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George R. Harrison Spectroscopy Laboratory

Massachusetts Institute of Technology

Research Report

Light scattering spectroscopy for analysis of pre-cancer development

Martin Hunter and Maxim Kalashnikov, G. R. Harrison Spectroscopy Laboratory

Light scattering spectroscopy (LSS) is a promising non-invasive technique for studying epithelial tissue properties with sub-micron resolution. The technique is sensitive to refractive index variations and can therefore be used to extract optical properties, and particle size distributions in cellular and sub-cellular matrices. An important area of research at the Spectroscopy Laboratory is applying LSS for analysis of pre-cancer (dysplasia) development. LSS is well-suited to this task, given that the majority of human cancers are epithelial in origin [1], and that pre-cancerous progression is often correlated to significant changes in cellular morphology (e.g., nuclear enlargement and polymorphism) [2-6].

Here, we present an animal cancer study utilizing the LSS technique, to deter-

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Also in this issue:

Watt Webb to Give Lord Lecture on April 27

Professor Watt Webb

Watt Webb, a Professor of Applied Physics at Cornell University, has been selected as the 2004 Lord Lecturer. He will speak on April 27 on the topic, "Spectroscopies as Biophysical Tools from MilliHz to ExaHz".

Dr. Webb, a biophysicist, has a long and distinguished research career in studies of the dynamics of the biomolecular processes of life, and he has pioneered in the development of numerous optical methods to probe biological systems, including multiphoton microscopy, fluorescence correlation spectroscopy, nanoscopic molecular tracking and, most recently, nanostructured molecular dynamic probes.

Now in its thirteenth year, the Lord Lecture commemorates the achievements of Richard C.Lord. a pioneer in infrared and biochemical spectroscopy and director of the Spectroscopy Laboratory for 30 years. Each year's Lecturer is selected by a committee of chemists, physicists and engineers at MIT who are active in various fields of spectroscopy. Past recipients include Charles Townes, Carl Lineberger, Steven Chu and Britton Chance.

When asked to provide a few words about his career, Dr. Webb wrote:

"This Lord Lecturer first encountered spectroscopy from a background of total ignorance of the subject after an MIT B.S. degree in Engineering Administration diluted by a focus on extracurricular activities. I first encountered spectroscopy while managing an industrial development laboratory where I needed to measure the plasma temperature of a closely confined 100-kilowatt electric arc. Study led me to atomic spectroscopy and ionization measurements of stellar temperatures, so I acquired the spectra through our sapphire single crystals to illuminate a two meter Rowland Ring. It worked, yielding about 5,500K, about like the sun. This motivated a 3-year interlude at MIT for an Sc.D., followed by return to industry to manage basic research leading to more high temperature physical chemistry to make perfect ultra-strength nano-crystals. Abandoning industry for Applied Physics at Cornell, I found milliHertz fluctuation spectroscopy in superconductors and critical phenomena at temperatures down to ~0.4 Kelvin to be lots of fun. Later I was drawn by my colleague Elliot Elson into "impossible problems" of molecular biophysics as we recognized the sensitivity of molecular fluorescence of individual molecules from our invention of Fluorescence Correlation Spectroscopy. Now my laboratory is applying diverse spectroscopies - from milliHertz to exaHertz - to understand molecular dynamics in biological systems. Nonlinear spectroscopies have been motivated by our invention with Winfried Denk of Multiphoton Microscopy, reported in 1990; and more recently by very useful second harmonic imaging of living structures and signals. Examples of that research will comprise the theme of my Lord Lecture."

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mine its potential as a pre-cancer diagnosis method. The work relies on a well-established rat esophagus cancer model, using carcinogen-treated Fisher 344 rats [7-9]. The rats were sacrificed 20 weeks after being dosed with the carcinogen nitrosomethylbenzylamine (NMBA), and their esophagi extracted and studied by LSS within 1 hour after the rats' deaths. Two locations (10mm^2 each) were studied for each rat tissue, and there were 5 rats sacrificed for each of the following study groups: (i) Normal; (ii) curcumin-treated; (iii) NMBA-treated, and; (iv) NMBA- and curcumin-treated rats. Curcumin was included in this study as a possible chemopreventive agent. Immediately after analysis by LSS, the rat tissues were fixed and stained for histopathological analysis (Figure 1).

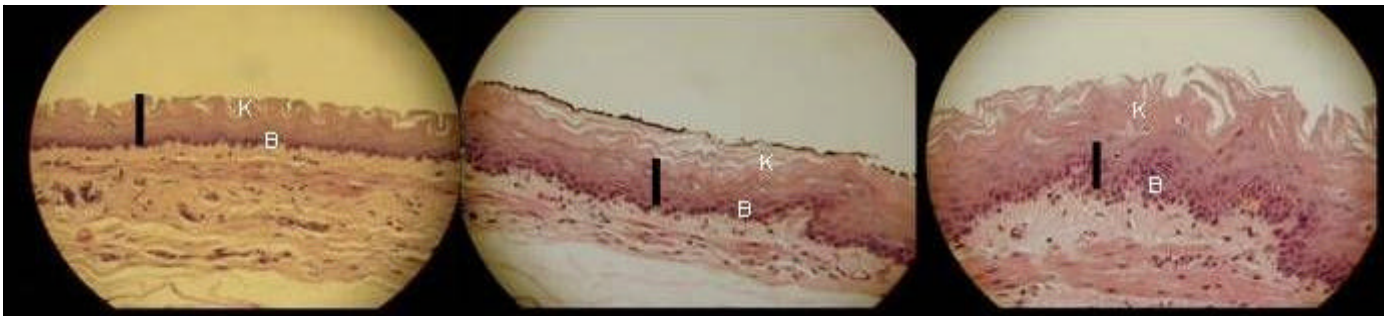

Figure 1. *Rat histology, at 20x magnification: (a) Normal tissue; (b) moderate dsyplasia; (c) severe dysplasia. B-basal cell layer, K-keratin layer. All of the images are on the same scale. The scale bar is 100 mm.*

Our LSS technique is based on illuminating a tissue sample with a polarized, collimated beam of white light from a Xe arc lamp source (Figure 2). The backscattered light from the tissue is collected over a range of polar backscattering angles θ=0-5^o, and dispersed in a CCD imaging spectrograph for spectral analysis in the range λ=450-700nm [6]. Two polarization components of the backscattered light, parallel and perpendicular to the incident beam polarization, are collected for discrimination against the large diffuse scattering signal inherent in turbid biological tissue samples. The polarized residual signal has been shown to provide scattering information from the topmost layer of tissue (optical depth <2), and thereby provides scattering properties specific to the tissue epithelium.

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The Spectroscopy Laboratory houses two laser research resource facilities. The MIT Laser Research Facility, supported by the National Science Foundation, provides shared facilities for core researchers to carry out basic laser research in the physical sciences. The MIT Laser Biomedical Research Center, a National Institutes of Health Biomedical Research Technology Center, is a resource center for laser biomedical studies. The LBRC supports core and collaborative research in technological research and development. In addition, it provides advanced laser instrumentation, along with technical and scientific support, free of charge to university, industrial, and medical researchers for publishable research projects. Call or write for further information or to receive our mailings.
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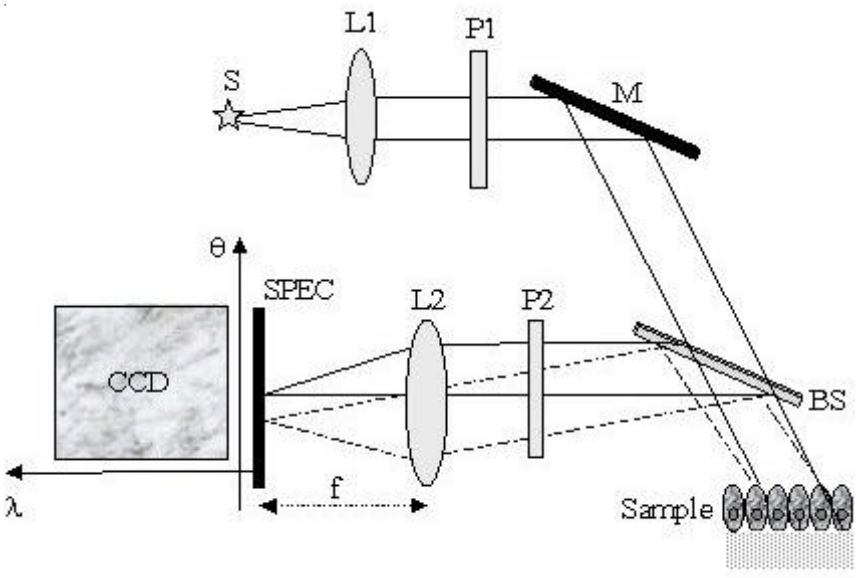

Figure 2. *Schematic of the LSS instrument. S - source of unpolarized white light, L1, L2 – lenses, P1, P2 - polarizers, M - mirror, BS - beam splitter, SPEC - spectrograph. The CCD records the scattered intensity distribution with respect to scattering angle q ?and wavelength l.*

The LSS spectra shown on Figure 3(a) were obtained at exact backscattering (θ=0^o), and are representative of LSS spectra obtained at other polar scattering angles. Spectra for individual LSS polarizations were normalized relative to a diffuse reflectance standard spectrum, as in [5,6]. The normalized perpendicular LSS spectra were linearly

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Personality Profile

Professor Bill Green

William H. Green, Associate Professor of Chemical Engineering, has been interested in public policy, and in love with lasers and chemical kinetics, ever since he was a child growing up in the Philadelphia suburbs. He was an avid reader of the current events section of the *Wall Street Journal* before he entered the third grade, and he circulated a petition to ban CFC's in his grade school classroom only a few months after Molina and Rowland's *Nature* article on the chemical kinetics of ozone destruction. He recalls that when he was in grade school, he read a popular science book called *The Amazing Laser*, and immediately tried to build his own, but had to back down when his father wisely refused to allow him to bring high voltage equipment into the house.

In high school, Prof. Green had a charismatic Ph.D. physical chemist as a high school teacher. That teacher's passion for physical chemistry confirmed him on his career path. Prof. Green majored in chemistry and physics at Swarthmore College, and for his undergraduate thesis he constructed a crossed molecular beam machine to study the kinetics of NO with ozone. While in college, he was the news editor of the campus newspaper, active in nuclear war education politics, and attended frequent lectures and discussions on *Physics and Public Policy* arranged by physics professor Rush Holt (who now represents New Jersey in Congress). When he was considering graduate schools, he immediately decided when he saw his first tunable ring dye laser in Prof. Bradley Moore's laboratory at U.C. Berkeley. While in graduate school, he was the editor of the *Berkeley Chemists for Peace* newsletter, and active in anti-war groups working with refugees from Guatemala and El Salvador. His thesis research using lasers and molecular beams focused on the spectroscopy and kinetics of highly excited molecules, and provided crucial experimental tests of competing reaction rate theories which are now discussed in several textbooks.

Prof. Green was awarded NATO and NSF postdoctoral fellowships to study theoretical chemistry at Cambridge University with N.C. Handy, where he was appointed The Charles and Katherine Darwin Research Fellow of Darwin College. His first son,

Professor William (Bill) Green

John, who was born in England, has neurological problems and related learning disabilities; as a result Bill and his wife Amanda have become actively interested in and engaged with a whole range of educational public policy issues. Prof. Green continued to work at the interface of theory and experiment during a brief spectroscopy postdoc with M.I. Lester at the University of Pennsylvania, and then for six years as a principal investigator in chemical kinetics at Exxon's Corporate Research Laboratory in New Jersey. He worked at Exxon with an experienced kinetic modeler, A.M. Dean,

Bill Green continued on page 12

Spectral Lines

by Stephen R. Wilk

Dr. Wilk, a Visiting Scientist in the Spectroscopy Laboratory, contributes columns to The Spectrograph on a regular basis. Dr. Wilk is a published author whose interests range from optics to gargoyles.

Georg Christoph Lichtenberg

Everyone is a genius at least once a year. The real geniuses simply have their bright ideas closer together – G.C. Lichtenberg

Georg Christoph Lichtenberg (1742-1799) was Professor at Göttingen, specializing in optics, mathematics, astronomy, and natural philosophy (which we would call "physics"). He has been called "the first of the great German experimental physicists". He was also a noted wit. His book of aphorisms, **The Waste Book**, is still in print in its English translation. He commented at length on the graphic works of William Hogarth. And he made extraordinarily bad puns.

Lichtenberg was born on July 1, 1742 in Oberramstadt, near Darmstadt in the state of Hesse in Germany, the 17th child of Johann Conrad Lichtenberg, a noted theologian and pastor. The elder Lichtenberg was also known for his work in architecture, poetry, mathematics, and natural philosophy, and Georg seems to have followed in his footsteps.

After studying at the gymnasium at Darmstadt, Lichtenberg attended the University at Göttingen from 1763 to 1766. During this time he also made scientific excursions to central and northern Germany, and to Denmark. One object of these trips was to prepare astronomical charts for the sky as seen from the latitudes of George III of England's German holdings. He traveled to England in 1769, and again in 1774 with gifts for George III, who received him for several visits. While in London, Lichtenberg visited the theater frequently, collected artwork, and made general observations on city life. He published his observations on the English people in **Briefe aus England** ("Letters from England") in 1776-8.

He was made Extraordinary Professor at Göttingen in 1769, and Ordinary Professor in 1775, a post he held until his death. He was widely known as a witty and engaging lecturer, and he taught and performed research in geophysics, meteorology, chemistry, astronomy, mathematics, and physics. He is probably best known today for his work in electricity. He is believed to have installed the first lightning rod in Göttingen. In 1777 he was experimenting with discharging electricity into plates. He found that if he placed a very sharp needle perpendicular to a non-conducting plate of resin, ebonite, or glass and discharged a Leyden jar through the needle into the plate it created distinct patterns. The patterns could be made visible by sifting fine grains of sulfur and red lead over the plate. These patterns, called *Lichtenberg figures*, are often of great beauty. They seem to resemble branching trees or river deltas, an efficiently cover the plate with a non-intersecting fractal network.

But what endears him to me the most is his commentaries upon people and on Hogarth's engravings. Not only is he a keen observer and expert a seeing tiny revelatory details in the art, but he describes this in unfettered prose filled with his quirky humor. "It has not been my intention to make a footnote catalogue of all such plays on

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Research Report

Chemotaxis in Microchannels

Azadeh Samadani and Alexander van Oudenaarden
G. R. Harrison Spectroscopy Laboratory and Department of Physics, MIT

Chemotaxis, the ability of the cell to sense and move in the direction of higher concentration of chemicals, is an integral part of immune response [1]. Additionally it plays a key role in wound healing, angiogenesis, and embryogenesis. Chemotaxis and signal transduction by chemoattractant receptors play a key role in inflammation, arthritis and asthma [2].

The mechanism of chemotaxis in prokaryotic cells is known to be temporal [3-5]. However, the exact nature of chemotaxis is not known for eukaryotic cells. *Dictyostelium discoideum*, as a model system for eukaryotic cells, has been studied extensively over the past twenty years. The organism has unique advantages for studying fundamental cellular processes with powerful molecular genetic tools. Additionally because of a remarkable twist in the life cycle of *Dictyostelium*, this social amoeba is particularly an excellent tool for the study of chemotaxis. *Dictyostelium* is a free-living cell that lives in soil and feeds on bacteria. Upon starvation, large collections of cells are able to get together and form a single multicellular organism (Figure1). The process starts when starving amoebae emits pulses of chemoattractant inducing other amoebae to move in their direction [6]. The mechanism by which individual amoebae sense and moves towards each other is believed to be similar to the way white blood cells (Neutrophils) find bacteria in our blood stream. Neutrophils, our body's first line of defense against bacterial infections, fight bacterium by recognizing the chemicals produced by bacteria and migrate toward them.

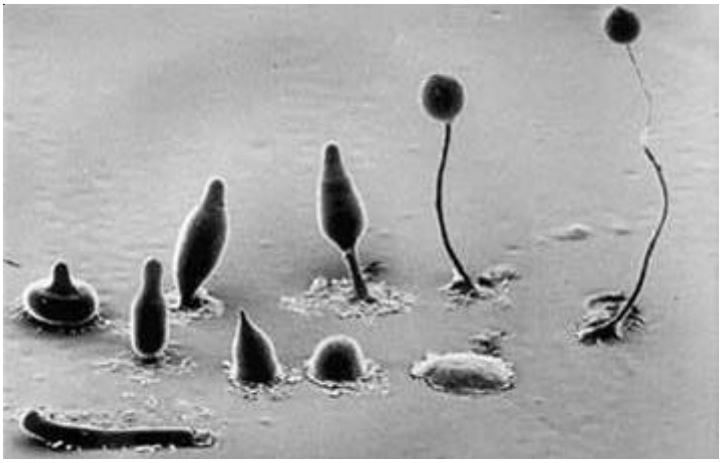

Figure 1. *Dictyostelium life cycle. After initial stages of starvation, individual amoebae chemotax and move towards each other to form a multicellular organism. They have evolved to do so in the event of starvation as a survival mechanism. (Image courtesy of R. Lawrence and M. Grimson, Texas Tech University)*

Recent theoretical modes of chemotaxing cell suggest a mechanism that involves the local excitation of the signal on the leading edge of the cell and a global inhibition of the receptor occupancy around the periphery [7-9]. Most theoretical models assume a series of assumptions about rate constants, substrate concentration and receptor dynamics. It is therefore necessary to verify the validity of this assumption by performing careful and quantitative experiments. The main focus of our experiment is to obtain quantitative data and compare our result to the existing models and hopefully create new models of eukaryotic chemotaxis.

In order to achieve a quantitative measurement of the response of the cell in an external gradient we need to create a chemical gradient that is linear, stable and easy to change over time. Traditional methods of creating chemical gradients involve the use of a single pipette. These methods lead to gradients, which are nonlinear, unstable over time, and limited in the shape of the gradient. Also these methods do not exhibit the spatial resolution that is on the order of a single cell.

We have utilized a microfluidc device using soft lithography techniques that was originally developed in the G. Whitesides group [10, 11]. Using this microfluidic device, we were able to achieve a spatial chemical gradient over many hundreds of microns over long periods of time. The gradient is well defined and has the high resolution needed for our experiment. Additionally in a linear gradient the concentration difference across the cell body is constant. This concentration difference is not constant in a gradient created by the micropipette.

Gradient generator

Figure (2a) shows a schematic of the microfluidic device. The microfluidic gradient generator is composed of embedded network of microchannels in PDMS (polydimethylsiloxane) bonded to a glass coverslip. The device consists of two major parts, the pyramid portion of the device which consists of arrays of serpentine microchannel with square cross section of 50 μm. The fluid mix by diffusion in the serpentine region and finally recombine in the large 600 μm wide channel result in a gradient that is perpendicular to the direction of the flow. There is a separate inlet for the cells on the side of the observation region. Figures (2b-2e) show the intensity of the fluorescein as it mixes further along the serpentine microchannels. We have used this technology to generate stable, soluble chemoattractant gradients of cAMP with different slopes.

Chemotaxis continued on page 9

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Lester Wolfe Workshop in Laser Biomedicine

Neural Imaging with Optics

Tuesday, April 13, 2004 4:00-6:00 PM

Wellman 1 Conference Room

50 Blossom Street, MGH Campus

Dynamic neural imaging is a growing field which is improving our understanding of neural structure and function from the level of single neurons to whole brain systems. This workshop will provide an introduction to this field and explore new optical methods for imaging changes in the brain.

Using Optical Microscopy to Study Synaptic Structure and Function
Venkatesh Murthy, Harvard University

Low Coherence Interferometry for Noninvasive Monitoring of Nerve Signals
Christopher Fang-Yen, MIT

Two-photon Imaging of Synaptic Morphology in the Visual Cortex In Vivo
Ania Majewska, MIT

Refreshments served at 3:30 PM

Sponsored by the G. R. Harrison Spectroscopy Laboratory, MIT, MGH Wellman Laboratories, the Harvard-MIT Division of Health Sciences and Technology, and the Center For the Integration of Medicine and Innovative Technology (CIMIT)

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Seminar on

Modern Optics and Spectroscopy

Spring Semester 2004

February 24	Joshua Vaughan & Thomas Hornung, *MIT* **Manipulating Light-Matter Interactions Via 2D Femtosecond Pulse Shaping**
March 9	Joseph Izatt, *Duke University* **Optical Coherence Tomography: Novel Systems and Molecular Contrast**
March 16	Thomas Brunold, *University of Wisconsin* **Spectroscopic and Computational Insights into the Biosynthesis and Reactivity of Adenosylcobalamin**
March 23	Abigail Haka, *MIT* **Diagnosing Breast Cancer: Raman Spectroscopic Real-Time Pathology**
March 30	Arthur Suits, *Wayne State University* **Chemical Dynamics with Ion Imaging**
April 6	Ed Grant, *Purdue University* **Frequency Domain Observations of Electron Orbital - Rovibrational Coupling**
April 13	Paul Barbara, *University of Texas at Austin* **F-V SMS: A New Technique for Studying the Structure and Dynamics of Single Molecules and Nanoparticles**
April 20	Jim Anderson, *Harvard University* **Lasers, Chemistry and Climate: New Developments in Fiber Lasers, High Finesse Cavities and Robotic Aircraft**
April 27	**13th Annual Richard C. Lord Lecturer** Watt Webb, *Cornell University* **Spectroscopies as Biophysical Tools from MilliHz to ExaHz**

TUESDAYS, 12:00 - 1:00 p.m., Grier Room (34-401)
Refreshments served following the seminar.

Sponsored by the George R. Harrison Spectroscopy Laboratory,
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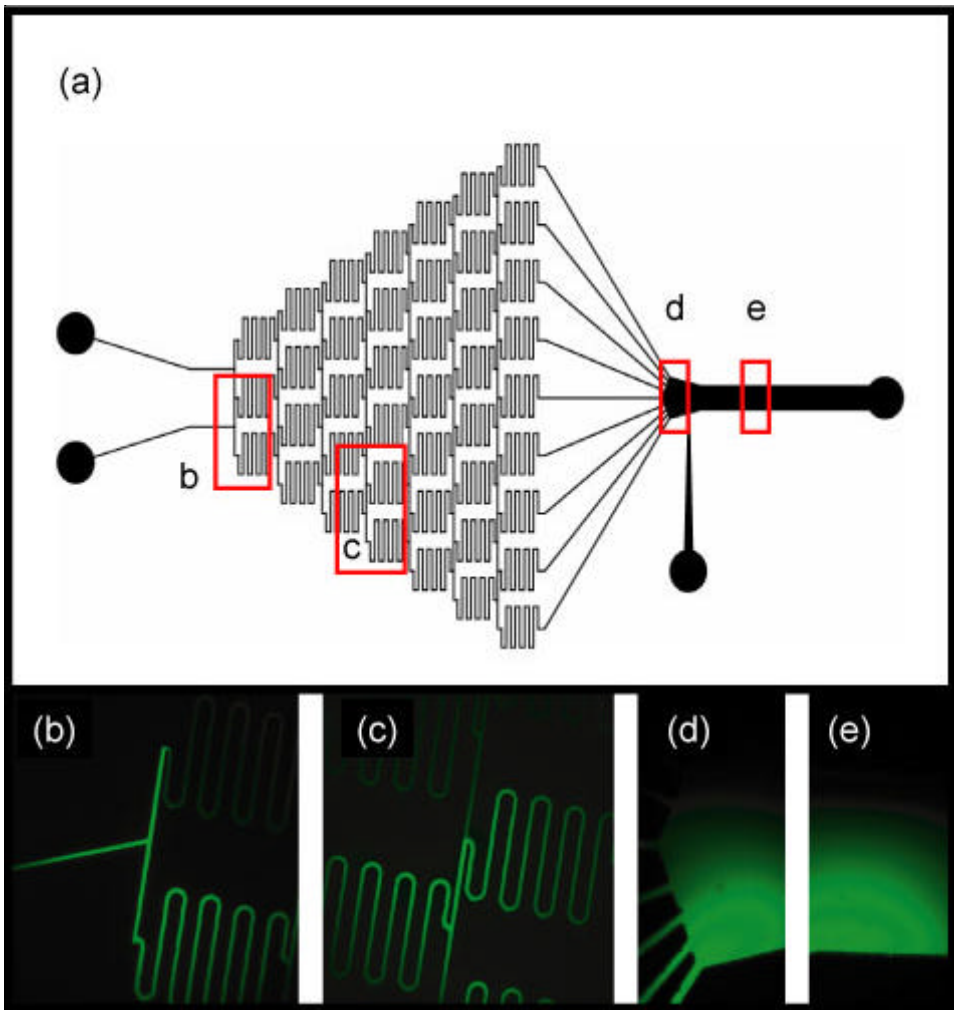

Figure 2. *Linear gradient generator: Fluids with different initial concentration is mixed along the serpentine channels by diffusive mixing of species in solution under low Reynolds number condition.*

Spatial gradient sensing and statistical analysis

We place a population of starved cells in the observation region of the device. Figure (3a) shows this initial random distribution of the cells in the gradient. The concentration of chemoattractant increases linearly from 0 nM/ml in the lower part of the image to 100 nM/ml on the top. Cells migrate towards the highest gradient concentration in about 2.5 hours in this particular experiment (Figure 3b.)

The position of each cell as a function of time was recorded with a CCD camera coupled to an inverted Nikon microscope. Images were taken every 30 sec using a phase contrast X20 objective. We tracked the position of each cells as a function of time using Metamorph software and analyze the information using Matlab. The tracks of cell position were used to calculate the quantitative statistical parameters that characterize the random walk and the directional bias of cellular movement.

Figure (3c) shows the tracks of the cells where the starting point of each track is collapsed into the center (0,0). The population of cells as a whole has moved to the higher concentration of chemoattractant. Note that the tracks resemble a directed random walk.

We define the chemotaxis index (CI) as , which is the angle that cells make at a particular time with respect to the established gradient and it is a measure of accuracy of chemotaxis. Our preliminary results show that *dicyostelium* amoebae can detect and move along a spatial gradient. The CI is relatively low for cells in a spatial gradient indicating the randomness of the motion. More quantitative experiments need to be done in order to study the effect of gradient and the absolute value of the concentration on the chemotaxis.

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Chemotaxis continued from page 9

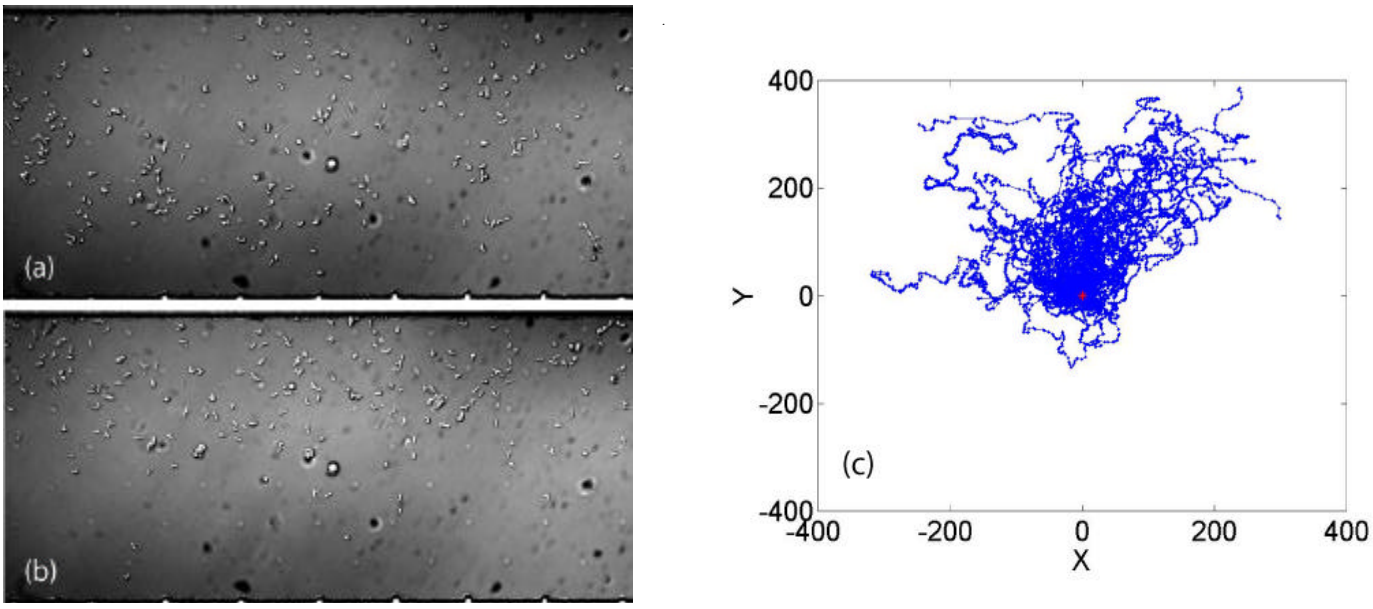

Figure 3. *Migration of Cells in a gradient of cAMP. The concentration of chemoattractant increases linearly from 0 nM/ml in the lower part of the image to 100 nM/ml on the top. Cells migrate towards the highest gradient concentration. Figures (3.a) and (3.b) show the initial and final position of the cells respectively.*

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Lichtenberg continued from page 3

words," writes a modern commentator on Lichtenberg, "I resort only occasionally and out of self-defense…Now and again Lichtenberg is, for the modern sensibility, an exasperating punster."

As an example of Lichtenberg's commentary, consider the following, from the series *Marriage-a-la-Mode*: "To compose a commentary on the steward's head, the meaning of his look, and the gesture of his hand would be the most inexcusable misuse of the alphabet. No letterpress in this world is cast for that. The two major divisions of the art of glossing would likewise perforce be doomed to failure in attempting such a text: both that whose aim is to aid comprehension, as well as the infinitely more learned one which aims at obfuscation. If I were to say: "Look, *this* is the very condition of His Grace's finances," and pointed at the figure of this household divinity, would anyone still ask, "Well, what *is* the condition of His Grace's finances?""

To finish up this brief account of Lichtenberg, I note that his knowledge of optics could still overcome his sense of artistic interpretation. Elsewhere in his commentary on *Marriage-a-la-Mode* he says, of the figure of the future Lord: "He is turned toward a looking-glass, but only because the glass hangs on that side where his betrothed is *not* sitting. He has in fact little or nothing to do with the mirror itself; the most he could glimpse in it would be a glint of silver brocade from his sumptuous sleeve. To assert (as does Mr. Ireland) that he could see himself or, indeed, even covertly eye his bride in the mirror, is a catoptrical impossibility." Yet modern commentators agree that the narcissistic young Lord *is* admiring himself in the mirror, whose placing might offend optics, but makes perfect viewing sense, just as the relationship between actor and mirror is frequently nonsensical in modern movies.

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weighted and subtracted from the parallel component, in such a manner as to eliminate the absorptive contribution of hemoglobin to the LSS spectra, and thereby minimize the diffusely backscattered LSS component. All residual spectra thus obtained were systematically well fit by an inverse power law, $I(\lambda) \propto \lambda^{-\gamma}$ (Figure 2(b)).

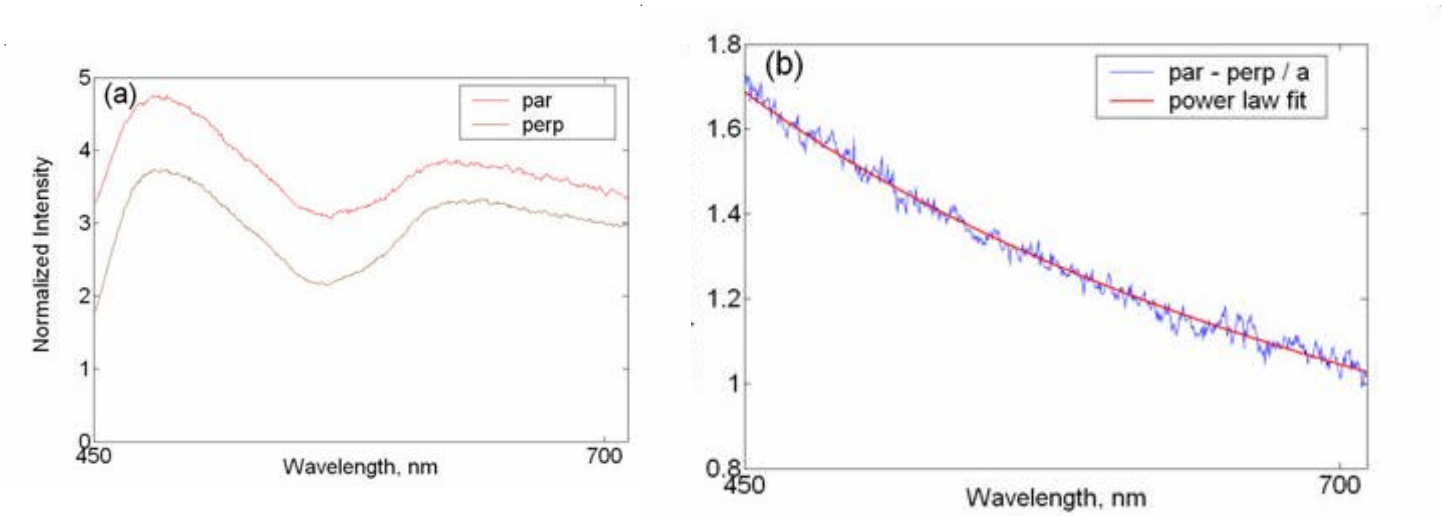

Figure 3. *(a) Parallel and perpendicular polarization signals normalized to diffuse reflectance standard for exact backscattering (q=0°). (b) Polarized normalized residual, with perpendicular component weighted (a = constant) to remove hemoglobin absorption band.*

Good correlation was found between the histopathology of the excised rat esophagi and the exponent of the inverse power law fit in their LSS residual spectra, γ (Figure 4). Rat esophagus tissue labeled as either moderately or severely dysplastic showed systematically lower values of γ than normal tissue. This result is significant as a potential marker of pre-cancerous evolution in epithelial tissue, and illustrates the potential of LSS as a quantitative and non-invasive approach to cancer diagnosis.

Work is also underway to explore the biophysical significance of the optical parameter γ. Mie theory simulations indicate that our inverse power law LSS spectra can result from an inverse power law in scattering particle size distribution, $N(d) \propto d^{-\beta}$, with particle diameters in the range $25nm < d < 1\mu m$ [10]. We note that the lower diameter limit thus obtained is significantly below the Rayleigh optical resolution limit. In addition, the parameter γ can be associated with fractal behavior of the scattering medium [11] and may thus shed light on the bulk organization and optical properties in normal and diseased biological tissue. Future research at the Spectroscopy Laboratory will explore these issues in greater depth.

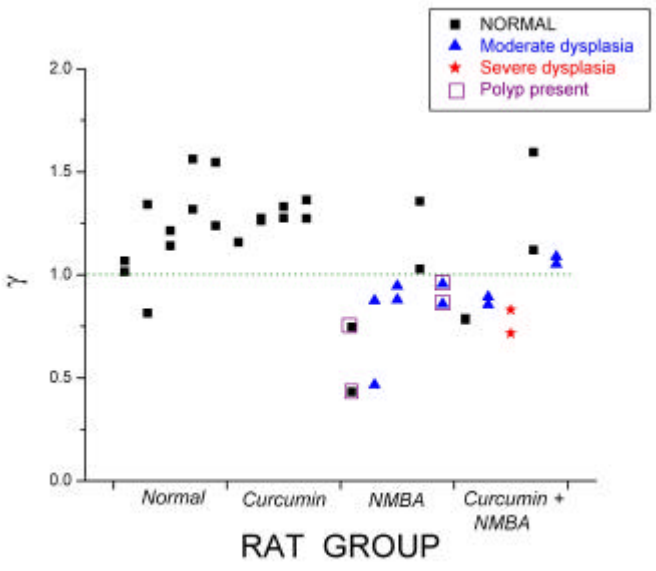

Figure 4. *Exponent γ vs. rat group. The symbols represent histopathological diagnosis.*

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who helped him to make the transition from working on the idealized systems studied by most physical chemists to the very complex systems engineers deal with. While at Exxon, Prof. Green set up a laser kinetics facility and developed new computational chemistry methods for predicting chemical reaction rates, but also dealt with systems as practical and messy as filter-plugging by soot-laden engine oil.

In 1997, Prof. Green left industry to join the Chemical Engineering faculty at MIT, where he has continued to do both theoretical and experimental work on chemical kinetics. He has developed some of the best methods for predicting chemical kinetics, and he and his students have applied these techniques to some extremely complex systems, notably novel engine designs. In 1999 he received the NSF CAREER award, and in 2003 he was appointed Associate Editor of the *International Journal of Chemical Kinetics*. Bill is one of the School of Engineering faculty who is actively engaged in the Spectroscopy Laboratory, where he has been working closely for several years with Chemistry Professor Robert Field on the laser spectroscopy and kinetics of free radicals important in combustion.

Prof. Green lives in Belmont with his wife Amanda and their three children (John, Paul, and David). He remains interested and active in public policy issues, and has been re-elected as a representative from his precinct to the Town Meeting several times. Prof. Freen writes that in addition to his interests in policy, lasers, and chemical kinetics, and despite his average size and poor outside shot, Prof. Green is an avid basketball player. He is proud of coaching John's 5th & 6th grade basketball team to the town championship game in 2003, and hopes to do the same with Paul's 3rd & 4th grade team this year.
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