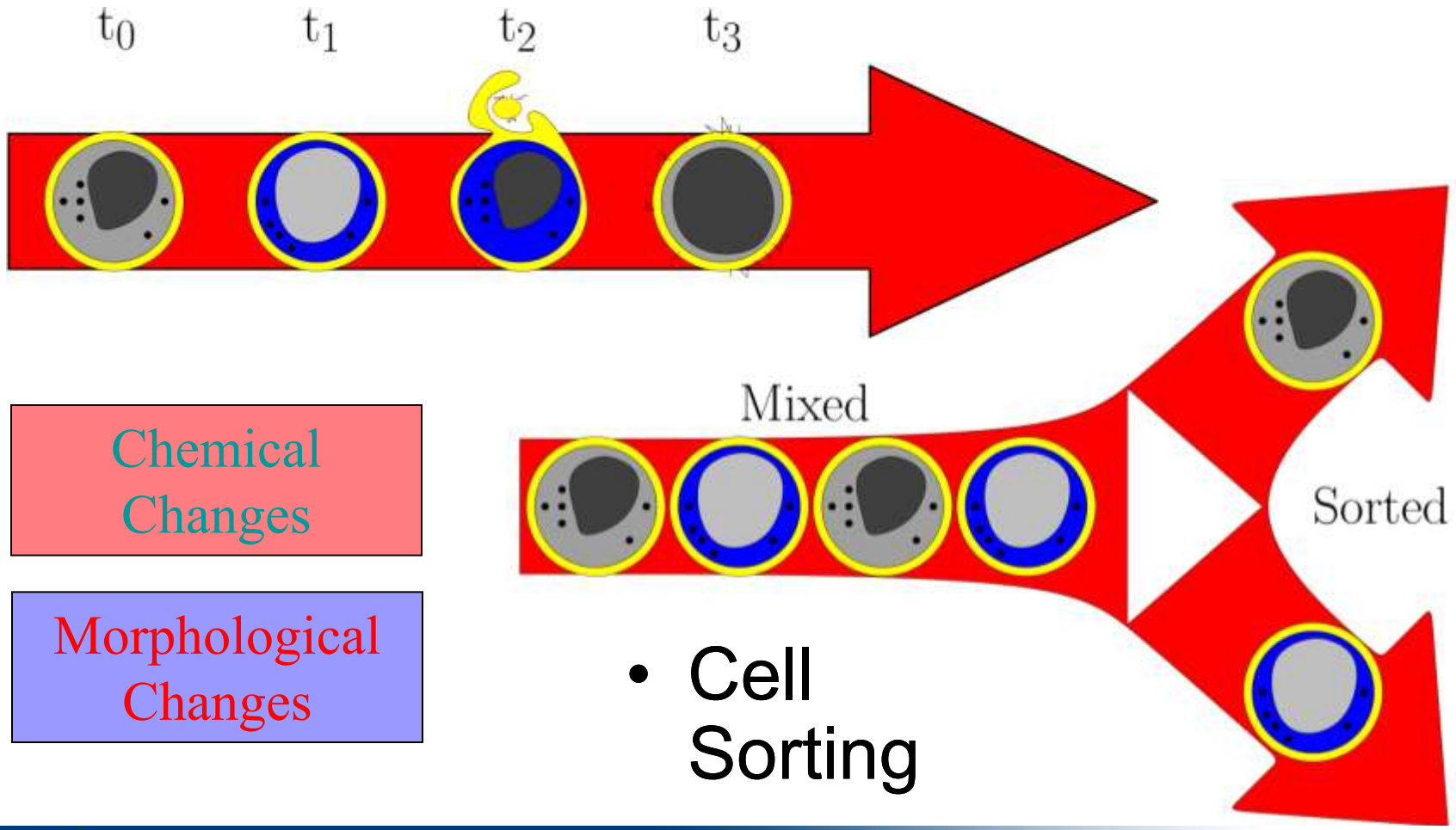
Zachary Smith

Motivation: study T-cell activation



Motivation: studying cells without labeling

- Single cell versus time

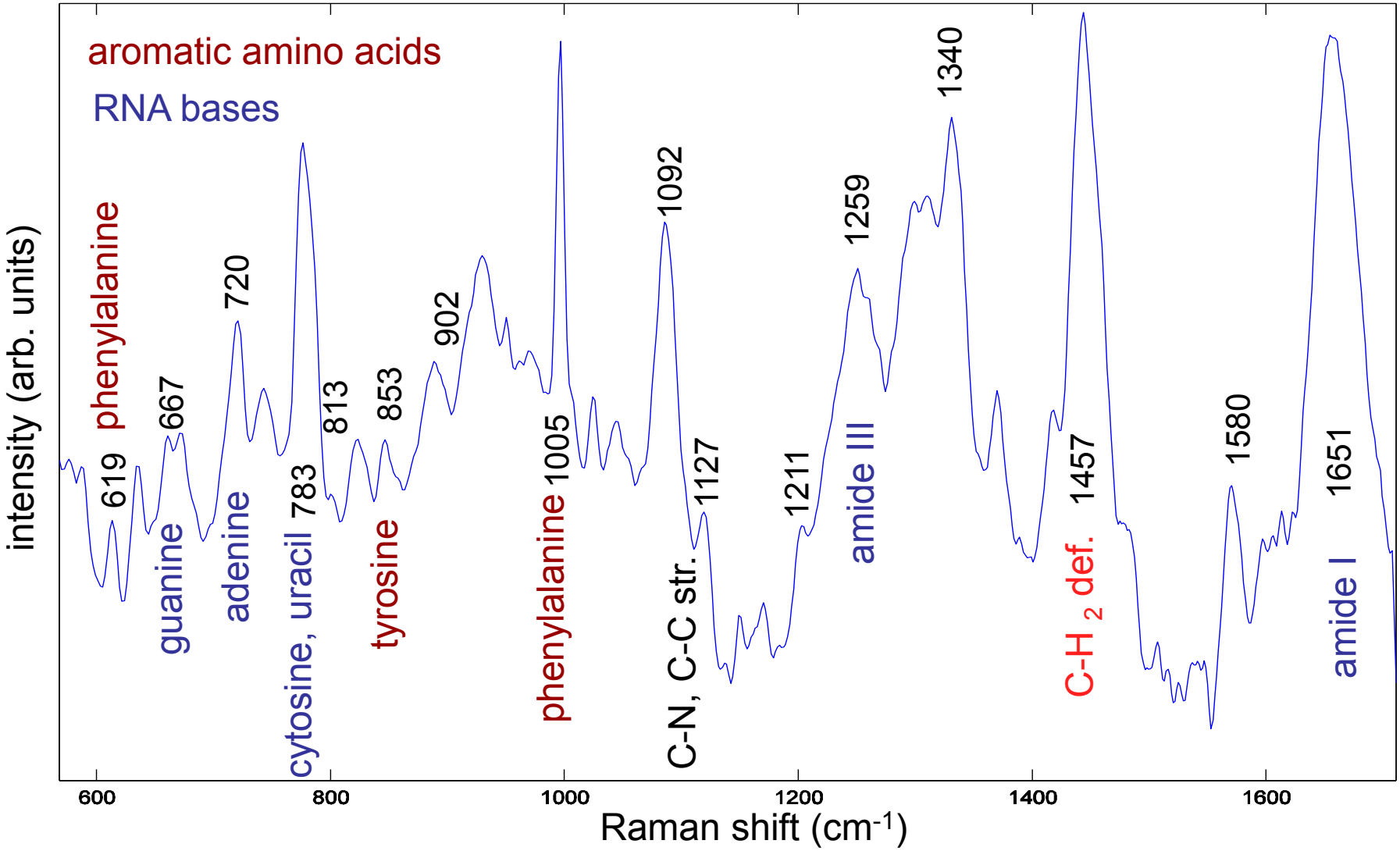


Chemical Changes

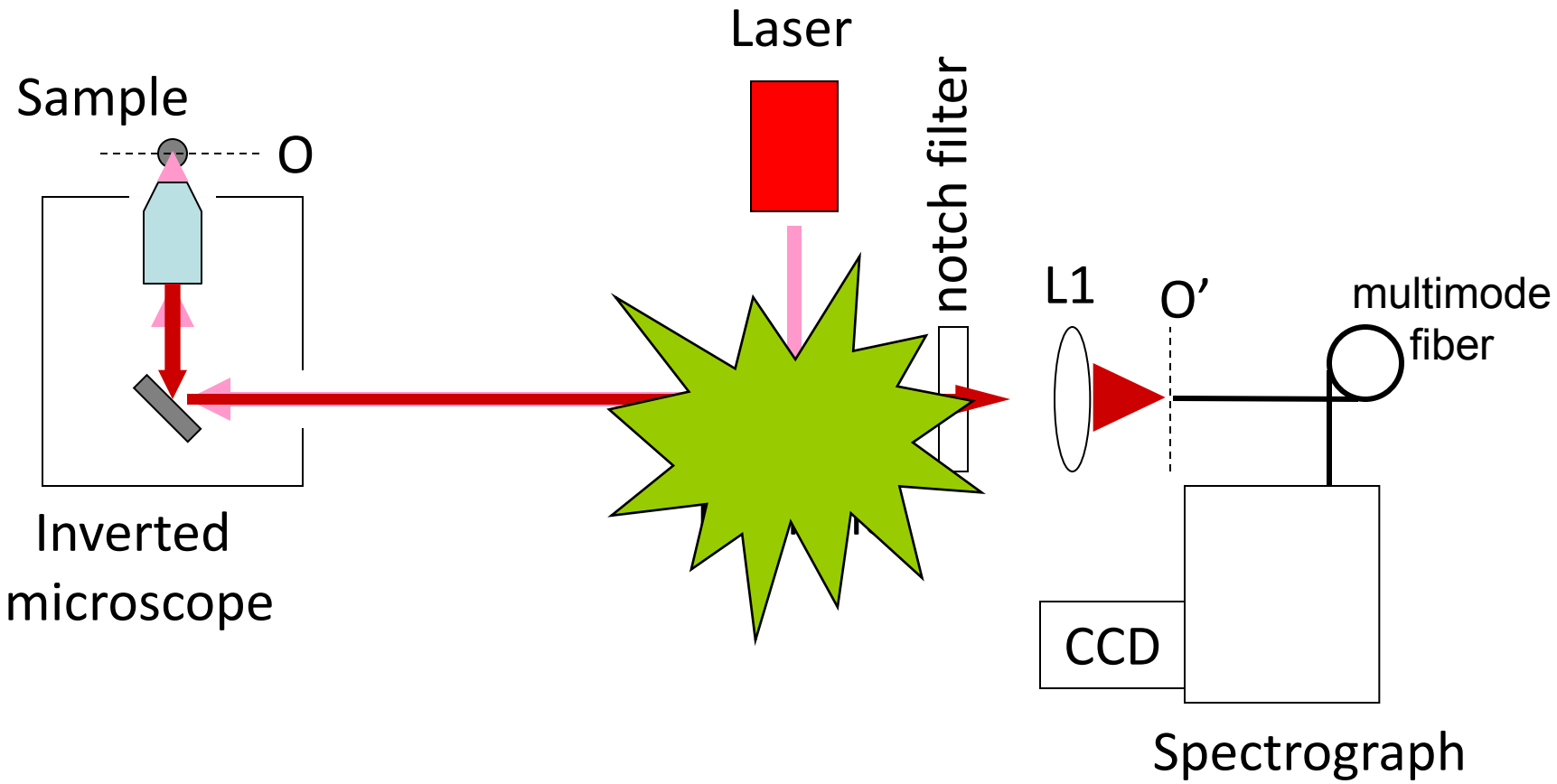
Morphological Changes

- Cell Sorting

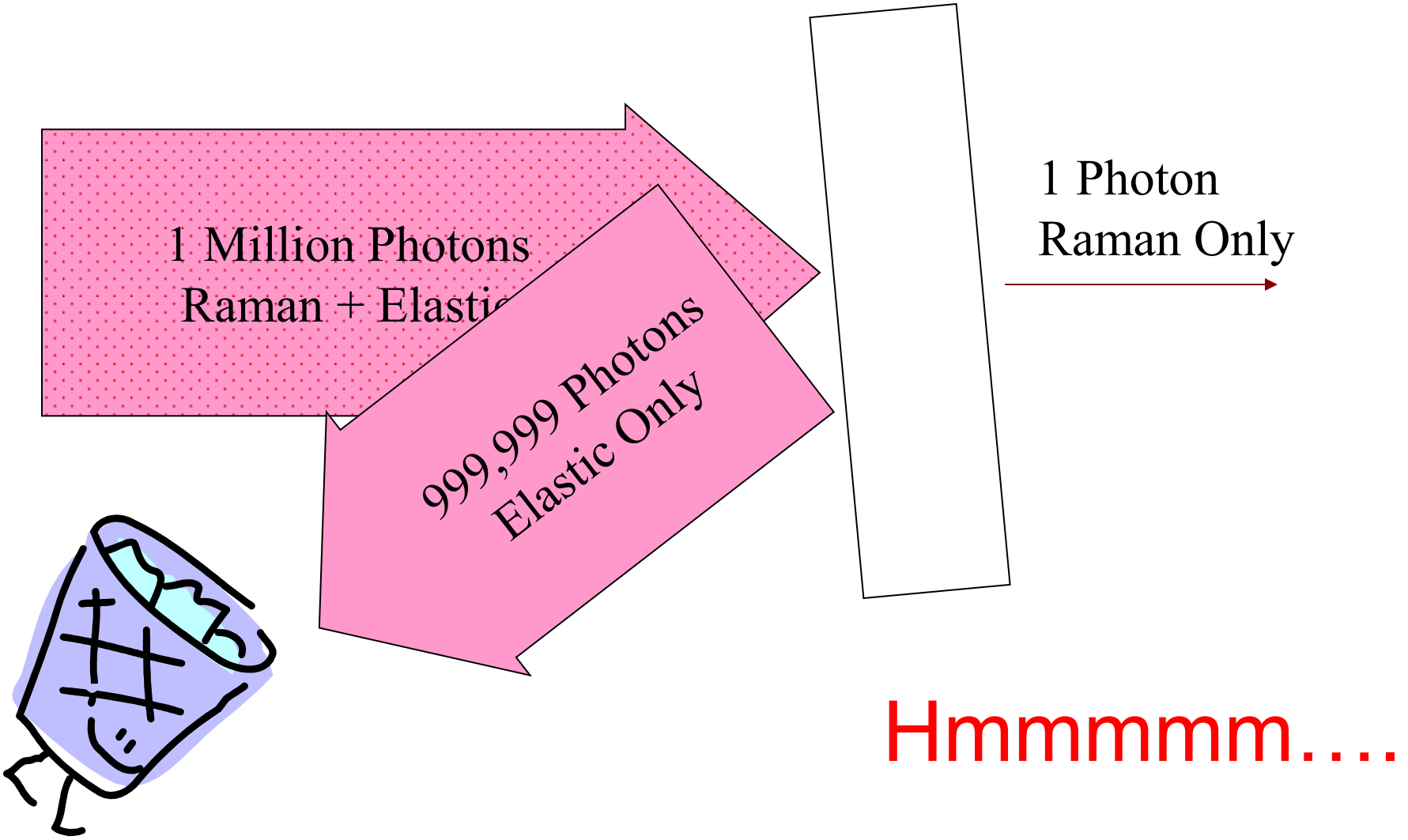
Starting point: Raman spectum of immune cell



Raman Microscope

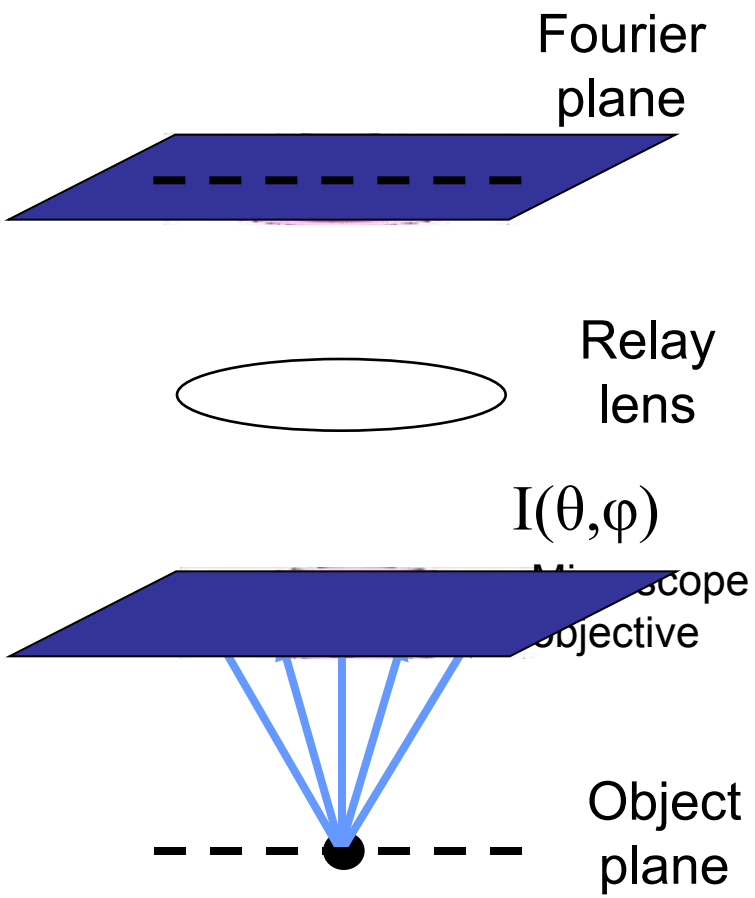


At the Dichroic Beamsplitter

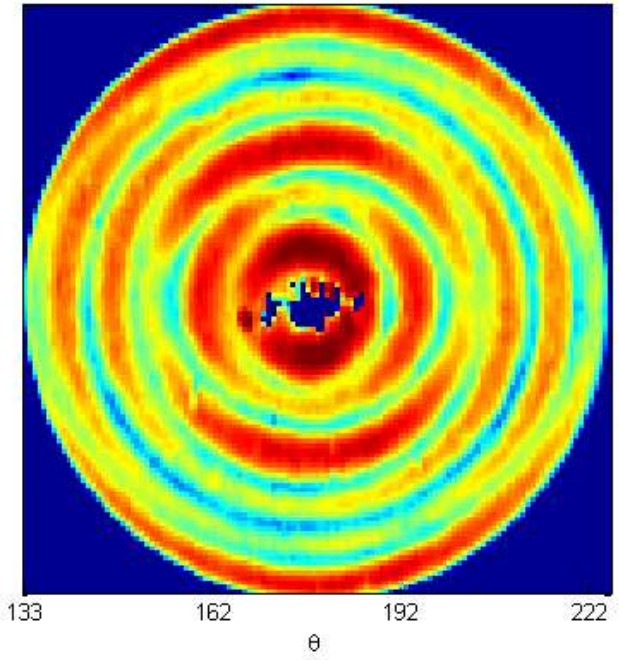


Hmmmmm….

Recording the angular pattern



Angle Mapped to Position

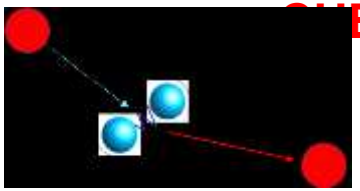


I(x,y) in Fourier plane = I(θ,φ) in object plane

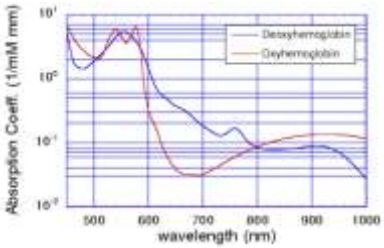
Summary of NIR interactions

biological sample

inelastic scattering:
CHEMISTRY

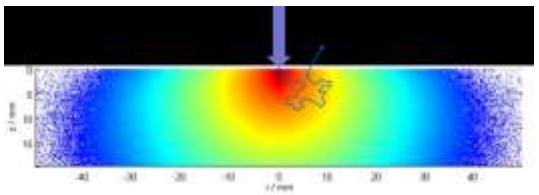


angle-dependent elastic scattering:
SIZE

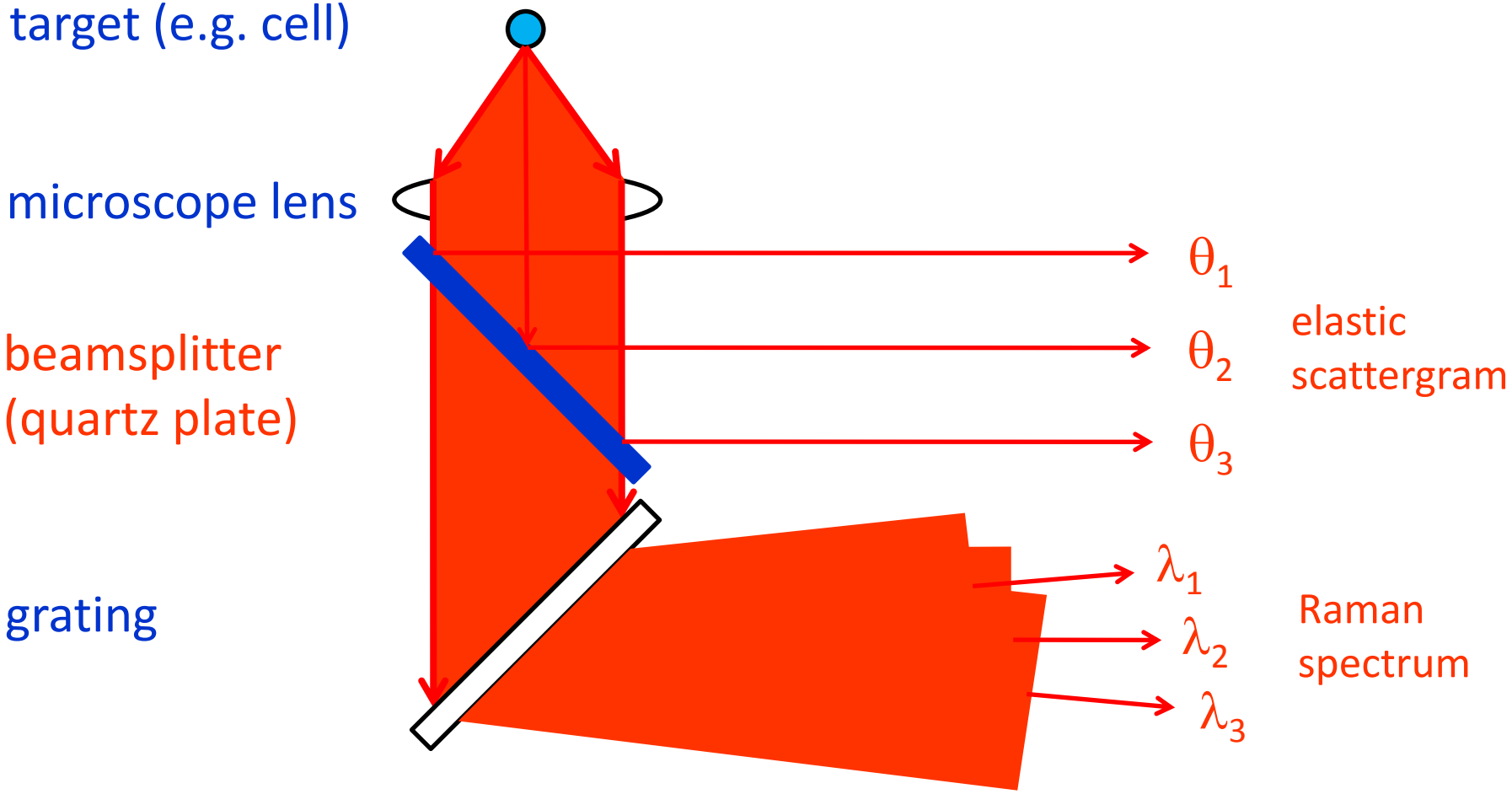


wavelength-dependent absorption:
BLOOD

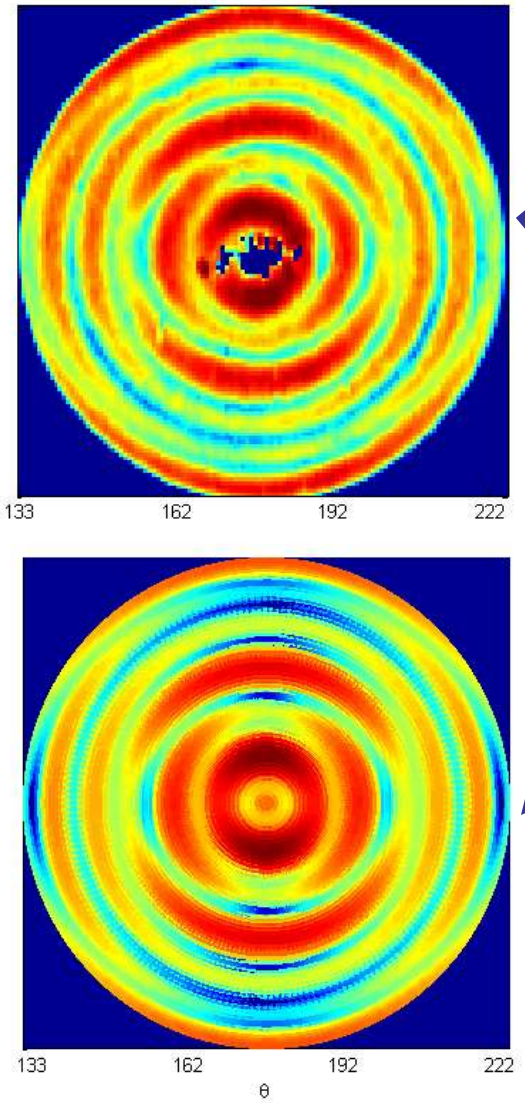
diffusive propagation:
DEPTH



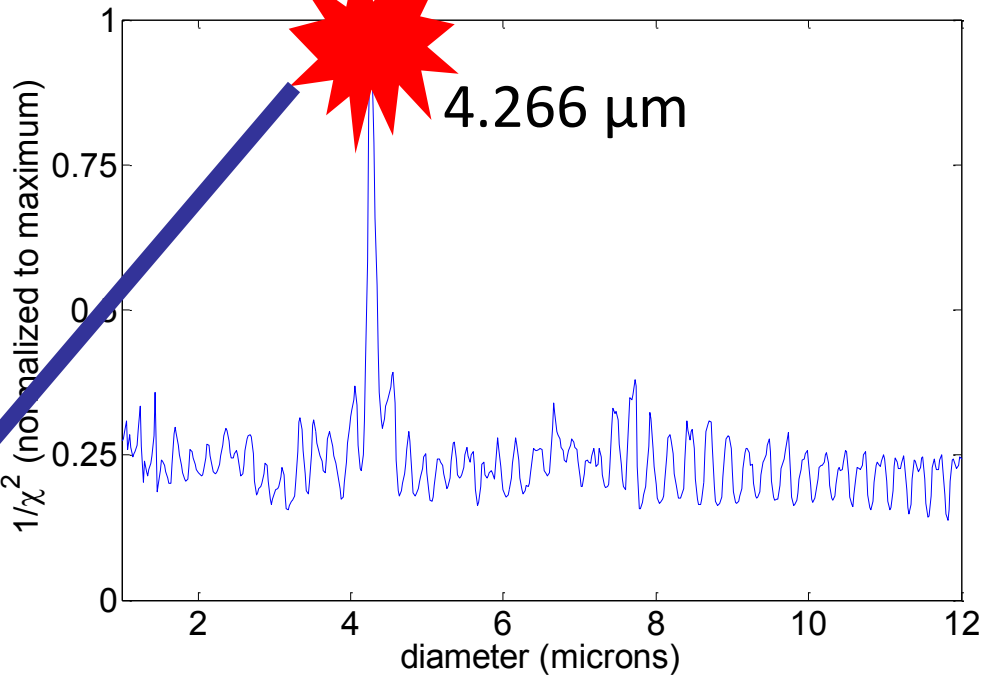
Combining two scattering modalities



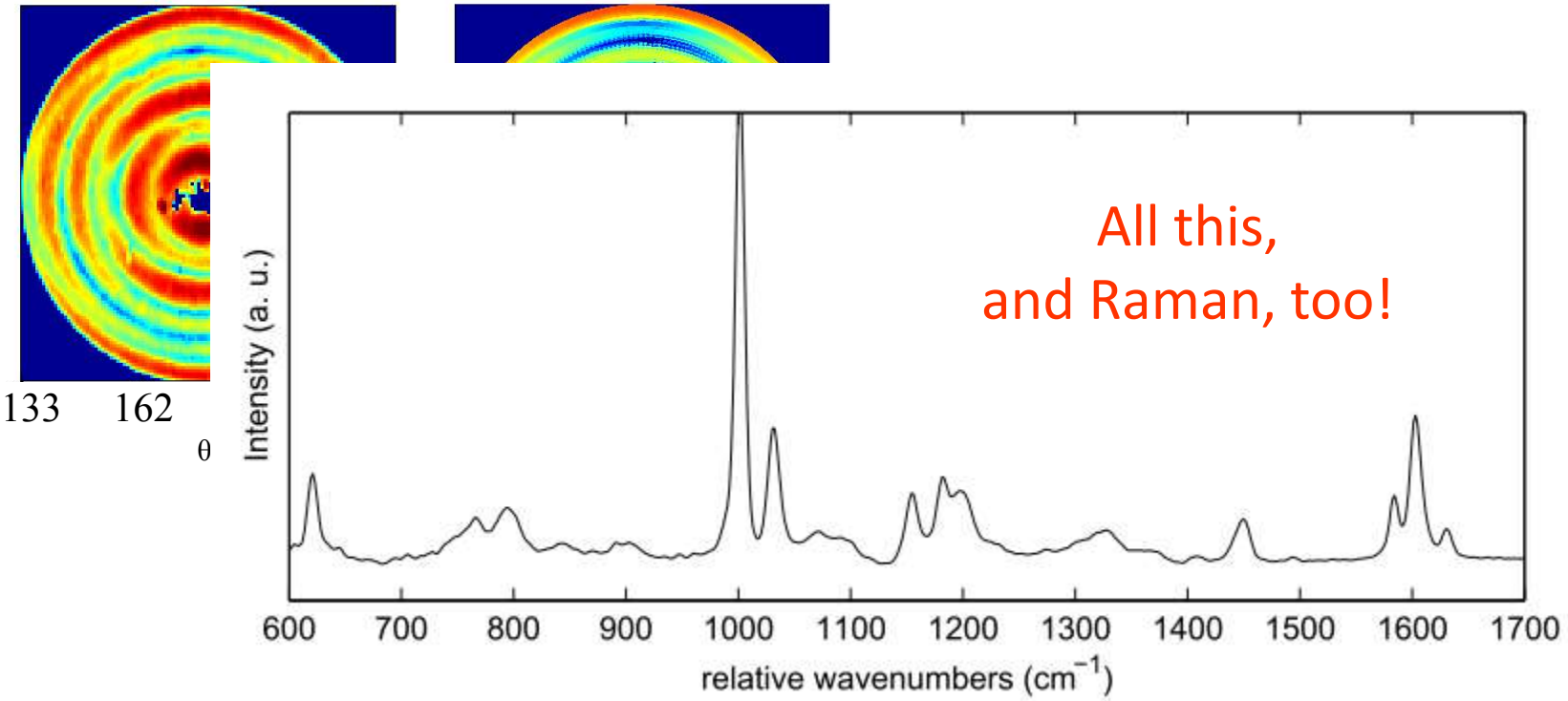
Scattergrams specify *size*



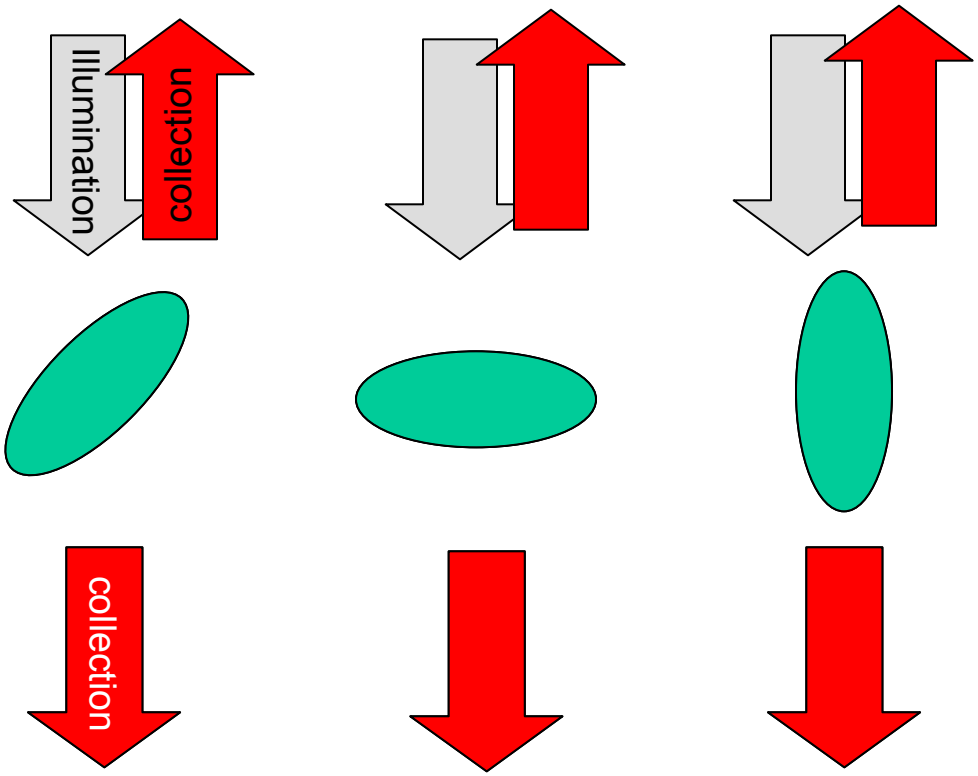
Automated comparison with theory



Sensing of slight size changes



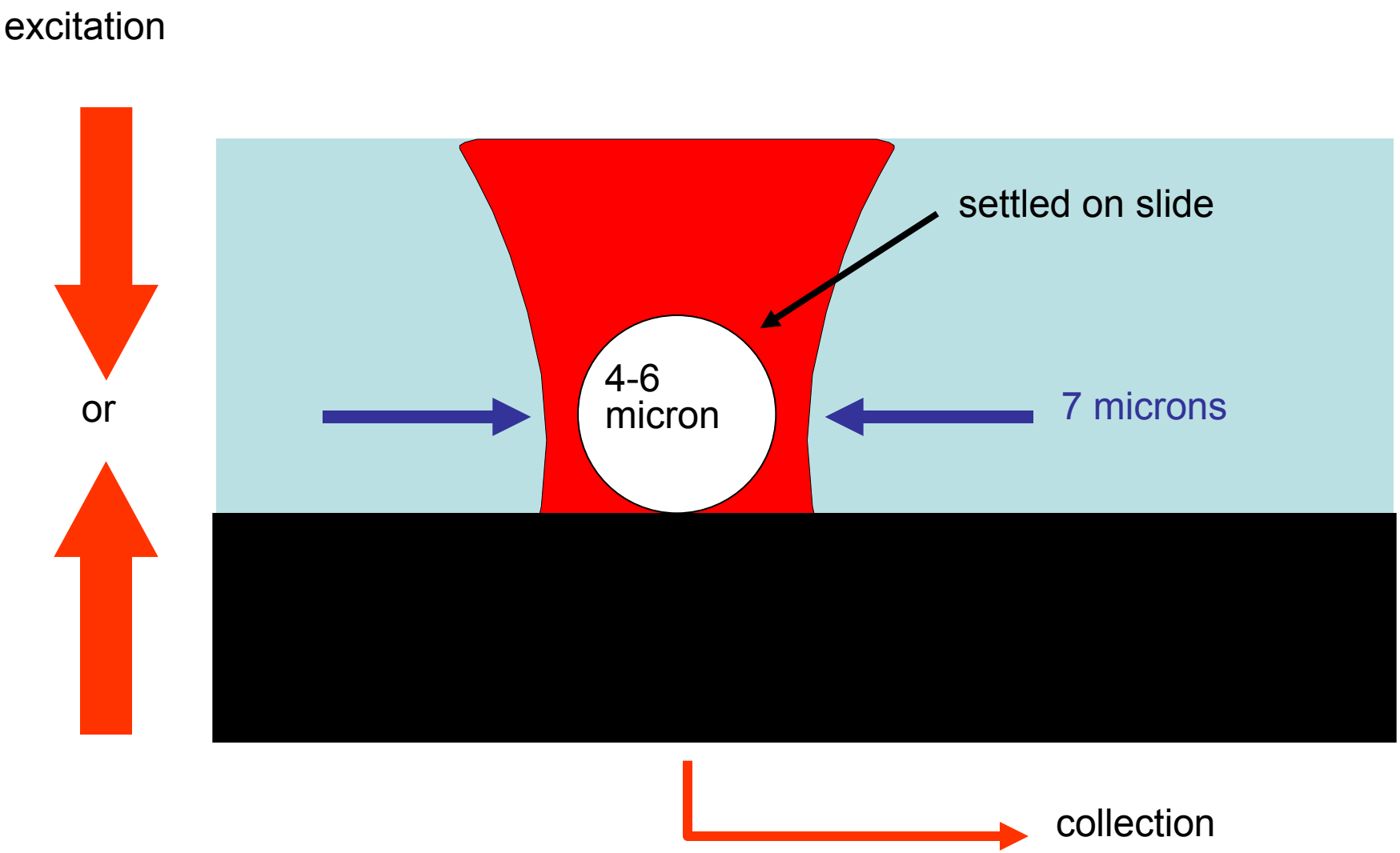
But organelles are not spheres!



Backward scattering highly sensitive to shape and orientation

Forward scattering insensitive to shape and orientation

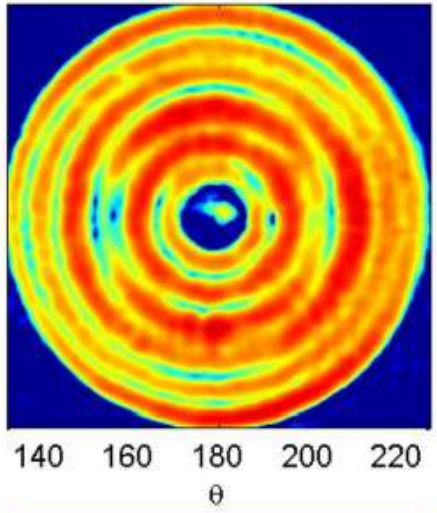
System test: sizing a single bead



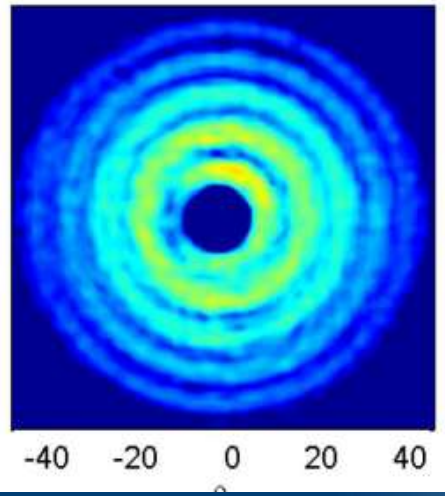
Forward vs. backward (epi) mode

Experiment

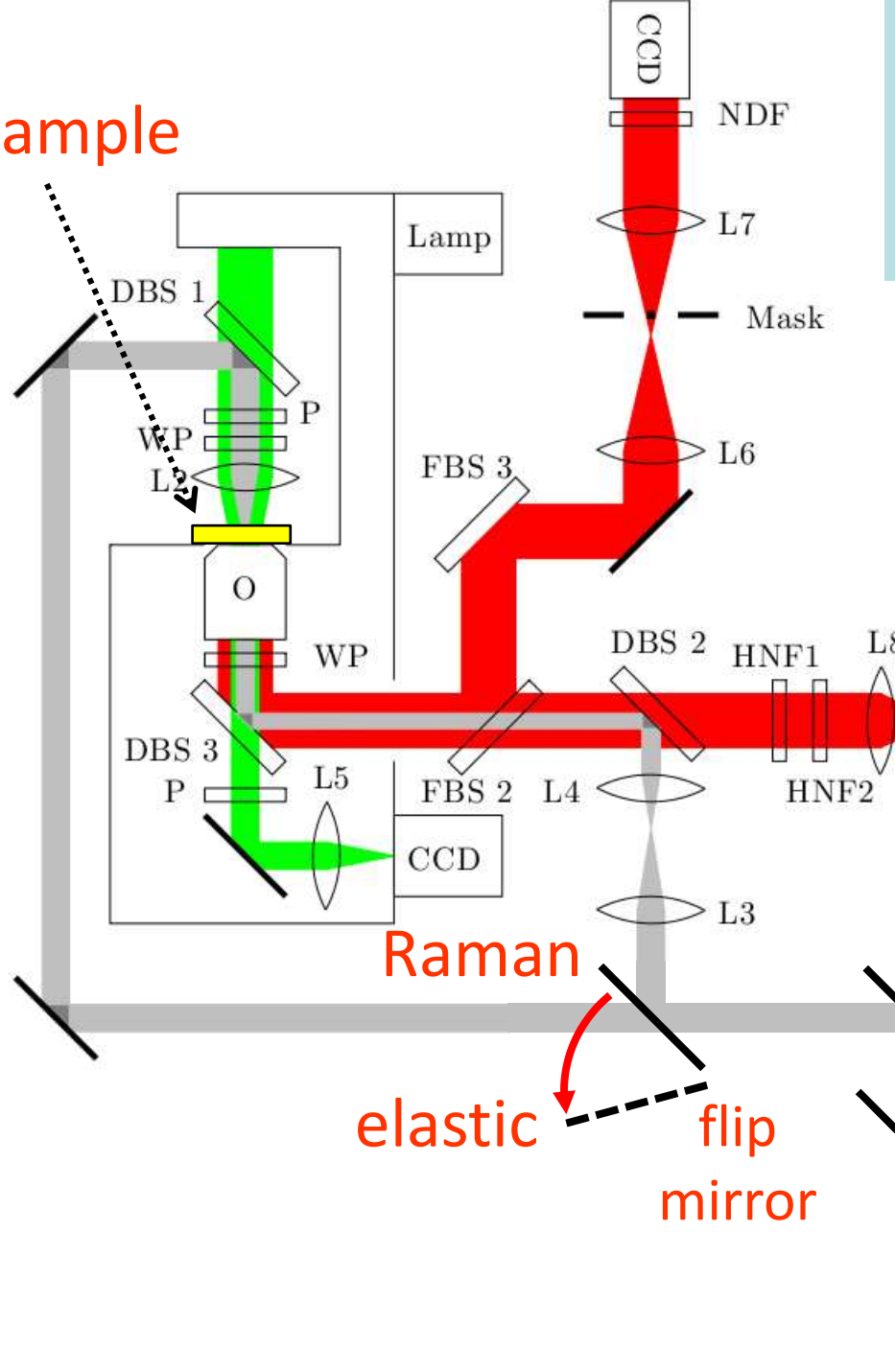
epi-mode



forward



Integrated system



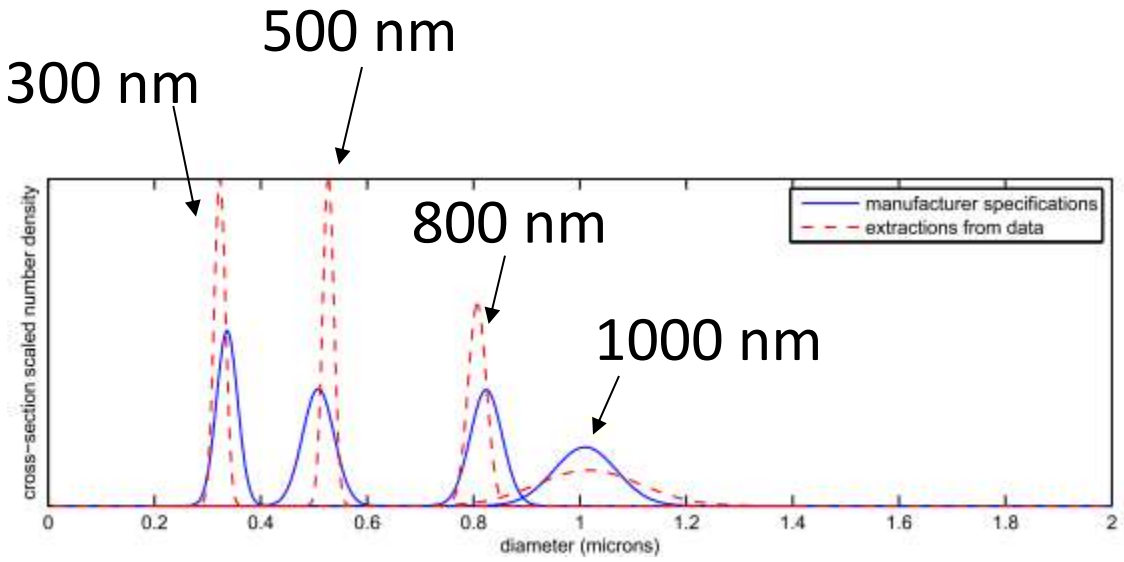
laser excitation

scattering

brightfield

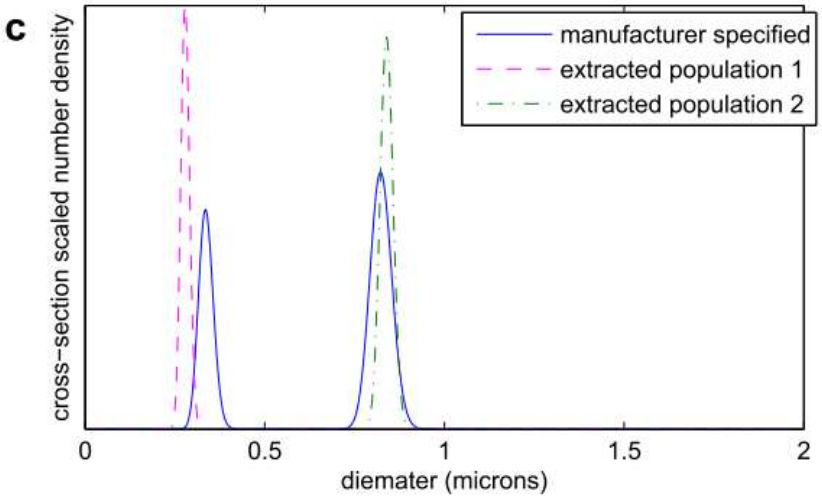
Smith and Berger, *Review of Scientific Instruments* **80** (4), 044302 (2009)

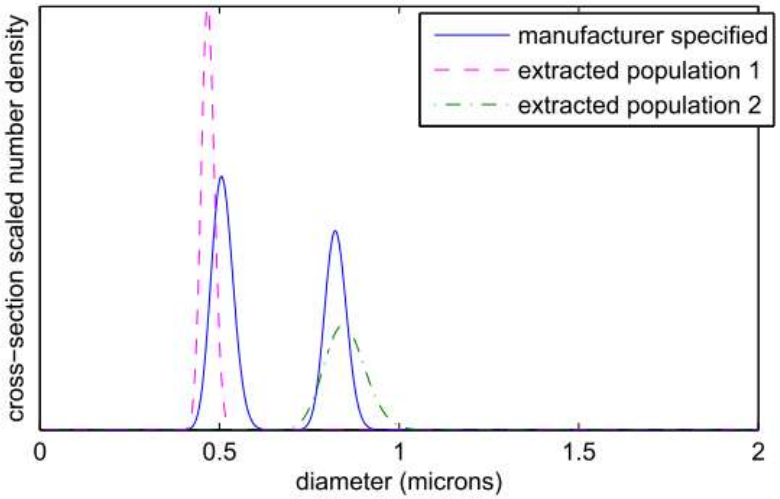
Single populations sized accurately

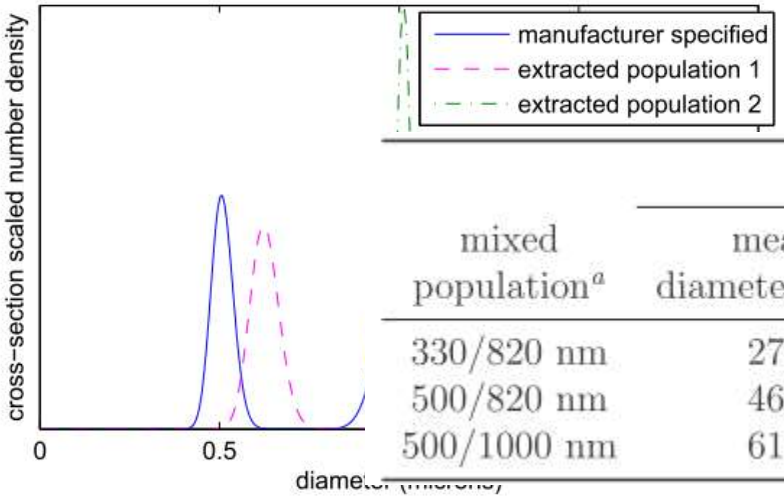


Manufacturer's Specification		IRAM extraction	
mean diameter (nm)	standard deviation (nm)	mean diameter (nm)	standard deviation (nm)
330	10	321	3
500	15	526	5
820	16	806	9
1000	30	988	50

Two-population mixtures



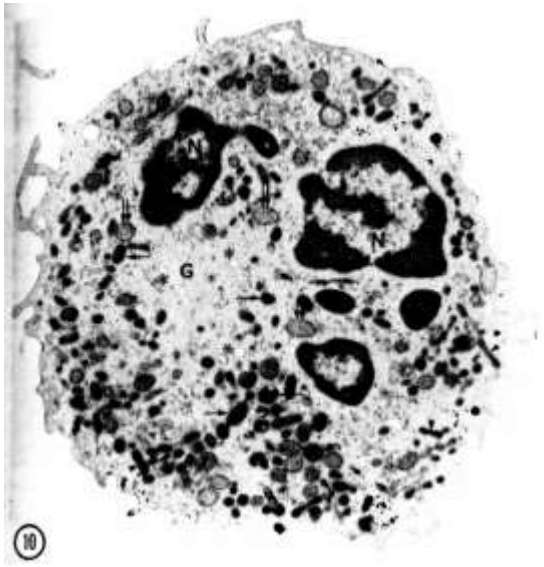




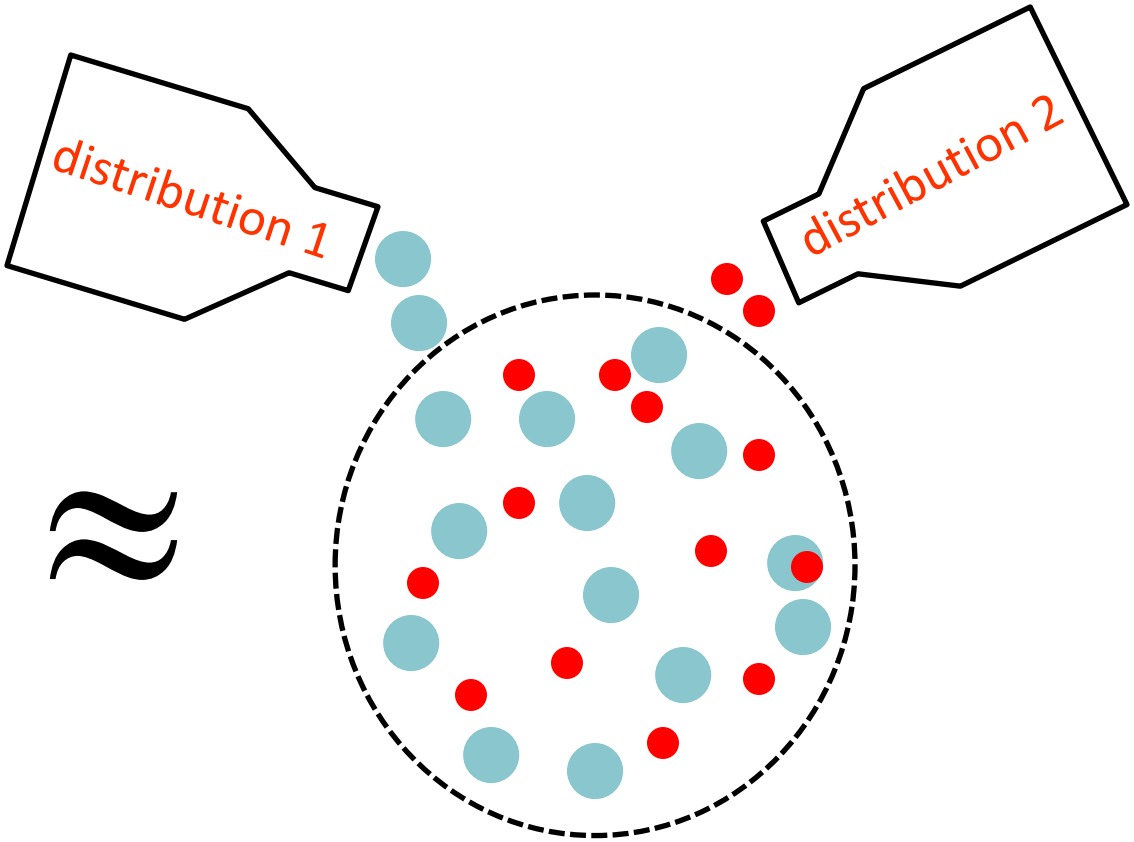
mixed population[a]	Population 1 mean diameter (nm)	Population 1 standard deviation (nm)	Population 2 mean diameter (nm)	Population 2 standard deviation (nm)
330/820 nm	276	6	838	9
500/820 nm	465	9	836	28
500/1000 nm	615	6	998	11

Approximating distributions in a cell

granulocyte

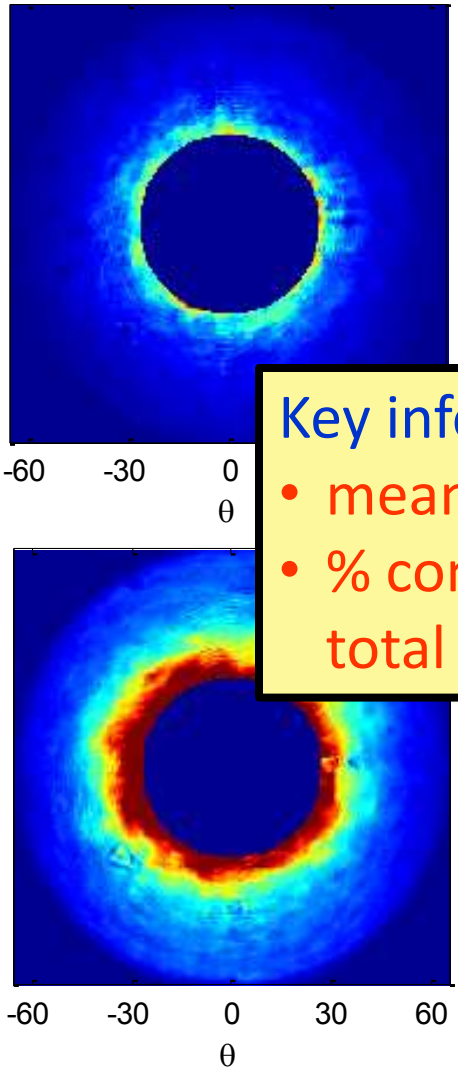


≈



P. Brederoo, J. van der Meulen, and A. M. Mommaas-Kienhuis, "Development of the granule population in neutrophil granulocytes from human bone marrow," Cell and Tissue Research 234, 469 – 496 (1983).

Lymphocytes vs. Granulocytes

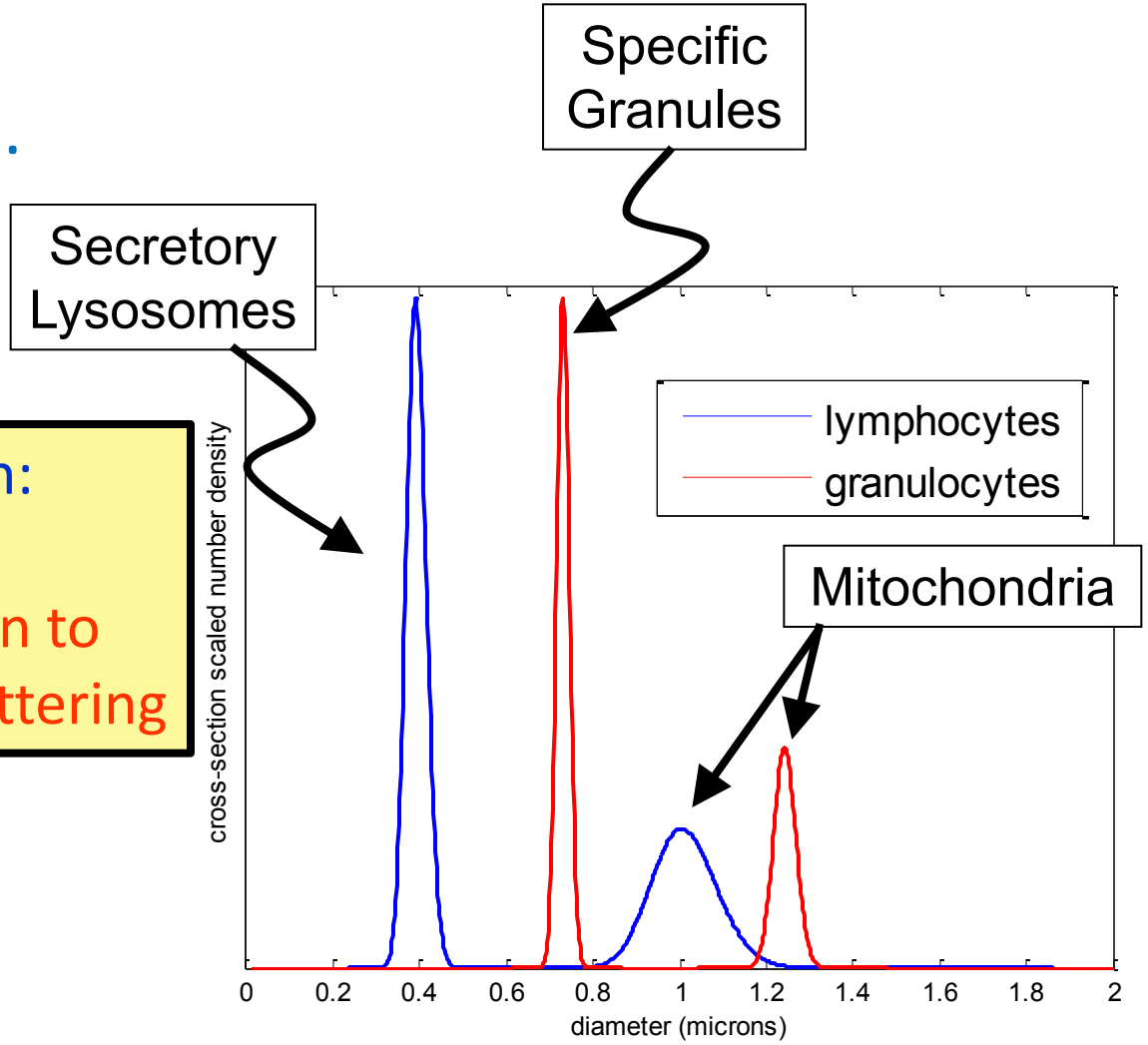


Lymph.

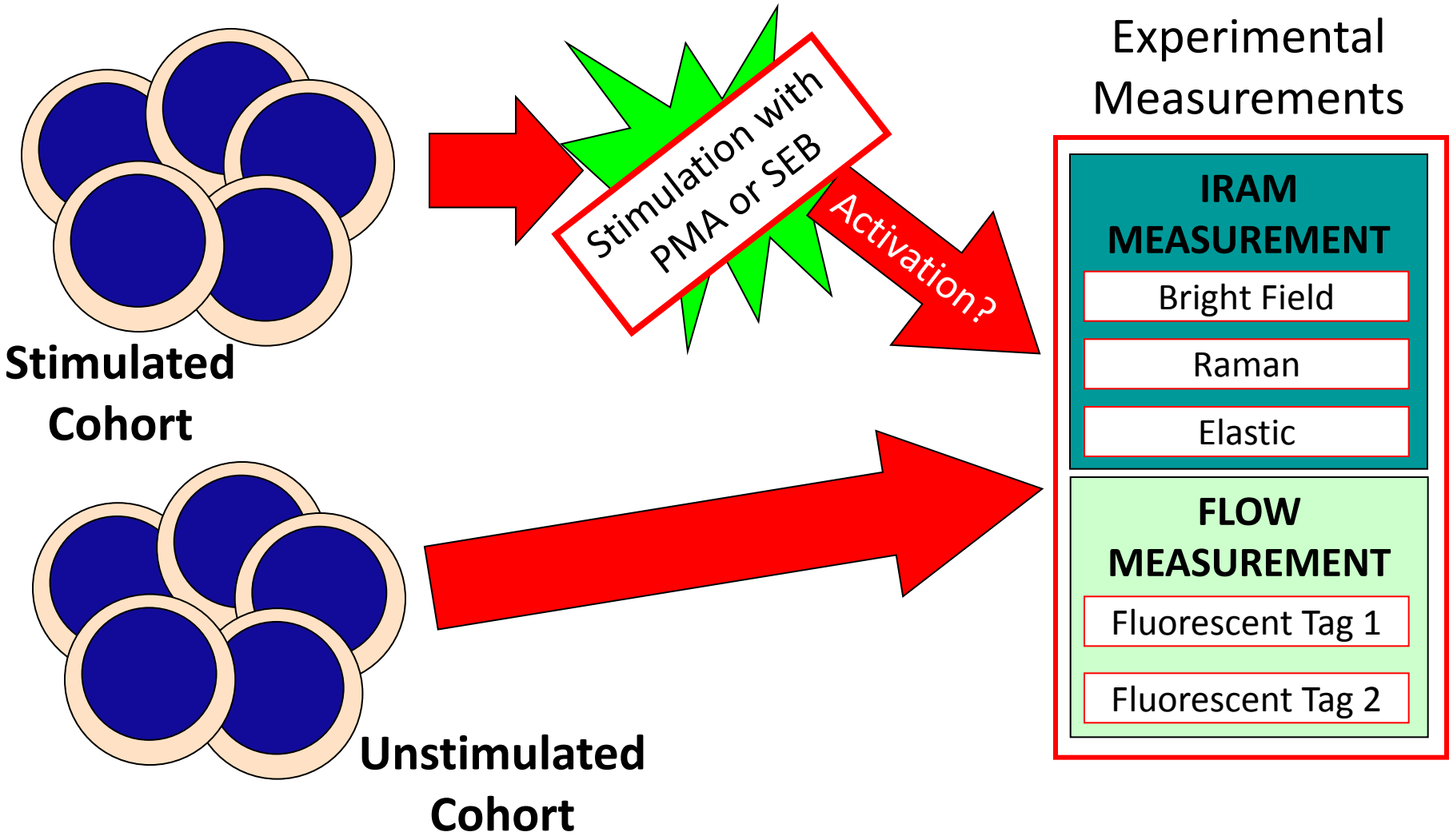
Gran.

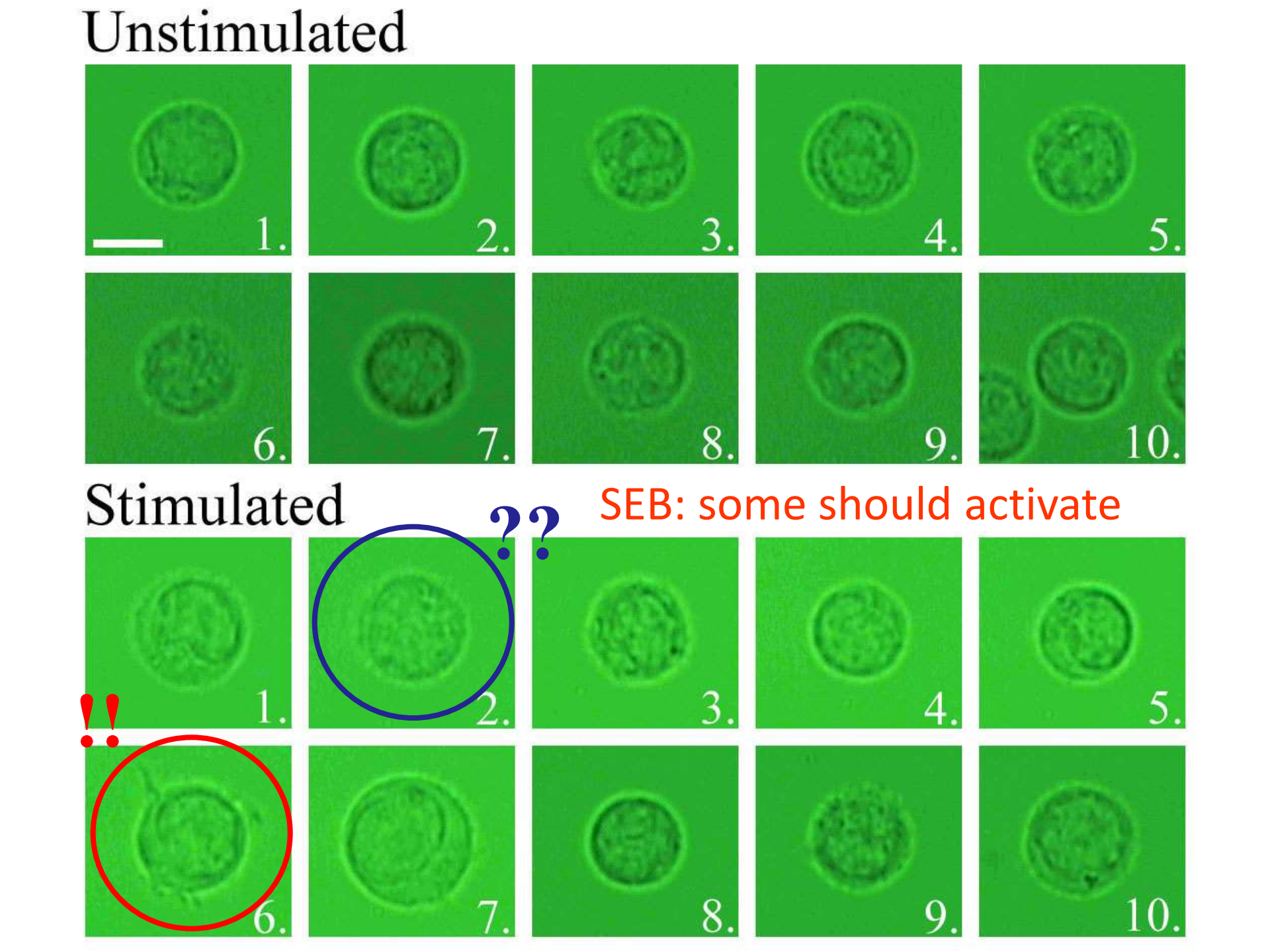
Key information:

- mean size
- % contribution to total light scattering

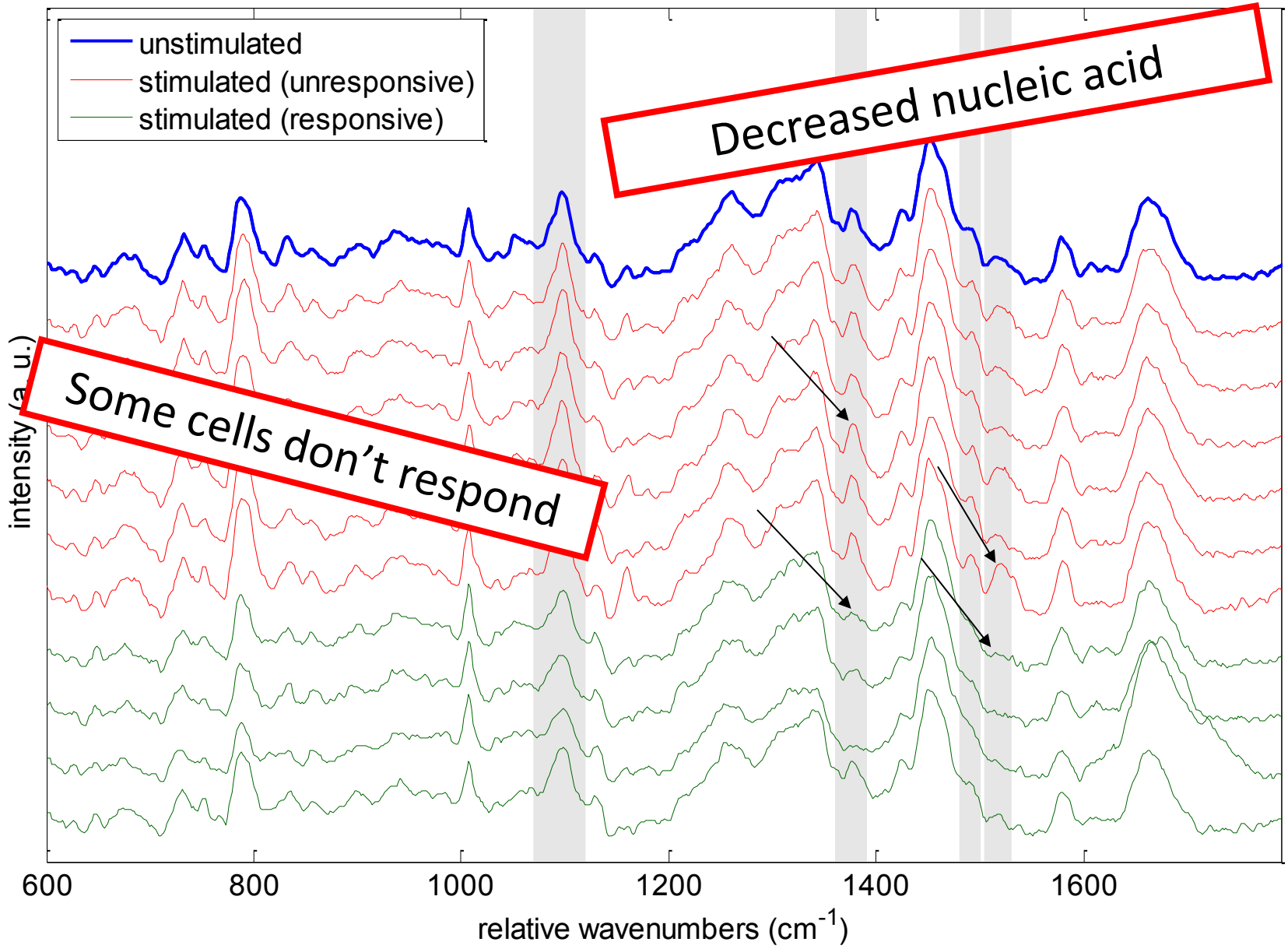


$CD8^+$ T-cell Activation

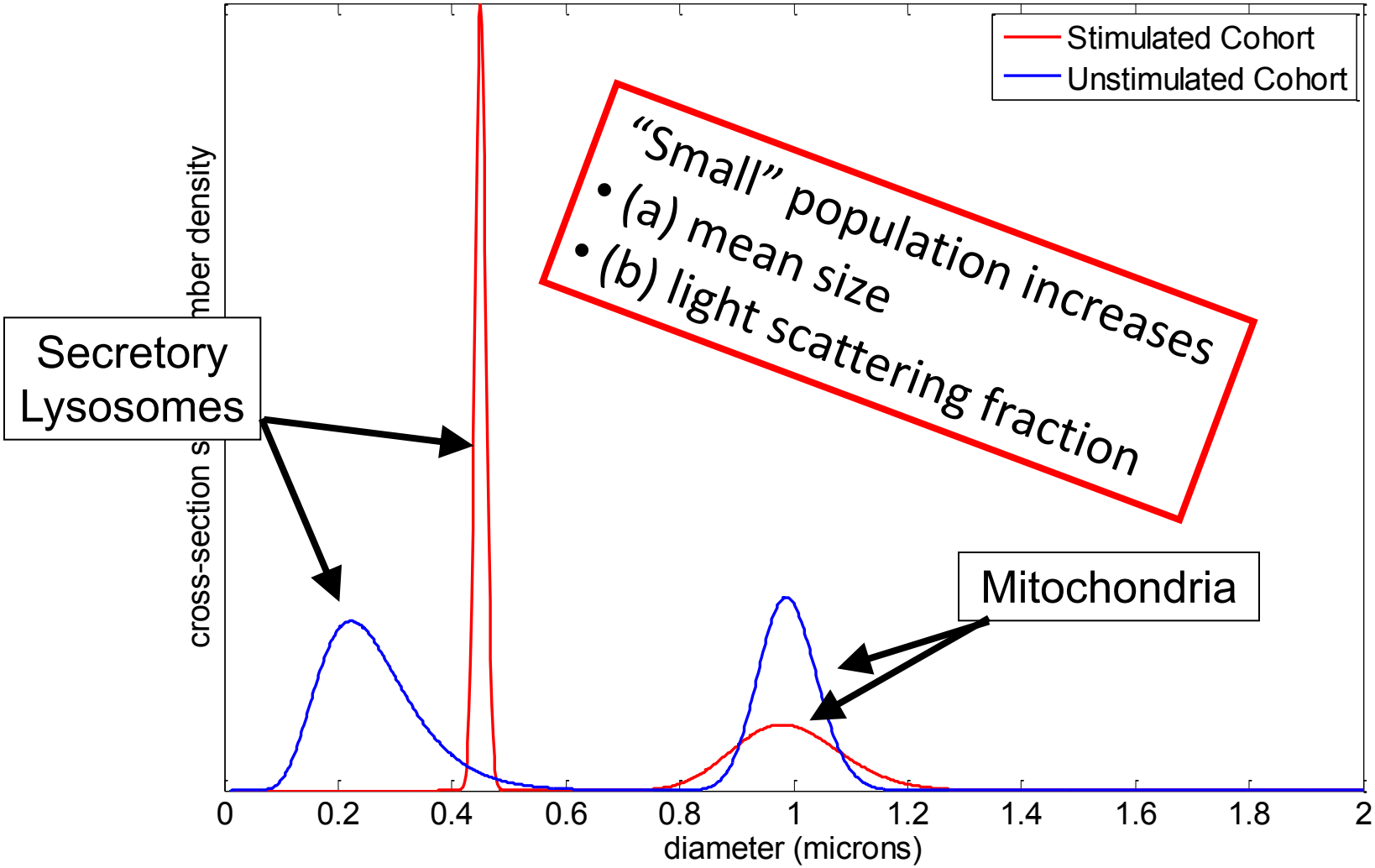



Unstimulated
1.
2.
3.
4.
5.
6.
7.
8.
9.
10.
Stimulated
??
SEB: some should activate
!!
1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

T-Cell Activation (Raman)

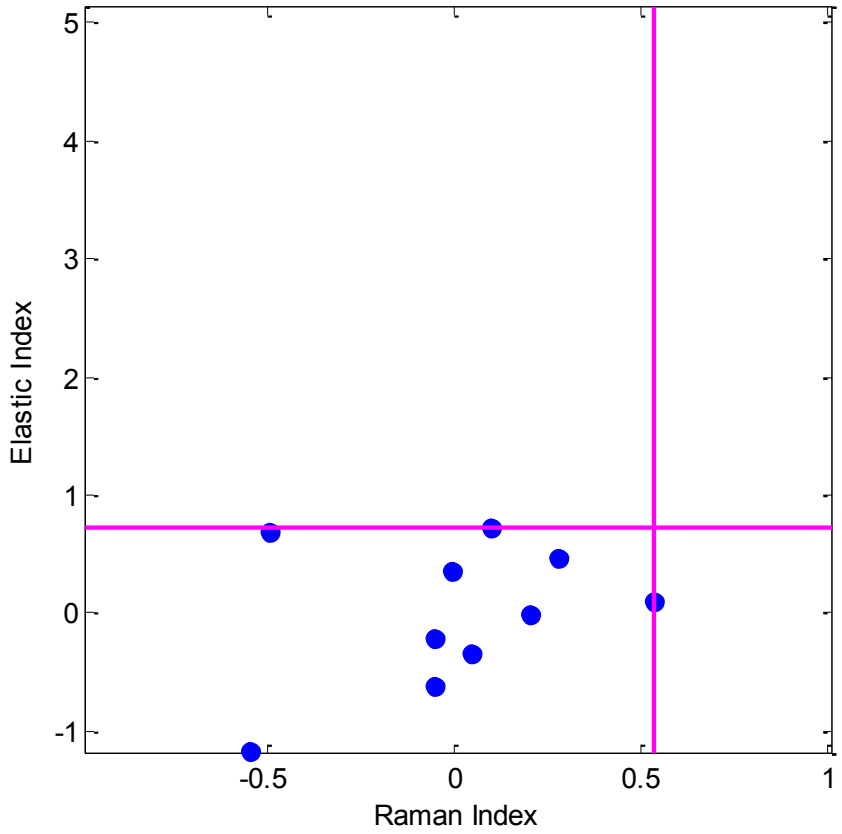


T-Cell Activation (Elastic)

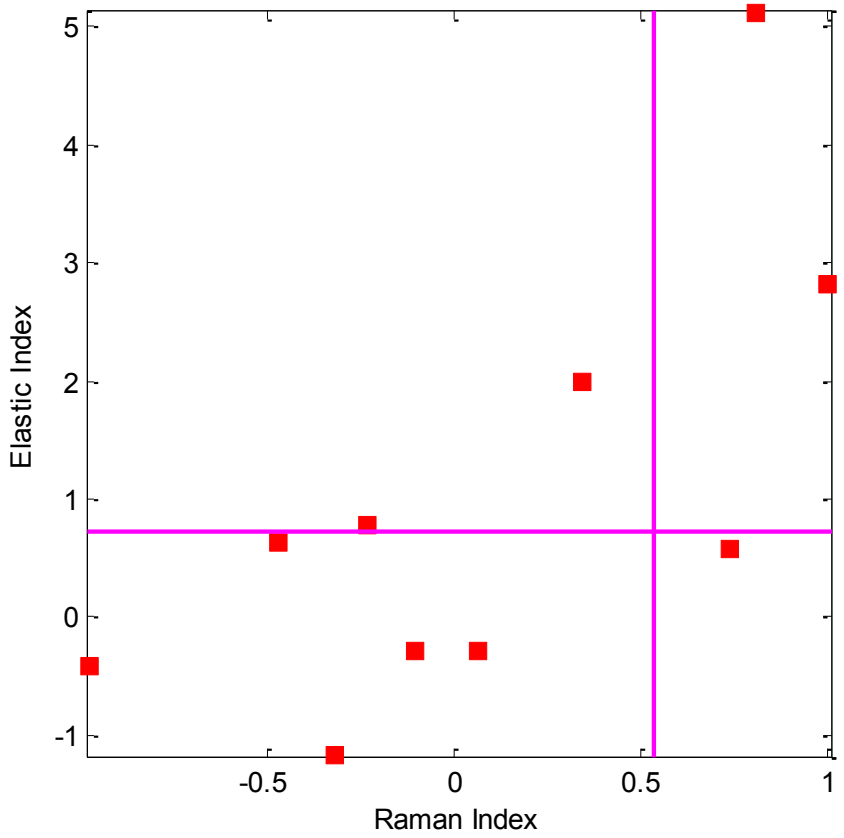


SEB T-Cell Activation (IRAM Index)

Unstimulated

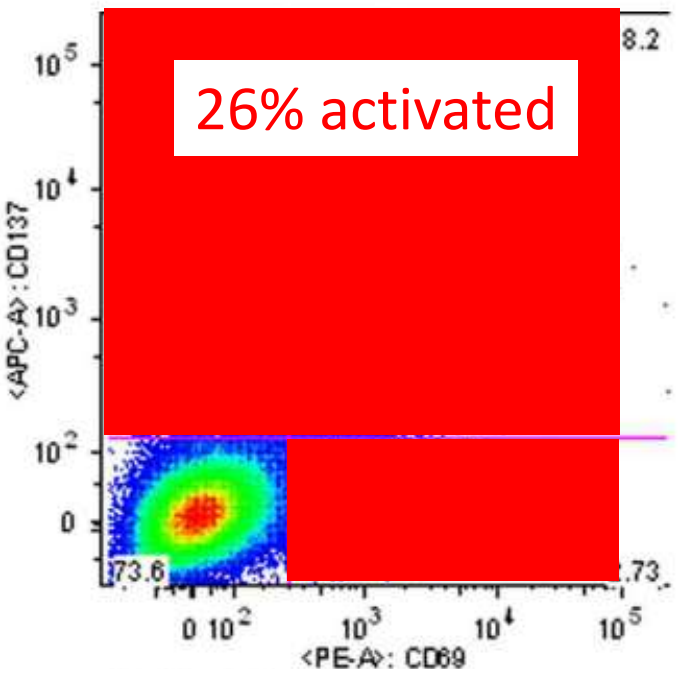


Stimulated

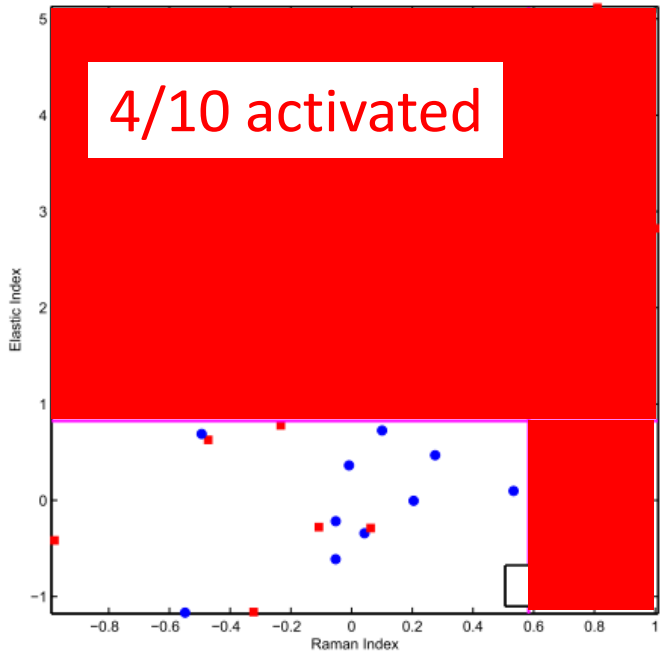


Flow cytometry comparison…

Flow cytometry

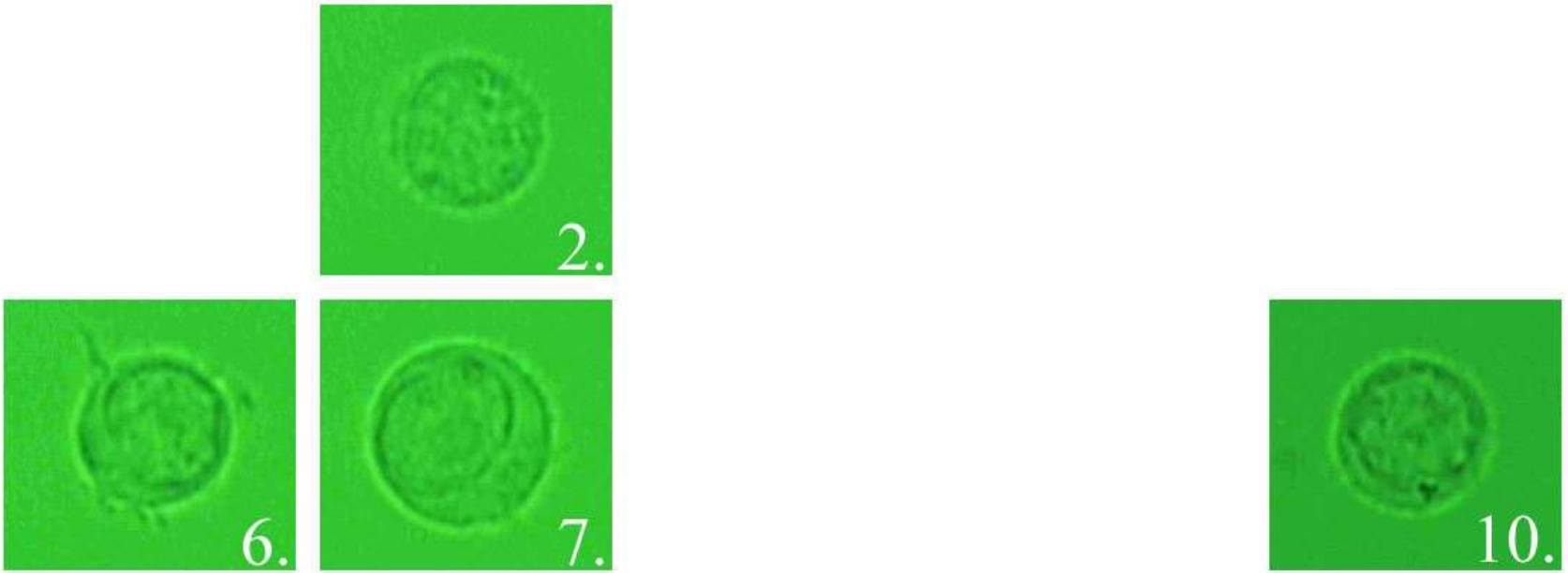


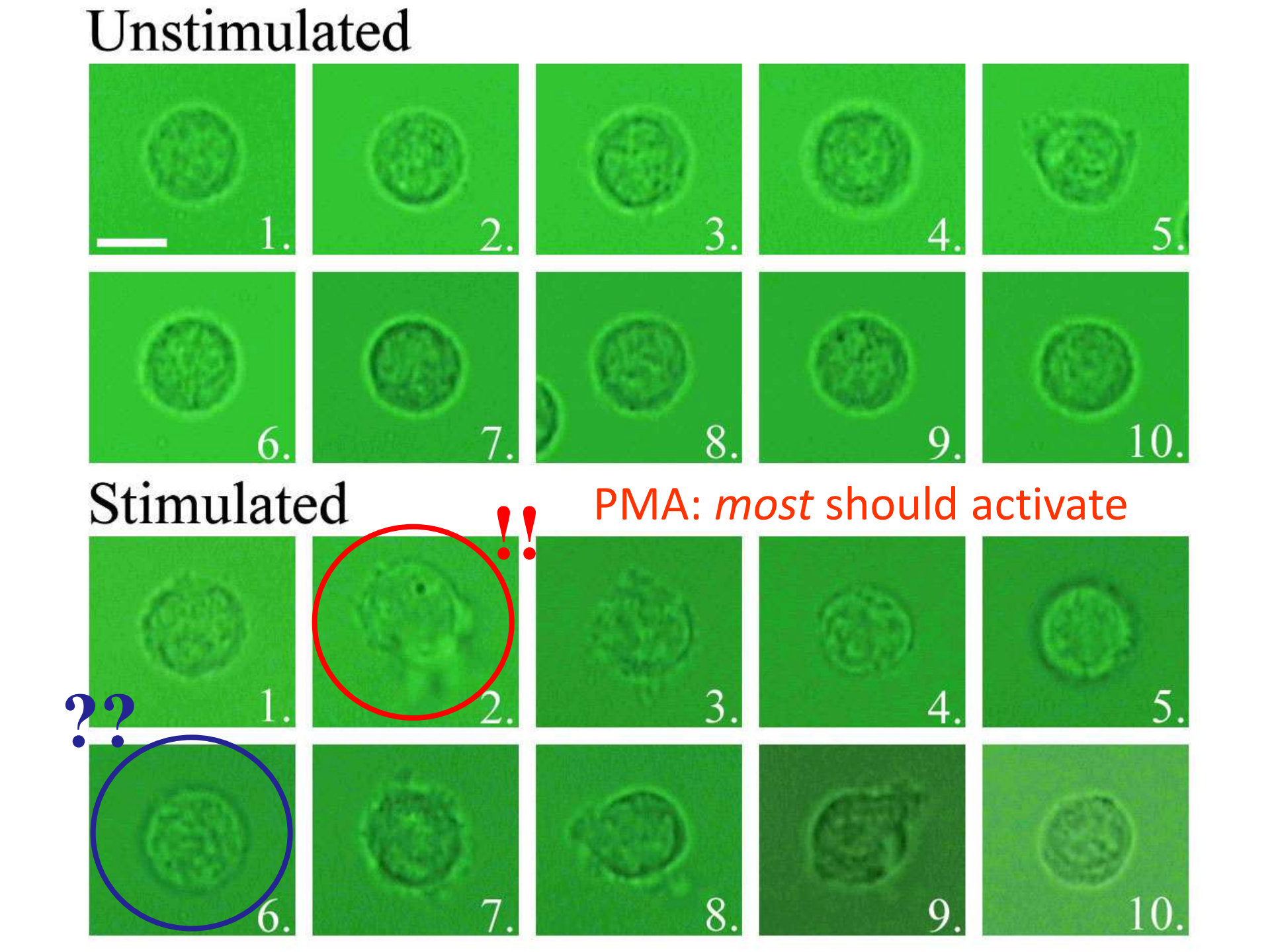
IRAM analysis



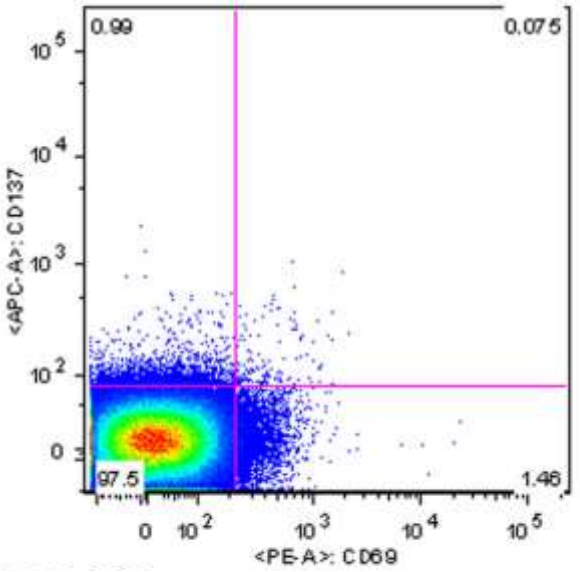
Guess the activated cells

Stimulated

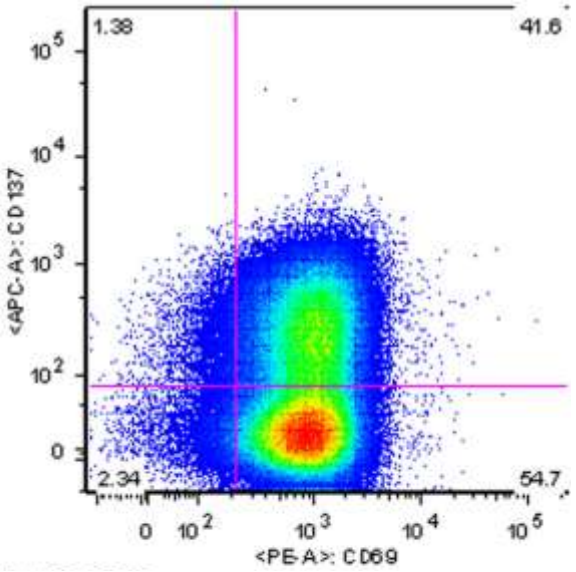



Unstimulated
1.
2.
3.
4.
5.
6.
7.
8.
9.
10.
Stimulated
PMA: *most* should activate
!!
??
1.
2.
3.
4.
5.
6.
7.
8.
9.
10.

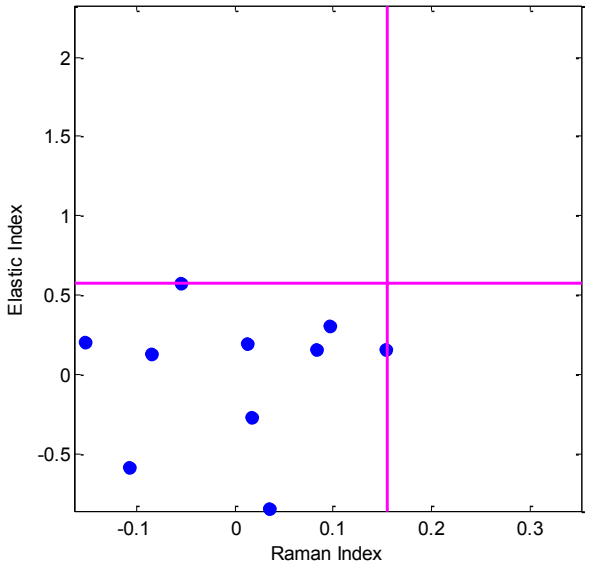
Unstimulated

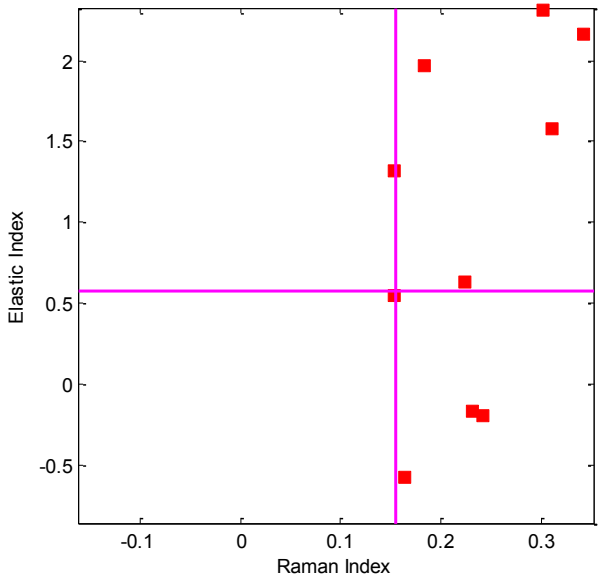


Stimulated



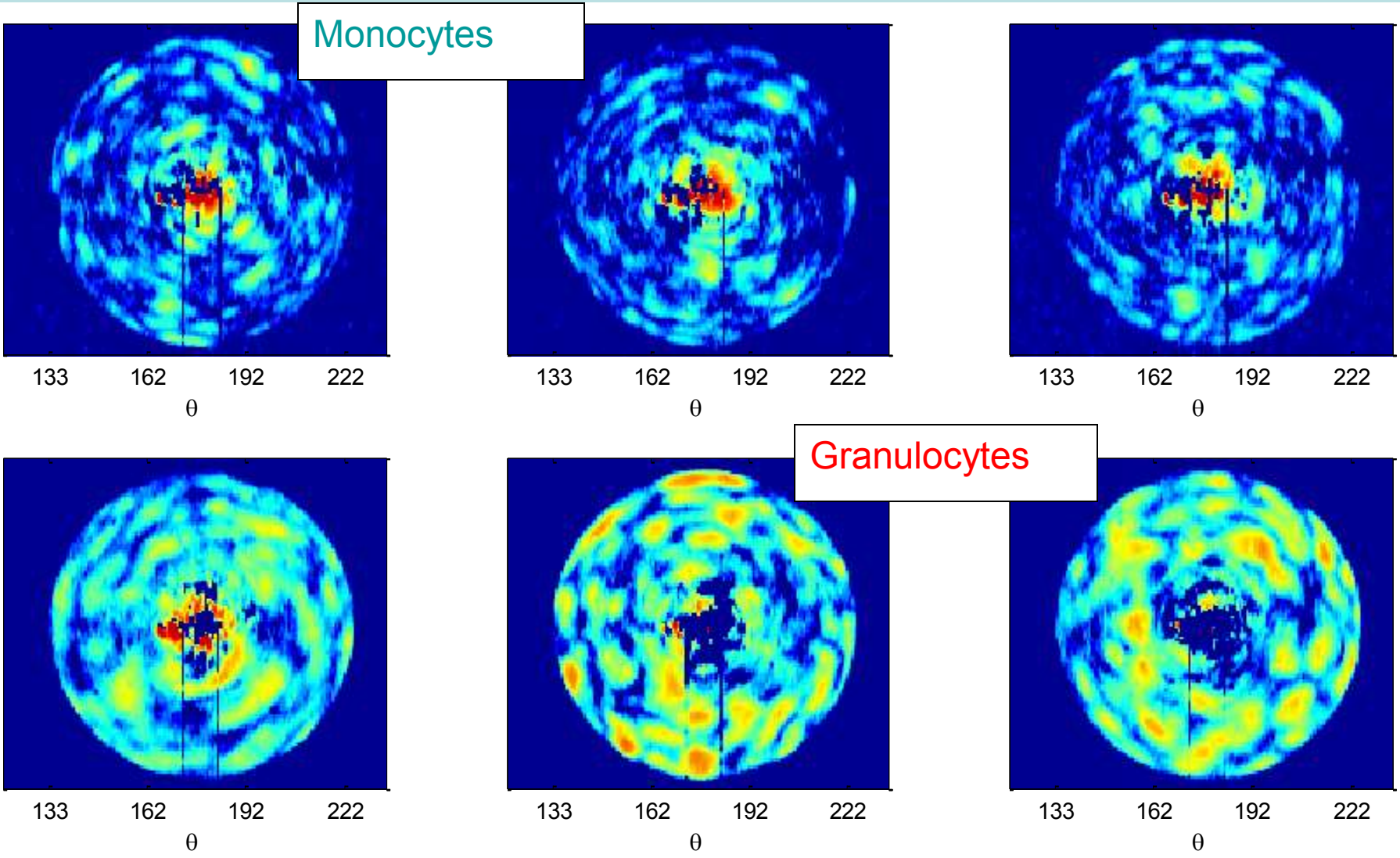
Flow cytometry (gold standard)





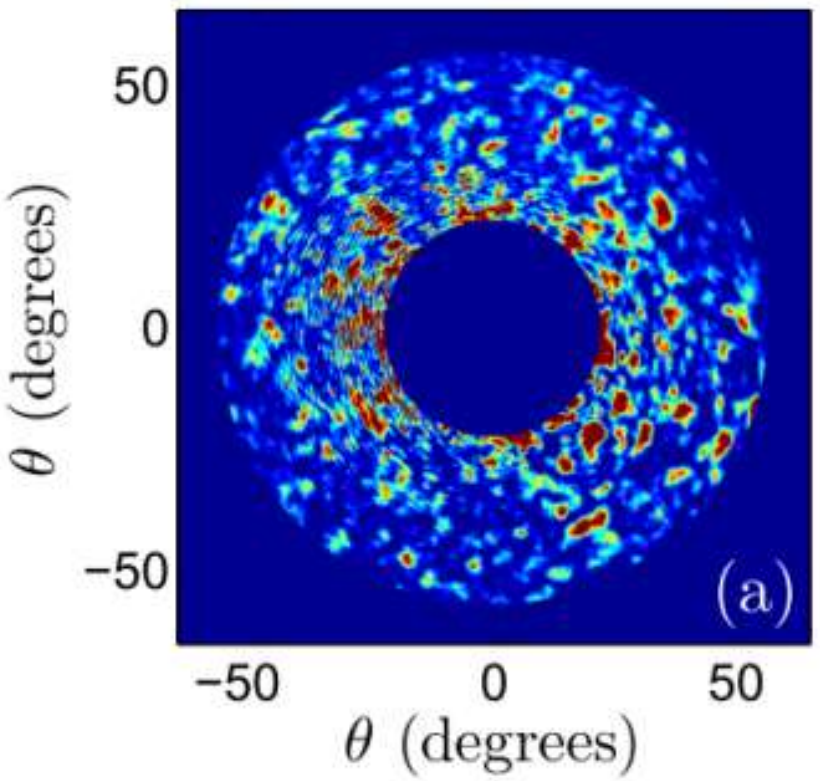
Smith et al., J. Biomed. Opt., 15(3), 036021 (June 2010).

Speckle from single immune cells

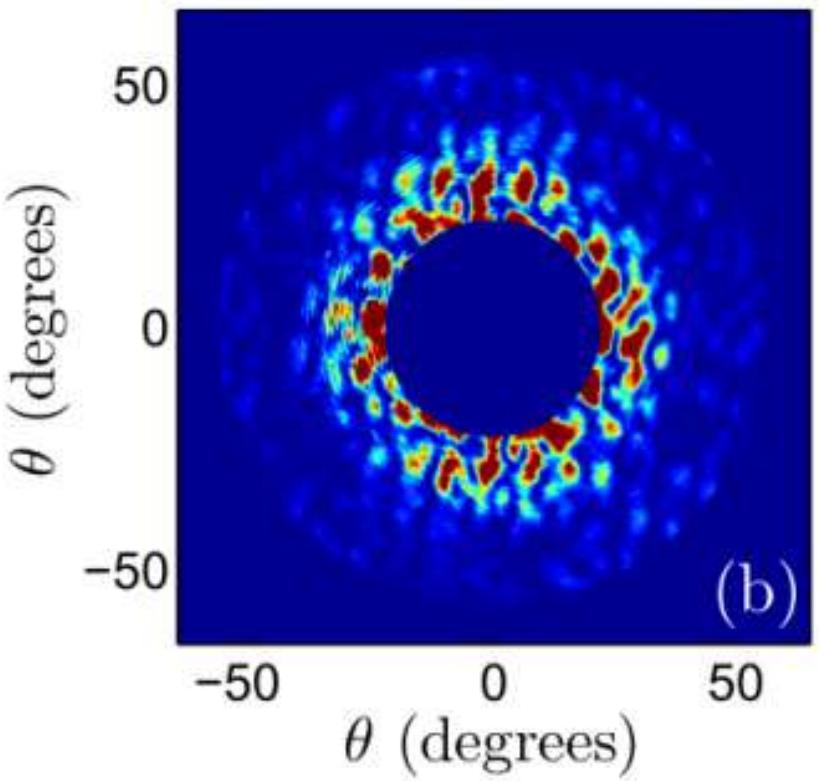


Current challenges: speckle

cancer cell

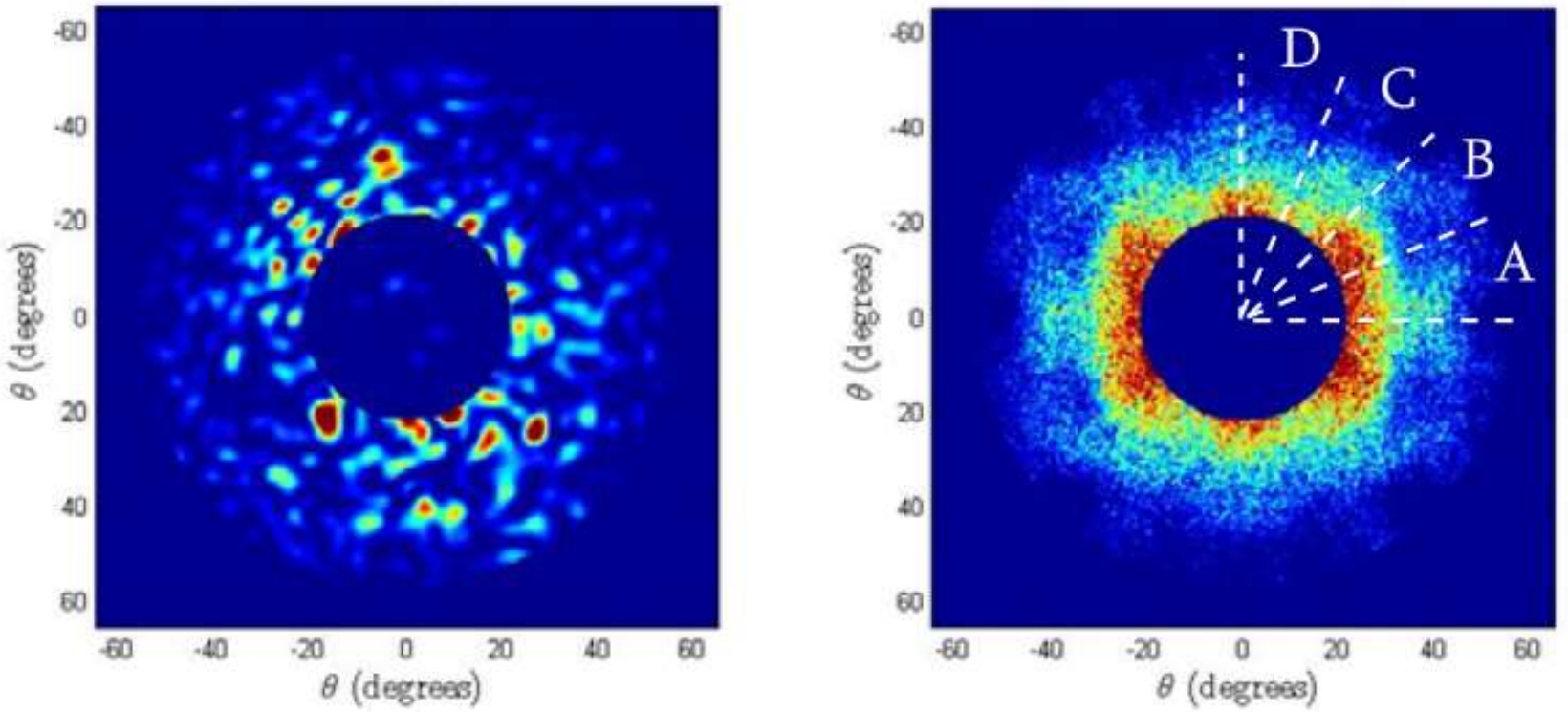


static beads

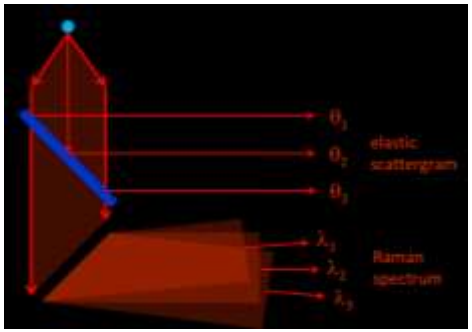


Speckle reduction

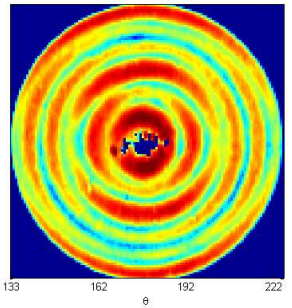
raw data → holographic processing

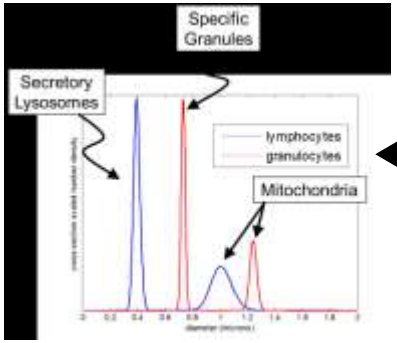


Summary: single-cell organelle sizing

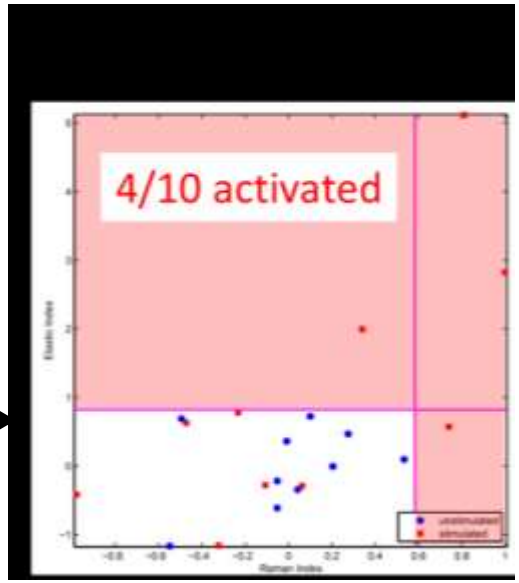


multimodal with
Raman spectroscopy





fit *angular scatter pattern*
to 2-size distribution



detect differences
or changes in
cellular response

James Goodwin

Welcome to the near-infrared

Measuring mouse bone quality

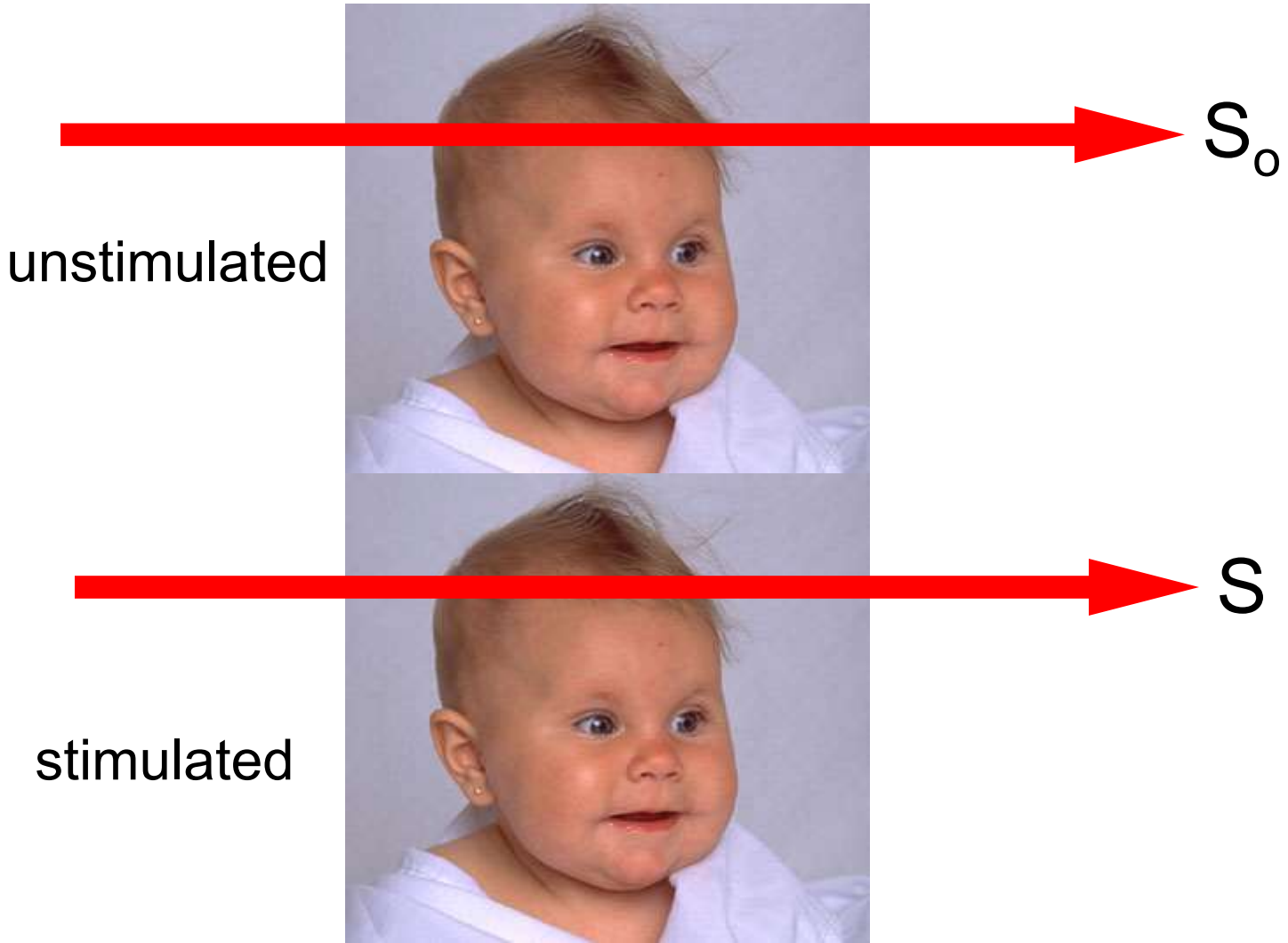
Sensing organelle size distributions

Sensing blood activity in the brain

Rolf Saager


?
vision
hearing
speech
motor/sensory

Infant cerebral studies



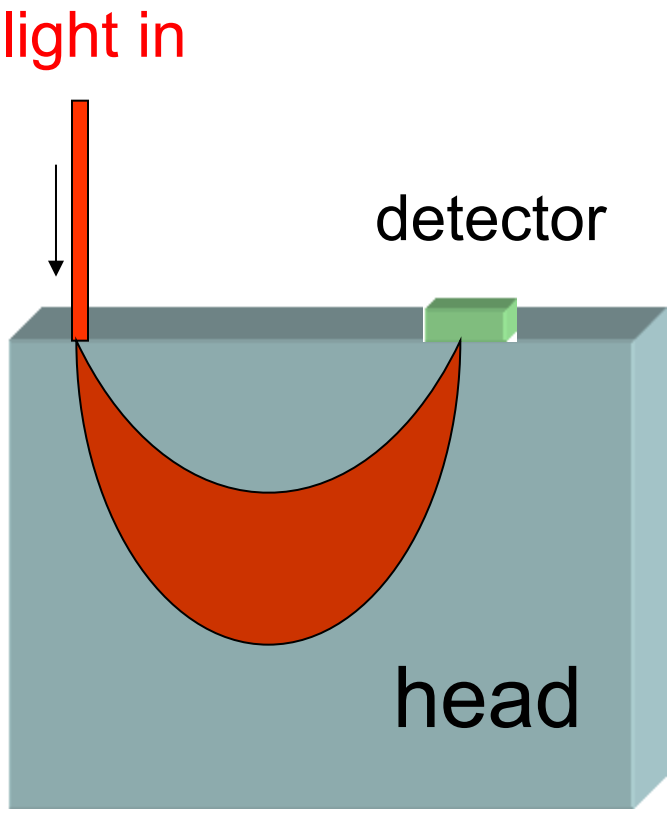
Diffuse reflectance geometry

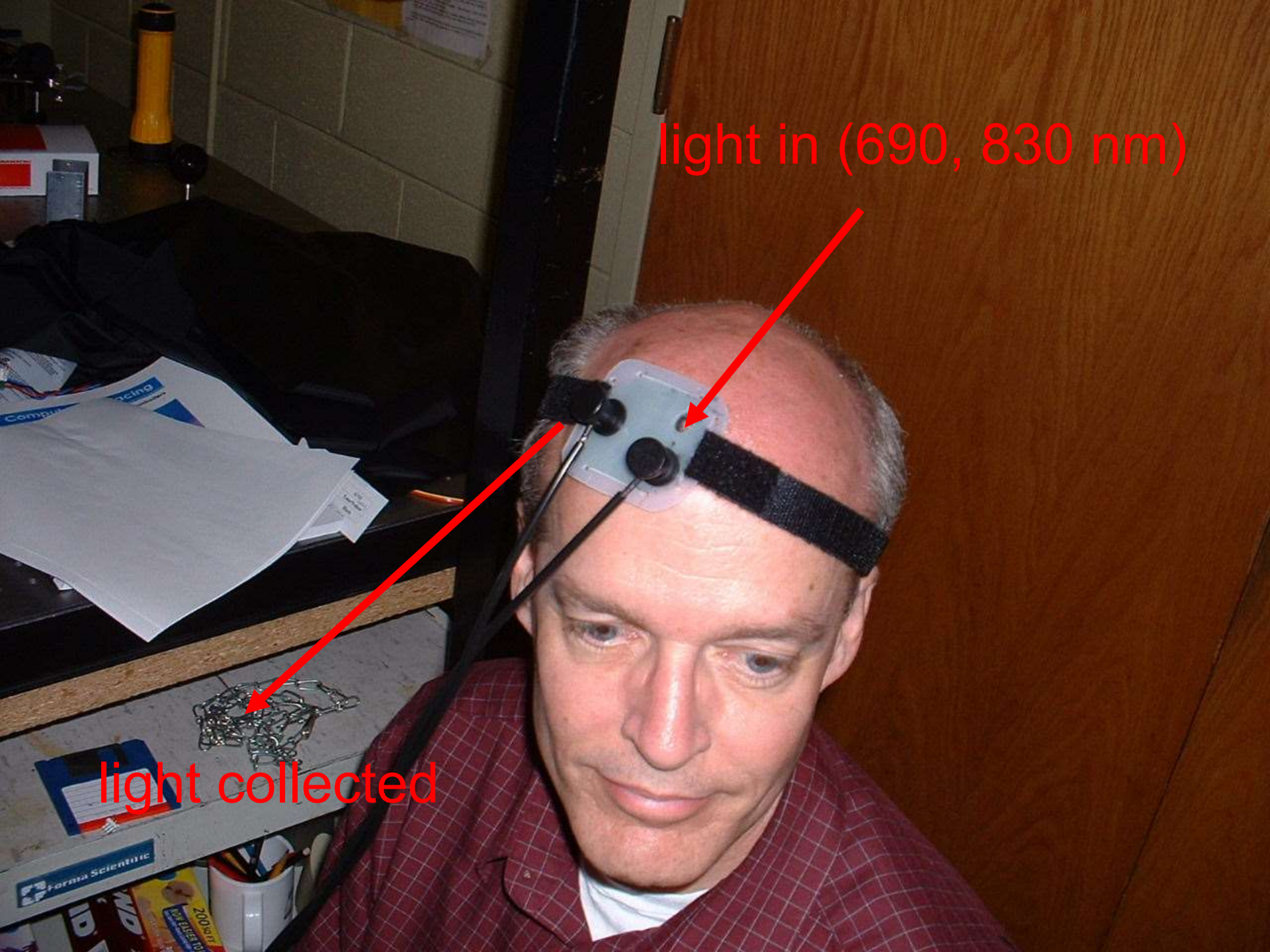
$S_0, S_1, S_2, \ldots S(t)$

incident


12859
Farmland
12859

The basic geometry

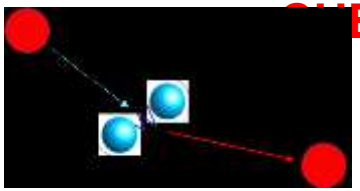



light in (690, 830 nm)
light collected

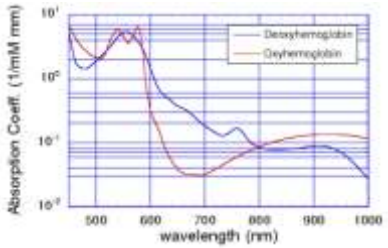
Summary of NIR interactions

biological sample

inelastic scattering:
CHEMISTRY

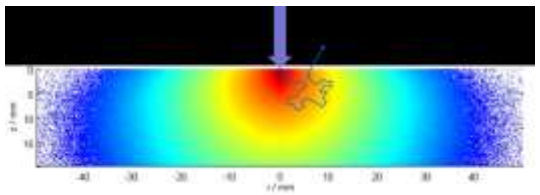


angle-dependent elastic scattering:
SIZE



wavelength-dependent absorption:
BLOOD

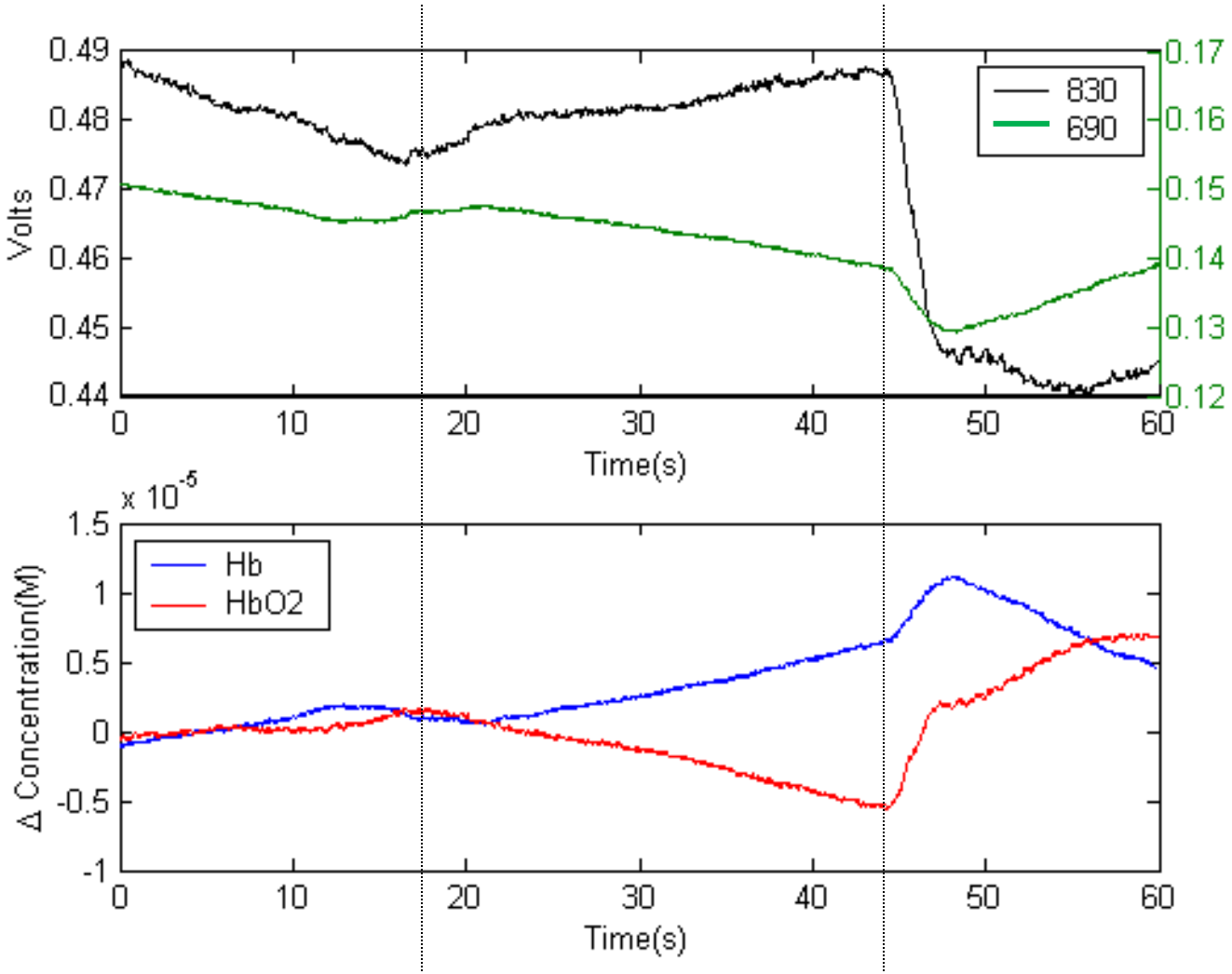
diffusive propagation:
DEPTH



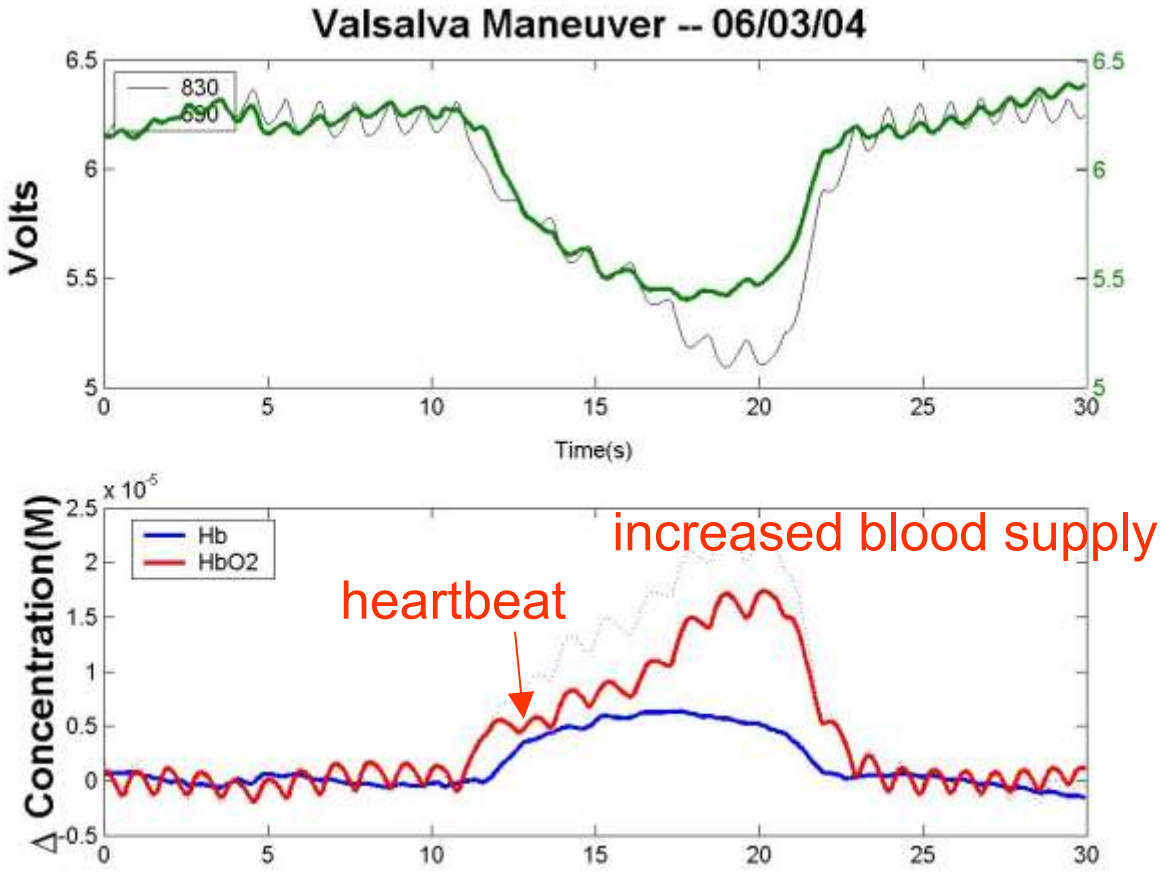
Hemoglobin sanity check: Pressure cuff data

raw data

Hb changes



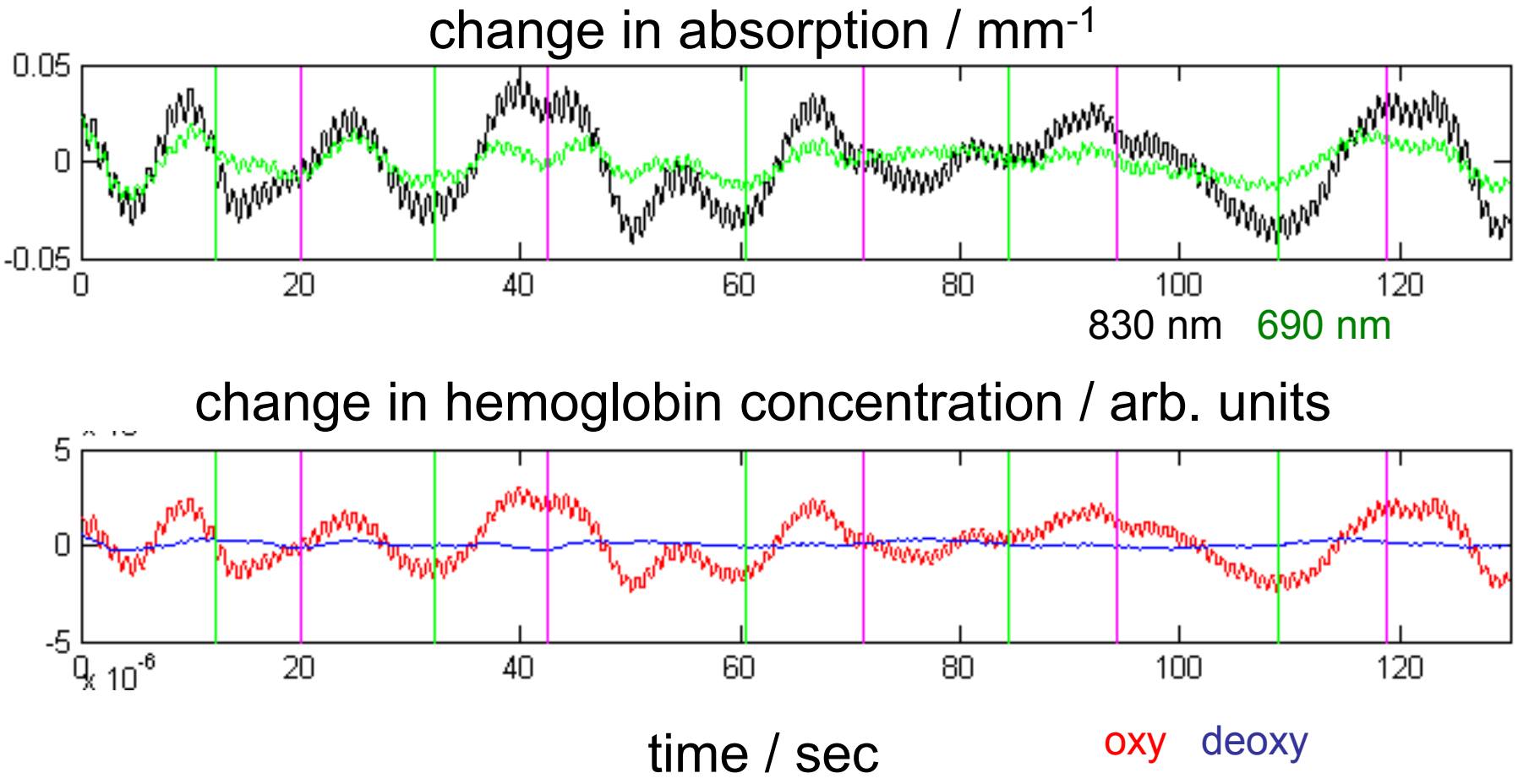
Noninvasive monitoring of hemodynamics



optical power measurements

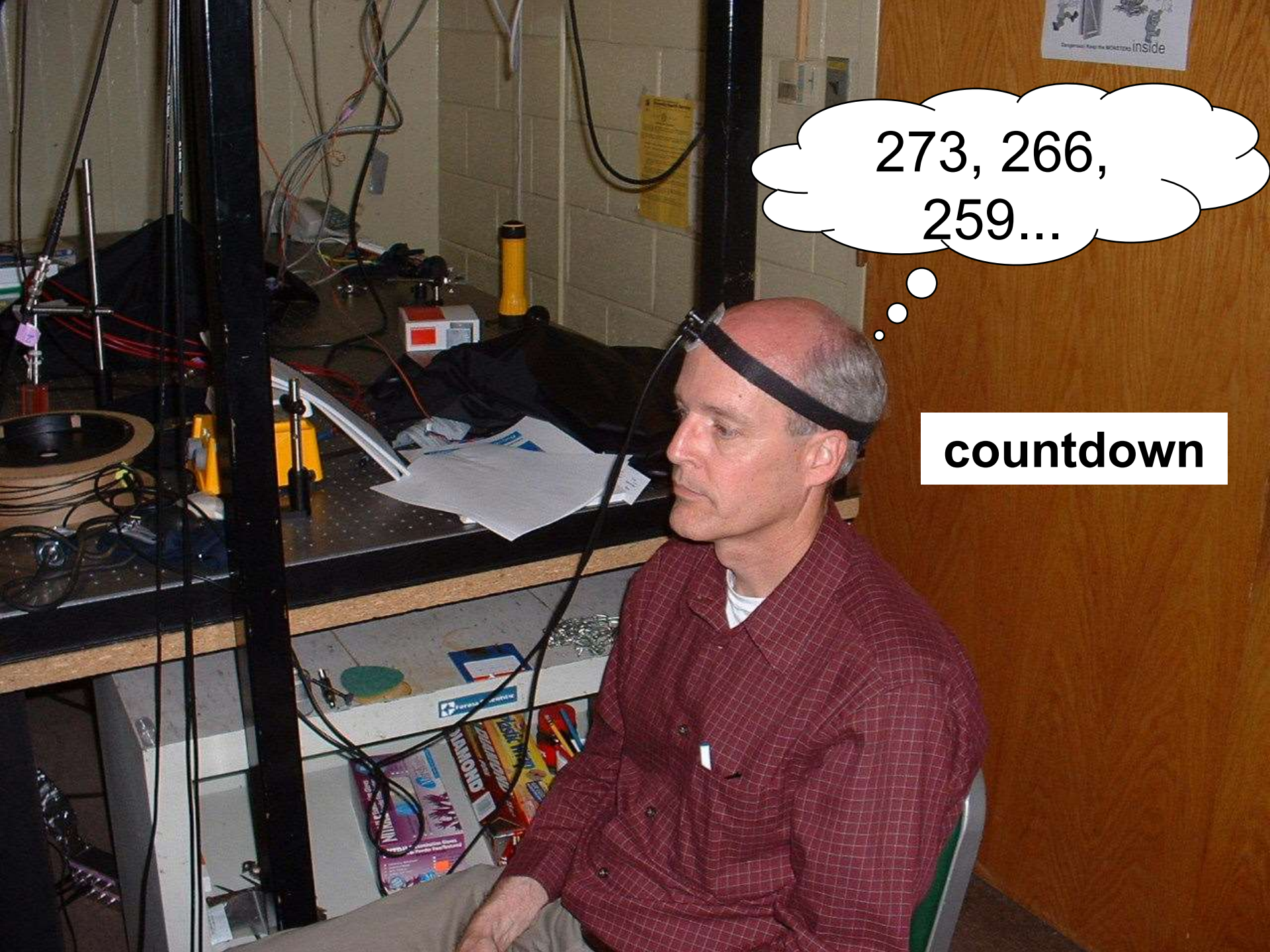
oxy and deoxy hemoglobin concentration changes

Typical measurements

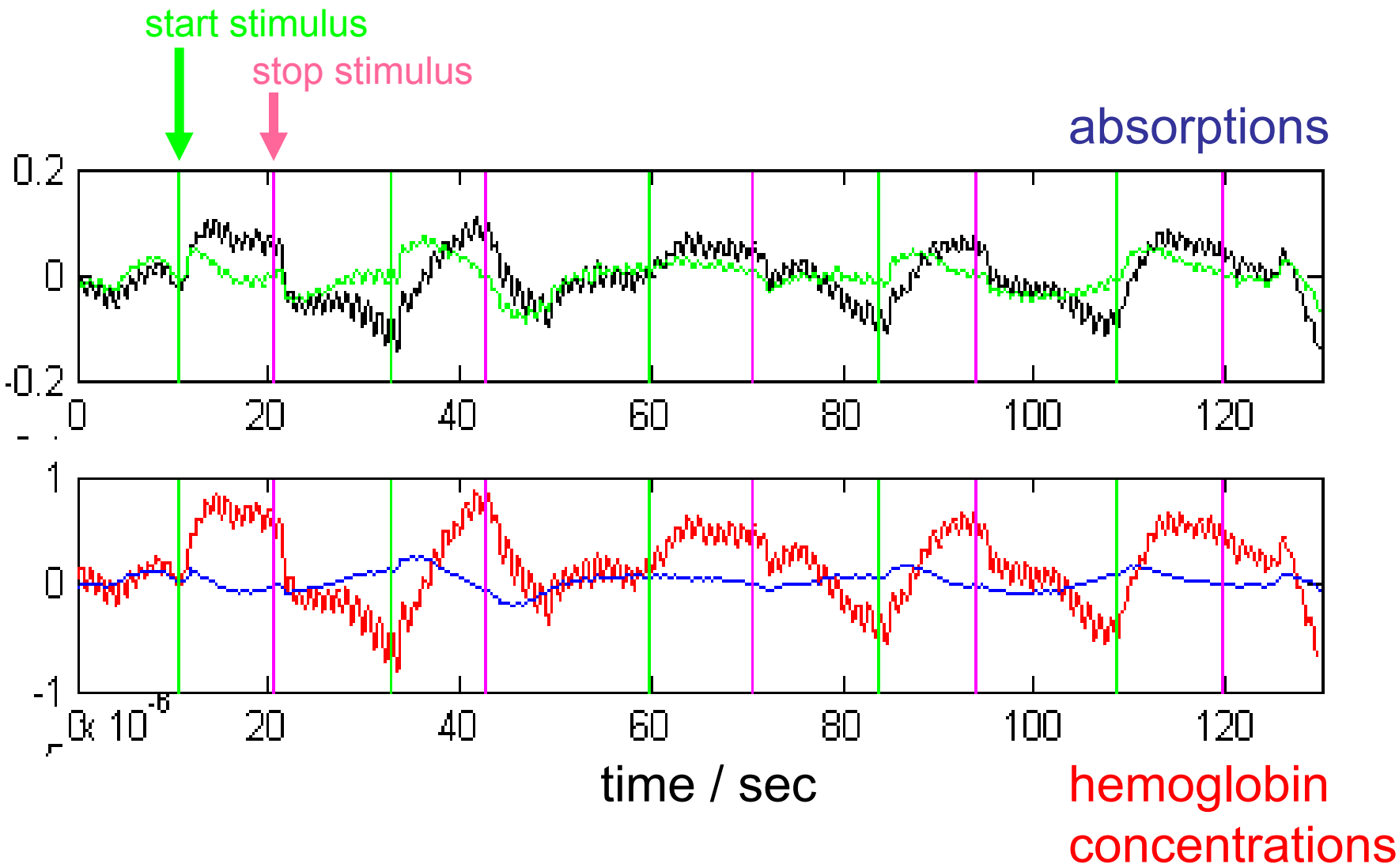


Why especially for infants?

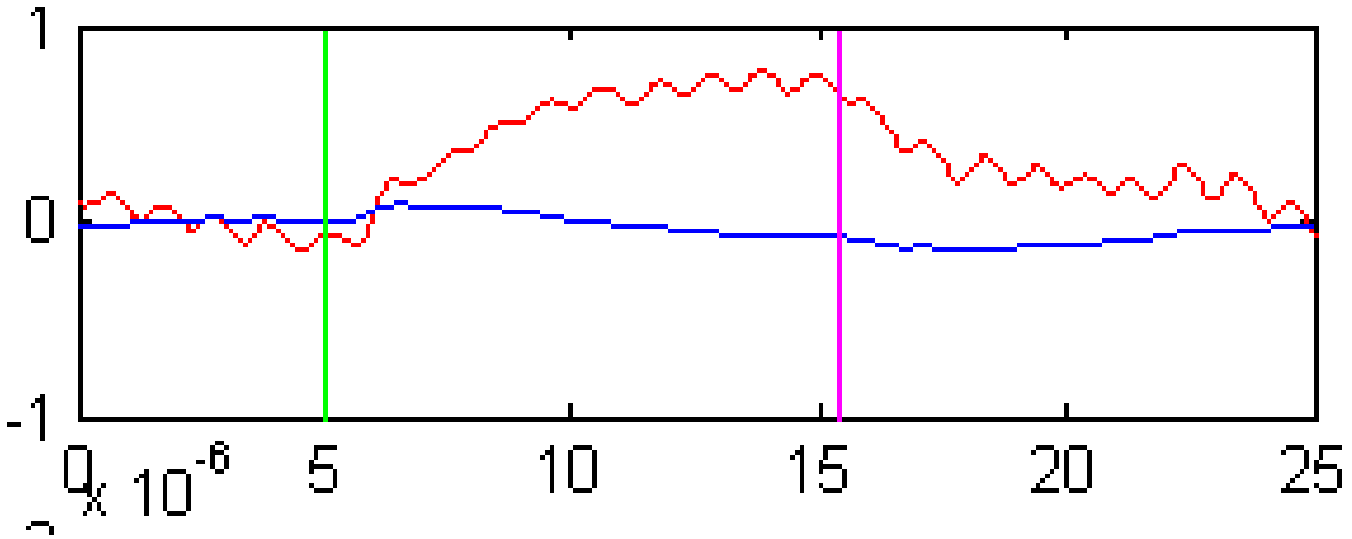
- small scale
- thin-skulled
- twitchy
- uncommunicative
- lots of developmental questions to ask


273, 266,
259...
countdown

Single subject countdown timecourse



Single subject, block average

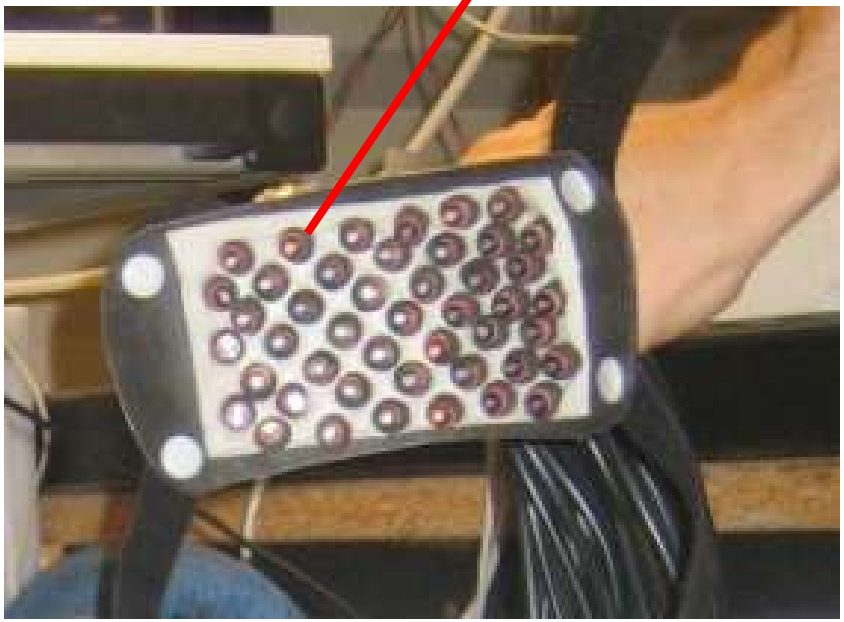


oxyhemoglobin

deoxyhemoglobin

Typical headpiece for adults

optical fiber bundles



First Nearest Neighbors 1.3 cm

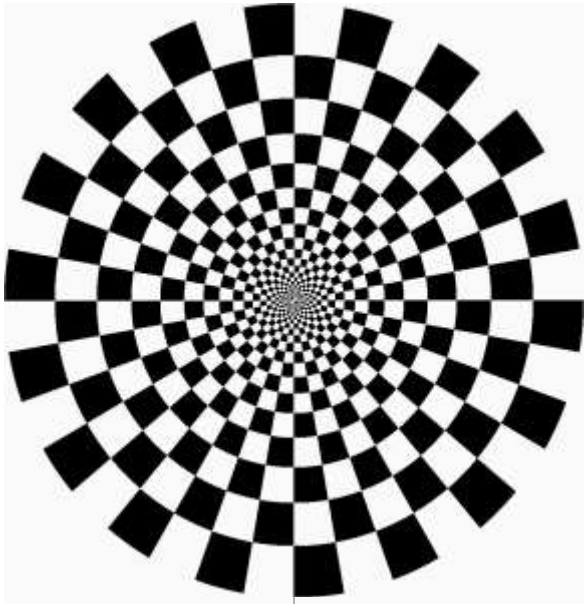
Second Nearest Neighbors 3 cm

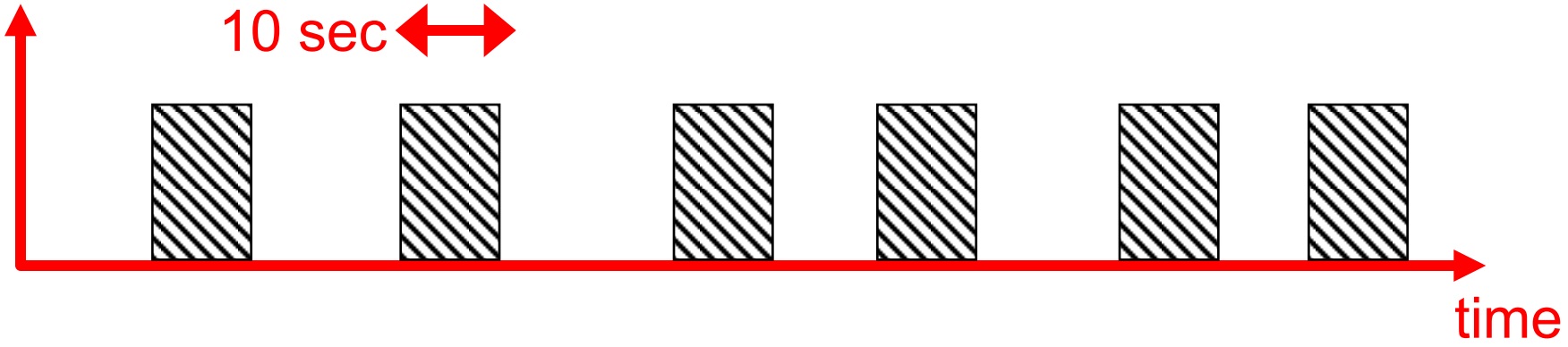
Third Nearest Neighbors 3.9 cm

Visual Stimulation Protocol

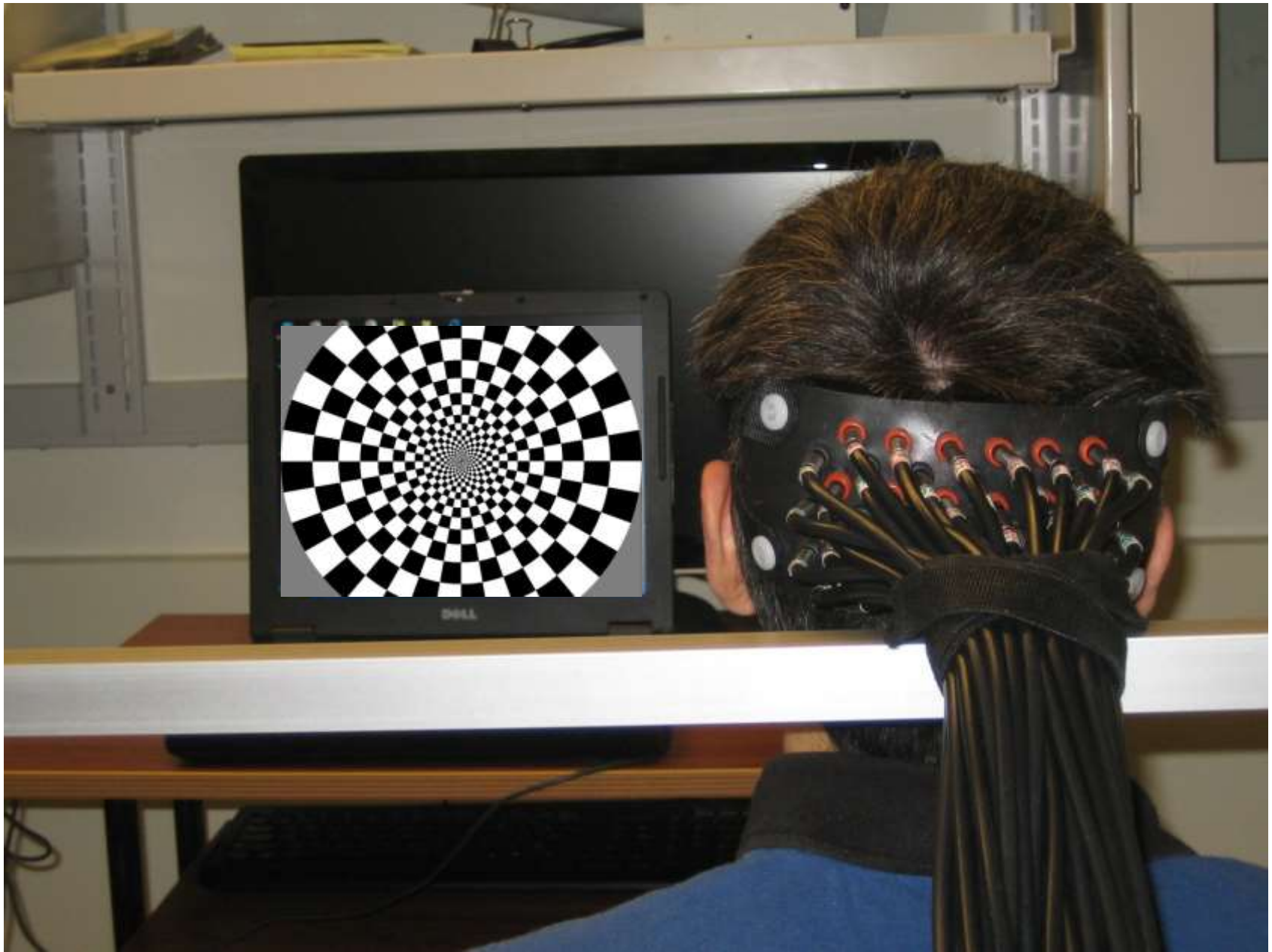
- 6 stimulus periods of pattern reversal at 10 Hz

  based upon code by Brian White and Joseph Culver, Washington University (St. Louis)

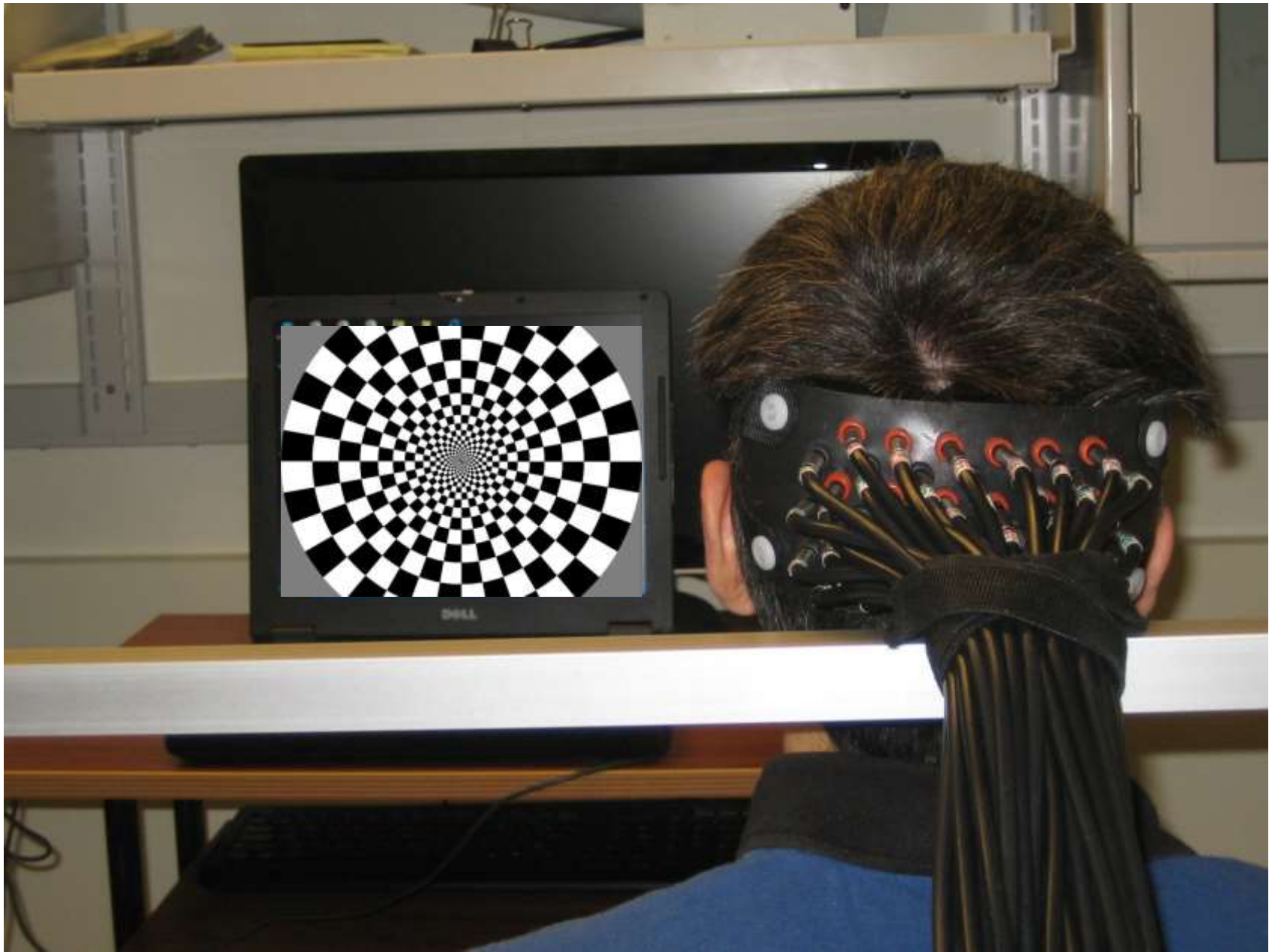




Example of a Stimulus

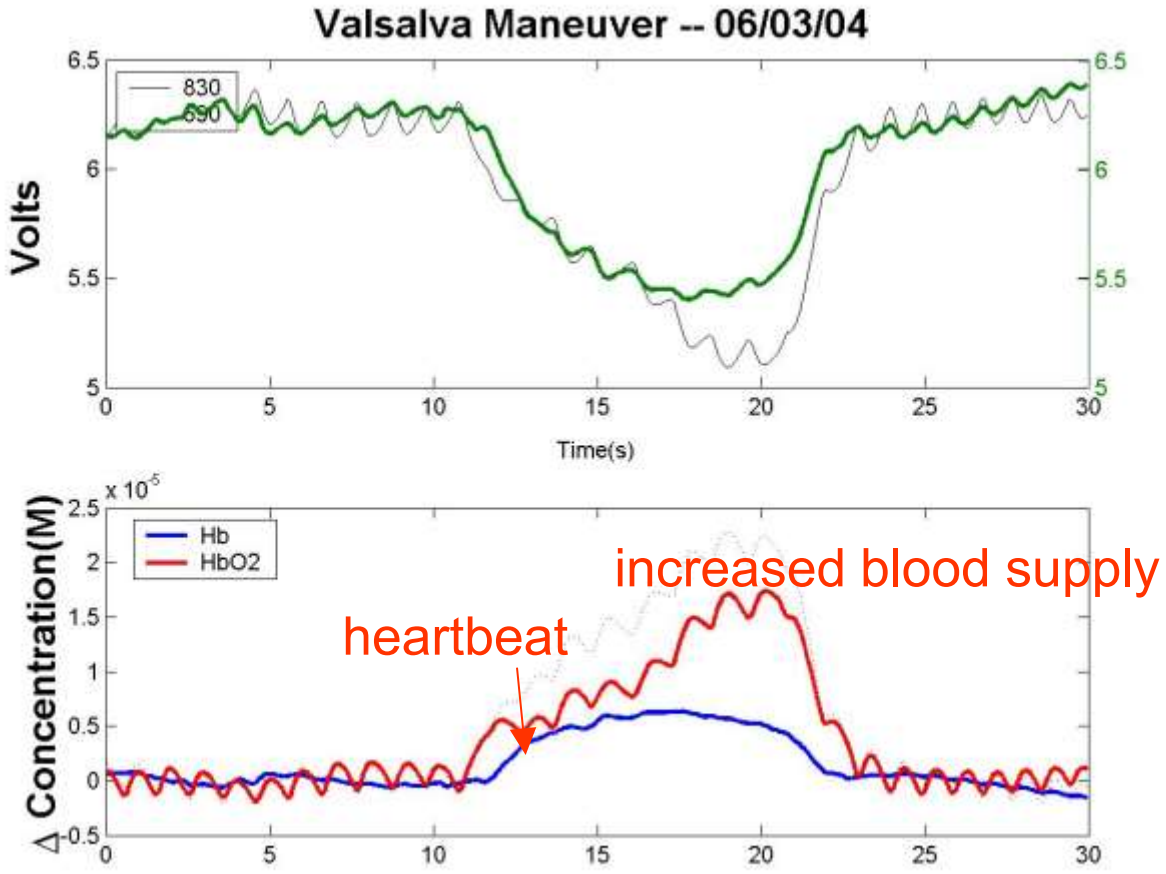


Example of a Stimulus



Hemodynamic response to stimulus

Problem: not all blood is in the brain!

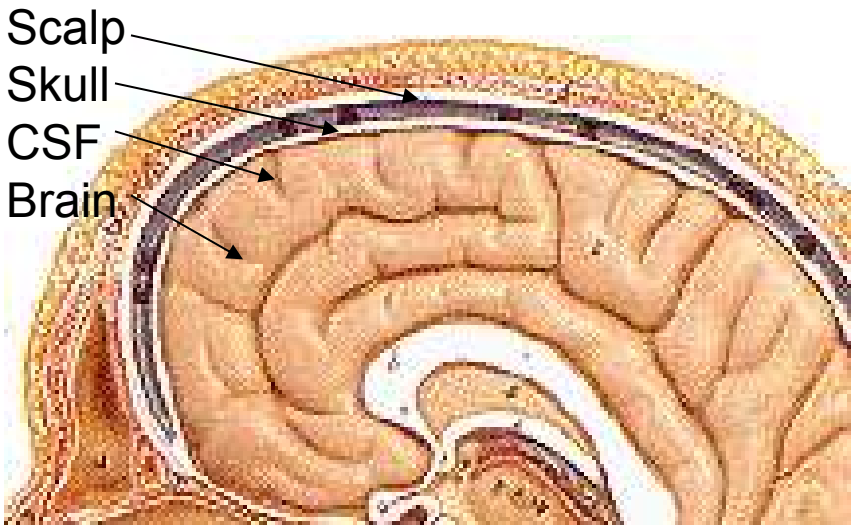


optical power measurements

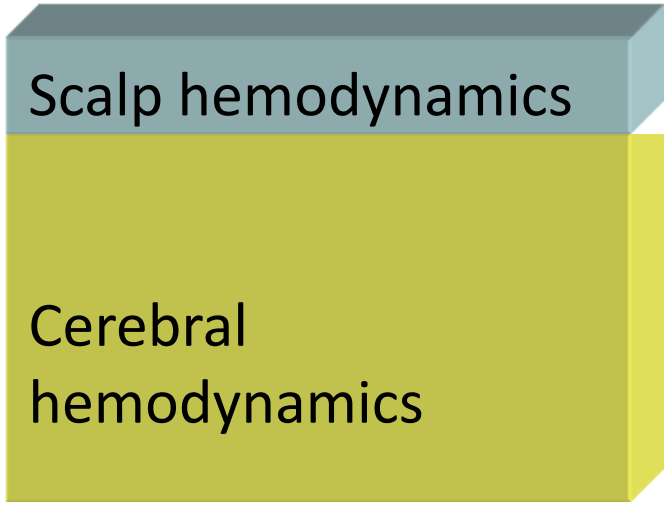
oxy and deoxy hemoglobin concentration changes

The optical geometry

A real head

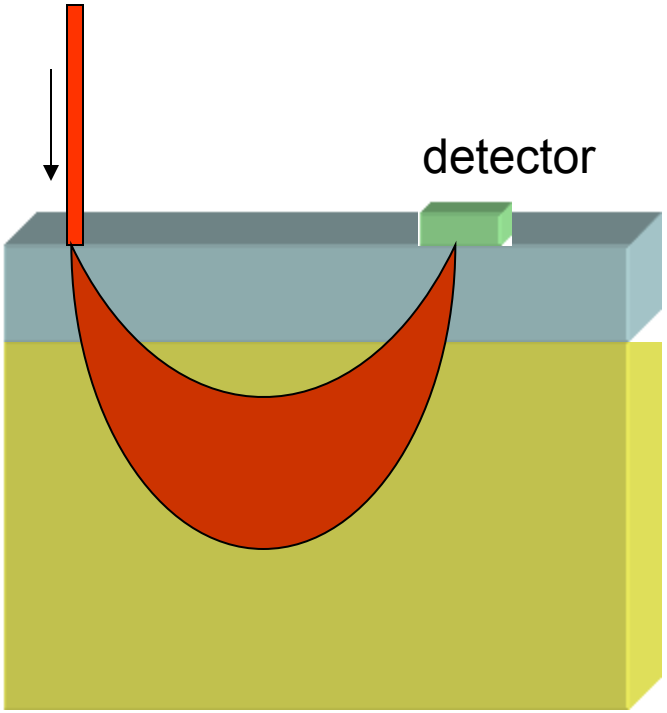


A physicist's head



Problem: not all blood is in the brain!

Saager et al., NeuroImage 55(4), 1679--1685 (April 2011)



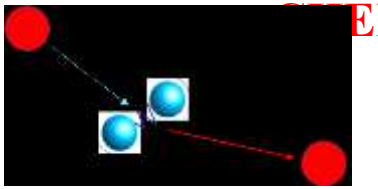
fNIRS measurement sensitive to both cortical and superficial hemodynamics

Want to isolate brain-specific trends

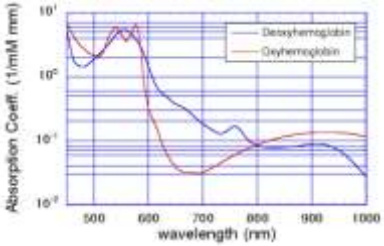
Summary of NIR interactions

biological sample

inelastic scattering:
CHEMISTRY

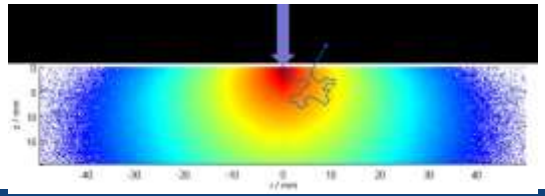


angle-dependent elastic scattering:
SIZE

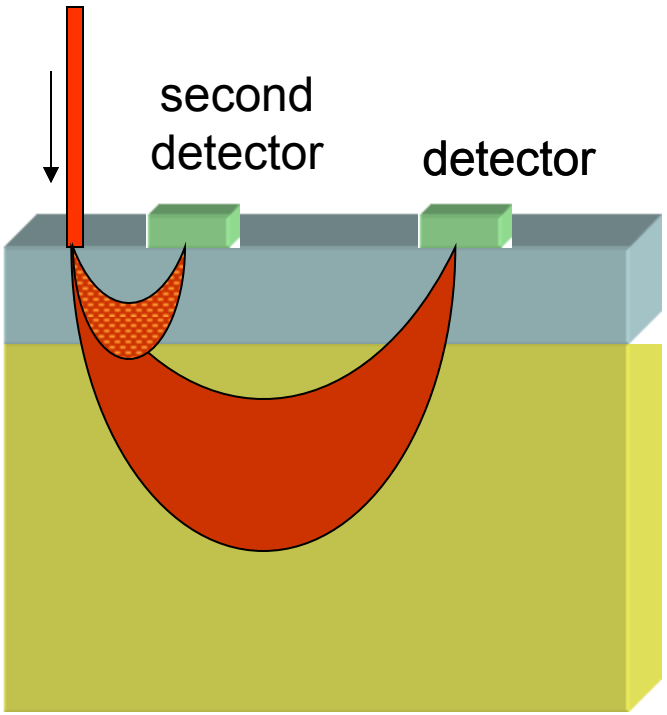


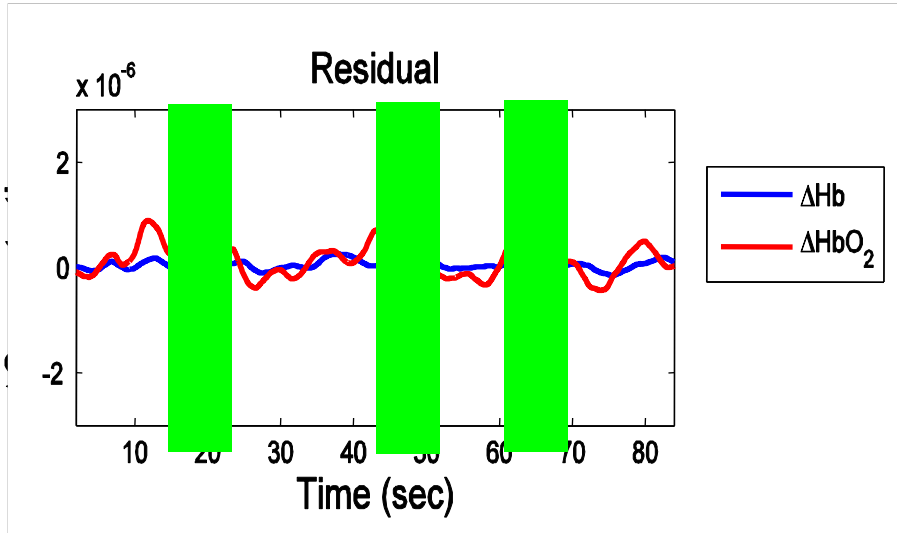
wavelength-dependent absorption:
BLOOD

diffusive propagation:
DEPTH



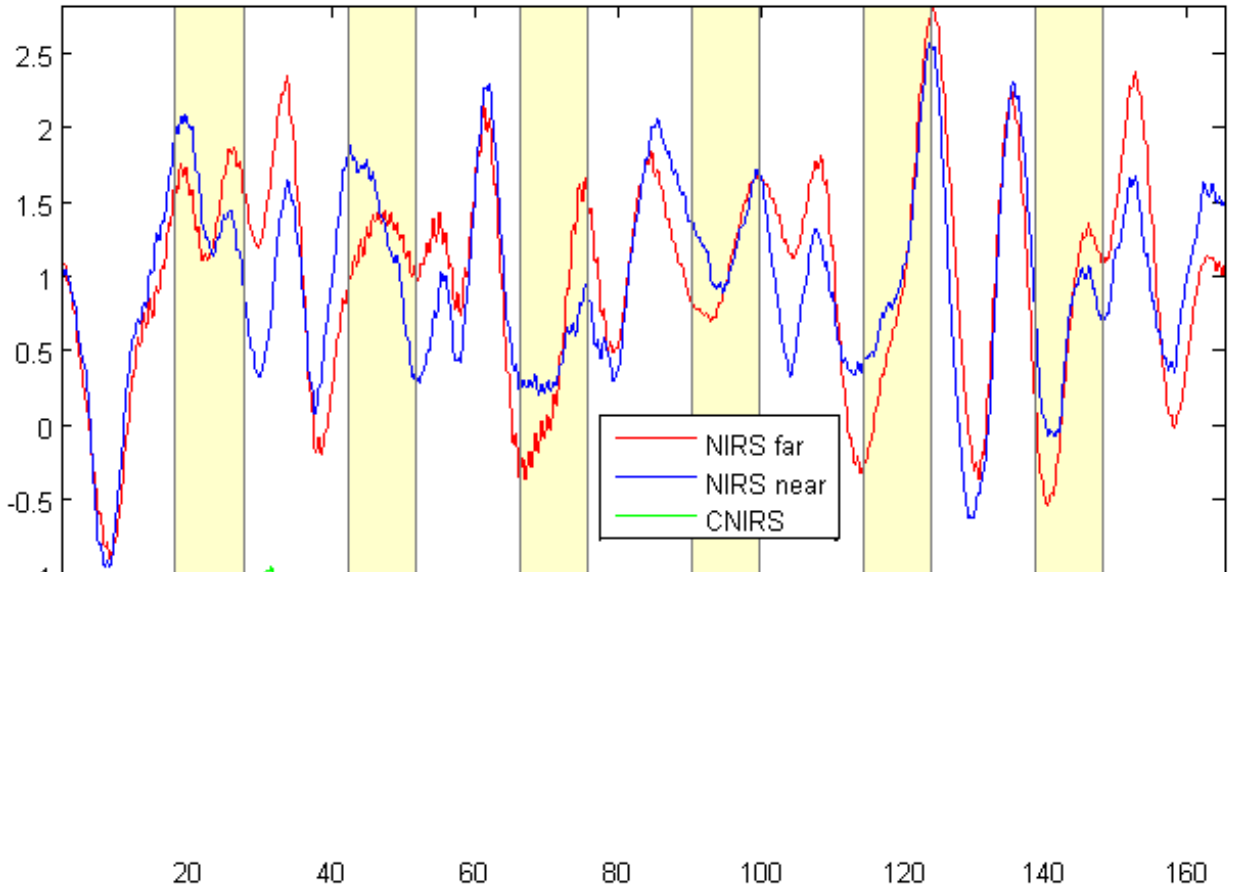
Explicit superficial monitoring



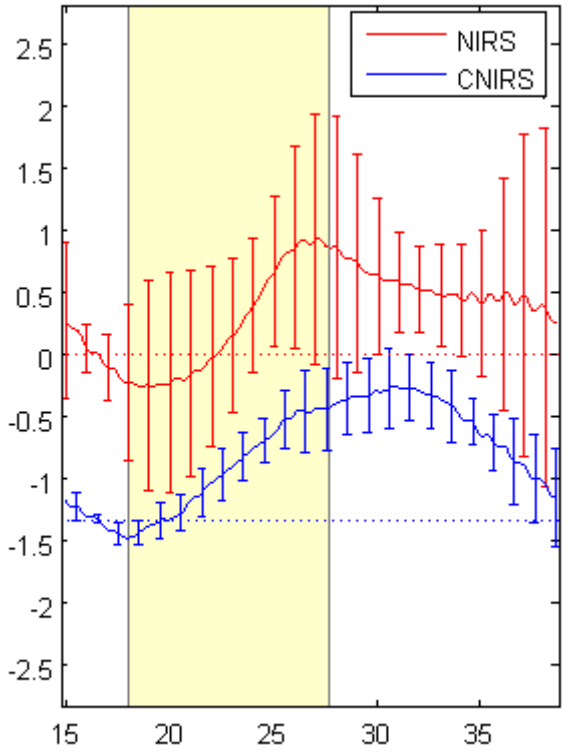


- least-squares residual
- uncorrelated with “near” trend
- C-NIRS, or
  “Corrected – NIRS”

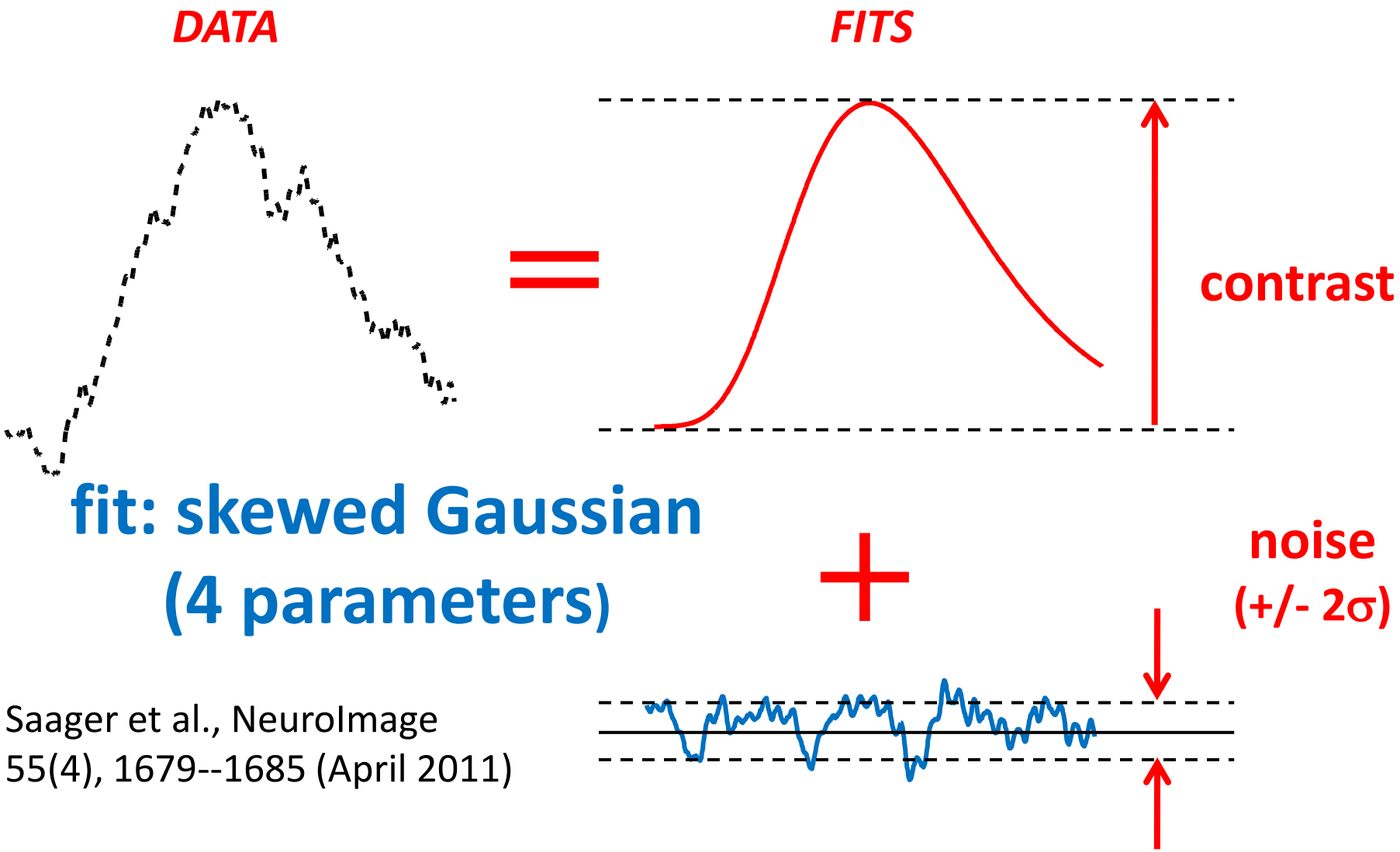
Improving signal-to-noise by subtracting “scalp” signal



time/sec



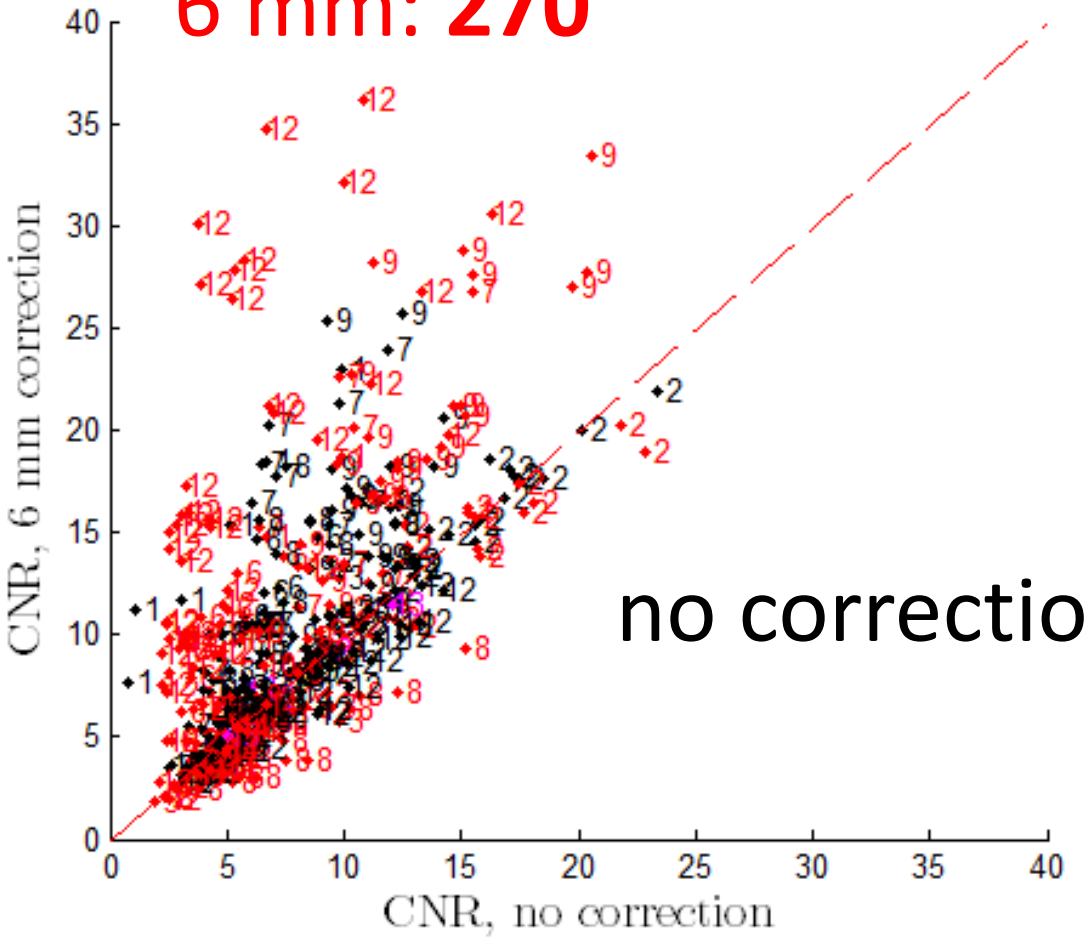
contrast and noise amplitudes



Saager et al., NeuroImage
55(4), 1679--1685 (April 2011)

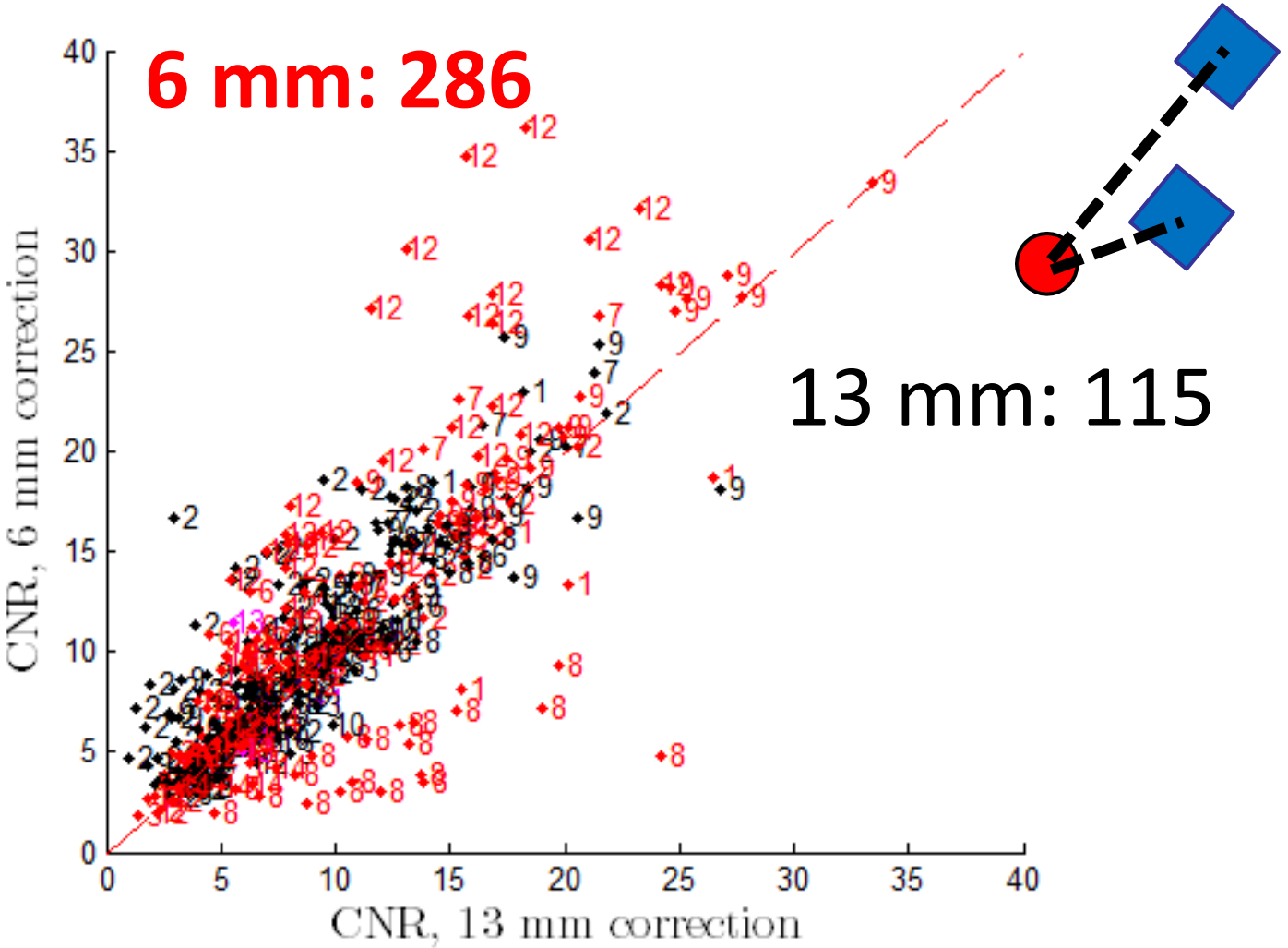
6 mm correction vs. no correction

6 mm: **270**

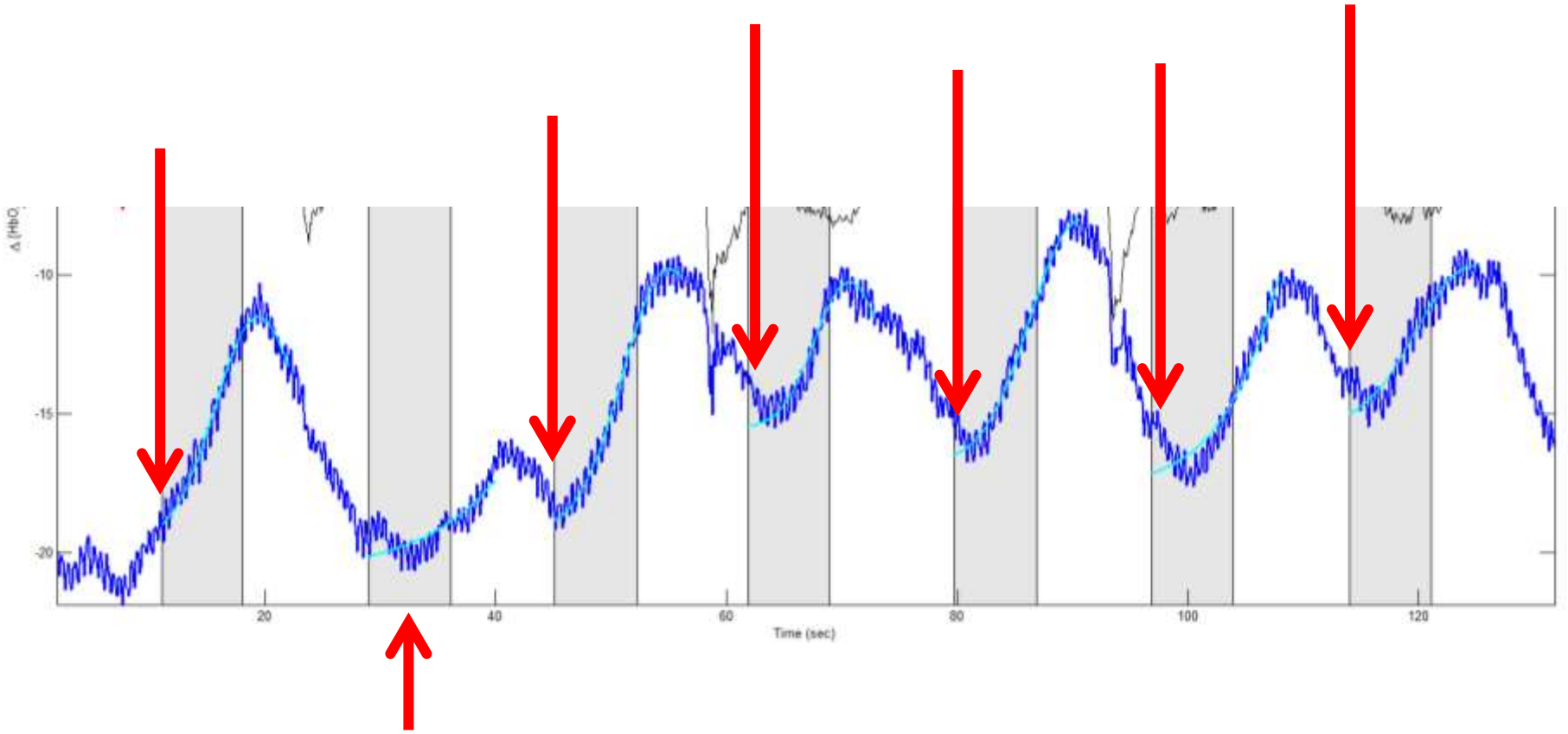


no correction: **131**

Comparing two “near” distances



Ongoing work: babies!

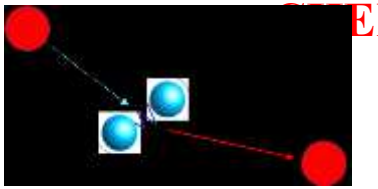


rest epoch

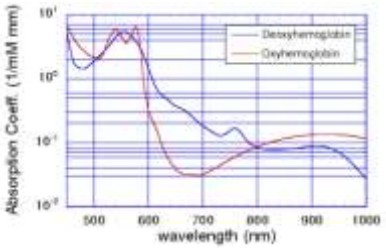
Conclusion

biological sample

inelastic scattering:
CHEMISTRY

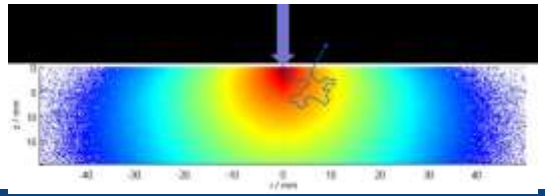


angle-dependent elastic scattering:
SIZE



wavelength-dependent absorption:
BLOOD

diffusive propagation:
DEPTH



To learn more

Tuesdays in January (7.1, 14.1, 21.1, 28.1), 2:00 pm, IPHT Sitzungssaal

Lecture 2 - Turbid tissue optics I: *Introduction*
Lecture 3 - Turbid tissue optics II: *Instrumentation and measurements*
Lecture 4 - Turbid tissue optics III: *Applications*
Lecture 5 - A different view of turbidity: *elastic scattering analysis*

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