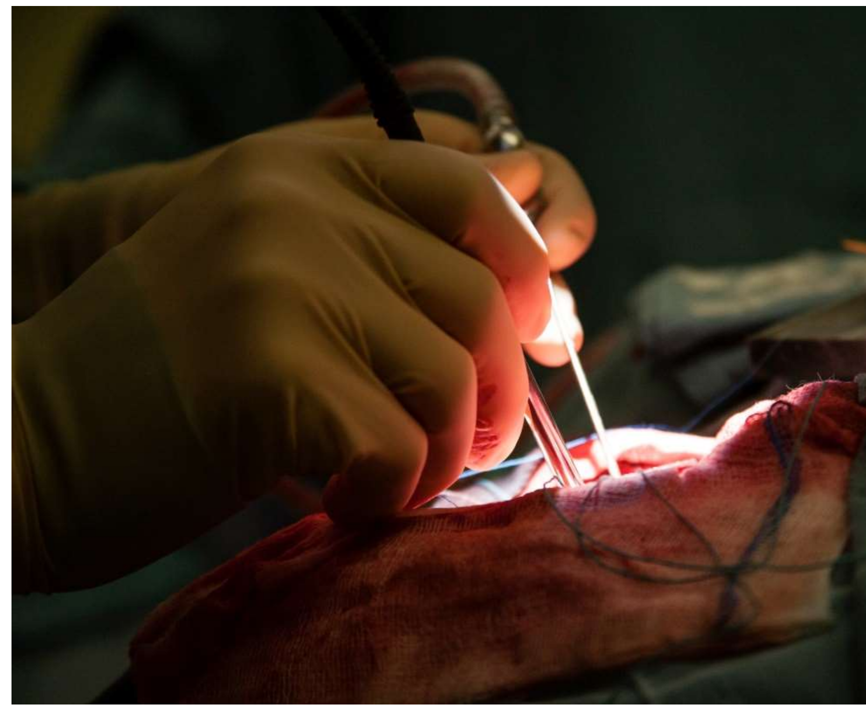
eloppement d’instruments médicaux en physique médi



Frederic Leblond, PhD

Director, Laboratory for Radiological Optics

ring Physics Department, Polytechnique Montreal

ch Center, University of Montreal Medical Center

POLYTECHNIQUE MONTRÉAL

WORLD-CLASS ENGINEERING

LABORATORY OF RADIOLOGICAL OPTICS

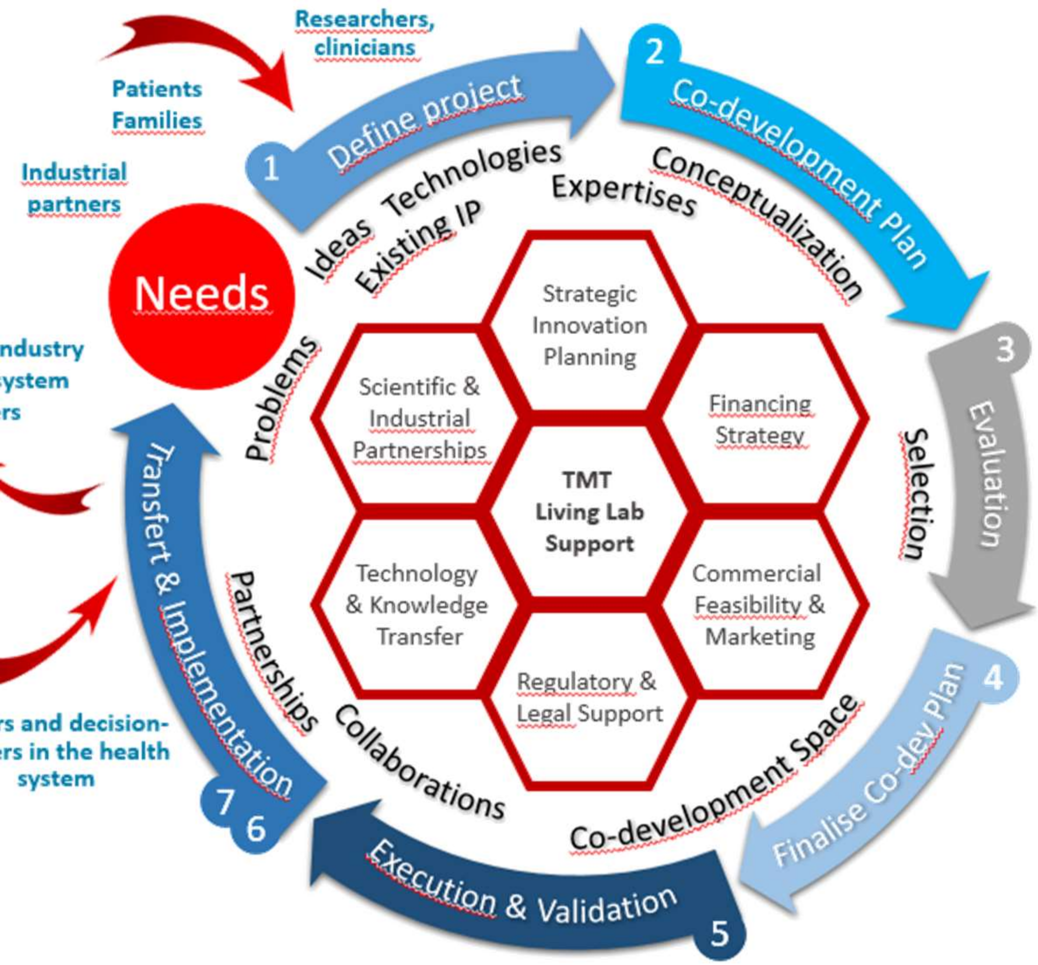
CRCHUM CENTRE DE RECHERCHE

LABORATORY FOR RADIOLOGICAL OPTICS

TransMedTech Institute of Montreal A consortium funded b

Canada First Research Excellence Fund (100M$, 7 years)

lized and dedicated



Supports the **development** & **validation** of n
generation medical technolog

Cardiovascular – Musculoskeletal - Can

to facilitate their **implementation** in the hea
system or indus

Train the next generation of profession
through HQP and student grants and personali
training progra

Living Lab mo
Transdisciplinary, intersectoral collabora
research, open innovation and creati

- HOW CAN LIGHT-TISSUE INTERACTIONS BE EXPLOITED OR MOLECULAR CHARACTERIZATION ?

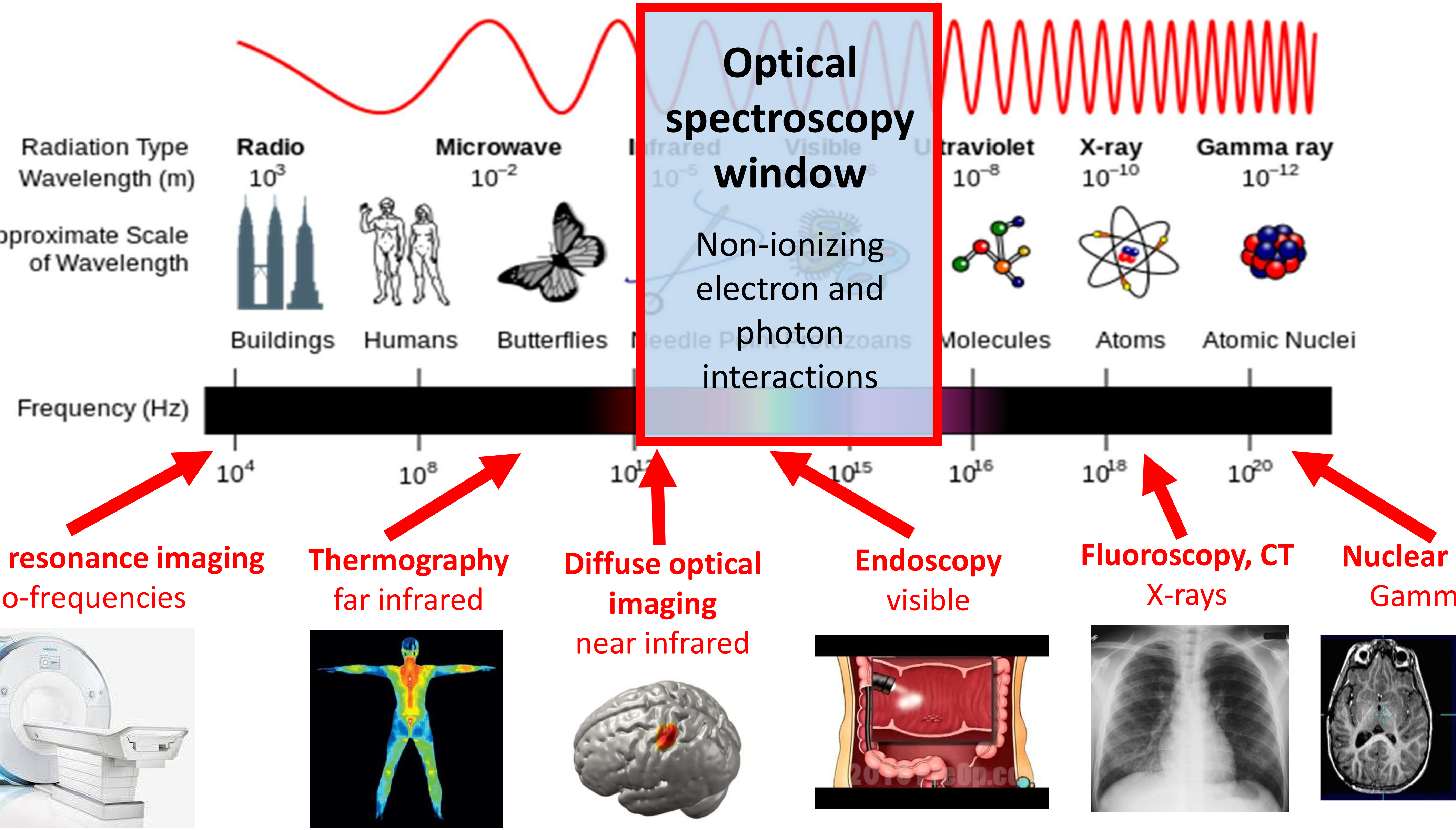
LABORATORY OF RADIOLOGICAL OPTICS

CRCHUM

CENTRE DE RECHERCHE

Centre hospitalier de l'Université de Montréal

MEDICAL IMAGING ACROSS THE ELECTROMAGNETIC SPECTRUM



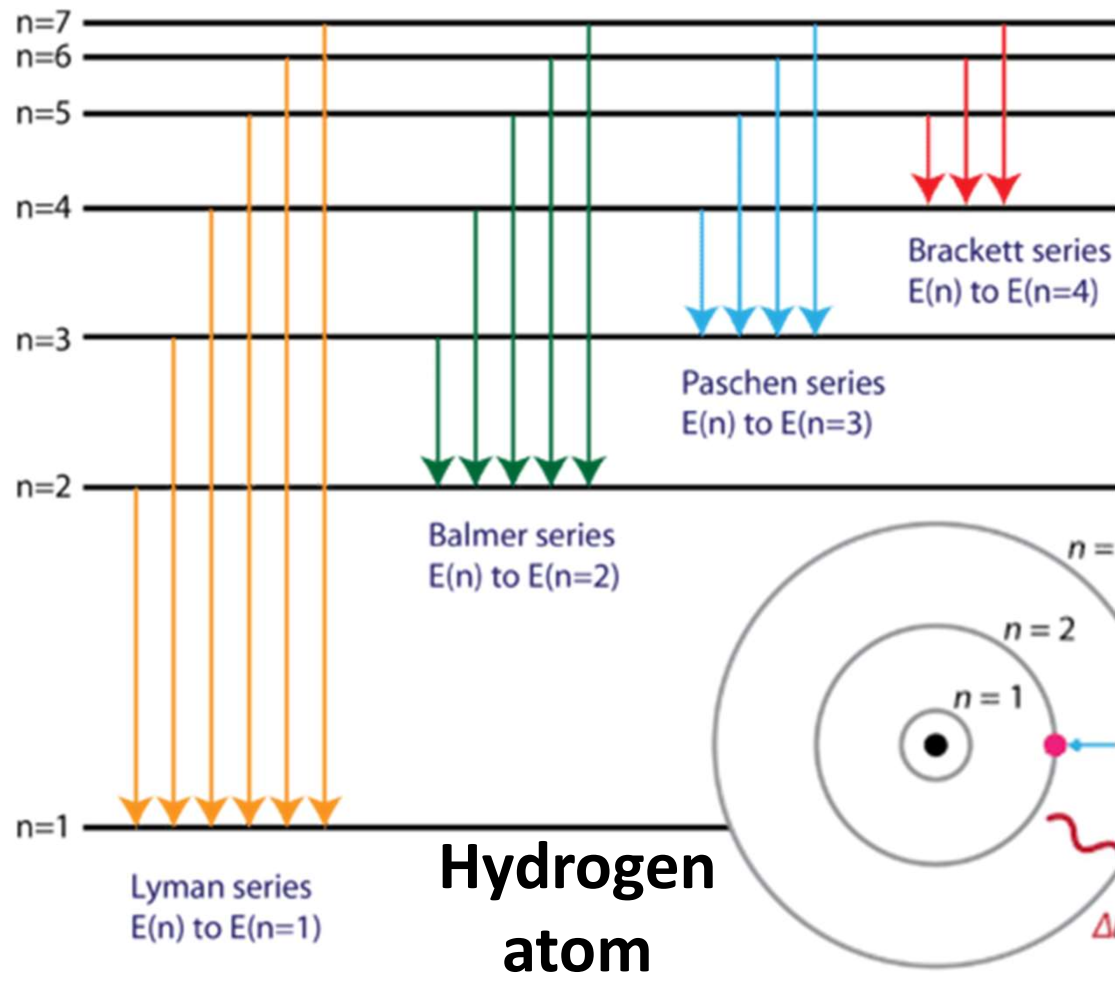
VERY SHORT INTRODUCTION TO QUANTUM MECHANICS
EXCITATION OF ATOMS AND MOLECULES

mentary particles are wave
ctions quantifying their **probability**
e a given location in space

tronic **energy levels** in atoms and
ecules are discrete

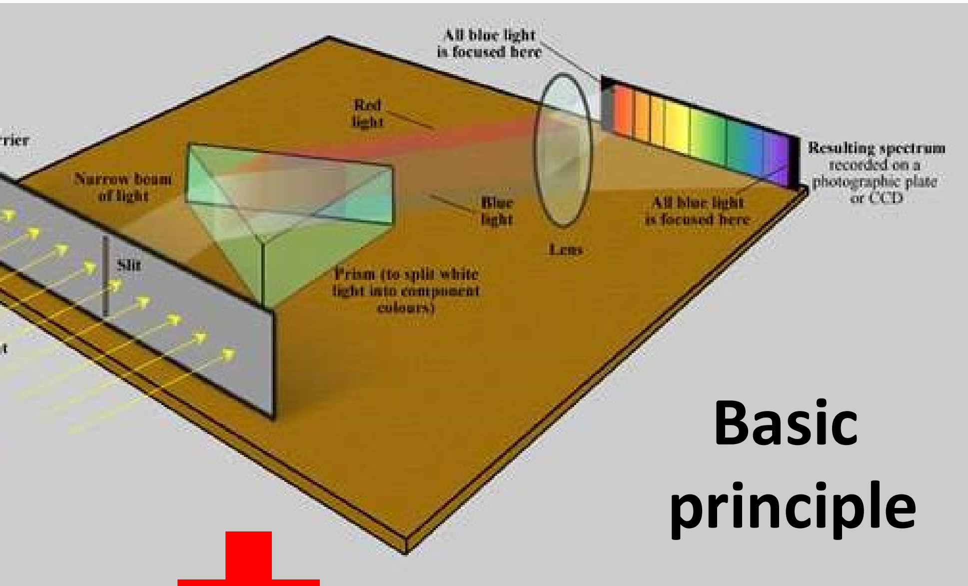
t is composed of discrete energy
kets with a frequency and a
elength : **photons**

ntum mechanics : **selection rules**
ating which **photons** can excite
trons in atoms and molecules



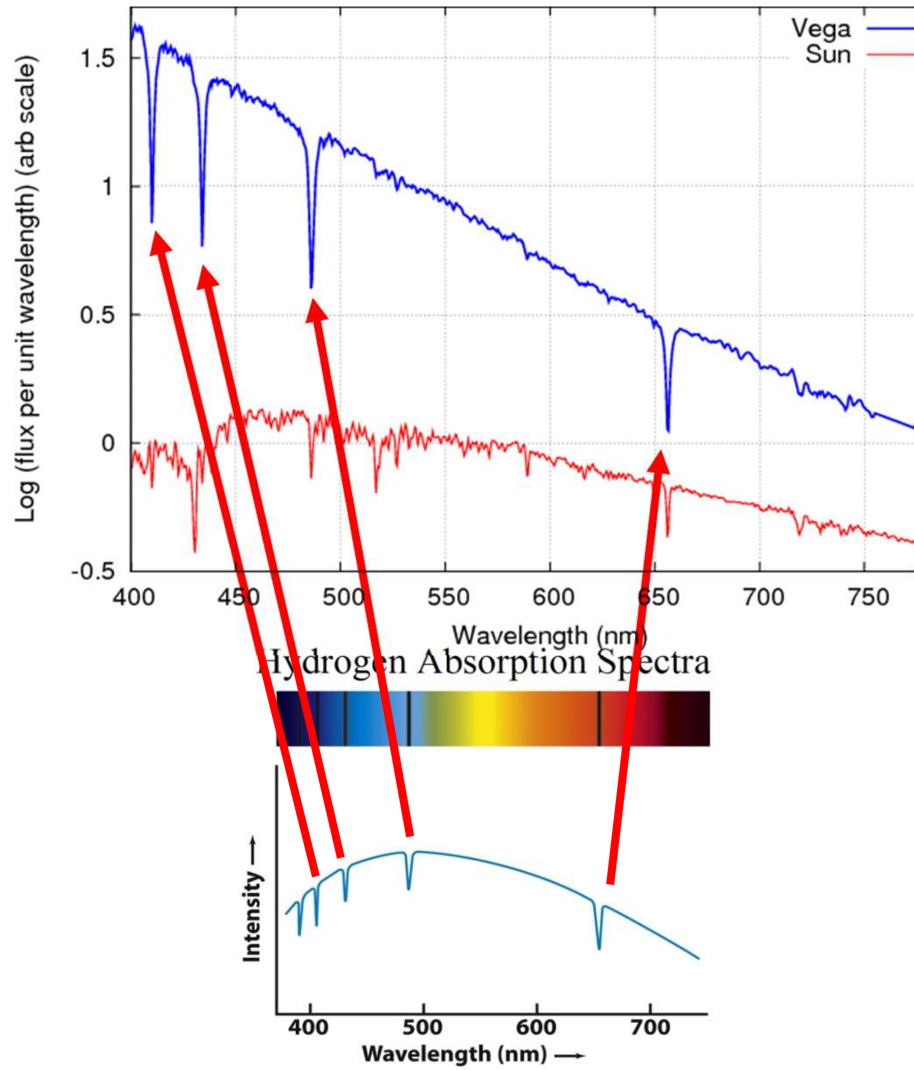
Credits: CK-12 Founc

WHAT IS SPECTROSCOPY ?



Basic principle

Absorption spectrum of a sta (electronic states)



THE MAKE-UP OF LIFE

Atoms

Complex biomolecules

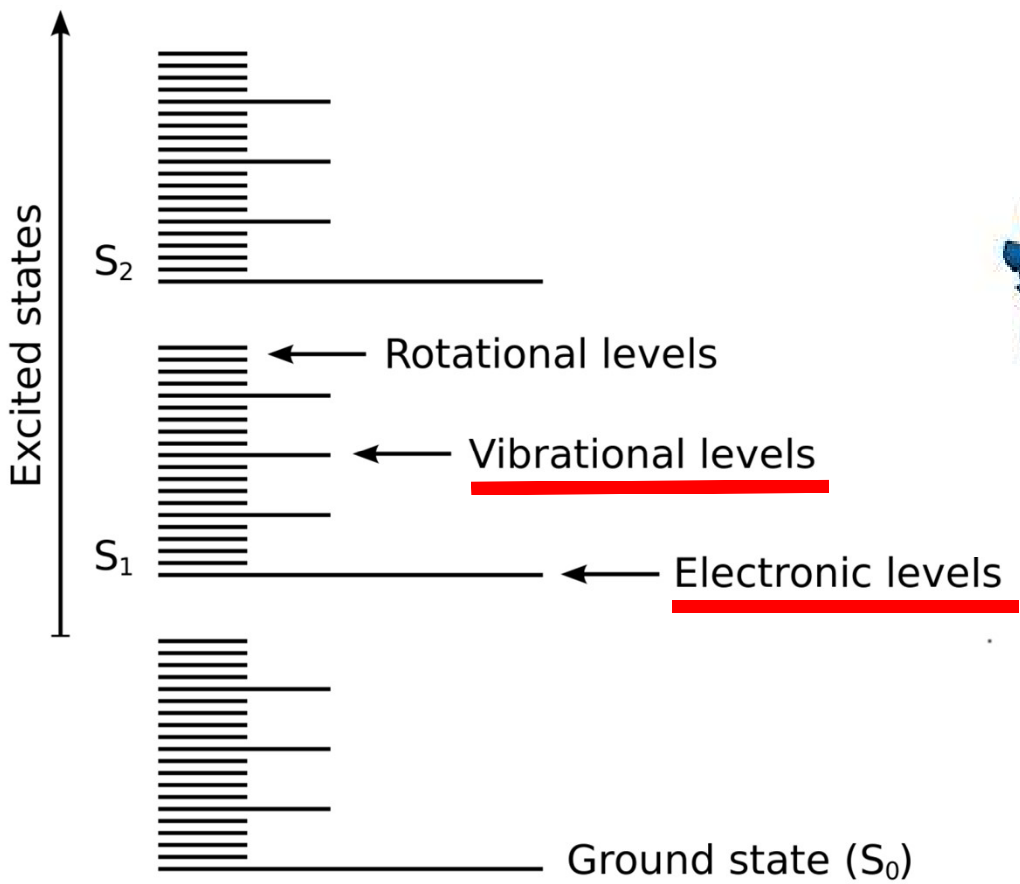
IMATE PERCENTAGE OF CHEMICAL SUBSTANCES IN A CELL

Main class of chemical substances	Approximate percentage composition	
Water	80.0	Inorganic
Inorganic salts	1.0	
Carbohydrates	1.0	Organic
Lipids	0.5	
Proteins	12.0	
Nucleic acids	2.0	
Other organic substances	0.5	

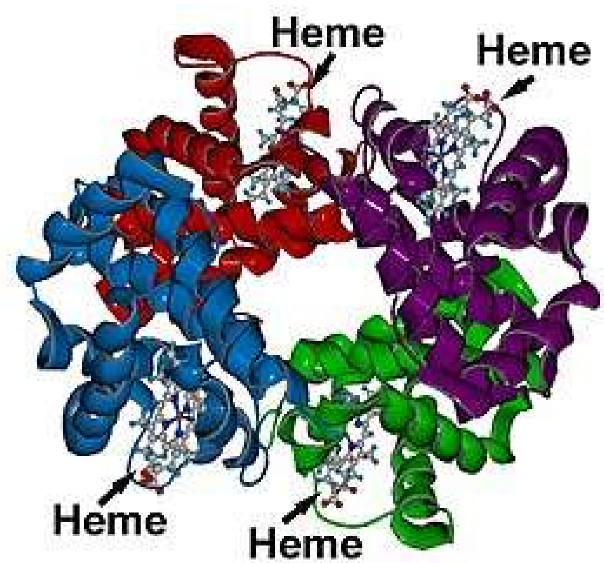
PROPORTIONS OF ELEMENTS OCCURRING IN A CEI

Elements	Approximate weight (percentage)		
1. Oxygen	62.00	About 95% major elements	Essential elements about 99.:
2. Carbon	20.00		
3. Nitrogen	10.00		
4. Hydrogen	3.00		
5. Calcium	2.50	About 4.25% minor elements	
6. Phosphorous	1.14		
7. Chlorine	0.16		
8. Sulphur	0.14		
9. Potassium	0.11		
10. Sodium	0.10		
11. Magnesium	0.07		
12. Iodine	0.014		
13. Iron	0.010		
14. Copper, Cobalt, Zinc, Silicon, Manganese, Aluminium Molybdenum, Florine etc.	0.756	About 0.75% trace elements	Trace elements about 0.7
	100	100	100

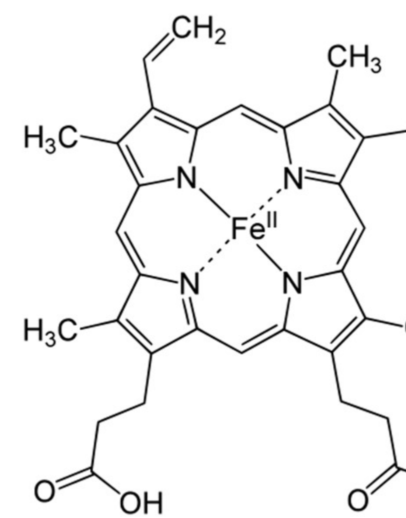
ELECTRONIC AND VIBRATIONAL MOLECULAR EXCITATION MODES



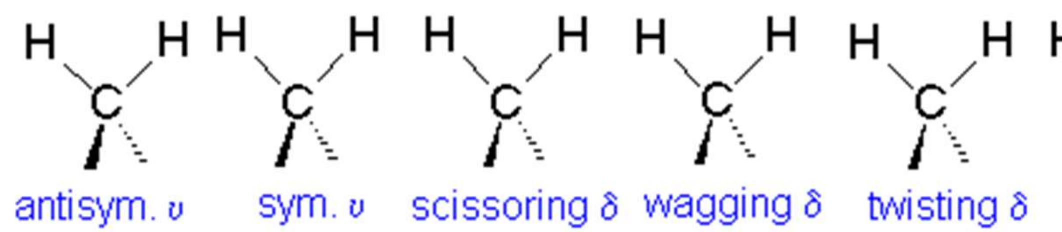
Hemoglobin



Heme sub-un

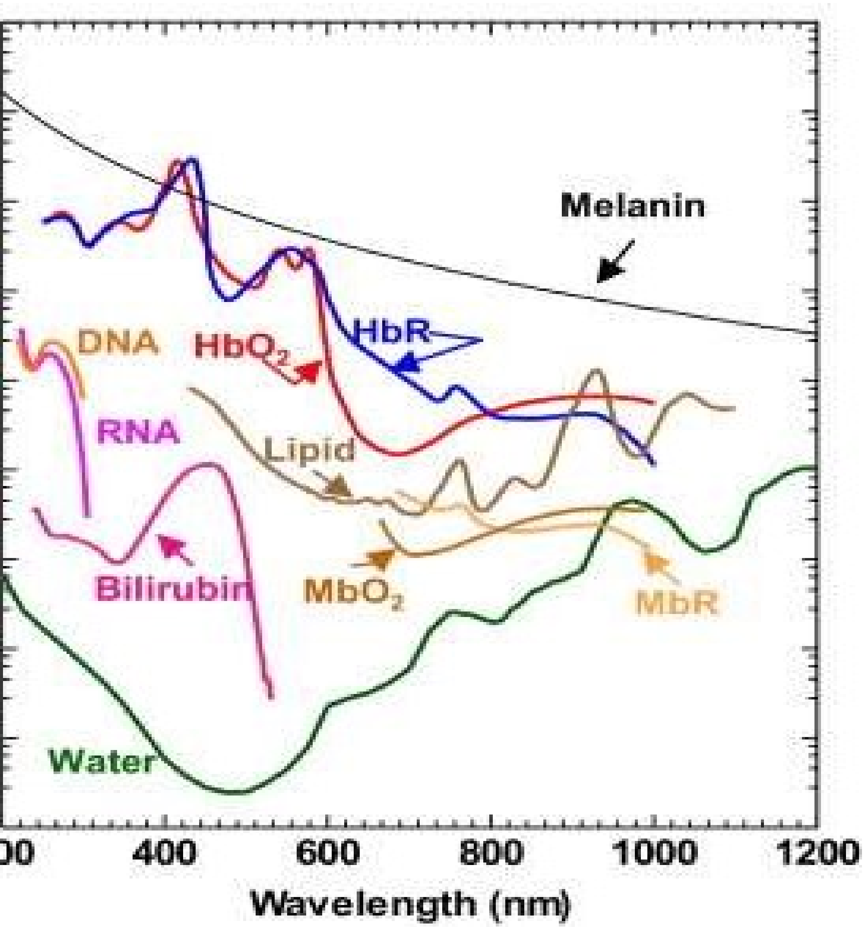


Vibrational modes : molecular bon



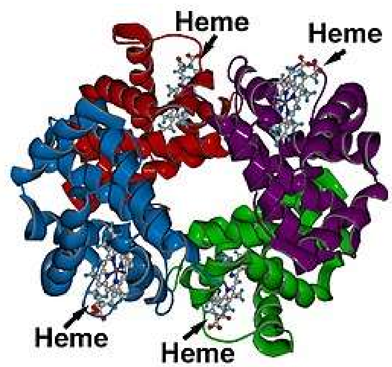
ABSORPTION SPECTRA OF COMPLEX MOLECULES : RESONANT PHENOMENON

Molecules have non-discrete excitation bands

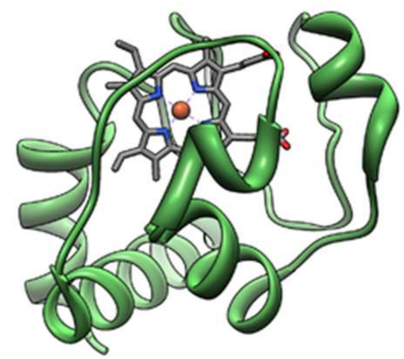


Important tissue absorbers (chromophores)

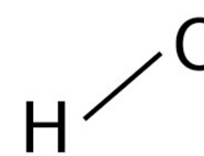
Hemoglobin



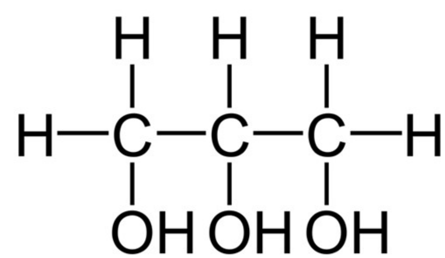
Cytochrome C



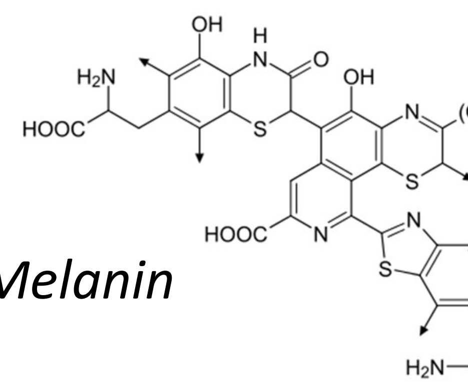
Wa



Lipids



Melanin

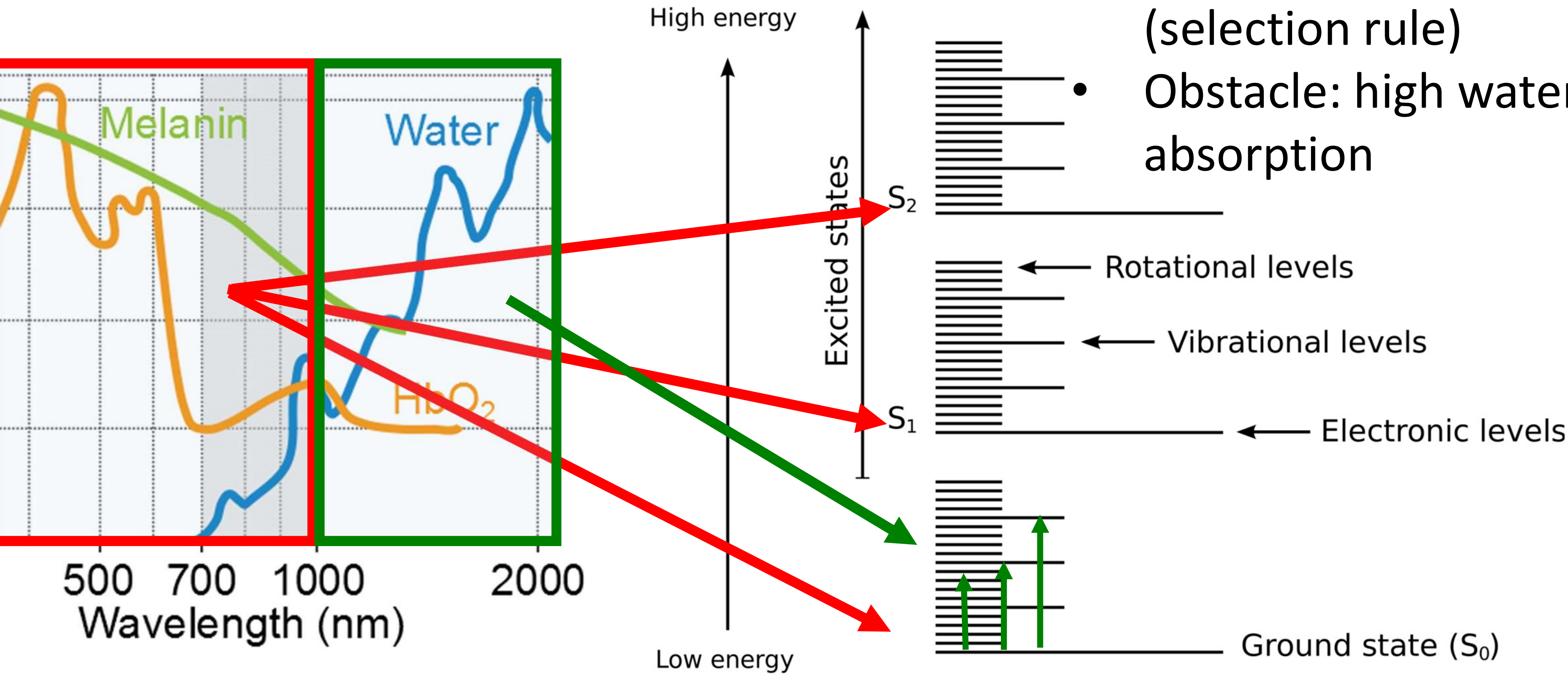


ABSORPTION AND VIBRATION MODES OF COMPLEX MOLECULES : RESONANT

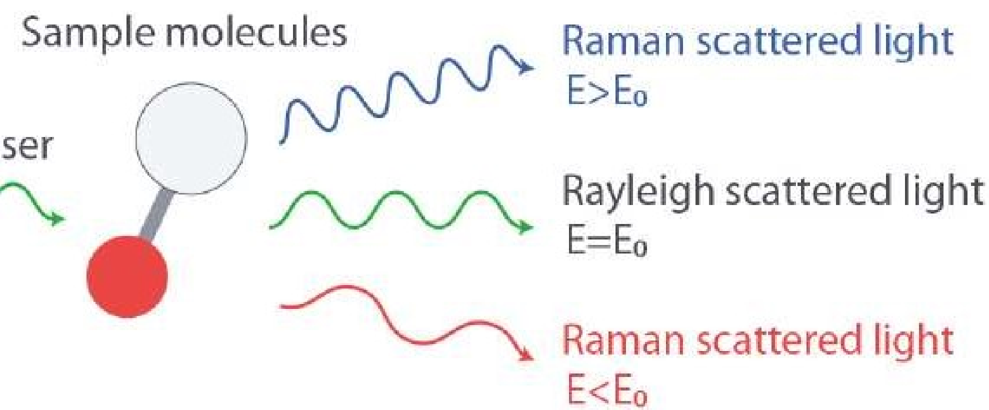
ronic levels can be imaged with UV, visible or NIR light

Imaging with mid-IR and

- Infrared spectroscopy
- IR-active molecular b
  (selection rule)
- Obstacle: high water
  absorption



NON-RESONANT PHOTON-ELECTRON INTERACTIONS : SCATTERING



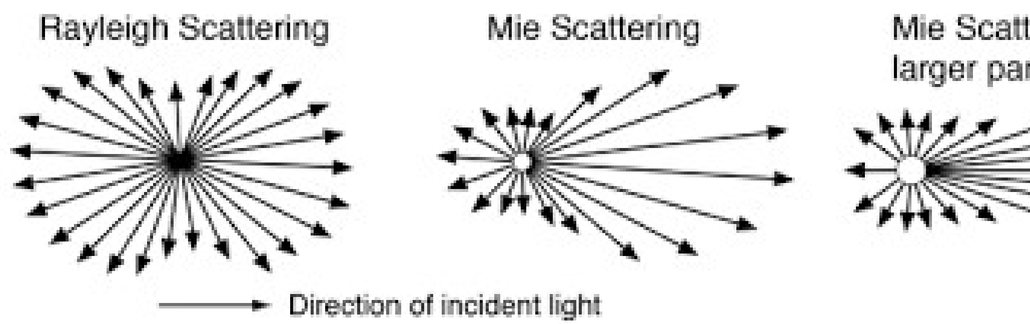
yleigh scattering (small particles)

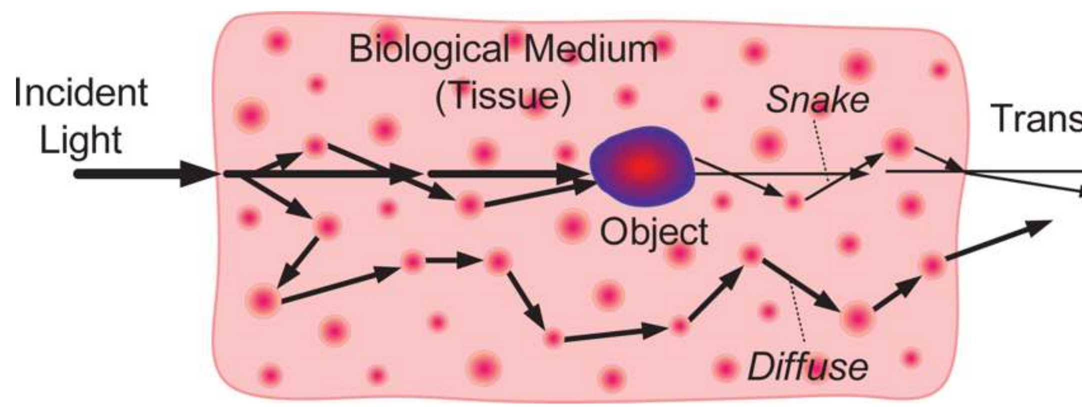
no. of scatterers — polarizability

$$\boxed{I = I_0 \frac{8\pi N \alpha^2}{\lambda^4 R^2}\left(1 + cos^2\theta\right)}$$

vavelength — distance

Mie scattering in biological tiss (larger particles)





Tissue : absorption + scattering

NON-RESONANT SPONTANEOUS RAMAN SCATTERING

man strength depends on molecular polarizability

$$\mu = \alpha_0 E_0 \cos 2\pi\nu_0 t + \frac{1}{2} E_0 Q_k^0 \left(\frac{\partial \alpha}{\partial Q_k}\right)_0 \left[\cos 2\pi(\nu_0 + \nu_k)t + \cos 2\pi(\nu\right.$$

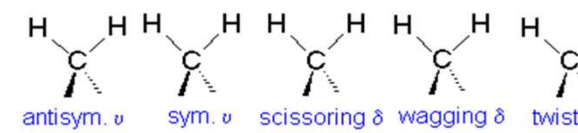
Rayleigh scattering

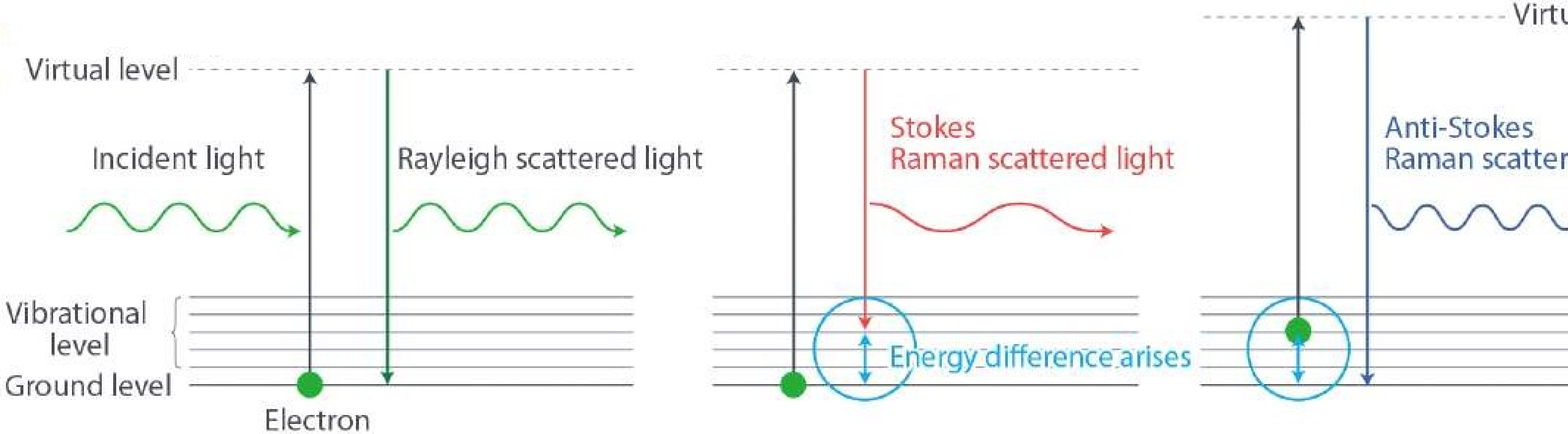
Anti-Stokes Raman scattering

Stoke scatte

and anti-stokes mpeting effects

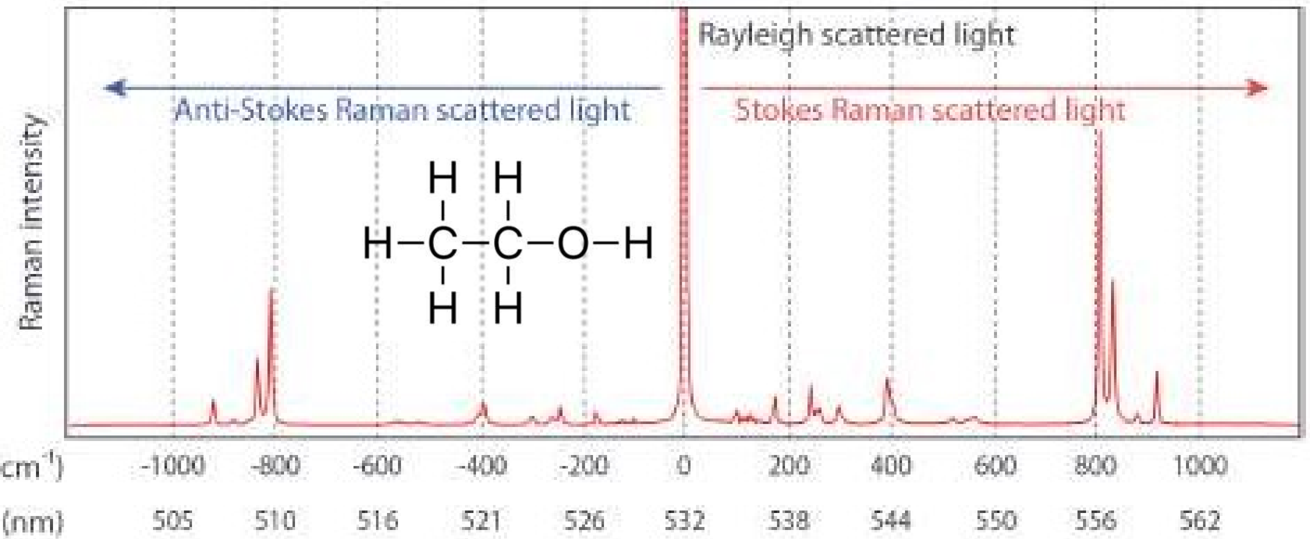
$$\frac{I_{\text{Stokes}}}{I_{\text{anti-Stokes}}} = \frac{(\nu_0 - \nu_{mn})^4}{(\nu_0 + \nu_{mn})^4} \exp(h\nu_{mn}/kt)$$





NON-RESONANT EXCITATIONS : SCATTERING IN TISSUE

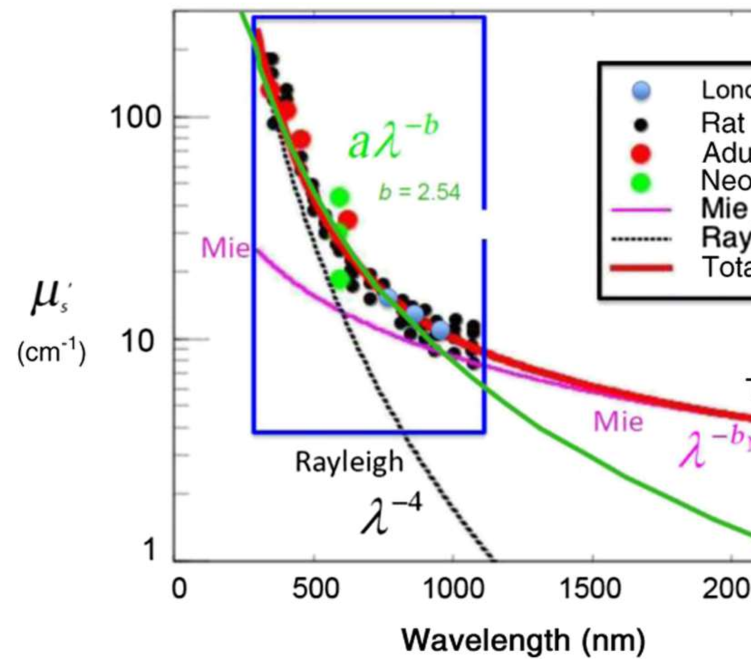
Stokes and anti-stokes



$$\left|\frac{\partial \vec{\mu}}{\partial Q}\right|^2 \qquad |\overleftrightarrow{\alpha}|^2 \qquad \left|\frac{\partial \overleftrightarrow{\alpha}}{\partial Q}\right|^2 \qquad \left|\frac{\partial \overleftrightarrow{\alpha}}{\partial Q}\right|^2$$

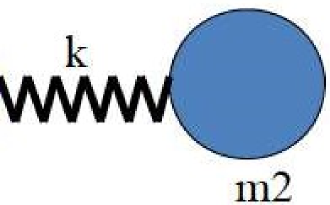
~~bsorption ctroscopy~~	Light scattering	Stokes Raman scattering	anti-Stokes Raman scattering

Rayleigh/Mie scatte

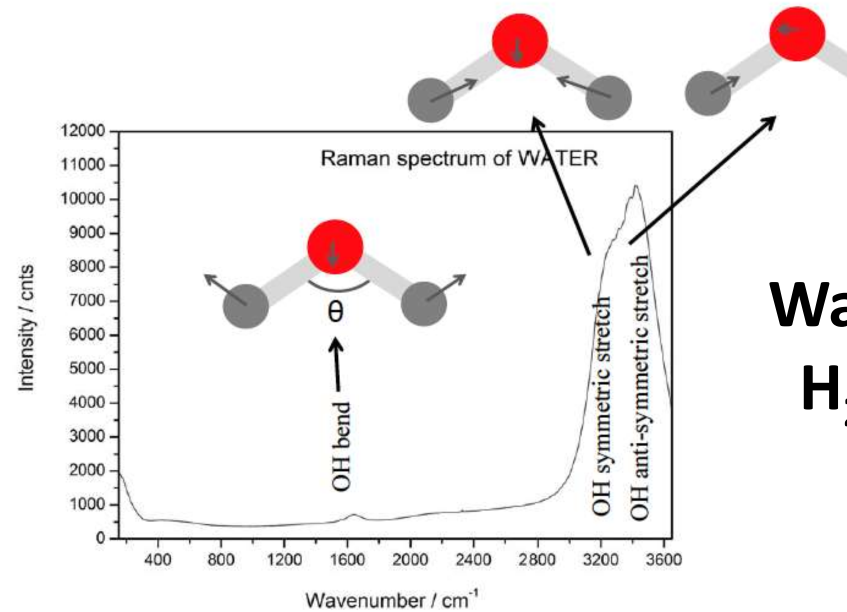


RAMAN SPECTROSCOPY : BIOCHEMICAL INTERPRETATION

ach vibrational mode can be modeled as a (an-)harmonic oscillator



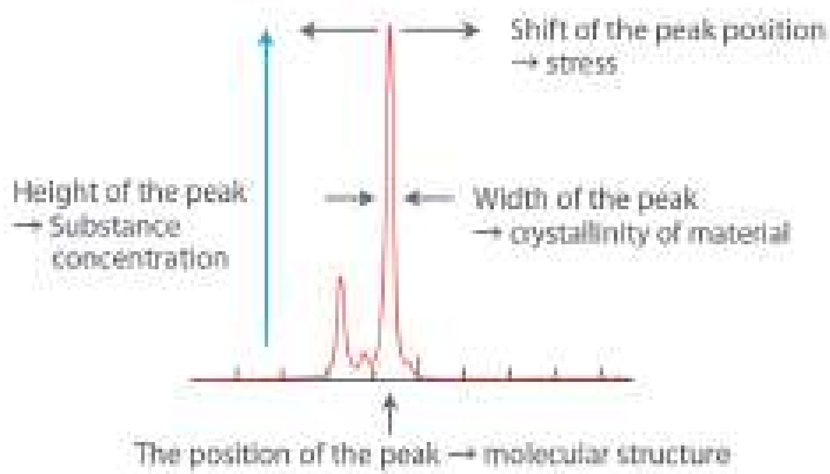
$$\frac{1}{\mu} = \frac{1}{m_1} + \frac{1}{m_2} \qquad \upsilon = \frac{1}{2\pi}\sqrt{\frac{k}{\mu}}$$



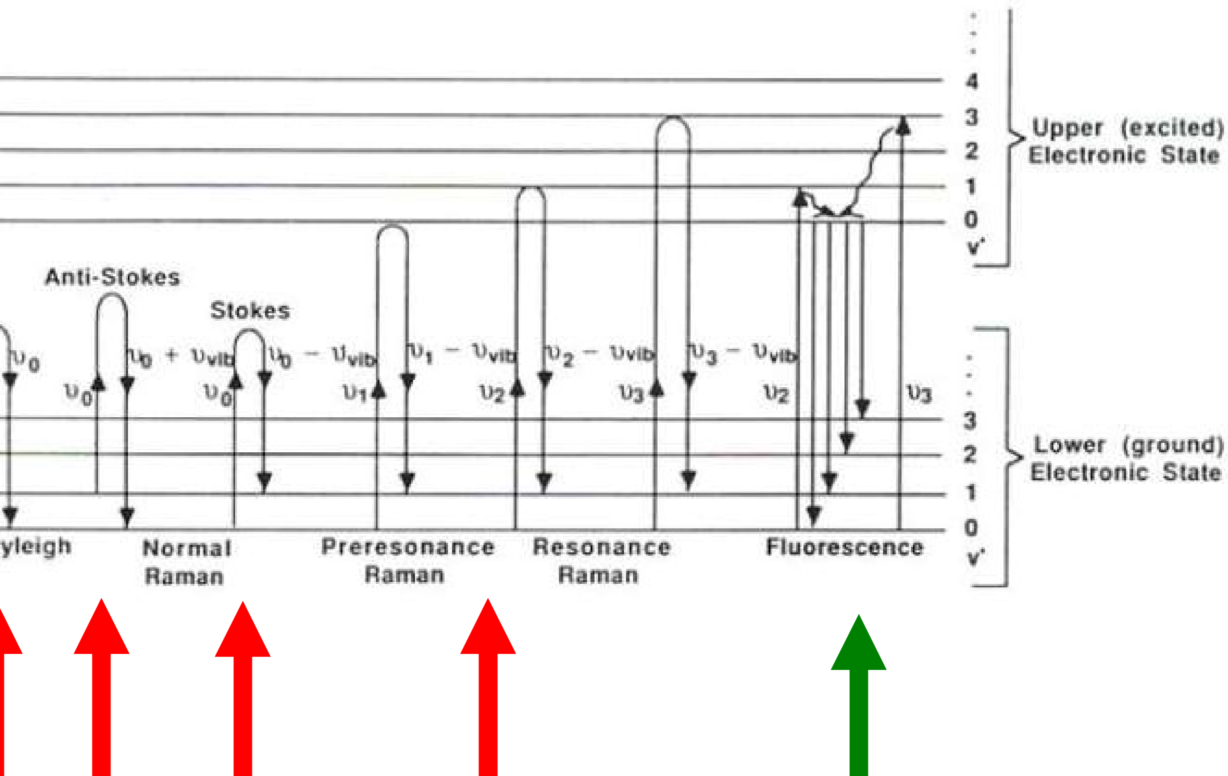
Wa
H

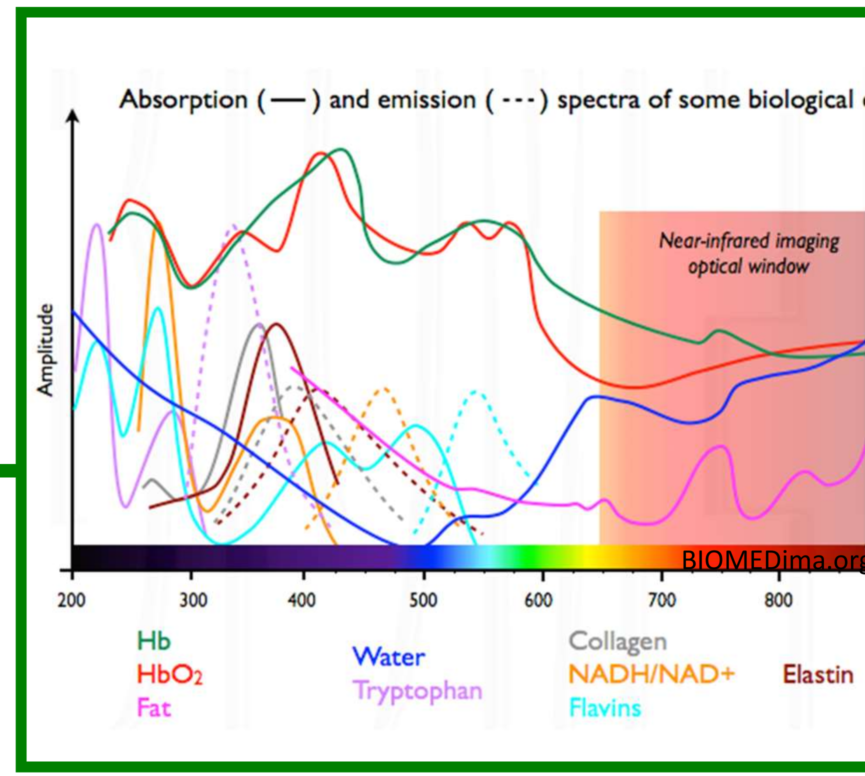
Frequencies : unique for molecular groups
Light atoms : larger frequencies
Stronger bonds : larger frequencies

Peak **shift** : pressure applied
Peak **width** : symmetry
Peak **height** : concentration
Peak **position** : molecular structure



ENDOGENOUS FLUORESCENCE : ANOTHERLIGHT-TISSUE NTERACTION COMPETING MECHANISM





ic (UV-Vis) Absorption spectroscopy:	10^{-20} m^2
cence spectroscopy:	Q x 10^{-20} m^2
nal (IR) absorption spectroscopy:	10^{-23} m^2
ice Raman spectroscopy:	10^{-29} m^2
onant Raman spectroscopy:	10^{-33} m^2

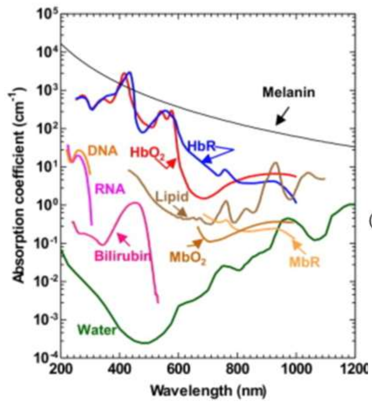
– DATA MINING AND TISSUE CLASSIFICATION

WHY ARE MULTIVARATE ANALYSIS USEFUL IN SPECTROSCOPY?

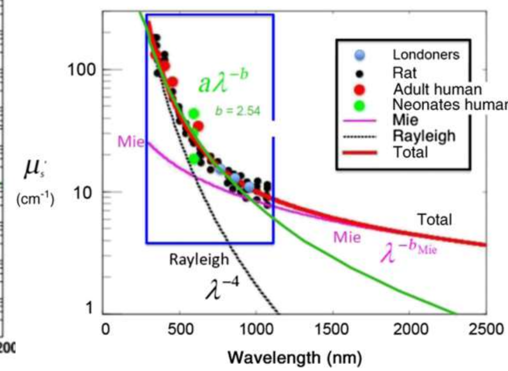
ssue spectra (Raman,
ffuse reflectance,
orescence) contain
mplex biochemical
formation

xture of molecules
ewed as a “pattern”
attern recognition)

Diffuse reflectance

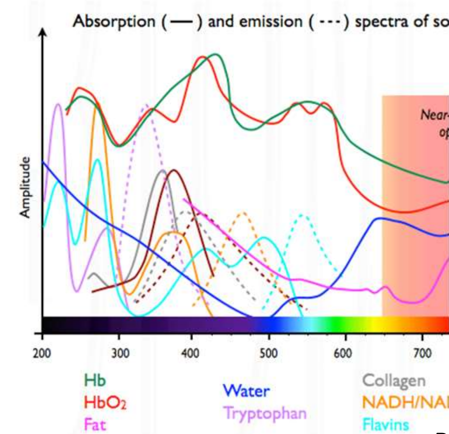


Yao et al, Photoacoustics (2014)



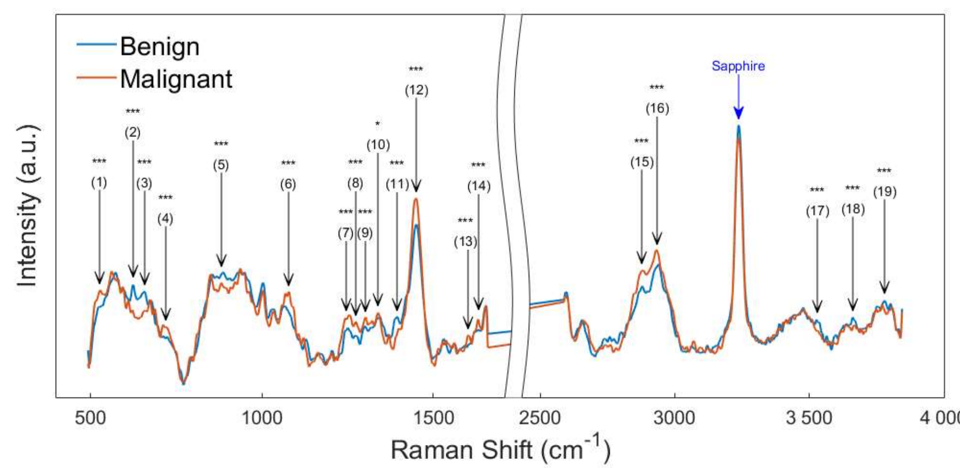
Tuchin et al, JBO (2016)

Fluorescenc



B

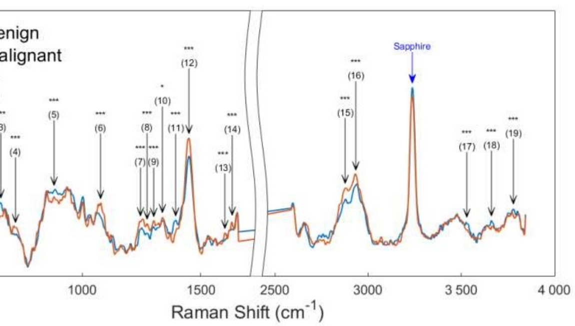
Vibrational spectroscopy

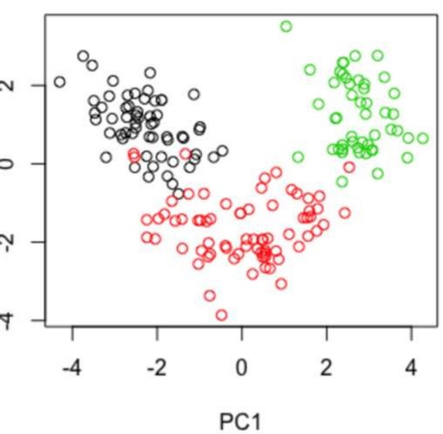


MACHINE LEARNING IN SPECTROSCOPY

Features selection

ect *N*-dimensional data on *M*-dimensional space)

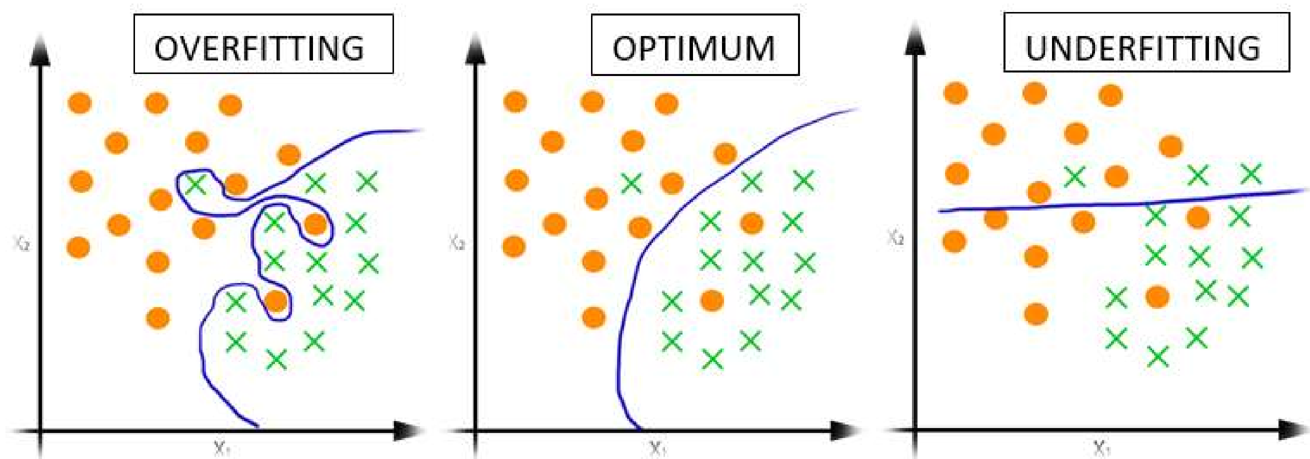




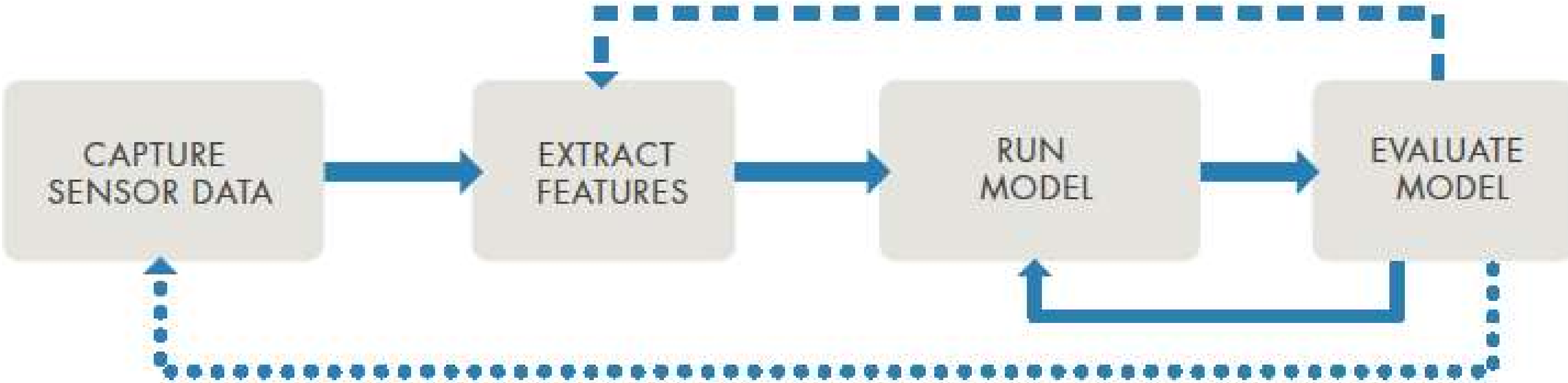
- Methods that can automatically detect patterns i data
- Uses uncovered patterns to predict future data, o to perform other kinds of decision making under uncertainty

Supervised learning and model building

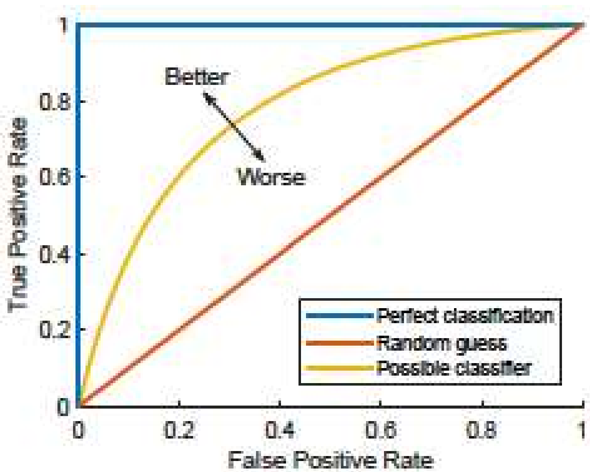
- each measurement is assigned a label
- logistic regression, singular vector machine



TERATIVE MACHINE LEARNING PROCESS



ceiver operating characteristic curve
false/true positives and negatives)



- Find classification model with no over-fitting
- Evaluate performance on an independent (hold-out) dataset : ROC curve

– BIOMEDICAL APPLICATIONS

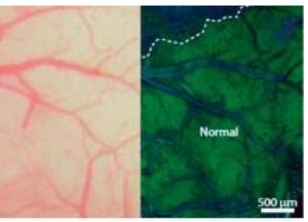
OPTICAL SPECTROSCOPY APPLICATIONS IN MEDICINE

reening and Diagnosis	*Treatment*	*Monitoring treatment respons and disease progression*
reening for early disease etection using optical ectroscopy of tissue or biofluids	***In situ* disease stratification** to inform treatment decision making	**Prognostication to better strat disease** and provide tailored treatment
tegrating optical techniques to clinical biopsy tools to avoid mplications and improve agnostic predictors	**Guidance for surgical resection** margin assessment/localization local drug administration focal therapy (*e.g.* brachytherapy)	**Monitor disease progression**, assess outcomes, and flag resid disease
omplementing current standard- -care diagnostic procedures by oviding additional information	**Optics-enabled treatment** using photochemical, photothermal, or photomechanical interactions to treat disease	**Monitor treatment safety**, especially for chronic condition and long-term treatments

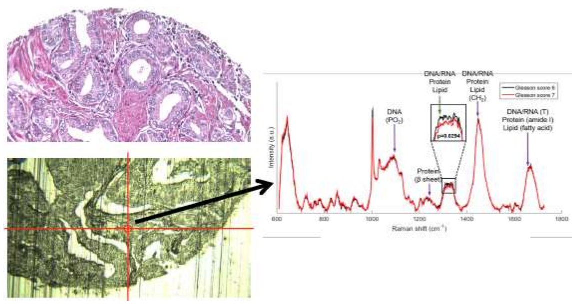
Jermyn, Leblond, Journal of Biomedical Optics (2018)

PLATFORM TECHNOLOGY : SPATIAL SCALES

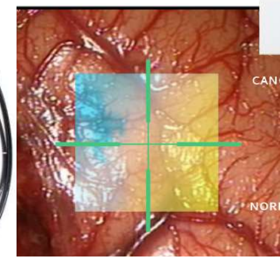
Probing tissue structure from microscopic to macroscopic scales



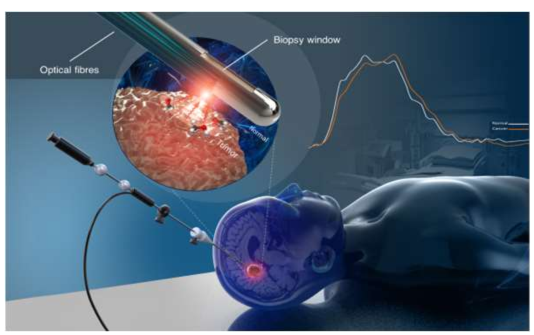
Microscopy
sub-millimeter

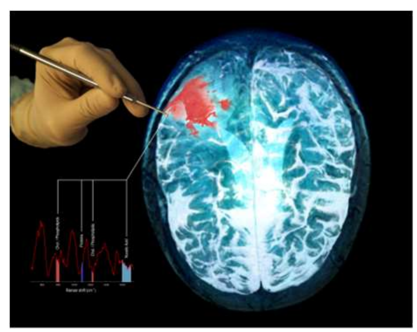


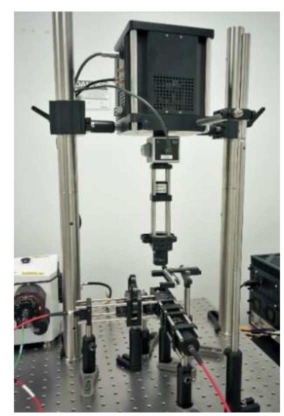
Macroscopy
centimer

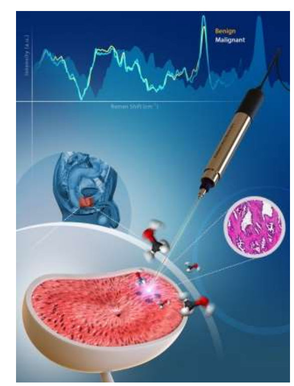


Mesoscopy
millimeter





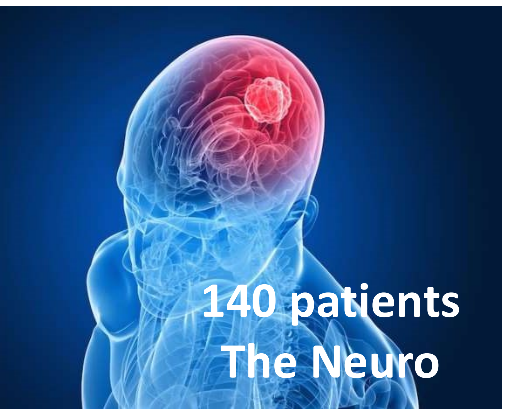




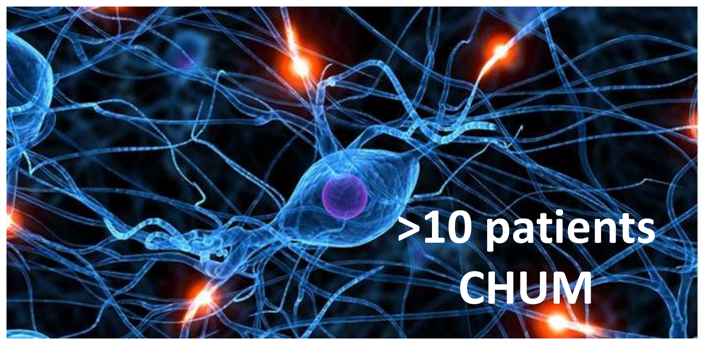
PLATFORM TECHNOLOGY : FINDING THE RIGHT APPLICATIONS

Designing statistic models across organ sites and diseases

Brain cancer

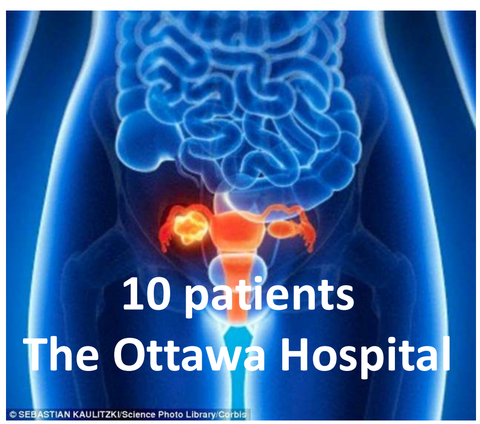


Epilepsy

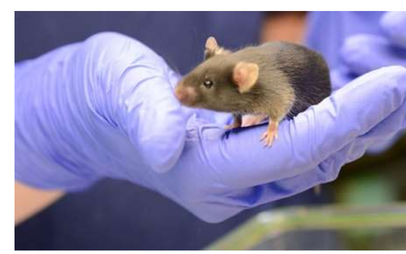


Prostate cancer

Lung cancer



Gynecologic cancers



CASE STUDY - PROSTATE CANCER DETECTION
STEP 1 : STUDY DESIGN

f patients	32
QR) age at RP, years	62 (58–66)
QR) preoperative PSA, µg/L	6.79 (5.33–8.50)
Gs, *n* (%)	
	4 (12)
	13 (41)
	7 (22)
	5 (16)
	3 (9)
ı (%)	
	0 (0)
	18 (56)
	9 (28)
	2 (6)
	3 (9)
al tumour stage, *n* (%)	
gan-confined)	13 (41)
xtra-prostatic extension)	15 (47)
eminal vesicle invasion)	4 (12)
f positive surgical margin, *n* (%)	10 (31)

e Group; IQR, interquartile range; RP, radical prostatectomy.

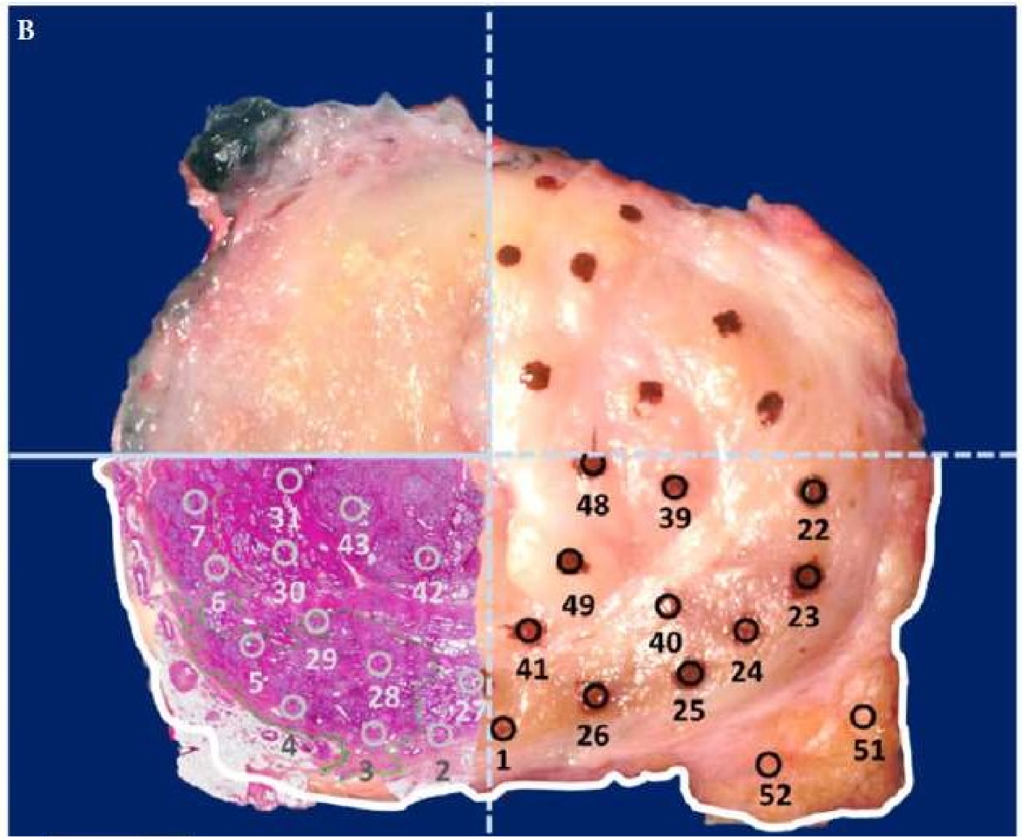
Journal of Urology (2018)

Objective – To improve safety and accuracy of prostatectomy proced

- Can spectroscopy detect cance in a highly heterogeneous background of normal tissue?
- Can spectroscopy distinguish prostate from extra-prostate tis

Clinical and pathologic characteristics of patie with prostate cancer incl in the study

CASE STUDY - PROSTATE CANCER DETECTION
STEP 2 : MEASUREMENTS

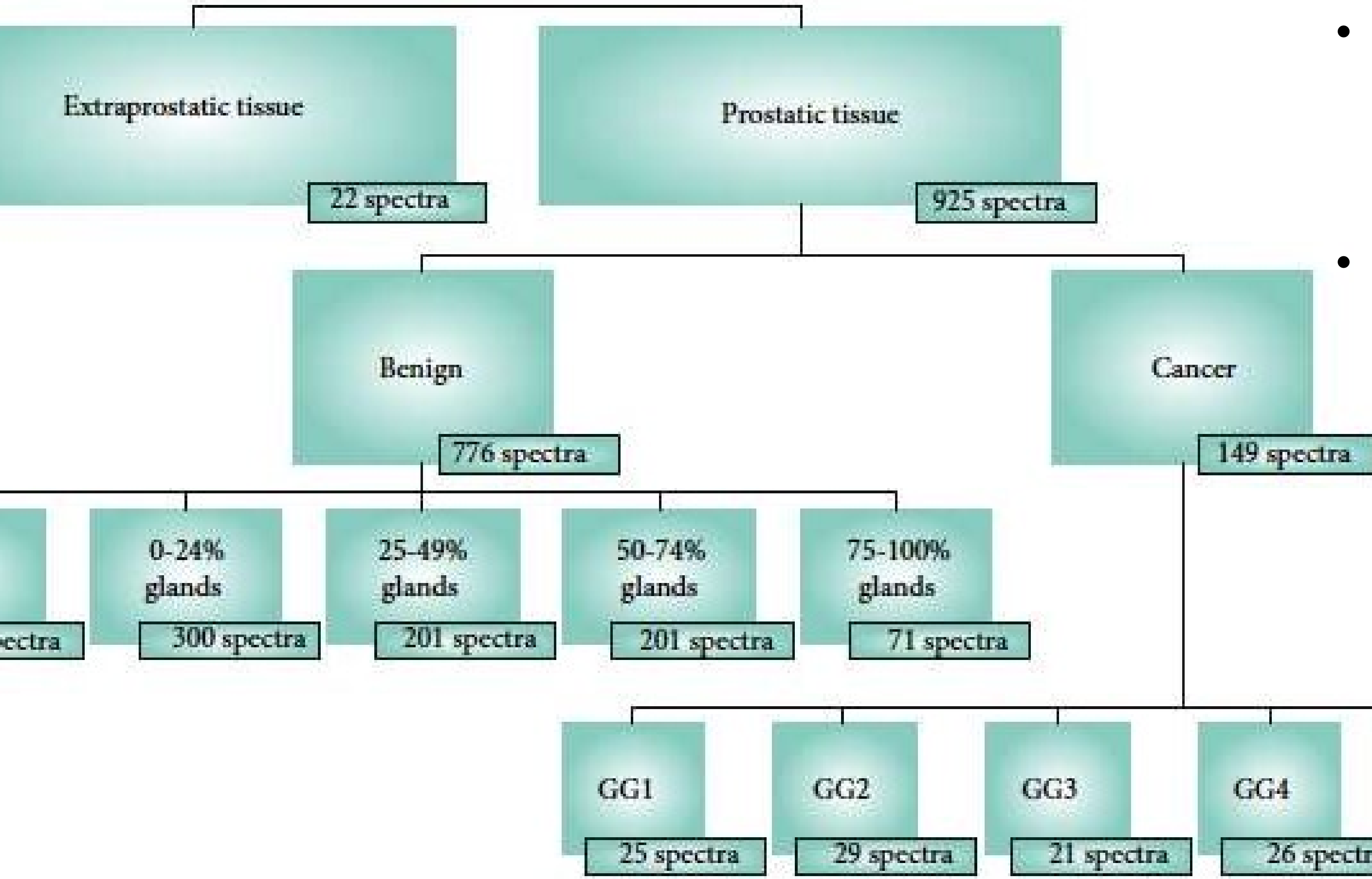


Intraoperative R
probe syste

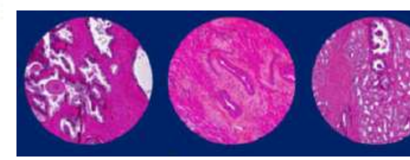
- real-time (0
  - 500 micro
diameter sar
  - contact m

British Journal of Urology (2018

CASE STUDY - PROSTATE CANCER DETECTION
STEP 3 : LABEL ASSIGNMENT

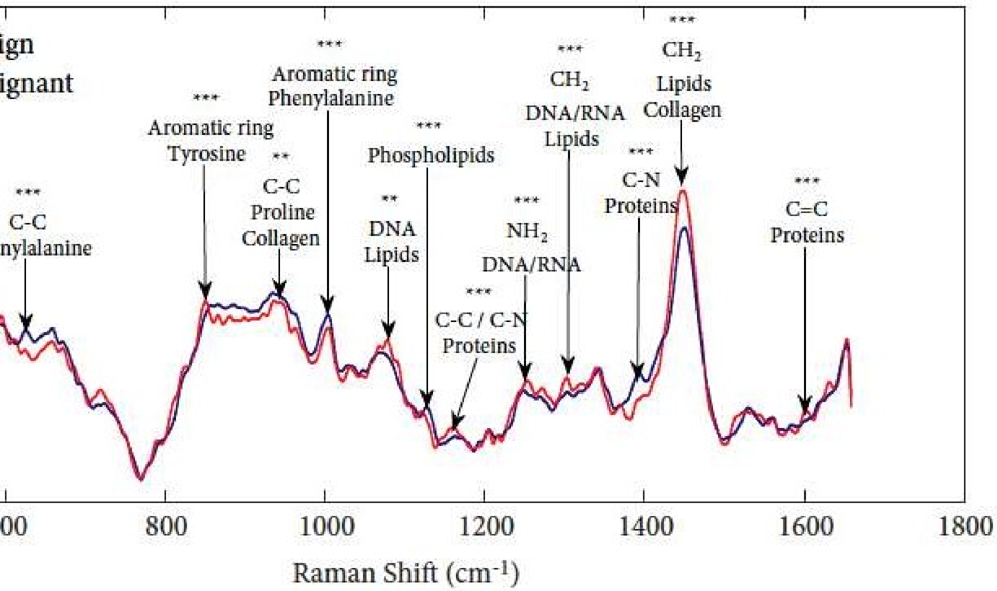


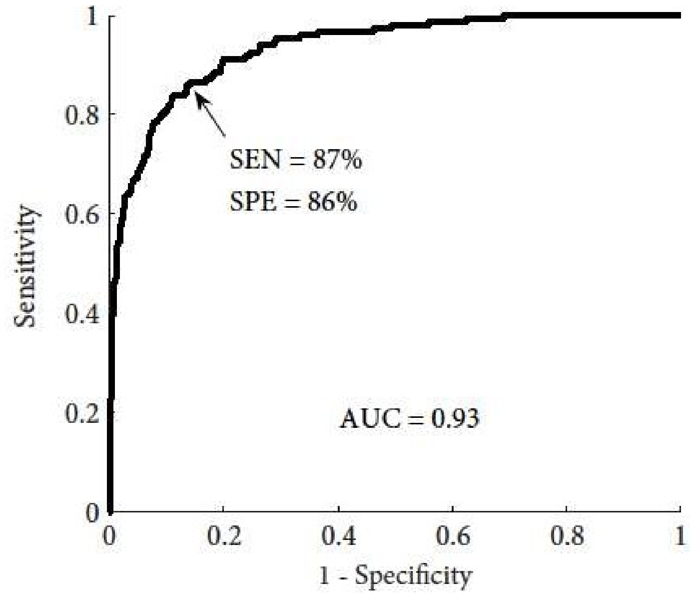
- Each measureme
  assigned with mu
  histopathology la
  (gold standard)
- Can lead to the
  production of mu
  classification mod



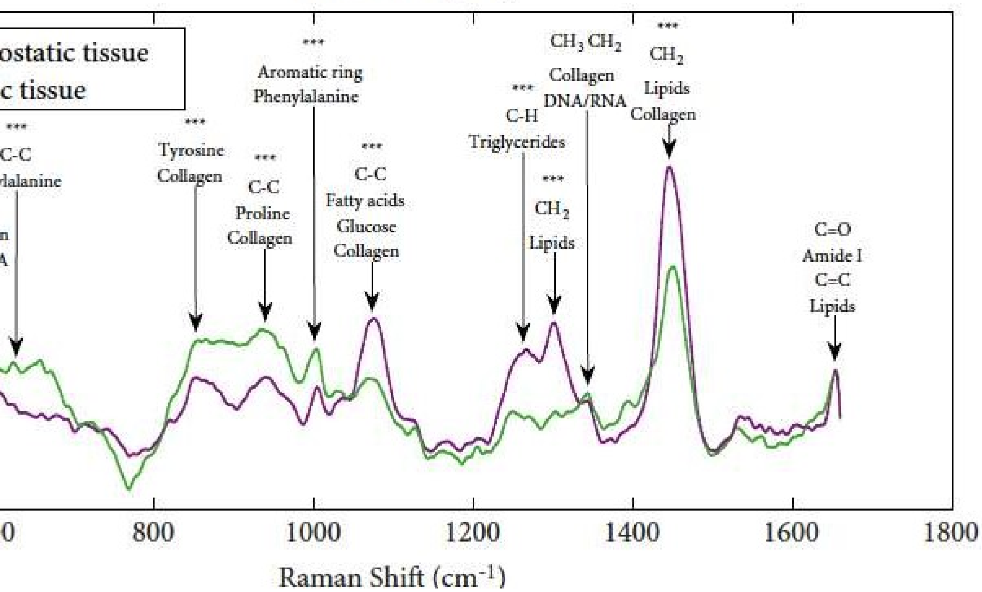
urnal of Urology (2018)

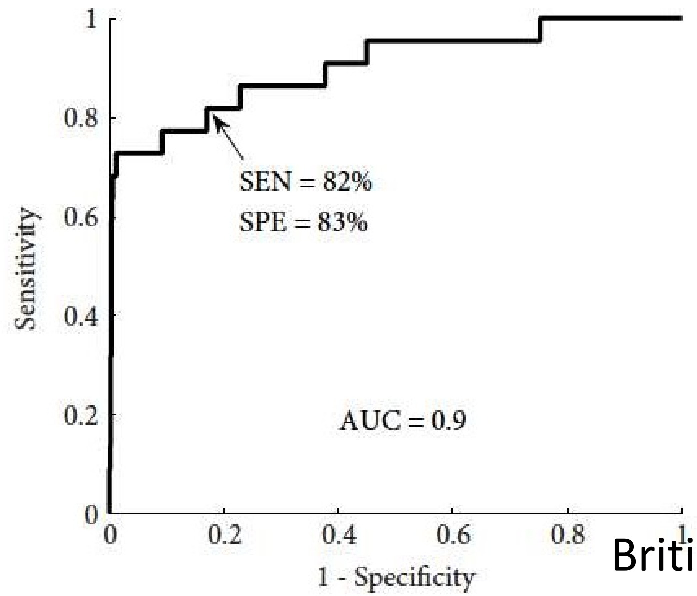
CASE STUDY - PROSTATE CANCER DETECTION
STEP 4 : MACHINE LEARNING MODELS





MODEL 1 :
Detection of res
cancer tissue
surgical marg





MODEL 2
Detection of pr
***vs.* non-prost**
tissue

British Journal of Urology

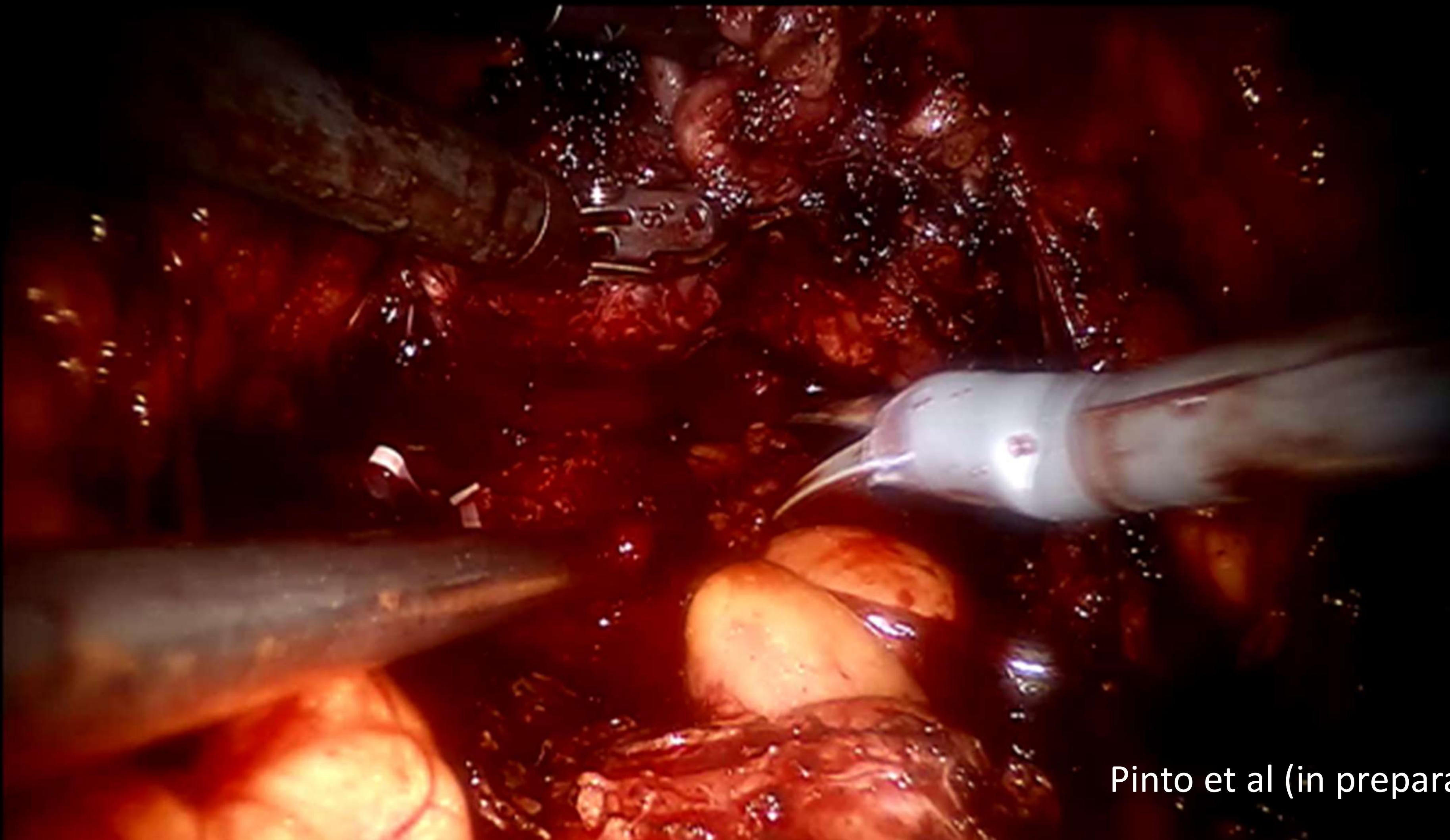
CASE STUDY - PROSTATE CANCER DETECTION
OPTIONAL STEP : BIOCHEMICAL INTERPRETATION

Tissue classes	Band centre, cm^{-1}	Molecular bond assignment	Dominant class	Molecular species	Specific molecules	P
Extraprostatic/ prostatic	573	C–S	Prostatic	Nucleic acids and proteins	DNA/RNA, Tryptophan	$<0.001^{***}$
	625	C–C	Extraprostatic	Proteins	Phenylalanine	$<0.001^{***}$
	856	C–C	Prostatic	Proteins	Collagen, Tyrosine	$<0.001^{***}$
	940	C–C	Prostatic	Proteins	Collagen, Proline	$<0.001^{***}$
	1 004		Prostatic	Proteins	Phenylalanine (breathing)	$<0.001^{***}$
	1 074	C–C	Extraprostatic	Lipids, Proteins, Carbohydrates	Fatty acids, Collagen, Glucose	$<0.001^{***}$
	1 267	C–H	Extraprostatic	Lipids	Triglycerides	$<0.001^{***}$
	1 302	CH_2	Extraprostatic	Lipids	Methylene	$<0.001^{***}$
	1 342	CH_3CH_2	N/A	Proteins and nucleic acids	Collagen, DNA/RNA	0.12^{NS}
	1 448	CH_2	Extraprostatic	Lipids and proteins	Collagen	$<0.001^{***}$
	1 654	C=O/C=C	N/A	Proteins and lipids	Amide I, lipid chains	0.82^{NS}
Benign/ malignant	625	C–C	Benign	Proteins	Phenylalanine	$<0.001^{***}$
	850		Malignant	Proteins	Tyrosine (Aromatic ring)	$<0.001^{***}$
	935	C–C	Benign	Proteins	Collagen, Proline	0.01^{**}
	1 004		Benign	Proteins	Phenylalanine	$<0.001^{***}$
	1 077	C–C/C–O/PO_2	Malignant	Nucleic acids and lipids	DNA	0.004^{**}
	1 127	C–N	Benign	Phospholipids	Biological membranes	$<0.001^{***}$
	1 160	C–C/C–N	Malignant	Proteins		0.001^{**}
	1 254	NH_2	Malignant	Nucleic acids	DNA/RNA	$<0.001^{***}$
	1 303	CH_2	Malignant	Nucleic acids and lipids	DNA/RNA	$<0.001^{***}$
	1 394	C–N	Benign	Proteins		$<0.001^{***}$
	1 448	CH_2	Malignant	Proteins and lipids	Collagen	$<0.001^{***}$
	1 602	C=C	Malignant	Proteins	Phenylalanine	$<0.001^{***}$
GG 1/GG5	655	O–C=O	GG1	Proteins	Histidine	0.001^{***}
	850	C–O–C	N/A	Carbohydrates	Polysaccharides	0.16^{NS}
	900	C–O–C	N/A	Carbohydrates	Monosaccharides	0.061^{NS}
	1 156	C–C/C–N	N/A	Proteins		0.008^{**}
	1 256	Amide III	GG5	Nucleic acids and proteins	DNA/RNA, Amide III	$<0.001^{***}$
	1 448	CH_2	N/A	Lipids and proteins	Collagen	0.79 NS
	1 517	C–C/C=C	GG1	Lipids	Carotenoids	$<0.001^{***}$
	1 604	C=C/	GG5	Proteins	Phenylalanine, Cytosine, Tyrosine	0.001^{**}
	1 654	C=C/C=O	GG1	Lipids and proteins	Lipid chains and Amide I	0.001^{**}

*Univariate analyses of prominent Raman peaks identified by arrows in Figs 3–5A. GG, Grade Group. ***P < 0.001, **P < 0.01, *P < 0.05 and NS, non-significant (P > 0.05). References for band centre, molecular bond assignment and potential molecules for specific peaks are provided in the reference list [17,28–37].*

CASE STUDY - PROSTATE CANCER DETECTION
STEP 6 : INTEGRATION IN SURGICAL WORKFLOW

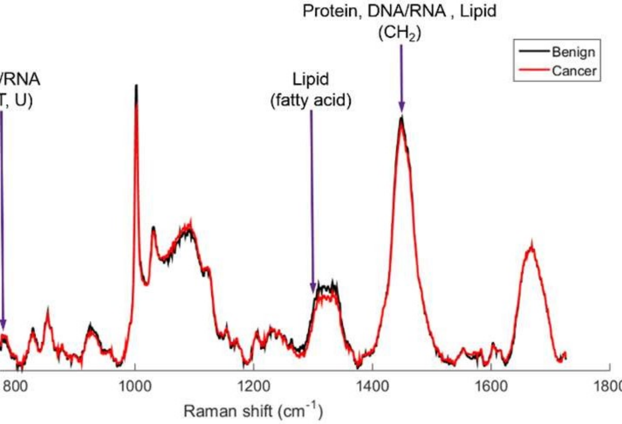
CASE STUDY - PROSTATE CANCER DETECTION
STEP 6 : INTEGRATION IN SURGICAL WORKFLOW



Pinto et al (in preparation)

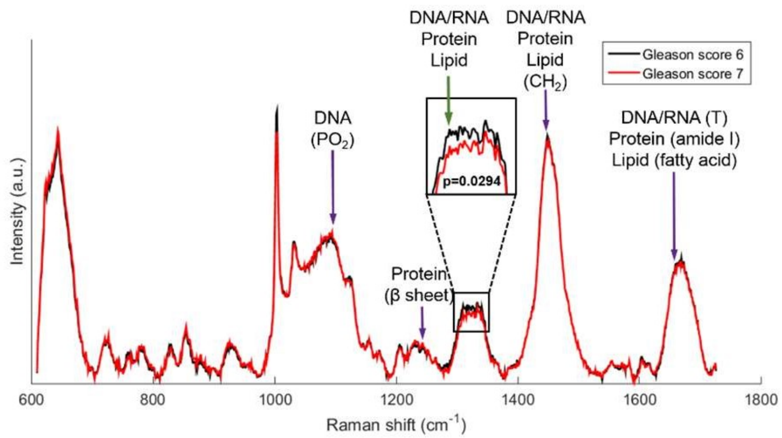
PROBING TISSUE AT MICROSCOPIC SCALES : PATHOLOGY APPLICATIONS IN PROSTATE CANCER

Diagnosis: Normal vs Cancer



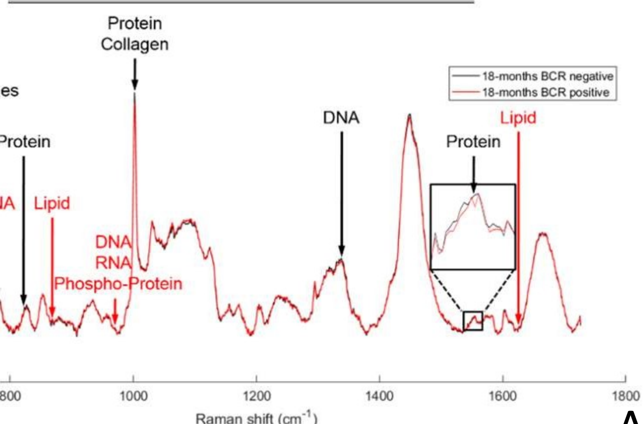
Sensitivity	Specificity	Accuracy
99%	100%	99%

Stratification: Gleason 6 vs 7



Sensitivity	Specificity	Accuracy
98%	96%	97%

Prognosis: Biochemical recurrence (18 months)

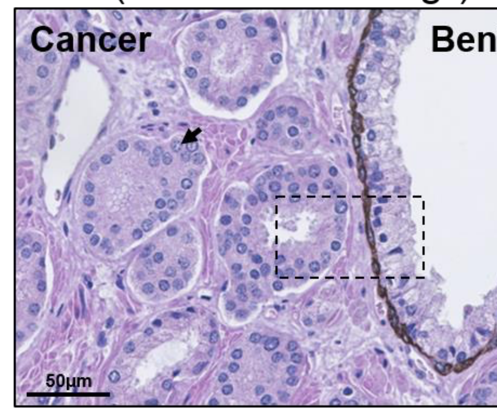


nsitivity	Specificity	Accuracy	AUC
34.0%	83.6%	83.7%	0.89

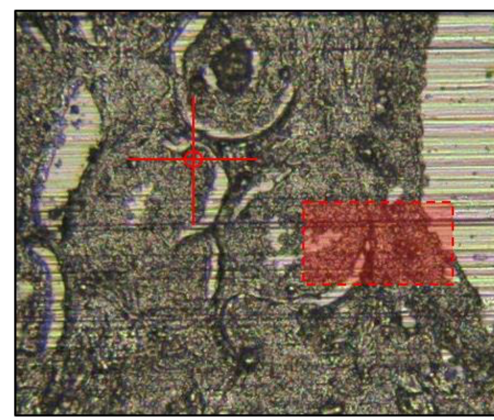
A.-A. Grosset, *publications in preparation*
Collaboration with Dr. Trudel's lab at CRCHUM

Stained slides mappe local Raman measure

Standard histology (H&E-IHC staining[1])

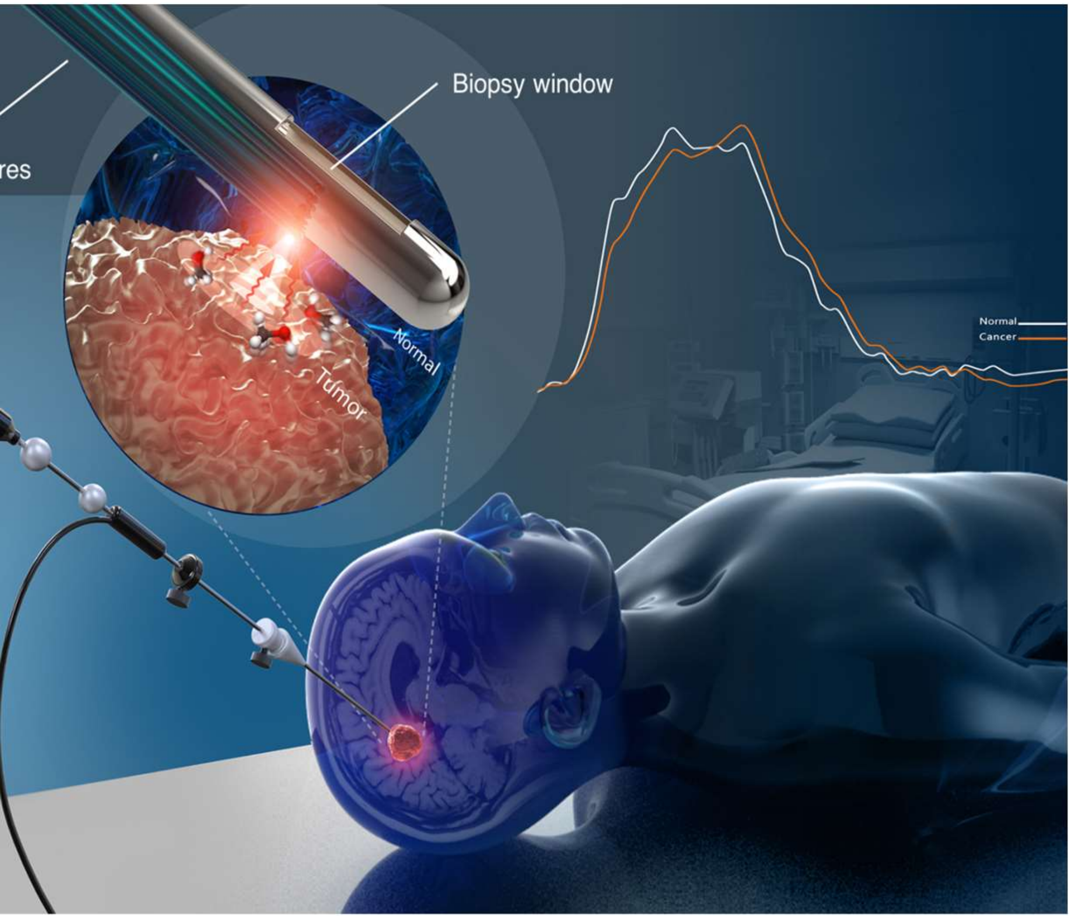


Targeted location for measurement

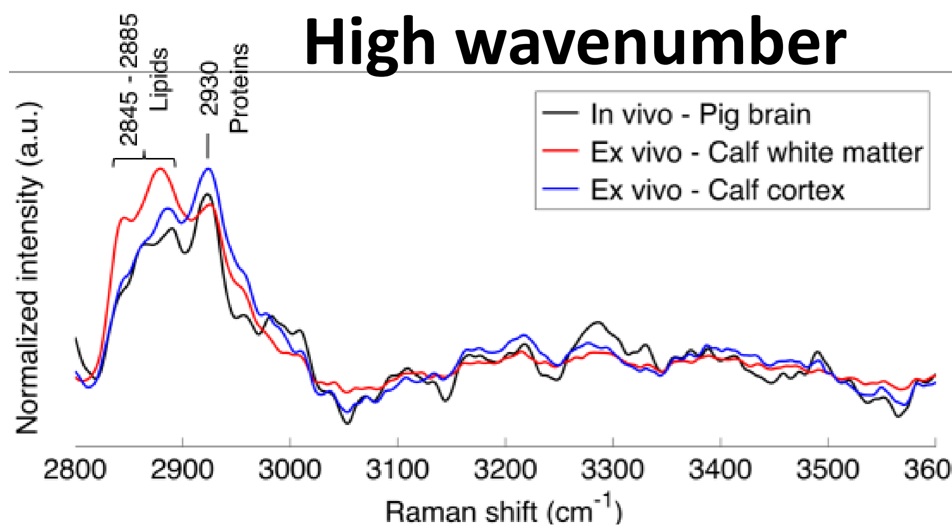


– INTRAOPERATIVE RAMAN DETECTION SYSTEMS AND SPECTS OF CLINICAL TRANSLATION

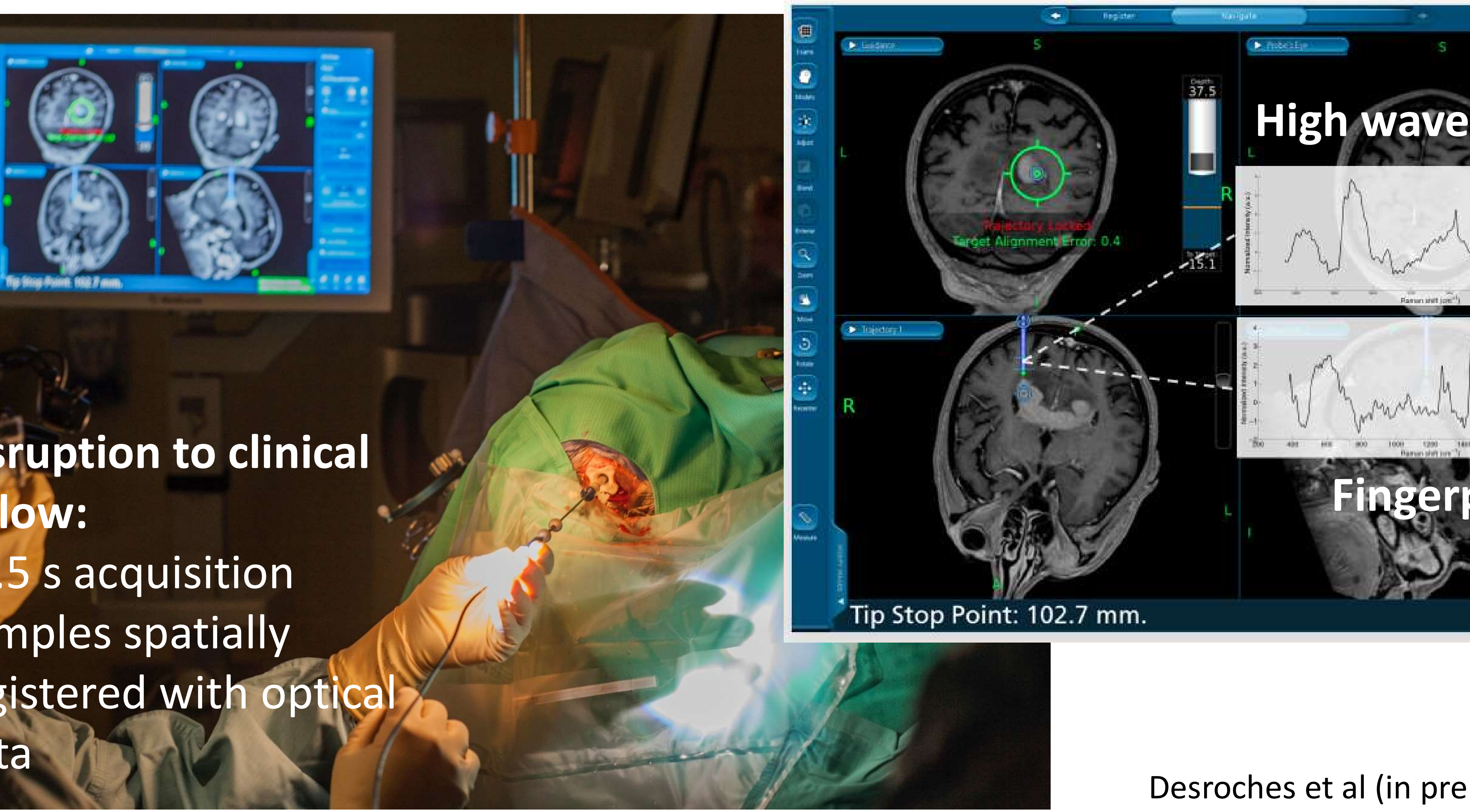
OPTICAL SPECTROSCOPY FOR TARGETED AND REAL TIME *IN SITU* TISSUE BIOPSY



fic Reports (2018)



NTRAOPERATIVE FIBEROPTICS SYSTEM INTEGRATED W
MMERCIAL BIOPSY NEEDLE



**sruption to clinical
low:**

.5 s acquisition

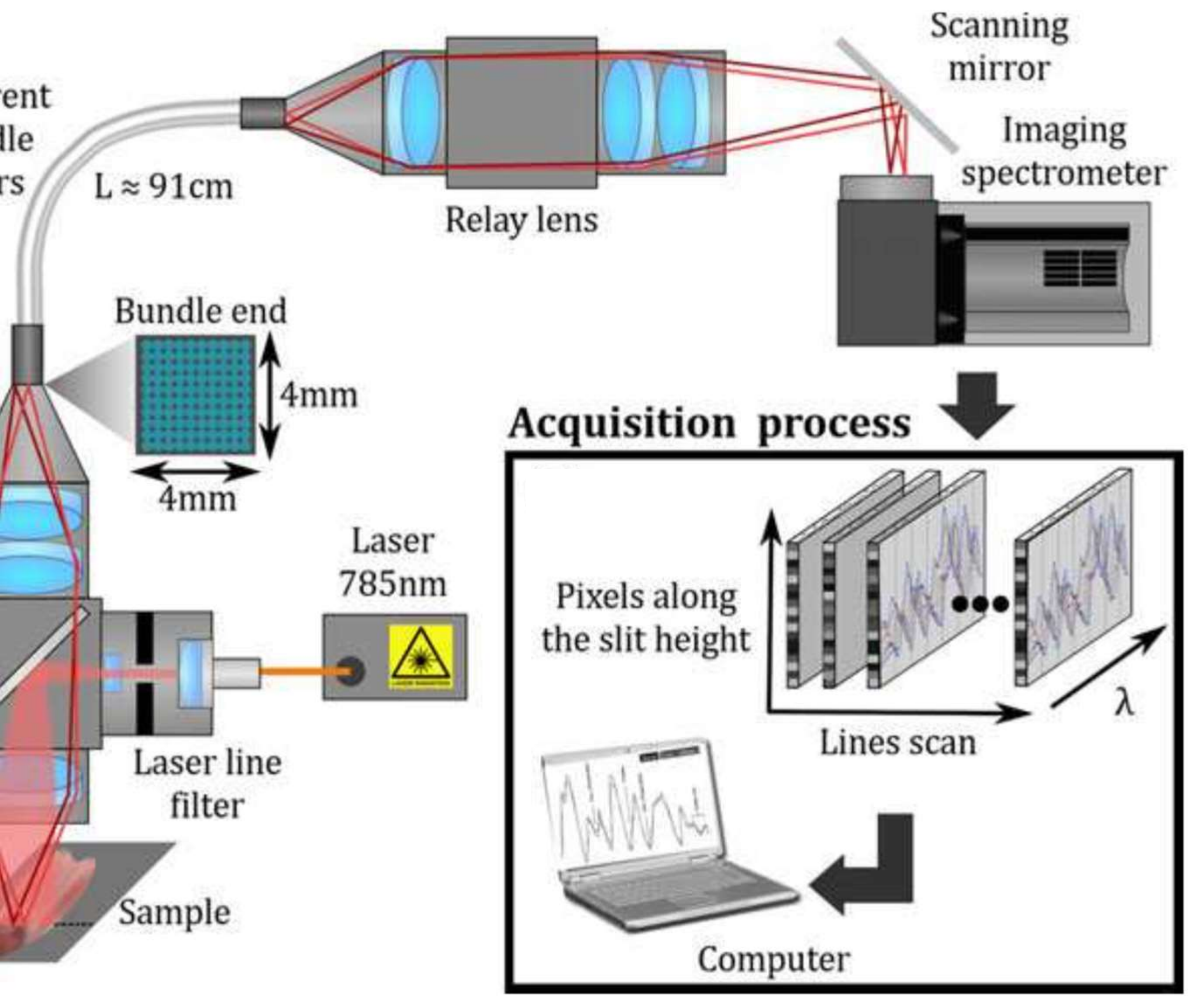
mples spatially

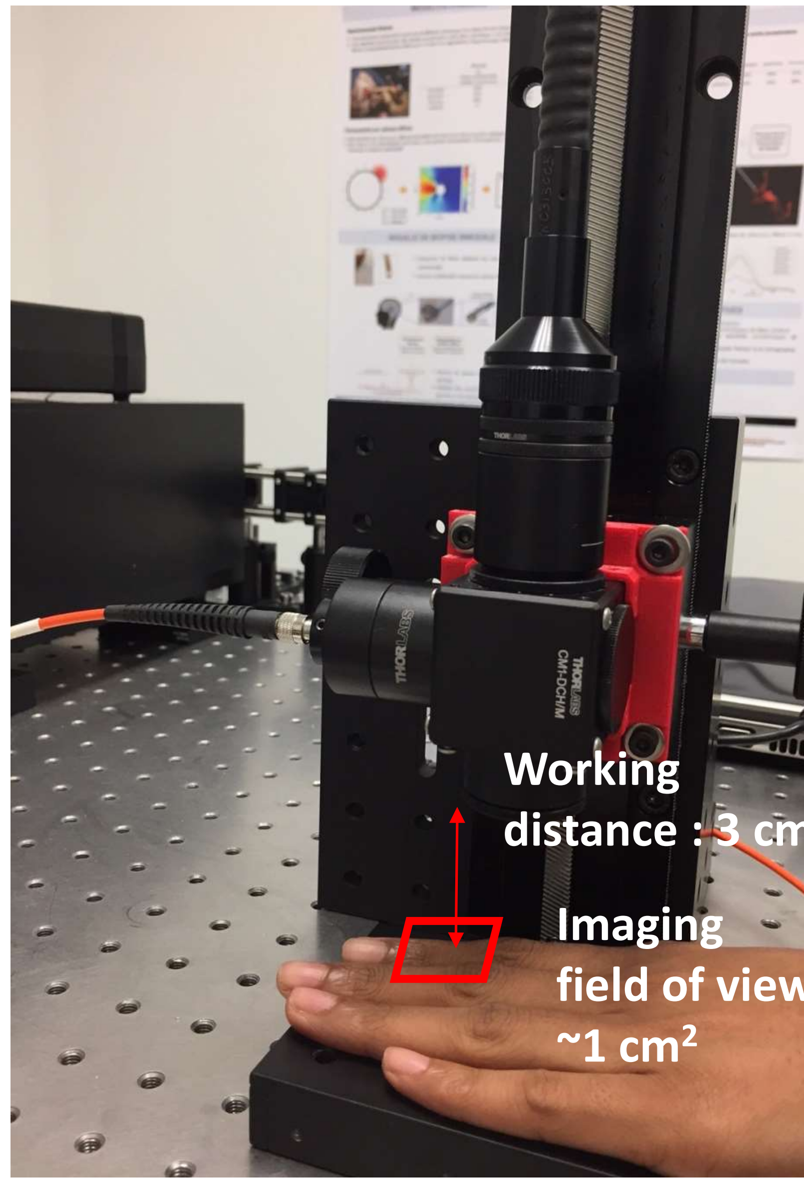
gistered with optical

ta

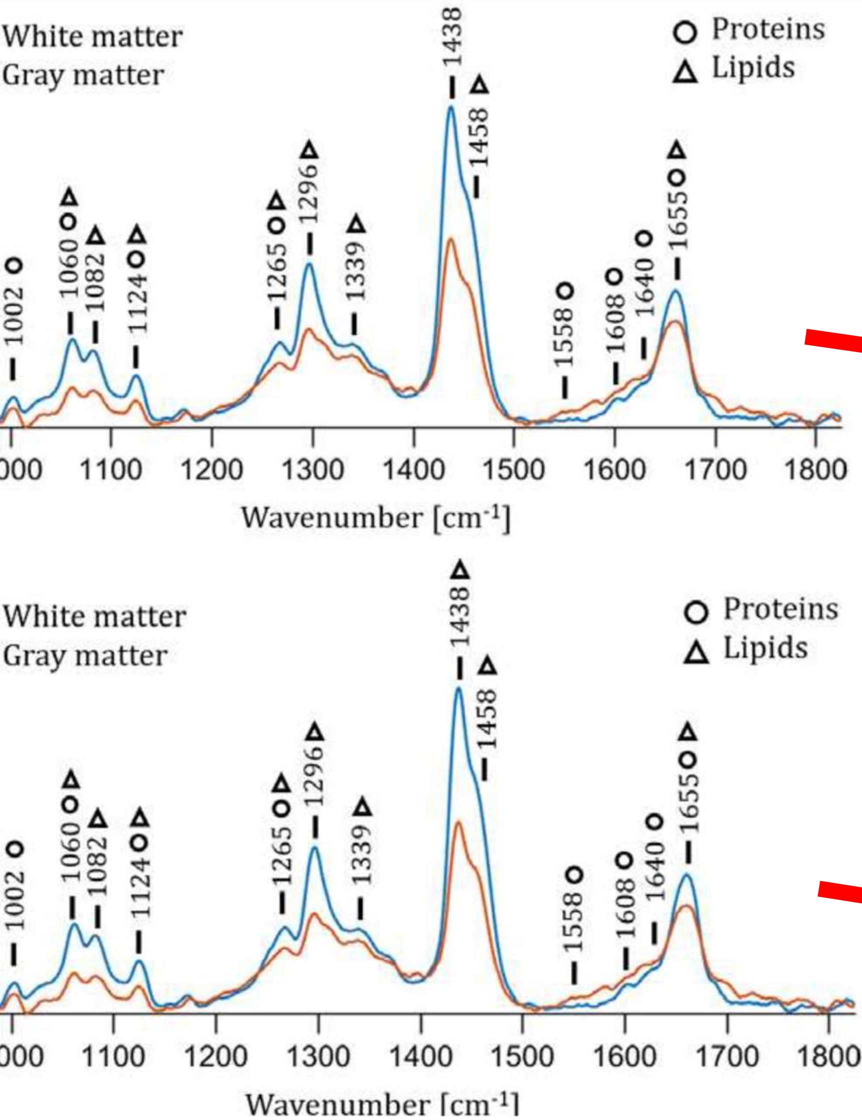
Desroches et al (in pre

WIDE-FIELD LINE-SCANNING RAMAN SPECTROSCOPY SYSTEM





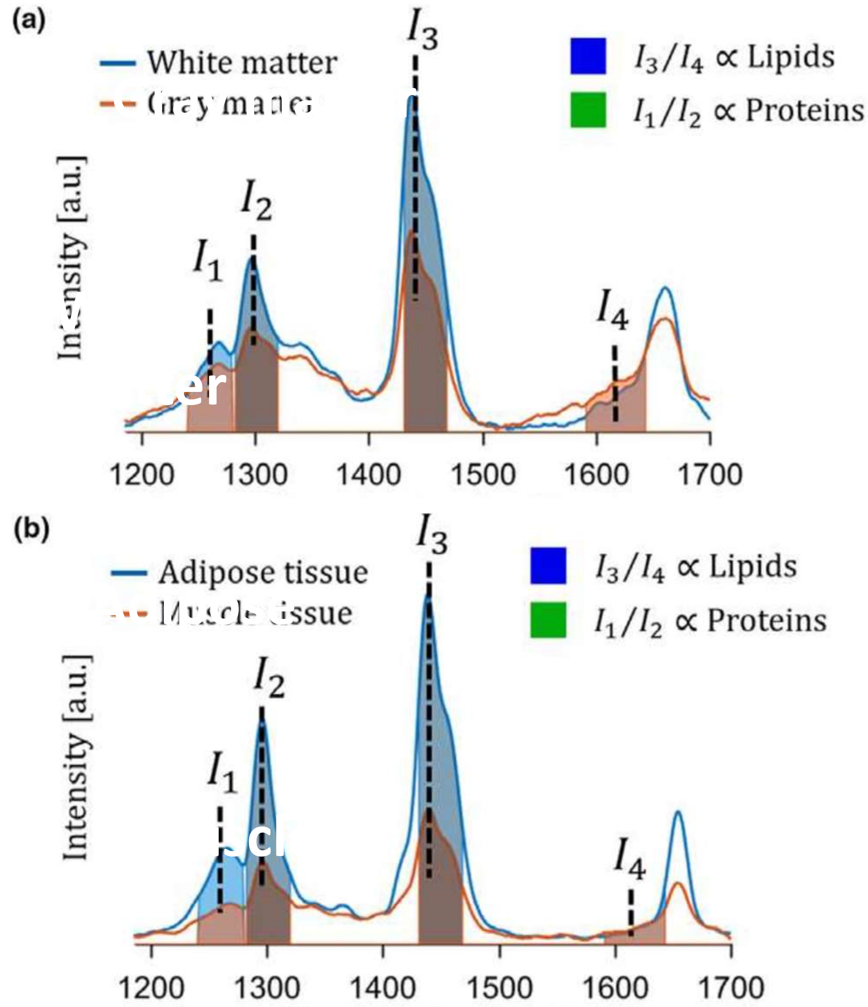
FEATURES EXTRACTION AND TISSUE CLASSIFICATION



tics Letters (2016) Medical Physics (2017)

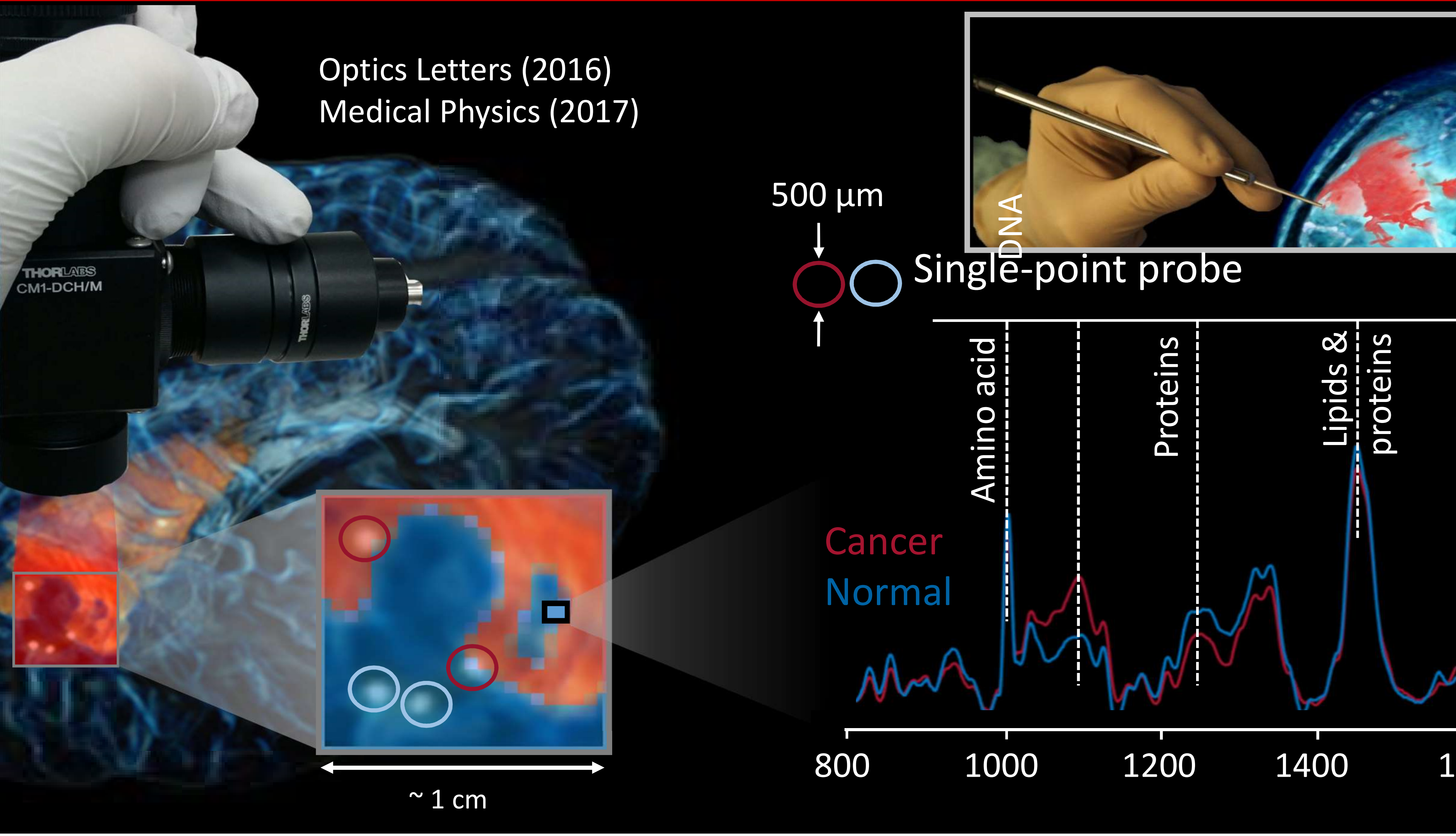
White-light
structure

Raman
molecular

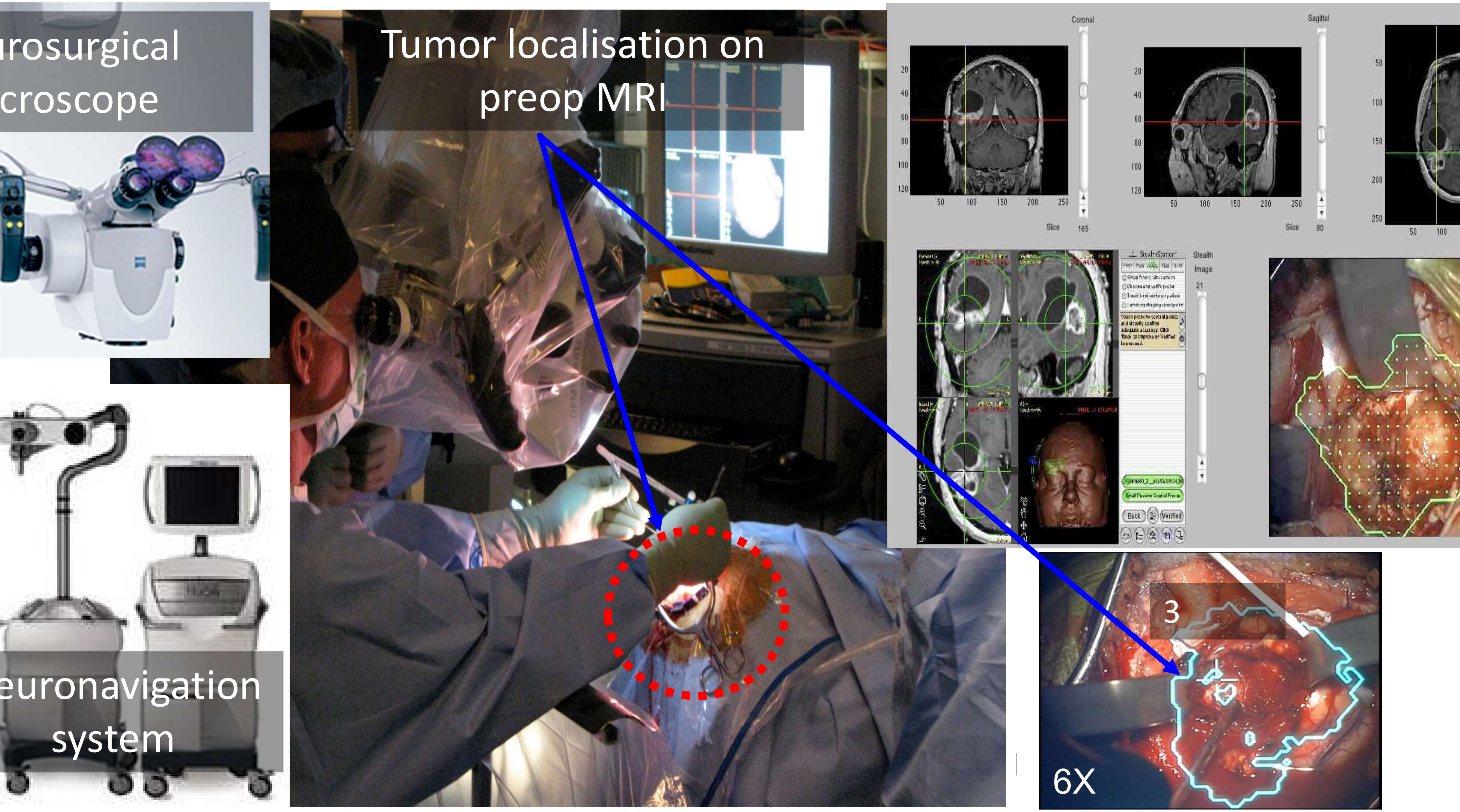


SPATIAL RESOLUTION MATCHES PROBE SYSTEM FOR PIXELIZED TISSUE CLASSIFICATION

Optics Letters (2016)
Medical Physics (2017)

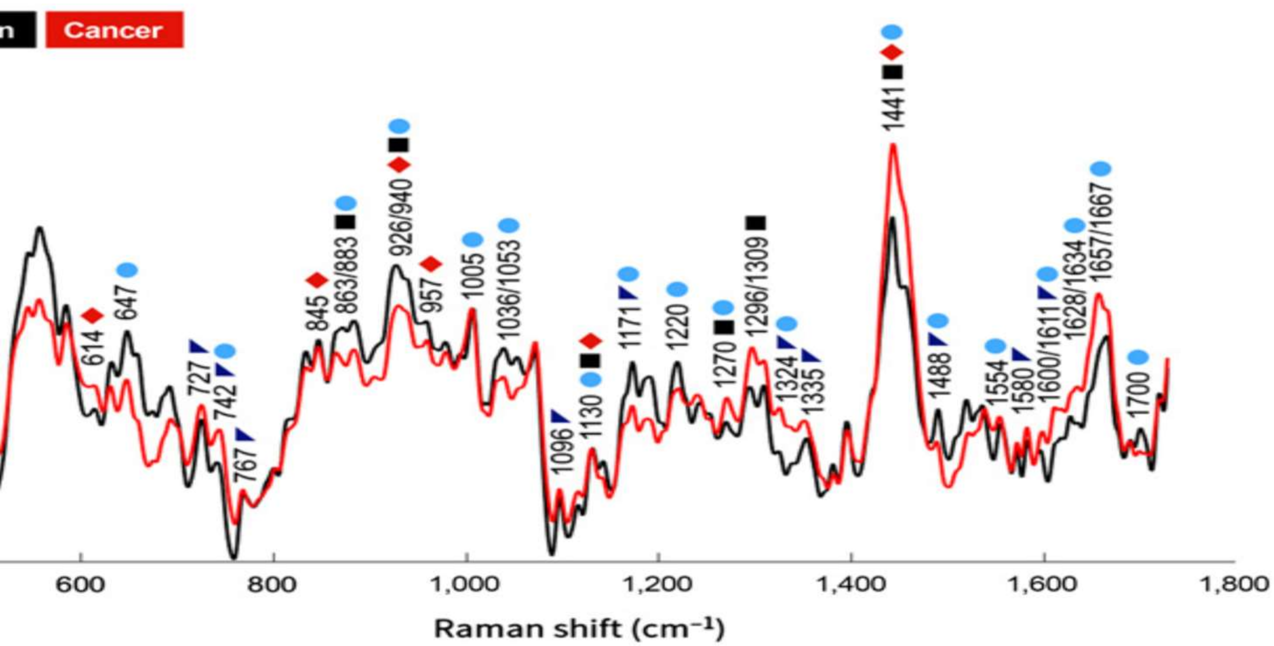


RESECTING TISSUE IN THE BRAIN : HOW-TO GUIDE

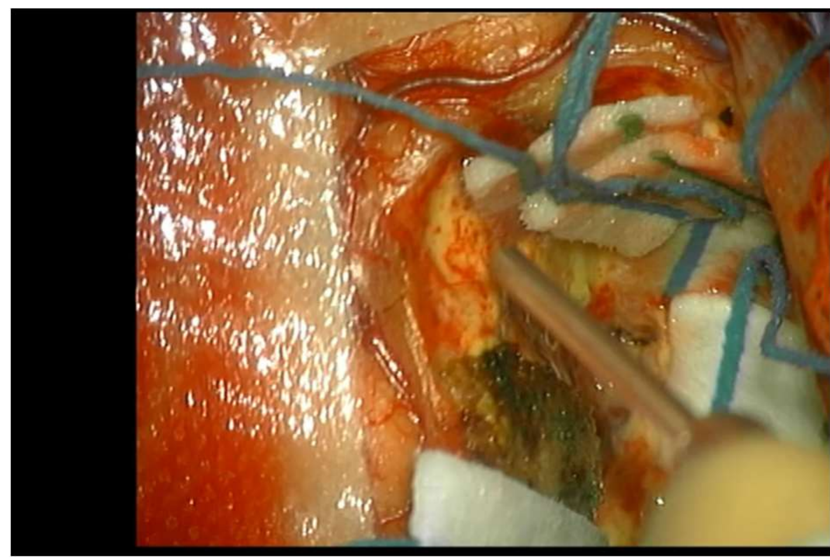


TUMOR RESECTION GUIDANCE IN BRAIN : RETROSPECTIVE CLINICAL STUDIES

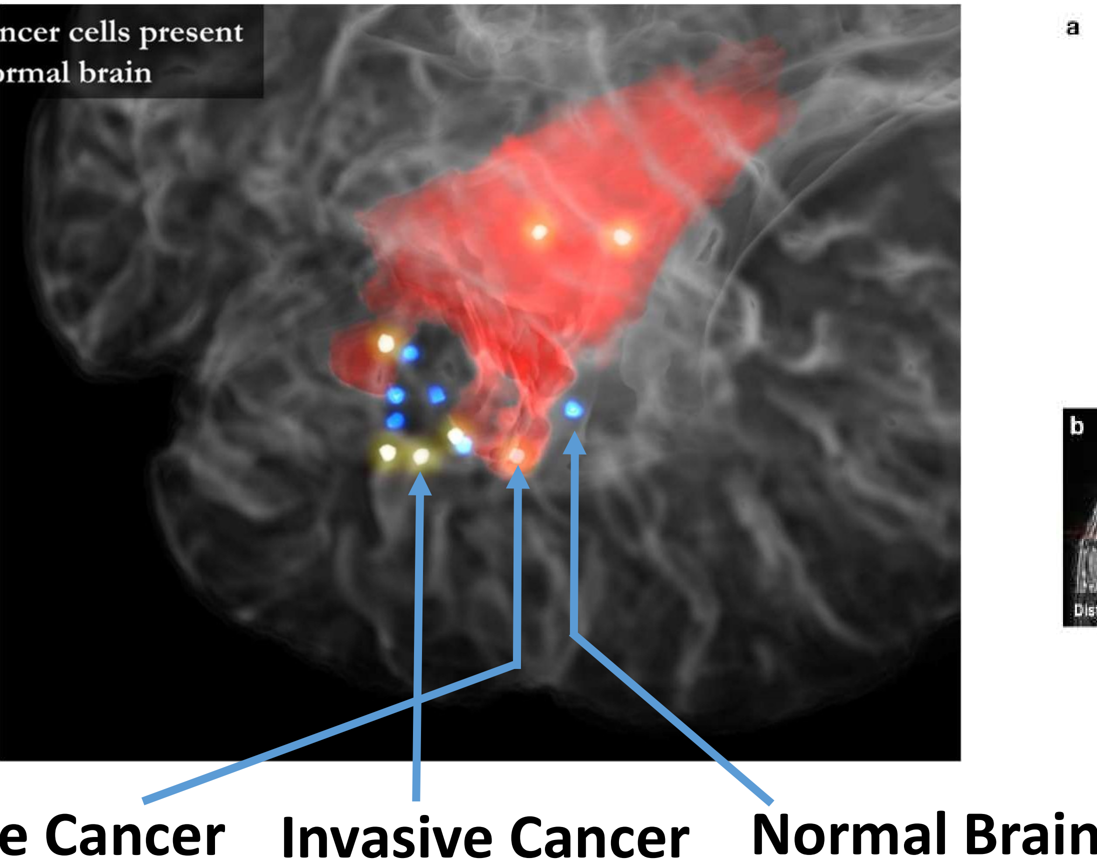
- an probe used *in vivo* for >**140 brain cancer nts** at the Neuro since 2013
- cancer detection sensitivity & specificity ding invasions **up to 2 cm beyond MRI contrast**

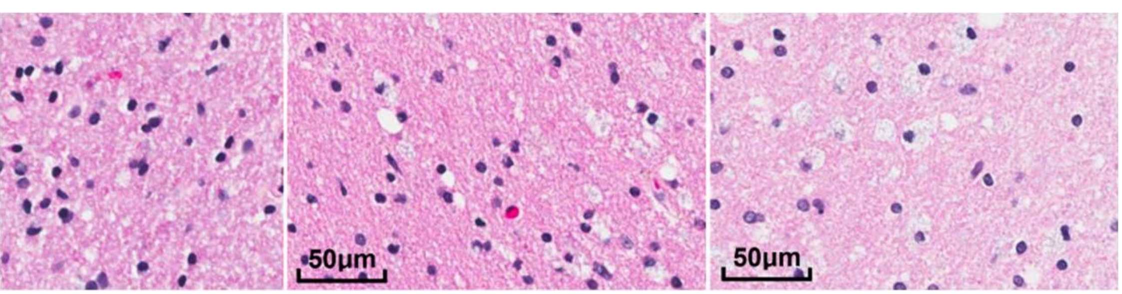


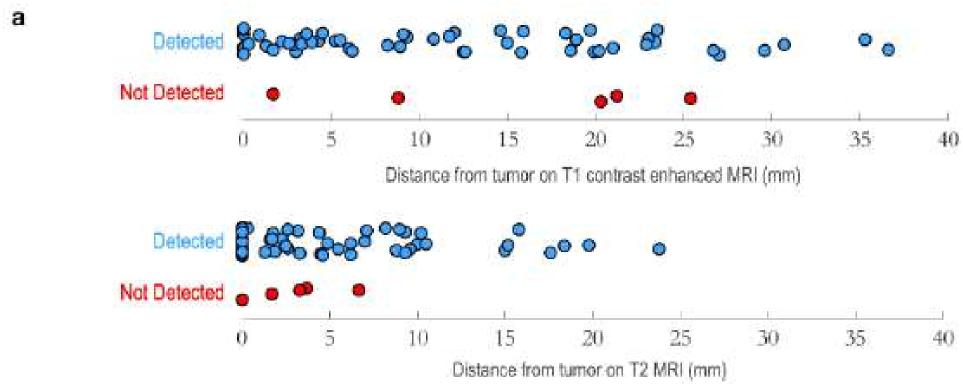
Translational Medicine (2015)
Research (2017)

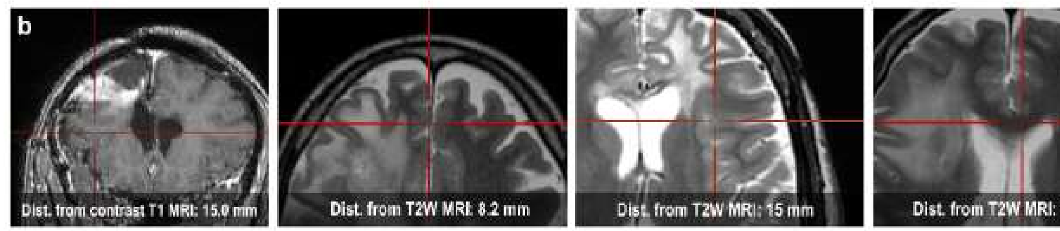


RAMAN SPECTROSCOPY DETECTS CANCER 2-3 CM BEYOND MRI ENHANCEMENT





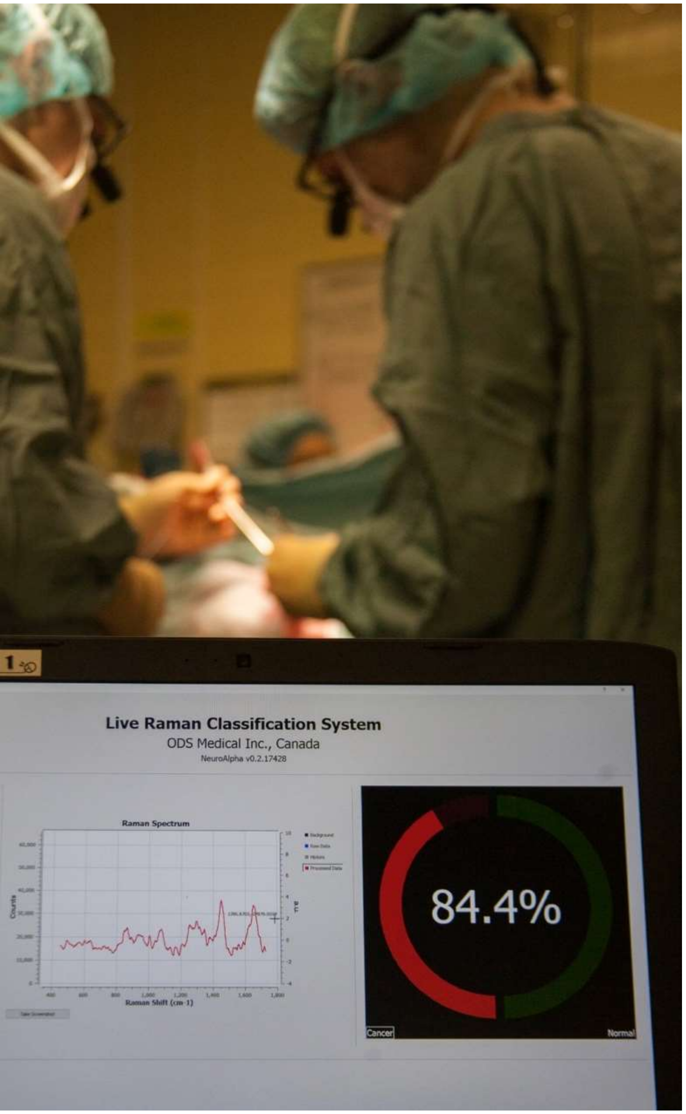




		N patients	*n* sa
WHO grade 2		2	4
	Astrocytoma	1	2
	Oligodendroglioma	1	2
WHO grade 3		4	12
	Astrocytoma	2	5
	Oligodendroglioma	1	1
	Oligoastrocytoma	1	6
WHO grade 4	Glioblastoma	7	44
Total		13	60

Biomedical Optics Express (2016)

ANDOMISED CONTROL TRIAL AT THE NEURO



- Recruitement of **32 glioma patients** (grade 2-4)
- Only first time surgeries
- Randomization at the end of the regular procedure
- Probe and **live ODS classifier** used for 50% of patie
- Tissue interrogation (cancer vs. normal) in **<1s**
- **Clinical metrics:** post-MRI contrast, weight of extra resected tissue, survival

Preliminary results:

- 25 patients completed
- Extra tissue resected in 40% of cases
- **Live classifier** achieves 85% specificity

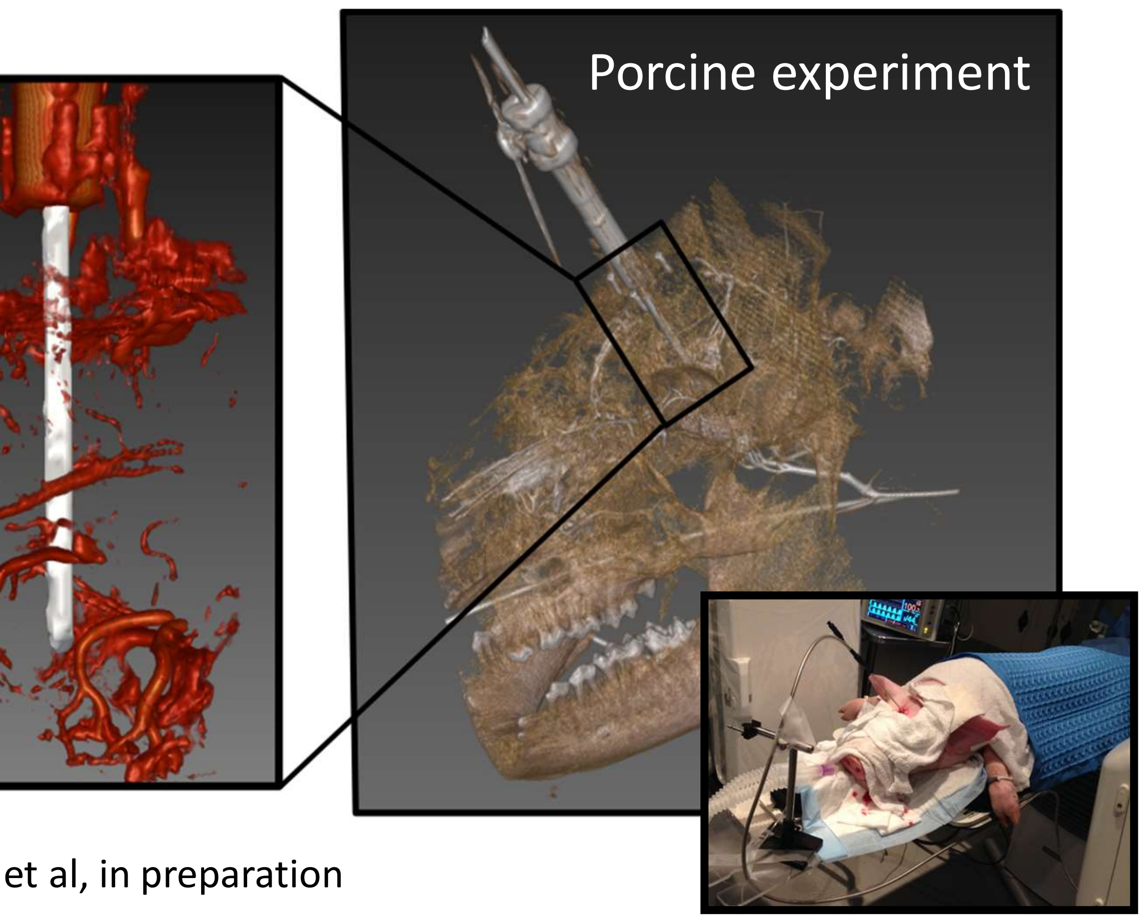
CLINICAL TRANSLATION OF A RAMAN SURGICAL TOOL : PROBLEMS AND SOLUTIONS

s	Ideal solution(s)	Practical solution(s)
odel performance consistency with training dataset tissue sampling y with pathology in statistical modeling	• Automated laser exposure/imaging time routines for SNR optimization • Minimize tissue background signal (*e.g.* AF photobleaching) • Ensure Raman SNR consistent with training dataset • Ensure training dataset captures full normal/benign/cancer tissue heterogeneit • Feature selection optimized with independent dataset • Spatial registration with histopathology and sufficiently detailed reports	
hting specific NIR contributions filter bleed-through	Turn-off all light sources • Only an issue for open surgical procedures	• Device-triggered light shut dow • Physical filtering of all light sou make OR optical device friendly
onse variability and scalability variations between study patients l centers	• Detailed calibration procedure (x-axis, NIST standard, laser power monitoring) • Implement at several time points including before and after sterilization • Monitor changes to ensure data consistency	
ng in surgical cavity uation from absorption mination from blood Raman	Ensure surgical cavity is clean prior to measurement • Possible in neurosurgery, likely unrealistic for several other applications	• Pressure applied with probe leaves negligibl blood • Classification models emphasizing only featu minimally affected by blood • Signal rejection based on presence of blood
nstrument depth sensitivity	Biophysical model for each instrument to evaluate system performance and predic under various tissue conditions	

– OTHER INTRAOPERATIVE IMAGING SYSTEMS : LUORESCENCE AND DIFFUSE REFLECTANCE

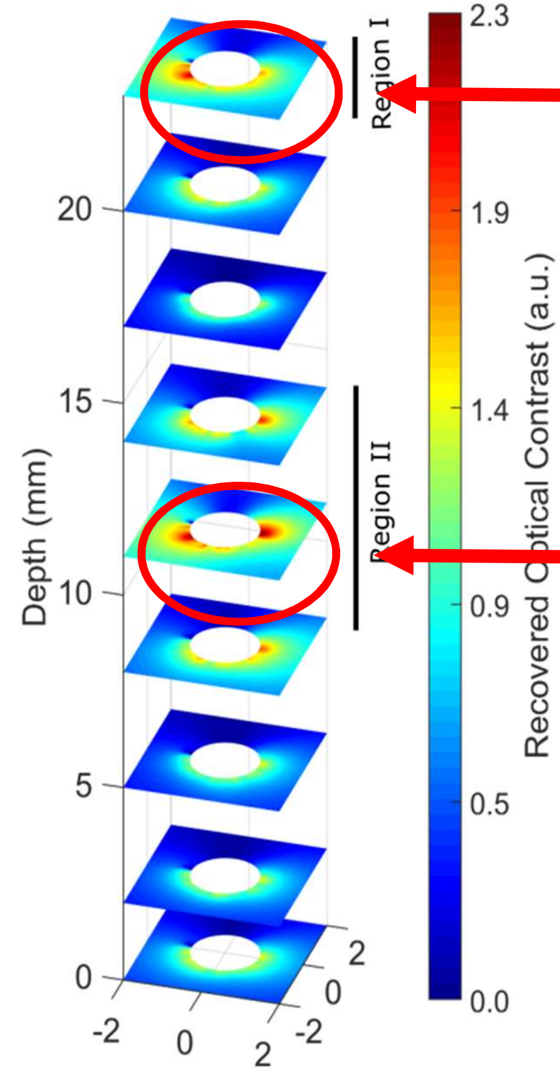
REDUCING HEMORRHAGE RISK DURING BIOPSY SAMPLE HARVESTING

T angiography as gold-standard for vessels detection

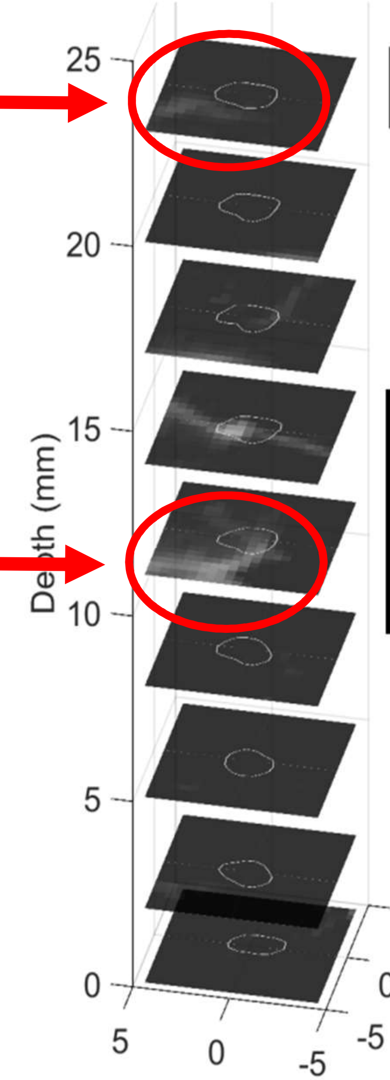


et al, in preparation

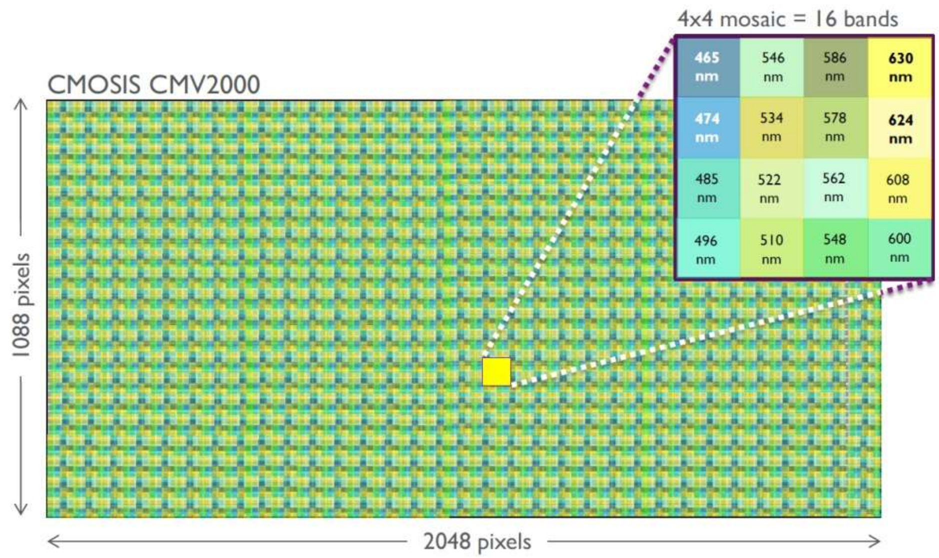
Optical tomography

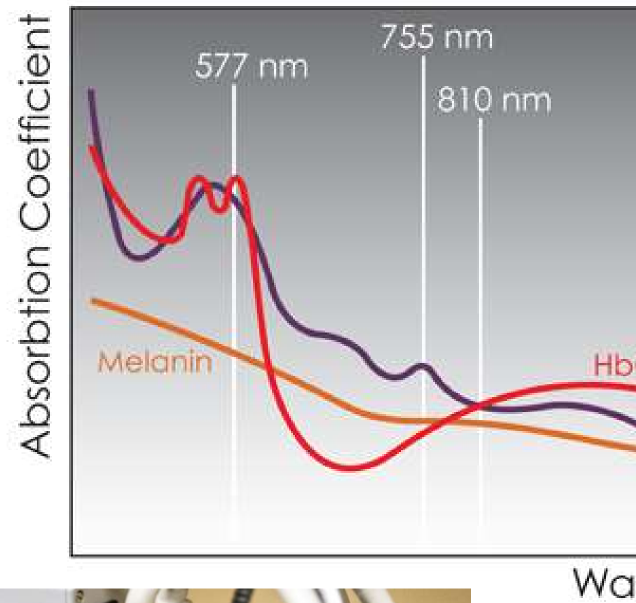


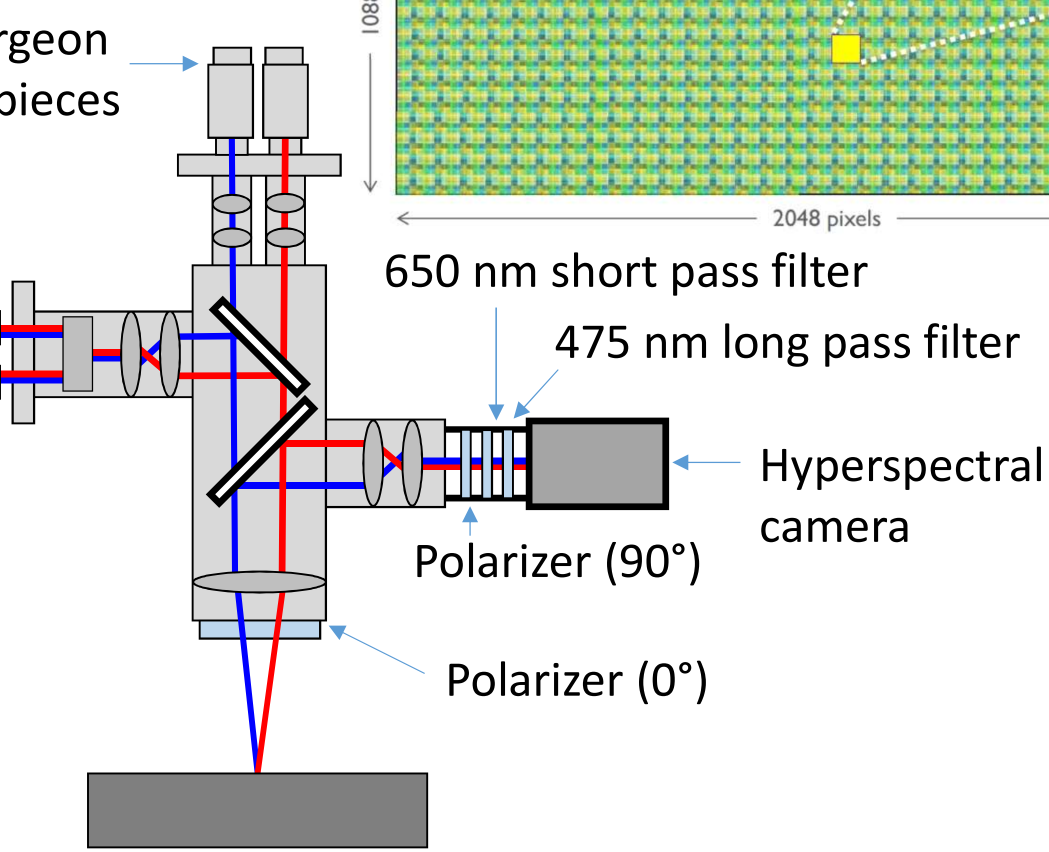
X-ray

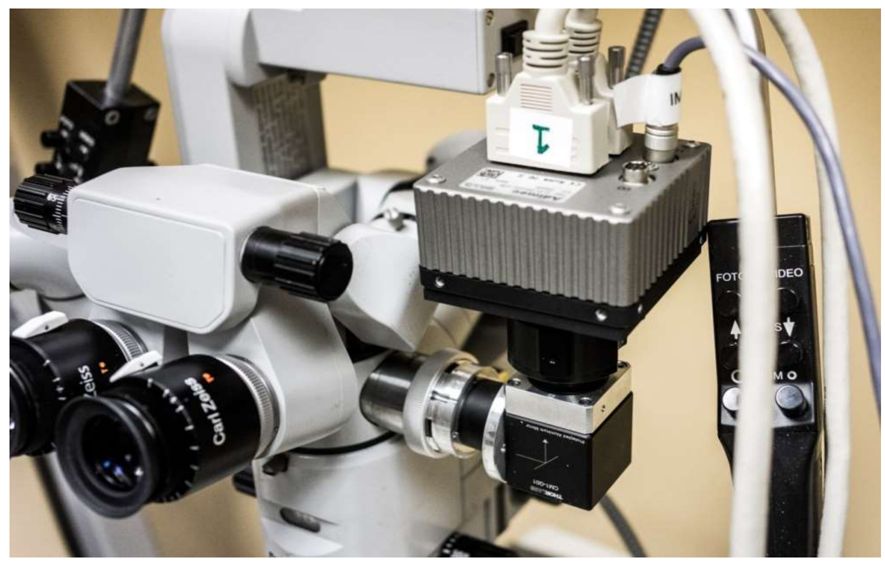


NTRAOPERATIVE HYPERSPECTRAL REFLECTANCE IMAGING

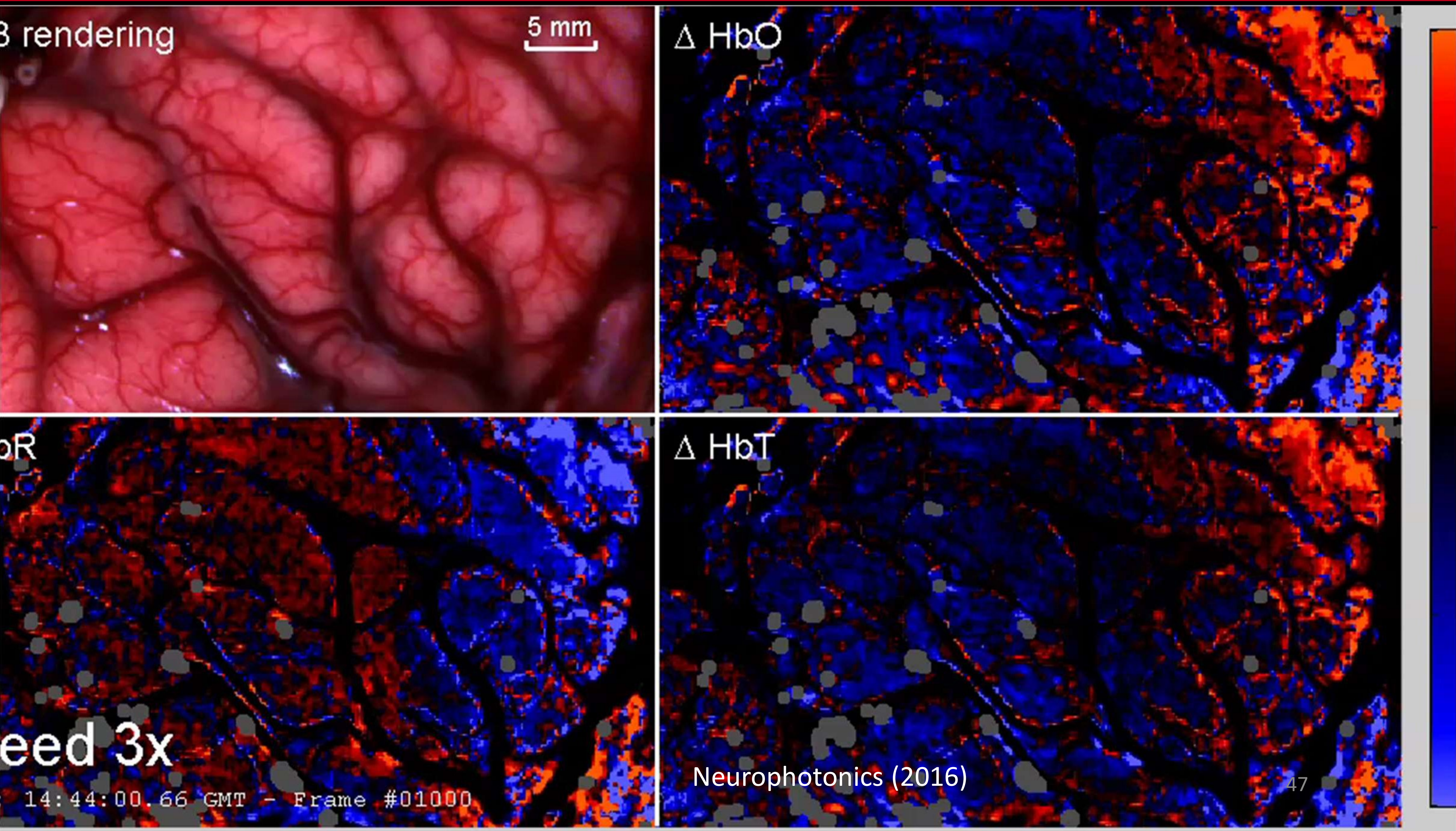






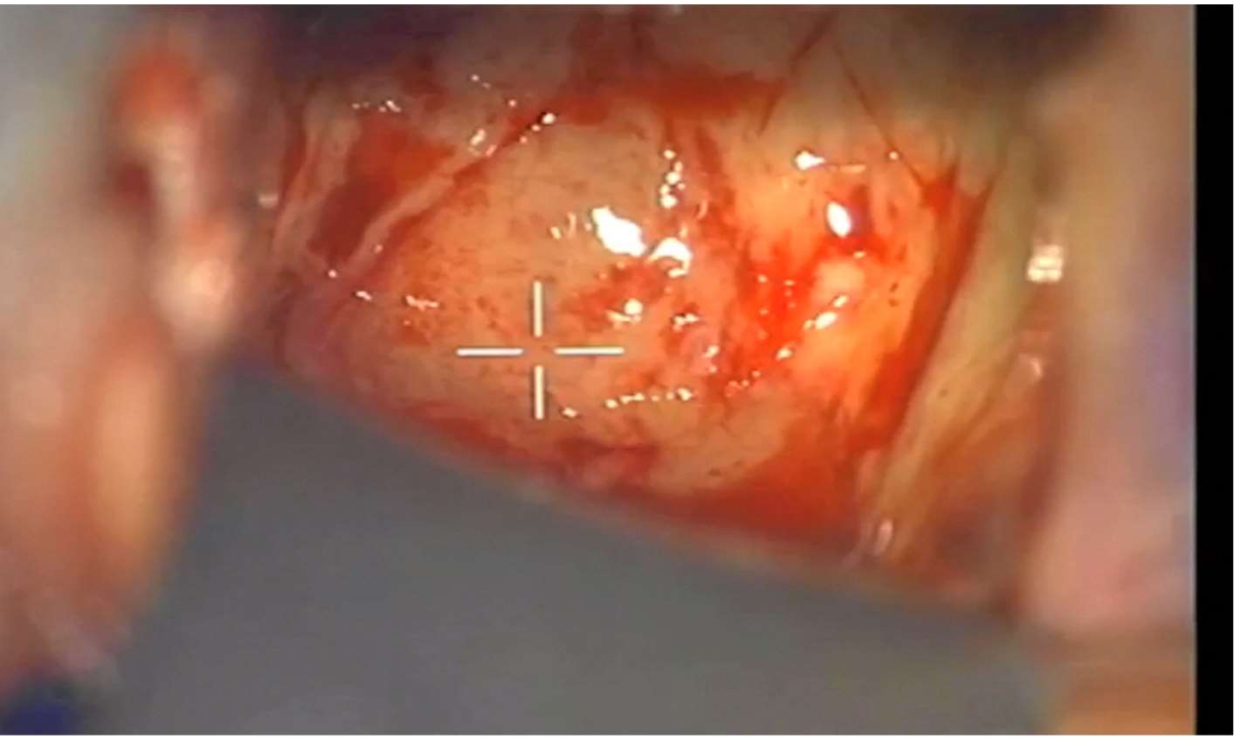


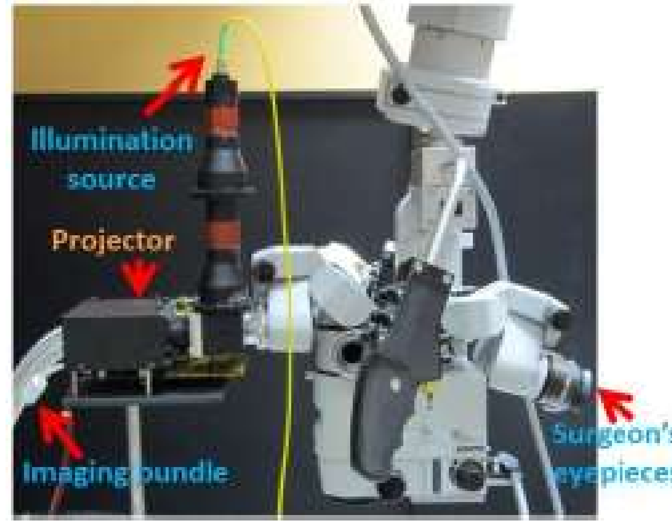
HEMODYNAMIC RESPONSE IMAGING

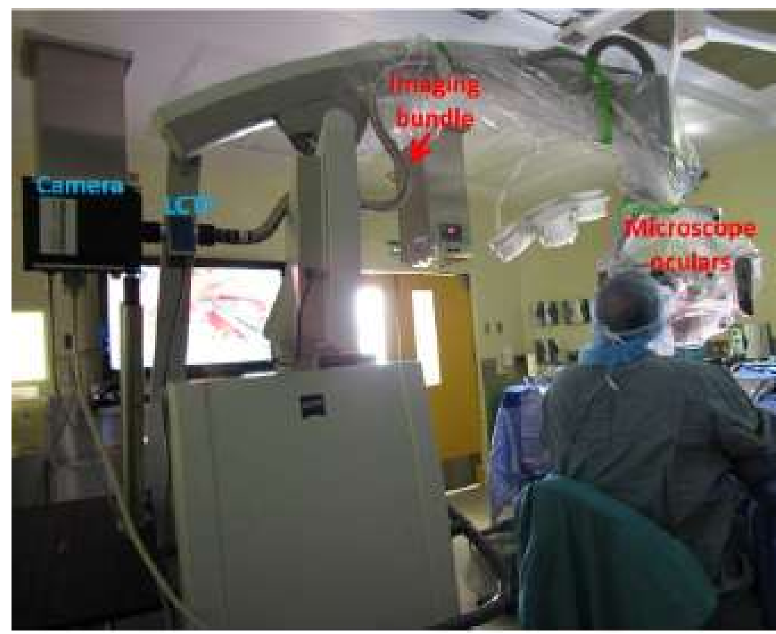


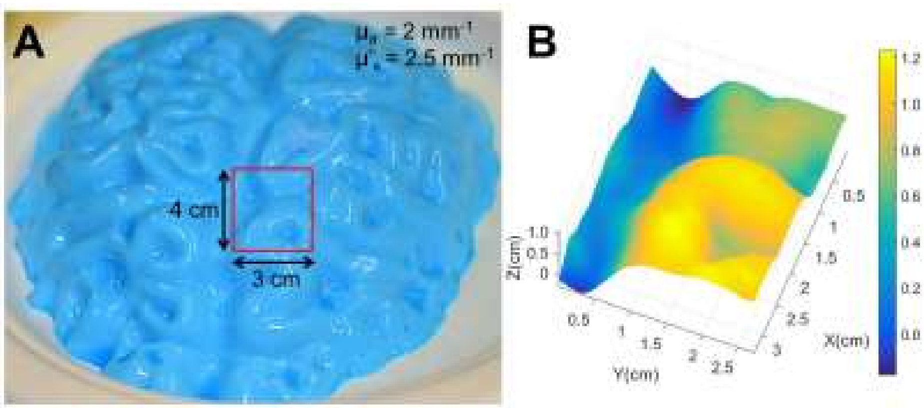
Neurophotonics (2016)

FLUORESCENCE-GUIDED SURGERY









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WORLD-CLASS ENGINEERING

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