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LLNL-TR-747181

Non-Invasive Optical Measurements Final Report CRADA No. TC-1070-94

L. Da Silva, L. Mace

March 2, 2018

Disclaimer

This work performed under the auspices of the U.S. Department of Energy by Lawrence Livermore National Laboratory under Contract DE-AC52-07NA27344.

Non-Invasive Optical Measurements

Final Report
CRADA No. TC-1070-94

Date: February 25, 1998 Revision:

A. Parties

The project is a relationship between the Lawrence Livermore National Laboratory (LLNL) and Novametrix Medical Systems, Inc.

University of California
Lawrence Livermore National Laboratory
7000 East Avenue, L-795
Livermore, CA 94550

Novametrix Medical Systems, Inc.
5 Technology Drive
P.O. Box 690
Wallingford, CT 06492

B. Project Scope

Development and evaluation of Optical Coherence Tomography (OCT) as a new non-invasive medical diagnostic tool for measuring concentration of absorbing species in highly scattering media. Although funding reductions prevented the completetion of the originally proposed project, the key deliverable of a detailed evaluation of OCT for quantitative spectroscopy was achieved.

C. Technical

The main accomplishments of this collaborative project were:

1. Designed and built a fiber based OCT system
2. Quantified the penetration limits of OCT in a variety of tissue including skin, heart, artery, and bone.
3. Designed and tested a dual wavelength OCT system which operated at 1.3 μm and 1.5 μm. Using this system we demonstrated the potential of OCT to measure water concentration in biological tissue.
4. Designed and tested a birefringence OCT system which accurately measured tissue birefringence. Using this system we demonstrated the potential of OCT to diagnose the extent of burn damage as evidenced by a significant reduction in tissue birefringence.

The lack of high-power broadband diode sources which operate at wavelengths below 800 nm currently prevents the development of an accurate OCT based blood oxymeter. However, this technology will soon exist and our current plans are at that time to submit a proposal to our industrial partner.

D. Partner Contribution

1. A pulse oximeter to be used as a blood oxygenation standard.
2. Evaluated OCT results and compared to existing pulse oximeter.
3. Conducted literature searches to identify medical applications of OCT.
4. Performed market studies of potential applications of OCT for medical applications, including battlefield medicine.

No subject inventions were created during the CRADA project.

E. Documents/Reference List

Patent application IL9617B *Multiple-wavelength spectroscopic quantitation of light-absorbing species in scattering media*

CRADA progress report FY95
CRADA progress report FY96
CRADA final report FY97

F. Acknowledgement

Participant's signature of the final report indicates the following:

1) The Participant has reviewed the final report and concurs with the statements made therein.
2) The Participant agrees that any modifications or changes from the initial proposal were discussed and agreed to during the term of the project.
3) The Participant certifies that all reports either completed or in process are listed and all subject inventions and the associated intellectual property protection measures generated by his/her respective company and attributable to the project have been disclosed or are included on a list attached to this report.
4) The Participant certifies that if real property was exchanged during the agreement, all has either been returned to the initial custodian or transferred permanently.
5) The Participant certifies that proprietary information has been returned or destroyed by LLNL.

Les Mace 4-6-98

Les Mace Date
Novametrix Medical Systems, Inc.

7/17/98

Luiz B. Da Silva Date
Lawrence Livermore National Laboratory

Attachment I Final Abstract
Attachment II Project Accomplishments Summary
Attachment III Final Quarterly Report
Attachment IV Diagrams

Non-Invasive Optical Measurements

Final Abstract
Attachment I
CRADA No. TC-1070-94

Optical low-coherence reflectometry (OCLR) is a non-invasive optical technique for imaging into highly scattering media. In this collaboration, LLNL and Novametrix Medical Sytems, Inc. evaluated the potential of OCLR to measure the concentration of blood constituents. A fiber optic scanning OCLR system was developed and used to measure the penetration limits into a variety of animal tissue. The results indicate that OCLR can probe up to 3 mm into tissue and accurately measure the transversed path length and the total attenuation coefficient. A dual wavelength OCLR system operating at 1300nm and 1500nm demonstrated the use of this technique to quantify water content in human skin. Additional optical sources operating at different wavelengths will allow OLCR to be combined with standard absorption spectroscopy techniques. Ultimately, this will provide a safe, inexpensive spectroscopic system able to non-invasively quantify blood constituents several millimeters into tissue.

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Technical Transfer Initiatives Program, P.O. Box 808 L-795, Livermore, CA 94551

Non-Invasive Optical Measurements

Project Accomplishments Summary (Attachment II)
CRADA No. TC-1070-94

Date: February 25, 1998 Revision:

A. Parties

The project is a relationship between the Lawrence Livermore National Laboratory (LLNL) and Novametrix Medical Systems, Inc.

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Wallingford CT 06492

B. Background

Although absorption of light in the wavelength range 600 nm to 1400 nm is low in tissue the high degree of scattering has prevented both imaging and accurate quantitative spectroscopic measurements. For this reason several techniques for discriminating between the scattered and unscattered photons have been developed in recent years. Ballistic photon imaging in which a ultrashort pulse (10^{-14} seconds), is used as the light source and time gated detector used to eliminate the delayed (scattered) photons have achieved good results but are not amenable to clinical systems because of their complexity and cost. Frequency domain techniques like optical low-coherence reflectometry (OLCR) rely on using continuous, broadband light sources and conventional optical detectors to produce a compact and modular device. OLCR in the form of optical coherence tomography (OCT) has been appliced to tissue imaging with demonstrated spatial resolutions of 15 μm in the longitudinal direction and several μm in the transverse dimension. Accurate blood constituent monitoring (O_2,CO_2, anesthesia, alcohol, and glucose) requires a precise measurement of absorption and the photon path length transversed through the tissue. Marrying OLCR with absorption spectroscopy will provide a safe, inexpensive spectroscopic system able to non-invasively quantify blood constituents several millimeters into tissue.

C. Description

The goal of this project was to develop and evaluate the potential of Optical Coherence Tomography (OCT) as a new non-invasive medical diagnostic tool for measuring concentration of absorbing species in highly scattering media. This involved constructing a dual wavelength fiber based OCT system, quantifying the penetration limits in a variety of tissue types and validating the underlying principles of quantitative OCT.

D. Expected Economic Impact

Although the lack of broadband spectral sources operating at the necessary wavelengths has limited the development of a practical new device, we expect this soon to change as the diode technology evolves. Ultimately quantitative OCT will play an important role as a low cost and accurate non- or minimally invasive diagnostic tool. This will provide the medical industry with a technique for immediate and continuous analysis and in many cases eliminate the need for expensive laboratory tests.

E. Benefits to DOE

OCT offers the possibility of imaging through highly scattering media with 10-15 μm depth resolution. Important applications of this technology which are important for DOE/DP include: diagnostic of high explosives, imaging inside weapons and battlefield medicine. This project also enhances LLNL's core competencies. For example, this project uses laser program personnel to advance a new technology and will offer a critical test of our radiation transport codes in scattering media. The optical and diagnostic techniques developed through this project are similar to those required for studying scattering in ICF plasmas. The scientists trained as part of this project can play important roles in ongoing DOE/LLNL programs.

F. Industry Area

Medical industry will benefit from this technology. Ultimately compact and inexpensive optical diagnostics will reduce diagnostic time and cost.

G. Project Status

The main accomplishments of this collaborative project were:

1. Designed and built a fiber based OCT system.
2. Quantified the penetration limits of OCT in a variety of tissue including skin, heart, artery, and bone.
3. Designed and tested a dual wavelength OCT system which operated at 1.3 μm and 1.5 μm. Using this system we demonstrated the potential of OCT to measure water concentration in biological tissue.
4. Designed and tested a birefringence OCT system which accurately measured tissue birefringence. Using this system we demonstrated the potential of OCT to diagnose the extent of burn damage as evidenced by a significant reduction in tissue birefringence.

The lack of high power broadband diode sources which operate at wavelengths below 800 nm currently prevents the development of an accurate OCT based blood oxymeter. However, this technology will soon exist and our current plans are that time to submit a proposal to our industrial partner.

H. LLNL Point of Contact for Project Information

Luiz Da Silva
Lawrence Livermore National Laboratory
7000 East Avenue, L-399
Livermore, CA 94550
(510) 423-9867
(510) 424-2778 (FAX)

I. Company Size and Point(s) of Contact

Novametrix Medical Systems Inc., is a publicly owned company with net sales of $28 million and approximately 200 employees.

Industrial Contact:

Les Mace
(425) 882-3500
(425) 869-1923 (Fax)

J. Project Examples

We have data which illustrates the ability of OCT to quantify water content in human skin. A picture of the OCT system and results is included with this package.

K. Release of Information

I certify that all information contained in this report is accurate and releasable to the best of my knowledge.

Karena McKinley, Director
Industrial Partnerships
and Commercialization

7/24/98
Date

RELEASE OF INFORMATION

I have reviewed the attached Project Accomplishment Summary prepared by Lawrence Livermore National Laboratory and agree that the information about our CRADA may be released for external distribution.

Les Mace — 4-6-98

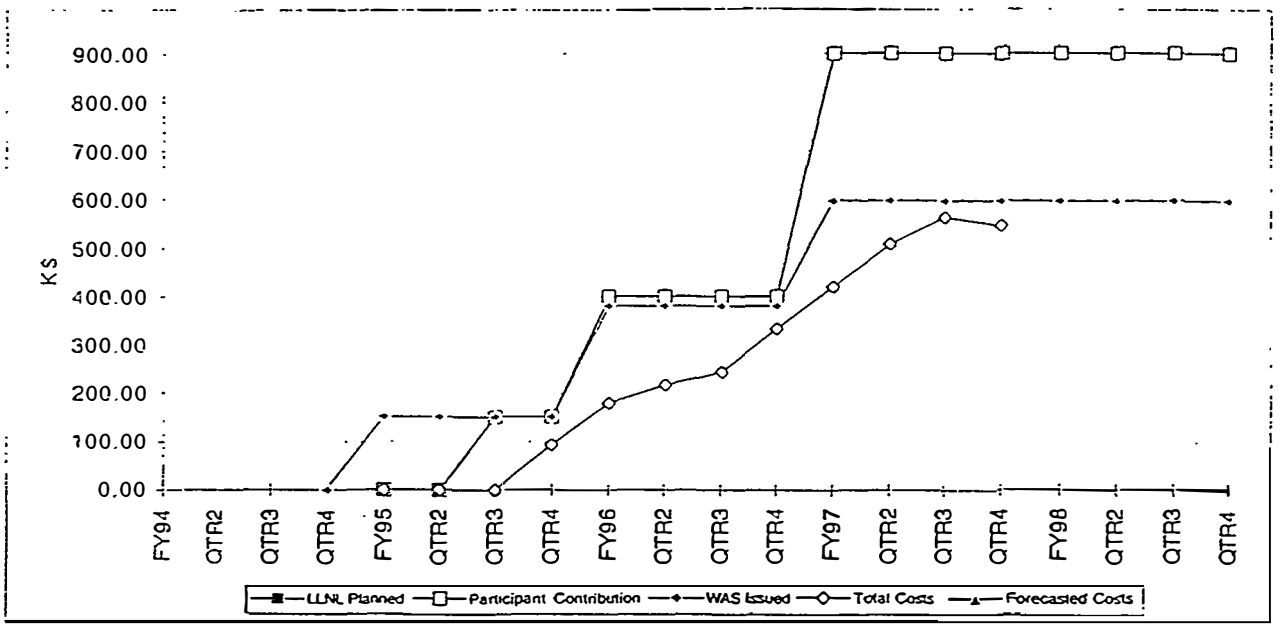
Les Mace — Date
Novametrix Medical Systems, Inc.

Lawrence Livermore National Laboratory

Title:	Non-Invasive Optical Measurements	Reporting Period:	07/01/96 - 09/30/97
Participant:	Novametrix Medical Systems, Inc.	Date CRADA Executed:	6/20/95
DOE TTI No.:	95-LLNL-070-HC	DOE Approval Date:	3/23/95
CRADA No.:	TC-1070-94	Scheduled Ending Date:	6/20/98
Account Numbers:	4755-20	Completion Date:	9/30/97
Accounts Closed:	N/A	B & R Code (S):	DP0301

Approved Funding Profile ($K)

	FY94	FY95	FY96	FY97	FY98	Total
LLNL Planned	0	150	250	500	0	900
Participant In-Kind	0	150	250	500	0	900
Participant Funds-In	0	0	0	0	0	0
WAS Operating	0	150	230	216	0	595
WAS Capital	0	0	0	0	0	0
Total Costs	0	92	241	214	0	547



DP0301	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	FYTD
FY94	0	0	0	0	0	0	0	0	0	0	0	0	0
FY95	0	0	0	0	0	0	0	0	0	29	30	34	92
FY96	33	29	25	27	2	8	15	10	2	19	39	31	241
FY97	17	28	42	22	39	27	20	20	14	-31	1	15	214
FY98	0	0	0	0	0	0	0	0	0	0	0	0	0

547

35DP03	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	Jun	July	Aug	Sep	FYTD
FY94	0	0	0	0	0	0	0	0	0	0	0	0	0
FY95	0	0	0	0	0	0	0	0	0	0	0	0	0
FY96	0	0	0	0	0	0	0	0	0	0	0	0	0
FY97	0	0	0	0	0	0	0	0	0	0	0	0	0
FY98	0	0	0	0	0	0	0	0	0	0	0	0	0

0

STAFF w/phone:

Lab Pt:	Luiz Da Silva (510) 423-9867	Participant:	Philip F. Nuzzo (203) 265-7701
Resource Manager:	Chris Skillern (510) 422-8812		
DOE OAK:	Jerry Scheinberg (510) 637-1653	DOE HQ:	J. Uecke (202) 586-5431

Milestones and Deliverables:

List the complete set of milestones for all phases of the CRADA. Continue on a separate page if necessary.
Report any changes from the original CRADA or previous quarterly report on the CRADA Change Form

	Completion Date: Scheduled	Actual
1a. A document describing a method for measuring optical path length in a non-invasive spectral analyzer	07-96	06-96
1b. A report of a laboratory experiment of a trial implementation method	07-96	06-96
2a. A document describing the design of a prototype OCO apparatus	07-97	09-97
2b. A report documenting experimental trials associated with the design	07-97	09-97
3a. A final report on results of the CRADA project	07-98	09-97

Verification of participants' in-kind contribution was made in accordance with LLNL policy. Explain basis of verification. Please initial YES X NO

List any subject inventions by either party (include IL# for LLNL inventions), additional background intellectual property, patents applied for, software copyrights, publications, awards, licenses granted or reportable economic impacts

Patent Application IL-9617 Dual-Wavelength Spectroscopic Quantitation of Light-Absorbing Species in in Scattering Media. Howard Nathel, Harry Cantland, Bill Colston Jr

Accomplishments

Describe Technical/Non-Technical lessons learned (address and be specific about milestones, participant contributions)
Summarize causes/justification of deviations from original scope of work. Continue on a separate page if necessary.

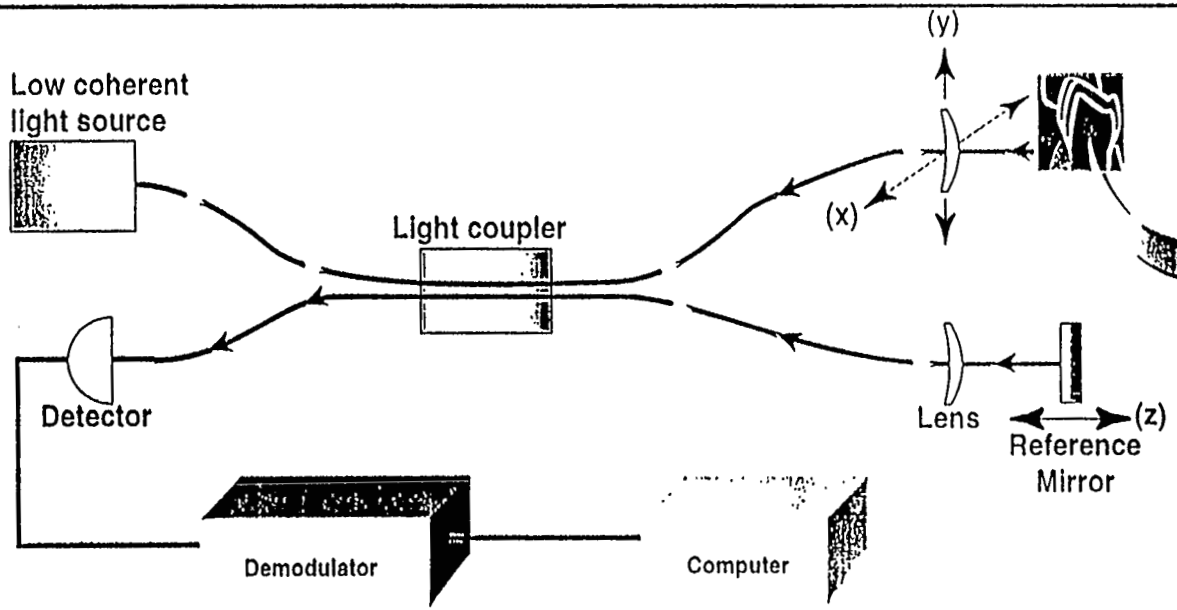
Optical coherence tomography (OCT) was used to measure the concentration of an absorber in a scattering media at a single wavelength. The results indicated, as hoped, that path length information is preserved even at relatively large scatterer concentrations. Thus the feasibility of Beer's Law type measurement using our system was demonstrated. The issue of penetration depth as a function of source power and wavelength was also investigated, using both scattering phantoms and tissue samples. The longer wavelengths, up to about 1300 nm, penetrated the furthest in tissue. Above this wavelength water absorption attenuates the light and limits penetration depth. Currently our penetration depth in tissue is around 1 mm, using a 140 microwatt superluminescent diode centered at 1300 nm wavelength. We are investigating the use of more powerful sources and better electronic filtering of the detected signal to increase this range. Using a 1500 nm wavelength source we have also been able to perform water quantization experiments which demonstrate the potential of OCT as a non-invasive medical diagnostic tool. The lack of high power broadband sources which operate at wavelengths below 800 nm currently prevents the development of an accurate OCT based blood oxymeter. However, this technology will soon exist which will make it possible to complete the CRADA goal. Overall this CRADA was extremely beneficial and gave LLNL and Novametrix the possibility of evaluating the potential of OCT for both medical and DP applications.

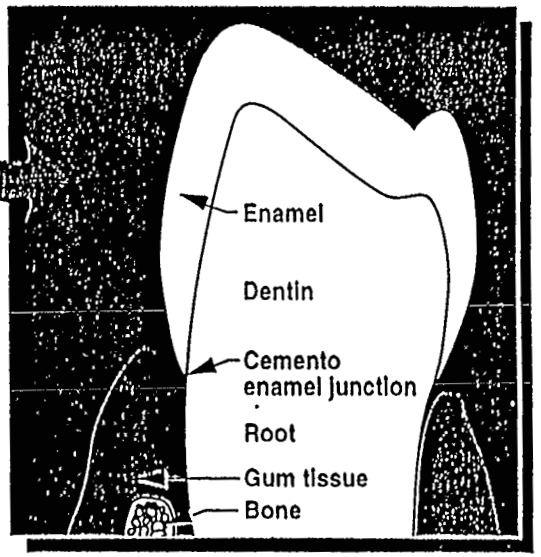
Reviewed by CRADA project Program Manager: Date:

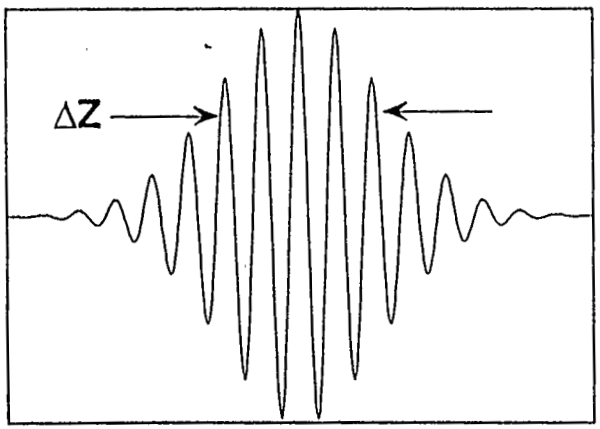
Reviewed by Karena McKinley, Director, LLNL/P&C: Karena McKinley Date: 7/24/98

Direct questions regarding this Report to IP&C Resource Manager, Carol Asher, at (510) 422-7618

We have developed an OCT system for imaging through scattering media





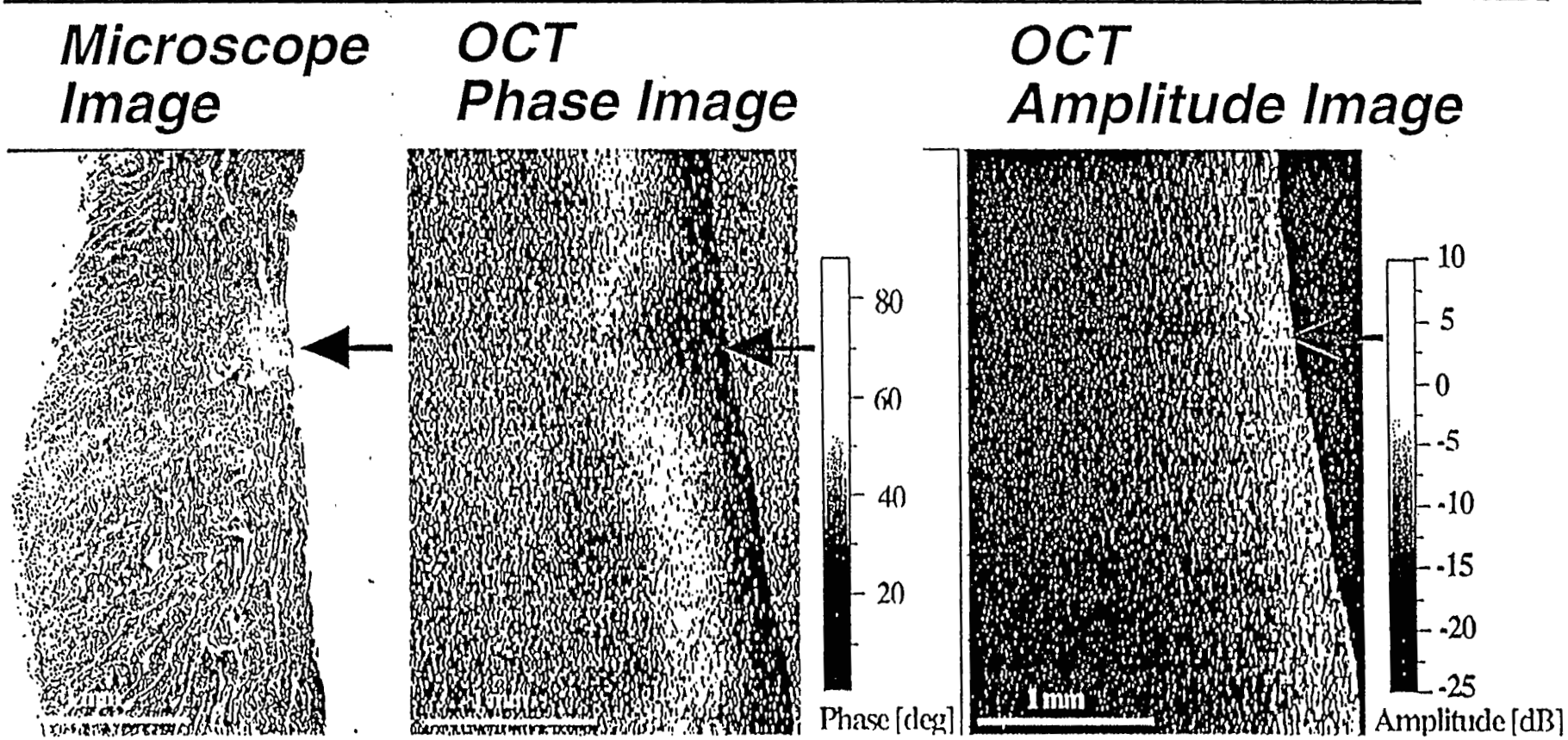


Pathlength mismatch

The spatial resolution is determined by the coherence properties of the light source

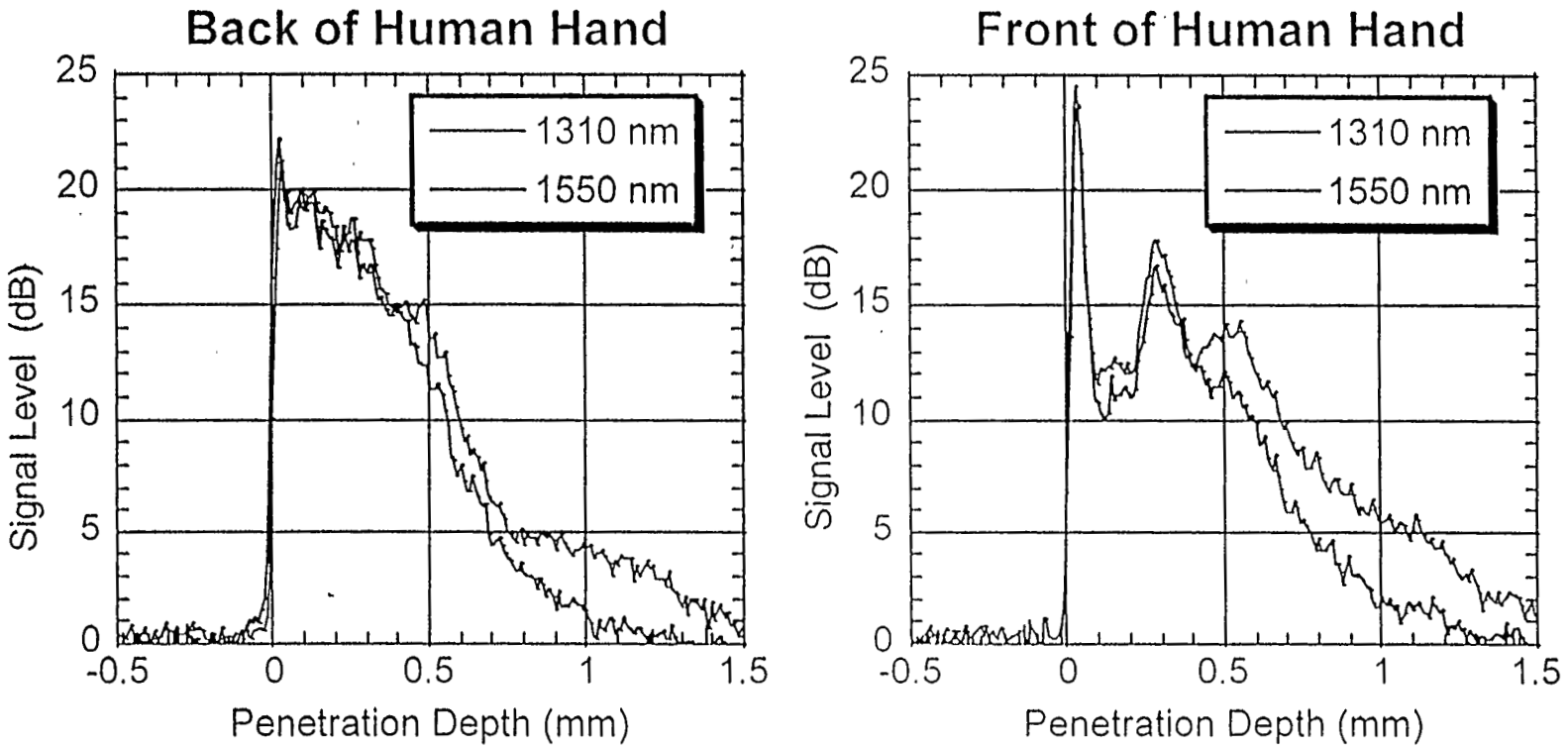
$$\Delta Z = \frac{\lambda^2}{\Delta\lambda} \sim 15\mu m$$

We have developed a dual channel OCT system to measure tissue birefringence



Laser heated region (arrow) shows clear evidence of damage. This diagnostic could be used for burn assessment and to guide treatment.

We have demonstrated a dual wavelength OCT system for water quantitation



Higher absorption of water at 1550 nm leads to faster decay of signal.