Charles Townes Honored as Third Annual Richard C. Lord Lecturer

On May 3, Dr. Charles H. Townes was honored as the third annual Richard C. Lord lecturer, describing his research on "Far Infrared Spectra of Galaxies". Dr. Townes is University Professor of Physics, Emeritus at the University of California at Berkeley. He is known for a variety of researches involving the interaction of electromagnetic waves and matter, and also as a teacher and government advisor. Dr. Townes' principal scientific work is in microwave spectroscopy, nuclear and molecular structure, quantum electronics, radio astronomy, and infrared astronomy. He holds the fundamental patent on masers and, with A. L. Schawlow, the basic patent on lasers.

Professor Townes was Provost and Professor of Physics at MIT from 1961-67. While at MIT, in addition to his work as the Institute's chief academic officer, Dr. Townes conducted research in the Spectroscopy Laboratory, where he discovered the stimulated Brillouin effect, conducted some of the earliest experiments on stimulated Raman scattering and, in collaboration with Ali Javan, performed the first Michelson-Morley experiment using lasers to study the anisotropy of space. In 1964 he received the Nobel Prize for Physics for his role in the invention of the maser and the laser.

The Lord Lectureship was created in honor of Richard C. Lord, a distinguished MIT physical chemist well-known for his research in infrared and Raman spectroscopy of polyatomic molecules. Professor Lord directed the Spectroscopy Laboratory from 1946 to 1976.

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Collision-induced energy transfer has been the subject of active study since the achievement of experimental resolution high enough to resolve variation in linewidths with pressure by the use of grating instruments in the 1930’s. Theoretical work has been extensive and it often seems that an understanding of the current literature requires knowledge of 30 years worth of results and mastery of all the attendant jargon. Theoretical models have included purely phase-changing models, perturbative models with inelastic and phase-changing contributions (Anderson theory variants), approximate non-perturbative methods (corrected sudden approximations, coupled states), and finally, full quantum mechanical calculations (coupled channels). Experimental studies have used many different techniques, and studied many different absorber-perturber combinations.

In spite of this long history, very little of the work has examined systems with “chemically relevant” amounts of energy: amounts of internal energy significant compared to chemical activation energies for unimolecular or bimolecular processes. This is the current frontier for energy transfer studies. Reactive and non-reactive collision events may compete when one of the partners is internally excited. Highly-vibrationally-excited molecules are somewhere on the road to ro-vibrational “chaos,” a hypothetical degree of excitation in which a molecule approaches the “bag of atoms” limit in which it is not possible to distinguish vibration from rotation.

As it becomes possible to study highly-excited systems, a whole new series of questions is opening up in this classical field. New work strives to understand how deactivation and energy transfer processes change as internal energy increases. This large question can be made more specific (some of these questions are especially relevant for CH₄, our current subject of study):

° How do ro-vibrational “propensity rules” and deactivation pathways change as the vibrational level density matches or exceeds the rotational level density for the ground state?
° What specificity remains in collision-induced changes in rigorous or approximate quantum numbers?
° Is there some preservation of “vibrational character?” Are small changes in vibrational quantum number preferred?
° Is vibrational angular momentum conserved?
° Is the nuclear spin at all coupled to the collisional process? Are vibrational swap processes (exchange of vibrational excitation between collision partners) rapid enough to equilibrate nuclear spin species before vibrational deactivation?
° How does the space-fixed projection of angular momentum (M) change?
° Is there a tendency to preserve centrifugal-distortion-induced quantum numbers like kₗ in CH₄?
° What are the general characteristics of the vibrational deactivation process?
° Vibrational levels often cluster because of near-degeneracy between different stretches, and between stretches and bend overtones (in CH₄, dyad, pentad, octad, ...). Are the vibrational levels populated in transitions between vibrational level clusters dependent on the initial level or does equilibration within a cluster occur rapidly, and transition non-selectively?
° Is the amount of energy lost in each collision event strongly dependent on the initial excitation?
° How does intra-cluster relaxation occur? Are there bottlenecks to energy transfer within a polyad?
How does final deactivation to the ground state occur?

CH₄ was chosen for the current series of experiments because of its significance in the analysis of energy transfer dynamics and spectral linewidths in the atmospheres of the outer planets Jupiter and Saturn. Energy transfer and deactivation are also important in combustion.

The current experimental design for the CH₄ experiments has been spectacularly successful. Many, but not all, of the questions we have listed above are explored and answered for CH₄ in this work, at least to some degree [Klaassen 1994]. This is especially important since previous results for vibrationally excited CH₄ exist only at vibrational resolution, with nothing at the single rotational resolution of our experiments. For these experiments, a new combination of pump-probe double resonance has been devised. The apparatus, in the Harrison Spectroscopy Laboratory, is shown in Fig. 1. It depends on

- A pulsed pump laser, the STI pulsed Ti-Sapphire laser (40 mJ, 2 nsec. Fourier Transform limited pulses (3 mJ at 4000 cm⁻¹ after Raman shifting).
- A CW IR probe — a liquid N₂ cooled MBE diode laser for about 3000 cm⁻¹ (CH₄ ν₃ region with a fast InSb detector.
- A trigger system to synchronize the locking dither signal on the diode laser to the firing of the pump laser. Also important were an isolation transformer to reduce electrical pickup, and narrowband optical filters to suppress scattered light.

The CH₄ vibrational levels that play a role in the current experiments are shown in Fig. 2. The dyad levels occur at about 1400 cm⁻¹; the pentad at about 3000 cm⁻¹, and the octad at about 4300 cm⁻¹. We have pumped transitions into the octad, and probed transitions from the ground state to ν₃ and hotband ν₃ transitions originating from ν₄. Both 3-level and 4-level experiments have been performed.

A 3-level double resonance experimental signal trace is shown in Fig. 3 which illustrates the key processes occurring during the relaxation. The pump transition populates a single rotational level in the octad, which is being probed on a hot-band transition originating from the dyad. Rotational relaxation occurs rapidly at the 0.800 mTorr pressure, and is followed by a series of deactivation processes.

The data that we have obtained is so extensive that we can only summarize the principle results on the four main subjects of study:
**PERSONALITIES**

**Dr. Stephen Coy**, a visiting scientist in the MIT Chemistry Department, has been working most recently with Professors Jeffrey Steinfeld, Robert Field and Robert Silbey. His interests include spectroscopy, intramolecular dynamics, and energy transfer in highly vibrationally excited (HVE) systems, the transition between regularity and ergodic or chaotic behavior in HVE systems, analytical models of HVE systems, and pattern recognition methods for the extraction of information from dense, practically unassignable, spectra.

Steve still thinks of himself as a Nebraskan, having grown up in Lincoln, even though he has lived in the Boston area since coming here as an undergraduate at Harvard. During graduate school, continuing at Harvard in Chemical Physics, he was a student of E. Bright Wilson, a great teacher who was acutely perceptive, and who accepted nothing but the highest level of integrity. His friendly and selfless but probing persona continue to be an inspiration. Steve’s other activities include squash, swimming, body surfing, and repairing motorcycles.

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**Dr. Jacques Van Dam** was born in Amersfoort, the Netherlands and came to the United States as a young child. He attended Rutgers University and received his Master's degree in Physiology & Biophysics from Hahnemann Medical College. Dr. Van Dam studied the role of the pancreas in endotoxic shock and for his Master's thesis, conducted a 3-year study of hypertension in primates (rhesus monkeys). He received his M.D. and Ph.D. (Physiology & Biophysics) degrees from Georgetown University School of Medicine in Washington DC. For his dissertation, Dr. Van Dam characterized the role 6-keto-PGE1, a metabolite of prostacyclin, in a variety of animal models and *in vitro* systems.

After moving to Boston in 1984 for his medical internship, residency, and clinical fellowship in gastroenterology, Dr. Van Dam completed a research fellowship in molecular endocrinology at the Wellman Laboratories of the Massachusetts General Hospital. A strong desire to return to gastroenterology led Dr. Van Dam to pursue a fellowship in advanced gastrointestinal endoscopy at the Cleveland Clinic Foundation where he was first introduced to endoscopic laser therapy. As part of his fellowship, Dr. Van Dam participated in an ongoing research project between the CCF and the Laser Biomedical Research Center exploring the clinical applications of laser-induced fluorescence spectroscopy in the gastrointestinal tract. On returning to Boston in 1991, Dr. Van Dam established a collaboration between the LBRC and the Brigham and Women's Hospital to continue locally the work in LIF-spectroscopy he first encountered at the CCF.

Dr. Van Dam became a visiting scientist at the LBRC in 1992 and was named chairman of the Medical Advisory Committee for the LBRC the same year. As chairman of the Medical Advisory Committee, Dr. Van Dam conducts regular meetings of basic medical researchers and clinical investigators that oversee the medical activities of the LBRC. He is currently an Assistant Professor of Medicine at Harvard Medical School and the Director of Endoscopic Gastrointestinal Oncology at the Brigham and Women's Hospital. Dr. Van Dam is a co-investigator (and principal investigator for the Brigham and Women's Hospital) for an NIH/R01 grant entitled "Real Time In Vivo Diagnosis of Dysplasia by Fluorescence". The grant supports a collaborative effort between the LBRC, Brigham and Women's Hospital, and the Cleveland Clinic Foundation to study the application of LIF-spectroscopy to detect premalignant, and therefore potentially curable disease in the gastrointestinal tract. To facilitate experiments to be conducted as part of the recently funded joint research proposal, a newly designed, state-of-the-art laser suite is nearing completion at the Brigham and Women's Hospital that will also serve as a satellite laboratory for LBRC clinical research.
Introduction Laser-induced fluorescence has been extensively investigated as a way of detecting and diagnosing cancer in human tissues. LIF provides significant advantages compared to traditional diagnostic methods, which require histologic examination of biopsy samples, because it has the potential to give information about the biochemical and morphological composition of tissue in real time without any need for tissue biopsy. The diagnostic potential of LIF-based techniques has been evaluated for different types of human tissues. [Alfano RR 1991, Richards-Kortum R 1990]. Detection of precancerous lesions is a particularly promising area, especially in the case of very common cancer types such as colon cancer. The American Cancer Society estimates that colorectal cancer is responsible for 61,000 deaths in the United States every year, and that most of these deaths could be prevented by early detection.

Colonoscopy, the visual endoscopic examination of the internal colon surface, is the standard method of screening for colon cancer. The precursor of colon cancer, known as dysplasia, can occur either as flat lesions or polyps (adenomas). Adenomas are easily detected because of their characteristic shape, but flat dysplasia is invisible to colonoscopy. The detection of flat dysplasia is an important, unsolved medical problem.

In two previous clinical studies [Cothren RM 1990 and 1994] we found that normal colon tissue and adenomatous polyps, excited by low intensity 370 nm light from a pulsed dye laser, exhibit distinct LIF spectra (Figs. 1 and 2). These spectral differences were used to successfully diagnose precancerous lesions. Diagnostic information was obtained empirically from two spectral features, the difference in peak intensity between normal and polyp tissue.
Seminar on

MODERN OPTICS AND SPECTROSCOPY

FALL SEMESTER, 1994

September 27  John Joannopoulos, MIT
The Wonderful World of Photonic Crystals

October 4  Kurt Gibble, Yale University
Laser Cooled Clocks and Cold Collisions

October 18  Michael Courtney, MIT
Periodic Orbit Spectroscopy in Quantum Chaos

October 25  Kyungwon An, MIT
The One-Atom Laser

November 1  Ted Orzekowski, Livermore National Laboratory
New Physics Issues in Indirect Drive Laser Fusion

November 8  David E. Pritchard, MIT
Mass Measurements on Single Trapped Ions

November 15  James Anderson, Harvard University

November 22  Robert Gordon, University of Illinois at Chicago
Passive and Active Control of the Photodissociation and Photoionization of HCl

December 6  Hermann A. Haus, MIT
On the Theory of Optical Quantum Measurement

December 13  David J. Norris, MIT
Using Size-Selective Spectroscopy to Study the Evolution of Quantum Dot Electronic States

TUESDAYS, 11:00-12:00, Marlar Lounge (37-252), Ronald E. McNair Building
Refreshments Served Following the Seminar

Sponsored by George R. Harrison Spectroscopy Laboratory,
Research Laboratory of Electronics, Schools of Science and Engineering,
Plasma Fusion Center and Industrial Liaison Program,
Massachusetts Institute of Technology
and the increased red fluorescence observed in polyps. Remarkably, the accuracy of the LIF diagnosis was as good as that achieved by standard histology. However, the underlying basis for this promising result was unclear.

**Morphological Model** We have embarked on a study to understand the spectral differences in terms of the biochemical make-up of the tissue, and to apply the results to the spectral detection of invisible flat dysplasia. The model we are developing relates the observed fluorescence of the tissue to its microscopic properties. The first step is to identify the morphological structures which fluoresce. Figure 3 shows a histologically stained section of colon tissue illustrating the morphology. The top layer, called the mucosa, consists of tubular “crypts” lined with epithelial cells which secrete mucin and absorb water. The crypts are surrounded by a delicate connective tissue called lamina propria. The lamina propria, mainly composed of collagen, contains tiny blood vessels and inflammation-fighting cells called eosinophils. Beneath this

**Figure 3.** Stained histology section of colon tissue. The important morphological structures are indicated.
MIT Laser Biomedical Research Center  
George R. Harrison Spectroscopy Laboratory  
An NIH Biomedical Research Resource Center

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Research facilities, along with technical and scientific supports, are available on a time-shared basis, free of charge, to qualified scientists, engineers and physicians throughout the US to conduct publishable research projects. Our researcher’s Guide contains detailed information about the equipment of the Center and an application form for initiating research project.

Research Snapshots

MIT physics graduate students Douglas Albagli (right) and Marta Dark studying the mechanism of pulsed ablation using a newly developed laser interferometer. The system provides nanosecond resolution of nanometer displacements of tissue undergoing ablation.

Spectroscopy Laboratory research scientist Dr. Ramasamy Manoharan (rear) and MIT physics graduate student George Zonios investigating biochemical and morphological features of human tissue at the LBRC microspectroscopy facility. Available techniques employ IR absorption, laser-induced fluorescence and near IR and UV resonance Raman spectroscopy.
MIT Electrical Engineering graduate student Jim Brennan conducting optical histochemical analysis of human arterial disease. Near IR Raman spectra, obtained via optical fibers with sub-second accumulation time, opens the possibility of in vivo diagnosis of atherosclerosis.

Professor Steven Lippard (right) and graduate student Joanne Yu, MIT Department of Chemistry, using the LBRC’s CW Raman Laboratory to study the mechanism and structure of intermediates in enzymatic reactions involving monooxygenases.

Professor Steven Tannenbaum (left) of the MIT Department of Chemistry and Dr. V. Bhaskaran Kartha using fluorescence line narrowing spectroscopy for quantitative detection of sub-femtomole samples of carcinogenic adducts of proteins and DNA.

Professor Tayyaba Hasan, Massachusetts General Hospital/Harvard Medical School, investigating the fluorescence lifetimes of porphyrin derivatives at the Ultrashort Pulse Laboratory.
Modeling Tissue Fluorescence …

tissue layer is the submucosa, a layer of connective tissue containing mostly collagen. Fluorescence photographs of colon tissue sections taken under a microscope reveal that the lamina propria, eosinophils, and dysplastic crypt cells are the fluorescing microstructures in the mucosal layer. (It is interesting that normal crypt cells do not exhibit fluorescence.) The submucosa also fluoresces quite strongly, but its contribution to the total tissue fluorescence is limited by the optical penetration depth of light within the tissue. The mucosal thickness of normal tissue is about 400 µm and should allow some contribution from the underlying submucosal tissue, but in the case of polyps the mucosa is much thicker, precluding any contribution.

The model contains three components, the fluorophore lineshapes, their relative intensities and spatial distributions, and transfer functions which describe light propagation in highly scattering colon tissue. We measured the lineshapes of the fluorescing structures from 5 µm thick colon tissue sections, using a microspectrofluorimeter with 364 nm excitation. We also measured the spatial distribution and relative intensity of the various fluorescent structures using microscopic digital imaging. Each image pixel was assigned to a particular fluorescence structure based on the pixel’s intensity. Light absorption and scattering were included by measuring the optical properties of colon tissue, and then simulating light propagation using Monte Carlo modeling to obtain transfer functions.

Fluorescence spectra taken from lamina propria have the spectral features of collagen, with the spectral peak located near 420 nm in both normal and adenomatous tissue. Eosinophils exhibit a characteristic broad spectrum peaking around 520 nm. Dysplastic crypt cells show two characteristic bands, one around 440 nm and another near 520 nm. The main differences in the fluorophore spatial distribution of normal and adenomatous tissue are the presence of the strongly fluorescent submucosal layer in normal tissue, which starts 400 µm below the mucosal surface, and the reduced fluorescence of adenomatous lamina propria compared to that of normal tissue. The contribution from eosinophil fluorescence was found to be very small. The absorption coefficient of adenomatous tissue was found to be twice that of normal tissue, due to increased hemoglobin content. This additional attenuation was taken into account through the Monte Carlo simulations.

The measured intrinsic fluorescence, fluorophore distributions and transfer functions were combined to predict the clinically observed spectra. The results are shown in Figs. 1 and 2. The model, which is based entirely on microscopic information, properly predicts all of the observed spectral features: (1) The position of the fluorescence maximum occurs at 460 nm, even though collagen, the dominant fluorophore, peaks at 420 nm; this shift is due to the absorption of hemoglobin. (2) The ratio of peak intensities between normal and adenoma is around 4, in excellent agreement with the average value of 3.5 observed in the clinical spectra. (3) The model predicts very well the increased red fluorescence in adenomatous tissue (Fig. 2). Our calculations indicate that approximately 40% of the peak intensity difference is due to the contribution of submucosal fluorescence, while the remaining 60% is due to reduced lamina propria fluorescence in adenomatous tissue and increased hemoglobin absorption.

This is the first time that a mathematical model has been used to accurately relate clinical LIF spectra to intrinsic microscopic fluorescence. This result is important in assessing the ability of fluorescence to diagnose flat dysplasia.

Conclusion We have developed a methodology for modeling LIF clinical spectra of colon tissue from microscopic information alone. The model accurately predicts the clinical spectra, and provides a basis for understanding the nature and origin of the individual features. The analysis places spectroscopic tissue diagnosis on a quantitative basis: the contributions from intrinsic fluorescence, gross architectural changes and microarchitectural changes are provided. Understanding these contributions is a key issue in developing improved diagnostic algorithms that enhance the contrast between normal and diseased tissue, both polypoid and flat. The results suggest several possibilities for future study. The spectral features differentiating normal and adenomatous tissue can be enhanced. An optimal choice of excitation wavelength could enhance the red fluorescence in adenomatous tissue, making it easier to discriminate against normal. In addition, the model can be used to select geometries of optical fiber probes for delivery/collection of light that limit the contribution of the strongly fluorescent submucosa, increasing the contrast between normal mucosa and flat dysplasia.

The LIF methodology presented here is a powerful and promising analysis tool for many types of human tissues exhibiting flat precancerous lesions. We are currently studying application of this modeling technique to bladder tissue.

References


Lester Wolfe Workshop Series in Laser Biomedicine

Optical "Biopsy"
Tuesday, November 15, 1994, 4:00-7:00 P.M.

LIF Diagnosis of Dysplasia:  What a Model Can Do!
Ramasamy Manoharan, MIT Spectroscopy Laboratory

Fluorescence Imaging of Early Lung Cancer
Stephen Lam, University of British Columbia and B.C. Cancer Agency

Raman Tissue Diagnosis
Richard L. McCreery, Ohio State University

Devil's Advocate:  A Pathologist Speaks
Thomas Flotte, MGH-Wellman Laboratories

Panel Discussion:  Optical Biopsy-Test of Reality
Michael S. Feld, Moderator, MIT Spectroscopy Laboratory

HST Auditorium (E25-111), Whitaker College Building, MIT
45 Carlton Street, Cambridge

Refreshments at 3:30 P.M.

Sponsored by MIT Laser Biomedical Research Center,
MGH Wellman Laboratories, MIT Industrial Liaison Program, &
Harvard-MIT Division of Health Sciences and Technology
1. Vibrational deactivation from the octad. Vibrational deactivation has been found to proceed largely through vibrational swap processes in which a single quantum of \( \nu_4 \) (causing deactivation to the pentad) is exchanged between the absorber and the perturber. Not all the pentad levels become involved in the process.

2. Rotational energy transfer in \( \nu_3 + \nu_4 \) shows parity and vibrational angular momentum conservation propensity rules.

3. Ground state rotational energy transfer has been studied in enough detail to allow a direct determination of the rates, and also shows a propensity for parity conservation.

4. Polarization measurements have shown that there is some tendency to preserve the space fixed angular momentum projection \( (M) \) and that elastic reorientation does occur.

This type of experiment represents a departure from traditional studies at low energy and is the beginning of a march to still higher energies in the studies of collision dynamics.

References

SPECTROSCOPY LABORATORY PUBLICATIONS

"15 Years of Reductive Coupling: What Have We Learned?", Carnahan EM and Lippard SJ. Accounts of Chemical Research, 26:90, (1993).


"[Ni$_2$(OAc)$_3$(urea)(tmen)$_2$](OTf) and [Ni(OAc)(urea)$_2$(tmen)]-[OTf], Model Complexes for the Enzyme Urease", Wages HE, Taft KL, and Lippard SJ. Inorg. Chem., 32:4985, (1993).


Spectroscopy Laboratory Publications


