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George R. Harrison Spectroscopy Laboratory

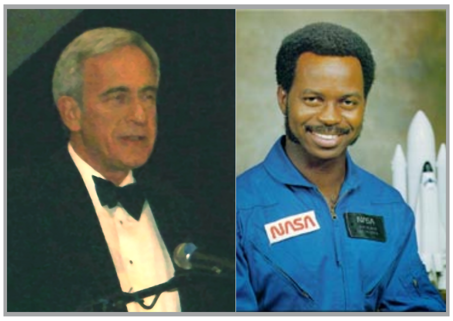
Massachusetts Institute of Technology

Good Vibrations!

Ali Javan will be inducted into the National Inventors Hall of Fame for "having made pioneering contributions to applied laser technology, Ali Javan's most significant invention is the helium-neon laser, the most useful, practical and profitable type of laser in use today," reads the citation. His invention, the first laser to operate continuously and the first to operate by converting electrical energy to light, attracted international attention almost overnight.

Daniel G. Nocera was one of the 10,001 torchbearers carrying the Olympic flame toward Turin, Italy, for the Torino Olympic Winter Games being held this month. He ran a 1 km stretch on December 8, the first day of the relay, as one of the participants for Italgas. Nocera received the 2004 Italgas Prize for Energy & Environment for developing photocatalysts to split water into hydrogen and oxygen and to make solar-energy conversion more efficient.

Mildred Dresselhaus was honored with the Heinz Award for Technolgy, Employment and the Economy, as well as honorary Doctorates at the University of Michigan and George Washington University. Millie was also elected as an Honorary Member of the Institute of Physics (UK), and received the Pender Award for "recent advances in the photophysics of carbon nanotubes." She is the first woman to receive these honors for her contributions to science.



Michael Feld commemorated the life and legacy of **Ronald McNair**, the nation's first black scientist astronaut, at the Inaugurial Gala of the McNair Educational Science Literacy Foundation. McNair, who received his Physics Ph.D. in Feld's group in 1976, perished on the space shuttle Challenger in 1986.

President George W. Bush congratulates **Stephen J. Lippard**, the Arthur Amos Noyes Professor of Chemistry, on receiving the National Medal of Science on Monday, Feb. 13, at the White House. Photo / Eric Draper, White House.

John Hall to Give Lord Lecture May 2

John Hall

JILA Fellow John Hall will deliver the 2006 Richard C. Lord Lecture on May 2, on "Optical clocks, combs and coherence: defining and measuring optical frequency."

Born in 1934 in Denver, Hall is an alumnus of the Carnegie Institute of Technology, where he received B.S., M.S. and Ph.D. degrees. He conducted postdoctoral studies at the Department of Commerce's National Bureau of Standards, now called National Institute of Standards and Technology (NIST). Along with 11 others, he moved to Boulder in 1962 to participate in founding the new Joint Institute of Laboratory Astrophysics, now known as JILA. He retired from NIST in 2004, but continues his JILA research enthusiastically. He has lectured at the University of Colorado at Boulder since 1967 and is currently a NIST Senior Fellow, Emeritus.

Hall is well known for developing and applying innovative laser techniques to the study of fundamental physical constants and theories, and to advance measurement science. He shared one half of the 2005 Nobel Prize in Physics with Theodor Hänsch. Hall is cited by the Nobel Prize committee for "contributions to the development of laser-based precision spectroscopy, including the optical frequency comb technique". The other half of the prize was awarded to Roy Glauber.

Hall has received many other honors for his pioneering work, including the Optical Society of America's Max Born Award "for pioneering the field of stable lasers, including their applications in fundamental physics and, most recently, in the stabiliza-

Lord, continues on page 2

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tion of femtosecond lasers to provide dramatic advances in optical frequency metrology." He is the sixth Nobel prize winner selected as a Lord lecturer. The others are Steven Chu, Theodor Hansch, William Phillips, Norman Ramsey, and Charles Townes.

Now in its 14th 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.

Also in this issue

THE SPECTROGRAPH
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Personality
Maryann Fitzmaurice

Maryann Fitzmaurice

Maryann Fitzmaurice is an M.D. with a B.S. in Biochemistry and Biophysics and a Ph.D. in Experimental Pathology. This may seem to be ideal preparation for a career in medical spectroscopy. However, looks are sometimes deceiving, and it was accident rather than design that led her to the G.R. Harrison Spectroscopy Laboratory.

Maryann grew up in Iowa and began her career in biomedical research as a National Science Foundation Summer Undergraduate Research Participant at Iowa State University. Although she obtained her B.S. degree from ISU in Biochemistry and Biophysics, her interest at that time was in biochemistry not biophysics. Her first research project was in the then nascent field of immunology, in the laboratory of her undergraduate advisor, Carol Warner, where she studied the then newly described phenomenon of immunological tolerance, using amino acid polymers as tolerance-inducing antigens (here's where the biochemistry comes in) in tetraparental chimeric mice (mice that are a mosaic of cells derived from two different sets of parents) created using a primitive embryo fusion technique that is a fore-runner of current in vitro fertilization techniques.

She continued her immunology research while pursing her Ph.D. degree in Experimental Pathology as a National Institutes of Health-National Graduate Medical Sciences Trainee in the combined M.D.-Ph.D. Medical Scientist Training Program at Case Western Reserve University in Cleveland. There she was introduced to fluorescence microscopy in her doctoral research on the pathogenesis of autoimmune bullous skin diseases, under Sharad Deodhar in the Department of Immunopathology at the Cleveland Clinic Foundation (CCF). Fluorescence microscopy is an important clinical diagnostic tool in the bullous skin diseases, which are caused by autoantibodies directed against antigens in the patient's own skin that are detected in fluorescence microscopy-based assays using exogenous fluorescent dyes.

After receiving her M.D. and Ph.D. degrees at Case, Maryann completed a residency in Anatomic and Clinical Pathology and a Fellowship in Immunopathology at CCF. While in training there, she began research studies under Norman (Burr) Ratliff, a surgical pathologist specializing in cardiovascular pathology, investigating the role of immunologic injury in atherosclerosis. These studies also involved fluorescence microscopy and ultimately led her to Professor Michael Feld and the G.R. Harrison Spectroscopy Laboratory.

Feld was collaborating with Burr Ratliff and John Kramer, an interventional cardiologist at CCF and a Visiting Scientist at the Spectroscopy Laboratory, to develop a catheter-based system for laser angiosurgery as an alternative to percutaneous transluminal coronary angioplasty (PTCA) for treatment of coronary artery disease. In PTCA, a catheter is positioned in a critically narrowed (or stenosed) coronary artery and inflated, opening up the artery and restoring normal blood flow to the heart. However, PTCA is prone to restenosis following the procedure due to exaggerated healing/remodeling of the coronary artery, which is damaged by the balloon inflation. The researchers proposed that laser ablation of the thrombus or atherosclerotic plaque obstructing the coronary artery would lead to less damage than balloon inflation, and thus to less restenosis. It soon became clear, however, that if you blindly lased ahead through a stenosed coronary artery, you were as likely to perforate the artery as ablate the plaque. This led to the concept of a "smart" catheter through which laser-induced fluorescence spectroscopy could be preformed to interrogate the tissue to be ablated and guide the ablation procedure.

In November 1984, Prof. Feld and Spectroscopy laboratory colleagues were visiting Burr Ratliff at CCF, debating what structures within the artery wall might fluoresce and thus be useful for guidance. Conventional wisdom said that only nucleic acids fluoresced, and in the UV not the visible wavelengths being used for laser ablation. Burr Ratliff thought

Personality, continues on page 3

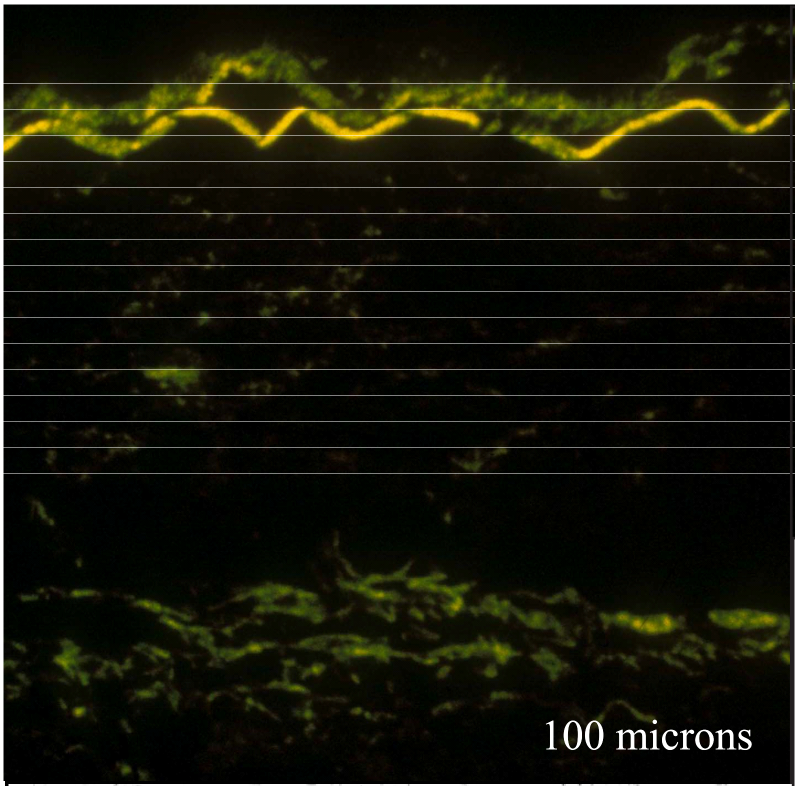

Figure 1: (left) Photomicrograph of yellow fluorescence of the structural protein elastin (arrow) in a normal coronary artery excited with 476nm excitation light from an argon ion laser and visualized using a 515nm barrier filter.

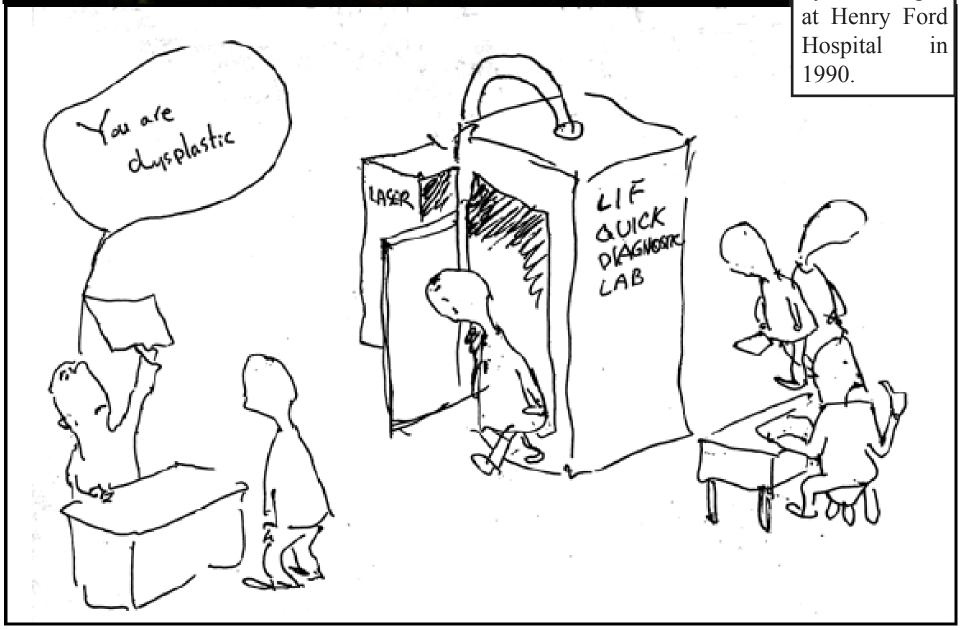

Figure 2: (below left) Cartoon illustrating the "future" of LIF diagnosis of dysplasia, drawn by a colleague at Henry Ford Hospital in 1990.

Figure 3: Abigail Haka, Ph.D., former Spectroscopy Laboratory graduate student, collecting Raman data from an excisional breast biopsy in the Mather Frozen Section Room at University Hospitals of Cleveland.

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otherwise. At that critical moment in the discussion, Maryann happened to pass by Burr's open office door. He knew that she had done fluorescence microscopy of normal and diseased coronary arteries as part of their studies of the immunology of atherosclerosis, and hoped she could resolve the dispute. She said that many structures in normal artery and atherosclerotic plaque fluoresced in the visible, and she could prove it. A few minutes later, the group was crowded around a fluorescence microscope in a darkened closet looking at arteries fluoresce. And that, as they say, was history. A few weeks later, Maryann made her first visit to the Spectroscopy laboratory. This led to the first study of laser-induced fluorescence (LIF) in the aorta and coronary arteries (Fig. 1).

That began a now 20-year plus collaboration with the Spectroscopy Laboratory and its Laser Biomedcial Research Center. Although still based as Case, Maryann is a Visiting Scientist and frequent visitor to the Spectroscopy Laboratory. She has participated in several Lester Wolfe Workshops in Laser Biomedicine sponsored by the Spectroscopy Laboratory and sat on the thesis committees of a number of Spectroscopy Laboratory graduate students, some in the Harvard-MIT HST program. She is currently the Chief Medical Advisor to the LBRC and Co-Chair of the LBRC Medical Advisory Committee.

Over the intervening years, Maryann's interests and those of the LBRC spectroscopy group have moved away from laser ablation to development of techniques and instrumentation for real time in vivo disease diagnosis, using diffuse reflectance, light scattering and Raman as well as fluorescence spectroscopy. For many years this work focused on LIF for the diagnosis of epithelial dysplasia (a precursor to cancer in a number of organ systems),(Figure 2). However, Maryann currently focuses primarily on Raman spectroscopy of atherosclerosis, particularly vulnerable plaques prone to thrombosis (which are the cause of most acute coronary events such as heart attacks) and breast cancer (Fig. 3). In fact, the first *ex vivo* validation and in vivo feasibility studies of Raman techniques and instrumentation developed at the LBRC for the diagnosis of breast cancer were performed in Cleveland.

Maryann is also a practicing surgical pathologist, first at CCF, then briefly at Henry Ford Hospital in Detroit, MI and, now at University Hospitals of Cleveland, where she is also Medical Director of the Immunohistochemistry Laboratory. In 1992, Maryann joined the faculty of her alma mater, the School of Medicine at Case, where she is now an Associate Professor of Pathology.

Spectral Lines

If at First You Don't Succeed…

by Stephen R. Wilk
Textron Defense Systems
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Stephen R. Wilk

James Burke, in his PBS series and book Connections, observed that the history of science and technology is all too often treated as if it was a simple story of unimpeded progress, each step inexorably and inevitably leading to the next, so that our knowledge constantly increases in a direct and flawless fashion. Textbooks reinforce this view, telling the history of science in a linear fashion, going from discovery to successful theory in an apparently effortless story of unfolding knowledge.

Real life doesn't work that way. There are misconceptions and mistakes. There are long periods when no progress in understanding on a topic at all is made. There are heartbreaking cases where a discovery is made, only to be lost again, or credit is misattributed. All of this is too confusing and complex to be told in introductory texts, however. It's one of the reasons to keep studying one's subject, and re-reading the histories. One of the delights of Burke's work is seeing how unexpected and haphazard progress is. Stephen Jay Gould, Martin Gardner, and others have written about the lack of good reporting of mistakes, failures, and dead ends. There should be more coverage of the errors and false starts of science. They teach us how to pursue the truth, how to recognize a wrong turning wen we find it, and hearten us when we eel that we have reached such a turning ourselves.

Consider, since we are in the field of spectroscopy, the early history of the first great triumph of spectroscopy – unraveling the spectrum of the hydrogen atom. The hydrogen emission spectrum, with its very regular series of lines in the visible spectrum, was first given accurate wavelength values by Anders Ǻngstrom and Julius Plucher of Uppsala in 1853. Of all the observed spectra, hydrogen seemed to be the one most likely to have a simple mathematical progression to its lines. As the story is almost always told, everyone expected elemental spectra to consist of a fundamental and overtones, just as mechanical vibrations do, and as musical tones do. It remained (so the story continues) for a humble schoolteacher, J.J. Balmer, who had no such biases, to look at the data afresh and see a purely mathematical relationship that fit the data perfectly in 1885. Balmer did not himself understand the nature of the fit, but neither did anyone else until Neils Bohr formulated his Quantum Theory.

The story is practically the only way this important bit of spectroscopic theory is told, but it glosses over those failed attempts that filled the years between 1853 and 1885, and it doesn't quite get the rest of the story correct, either.

I was interested in this aspect of history because I vaguely recalled hearing that, in the interval, someone had actually come up with a formula that fit the observed hydrogen spectrum, and did it perfectly. However, it was erroneous, a dead end, and it represented a false lead in the history of science. What was this formula? How close was it? Was it perhaps an approximation to the correct formula, or was it, indeed, a completely incorrect guess that managed, against the odds, to perfectly fit the observations? If so, how did they know that it was false, and stop pursuing it?

After some searching, I found what I was after [1]. The characteristic spectral lines that provided a unique set of fingerprints for the elements (and provided a powerful tool for identifying new elements) also provided an exasperating and perplexing riddle. There seemed to be no obvious explanation or trend for the numbers, intensities, and especially the spacing of the lines. However, the lines were not without some trends that were noticed. In 1861-2 Alexander Mitscherlich of the University of Berlin noted that the spacing of the two principal lines in the spectra of barium chloride, barium iodide, and barium bromide were similar but varied as the atomic weight of the compound [2]. There was a relationship between the halides of the other alkaline earths, calcium and strontium, but this was an inverse relationship. There was clearly a connection of some sort, but it was frustratingly obtuse. Francois Lecoq de Boisbaudran, an unaffiliated scientist, noted in 1869 that the principal lines of potassium had spacing that increased in nearly geometrical progression [3] – 11.9:16.1:23.2.

The most striking fitting, however, which must certainly be the one that inspired the legend I had heard, was the work of George Johnstone Stoney, professor of Natural Philosophy at Queen's University in Dublin. Photographs show Stoney (1826-1911) with a patriarchal beard. If you look him up in the reference books little mention of this spectroscopic work is made. His real claim to fame is his pioneering work on the electron, to which he coined the name. Even here however, Thompson overshadows him.

Stoney, too, imagined that spectra must consist of harmonics of some fundamental frequency. Yet no obvious progression existed. Stoney's idea was that not all lines might be present, that some might be exceptionally weak or even absent, due to some sort of interference effect. He therefore tried to find numerical ratios between observed lines, and in the case of hydrogen, found both exceptional agreement and perverse anomaly.

The four visible emission lines of hydrogen were measured at 4102.37 Ǻ, 4341.68 Ǻ, 4862.11 Ǻ, and 6563.93 Ǻ (Stoney corrected the measured values to obtain the wavelengths in vacuum). Three of these (excepting the second) he found to be in the ratio of 20: 27: 32, indicating a fundamental vibration [4] of 131,277 Ǻ. He doesn't give the details of how he discovered this, but the agreement is phenomenal. Maddeningly, no other lines fit the series. Equally maddeningly, the line at 4341 Ǻ does not fit the pattern.

Looking to bolster his case, Stoney collaborated with J. Emerson Reynolds, Keeper of the Mineralogical Department of the Royal Dublin Society to measure and fit the absorption spectra of chlorochromic anhydride. They fit 31 lines, but not as well as in the case of hydrogen. It also required very high harmonics[5], up to the 733rd.

The iffy agreement of the chlorochromic anhydride and the high numbers required gave many pause, but J.L. Soret, editor of the Archives des Sciences Physiques et Naturelles was impressed with, as he put it, the "extreme precision", and tried his own hand at fitting the spectra of magnesium and cadmium.

Yet a complete and reliable theory explaining the spectral lines and the evident gaps did not emerge. Something was clearly wrong. The entire issue of such high-order overtones was addressed by Franz Arthur Friedrich Schuster, a German-born pioneering spectroscopist (who coined the word "spectroscopy") at the University of Manchester. In "On Harmonic Ratios in the Spectra of Gases" he explored the probability of such close fits between ratios of observed spectral lines occurring purely by chance [6] for ratios of numbers less than 100. Schuster was able to show that it was certainly possible to find ratios of pairs of number less than 100 that fit the observed spectra for sodium, copper, barium, and iron, and that, by probability alone, the fits are no better than one would expect by chance. There was therefore no compelling need to see an underlying physical law behind such coincidences [7].

Schuster's report had a chilling effect on the search for harmonics. At the June 12, 1885 meeting of the Berlin Physical Society, it as stated that the attempt to find simple harmonic relations between spectral lines was abandoned after Schuster's discussion [8].

Johann Jacob Balmer (1825-1898) was, it is true, a teacher at a secondary school for girls in Switzerland. However, he was also a lecturer in mathematics at the University of Basel. Just as Balmer was not restricted to high school teaching, he also was not unaware of prior work. He explicitly mentions the work of Stoney, his whole-number ratios corresponding to ratios of hydrogen wavelengths, and of his search for higher harmonics of a supposed fundamental frequency. As others had been, Balmer was distrustful of the large number often needed to obtain fits. Nevertheless, the low number ratios in the case of hydrogen intrigued him and convinced him that some simple law must be hiding there [9] Balmer noted that Stoney's ratios for the lines could be expressed as whole-number ratios of 9/5, 4/3, and 9/8.

He was able to express the fourth visible line as a ratio as well – 25/21, which, although larger, was still a ratio of small numbers. The fit of this fourth line to the ratio as as good as the others. Multiplying the numerator and denominator of two of these ratios by four gave the values:

$$\frac{9}{5},\frac{16}{12},\frac{25}{21},\frac{36}{32}.$$

The numerators form an ascending sequence of squares. Moreover, the denominators are all smaller than the numerators by four. Balmer concluded that he had found a formula that had a fundamental frequency – he called it a "key note" – of 3645.6 Å, but in which the harmonics were not simple multiples, but followed the relationship:

$$\lambda = 3645.6\frac{n^2}{n^2-4} = 3645.6\frac{n^2}{n^2-2^2}.$$

This is the Balmer Formula, which can be rearranged to give the Rydberg-Ritz formula, and which was confirmed by Bohr's atomic model. Balmer saw the possibilities to extend the formula by inserting other values of n, and of substituting other squares for the 4 in the denominator. He used the formula on the ultraviolet hydrogen lines measured by astronomer William Huggins and H.W. Vogel in the 1870s, and found very good agreement, to within 1 Å for Huggins' values and no more than 3.9 Å for Vogel's. The error was not with the formula, but the measurements. Improved precision in data newly measured by Alfred Cornu of Paris and Gustav Muller of Potsdam were fitted by Hagenbach in 1886 and yielded much better fits [10].

Balmer's formula doesn't agree with the form of harmonics in vibration or acoustics. Balmer himself saw it as a sort of Pythagorean progression, and the denominator does indeed resemble the equation for one of the legs of a right triangle. Nevertheless, the goodness of the fit and the predictive power of Balmer's formula was proven.

What's interesting here is that Stoney did indeed stumble upon an important relationship, but his own model of high-order harmonics with missing orders was not correct, and lead him to pursue other, less convincing fits. Schuster was quite right in dispensing with Stoney's chlorochromic anhydride, and Soret's data, with his statistical argument. In hindsight, it's easy to say that he went too far in dismissing Stoney's work on hydrogen as well, which agreed far better with the simple ratios than the other work, and which used harmonic numbers much smaller than the other fits that had been attempted. It was necessary to jettison the approximate fits, which were the result of coincidence, but the hydrogen spectrum data "baby" as thrown out with the bathwater. It remained for the unaffiliated Balmer, who had not been dissuaded by these arguments against harmonics, to take a fresh look (but an informed one, familiar with prior work, and not the naïve look of legend) and to discover the law of progression.

References

1. This material is drawn from Klaus Hentschel Mapping the Spectrum Oxford Univ. Press (2002), and William McGucken Nineteenth Century Spectroscopy Johns Hopkins Press (1969), and from other sources listed below.
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3. McGucken pp. 106-7
4. J.G. Stoney "On the Cause of the Interrupted Spectra of Gases" Philosophical Magazine, 41 pp. 291-6 (1871)
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6. First a brief notice in Nature 20 p. 533 (1879), then expanded into a longer article in Proceedings of the Royal Society of London 31A pp. 337-47 (1881)
7. McGucken, pp. 122-5
8. Nature 32 p. 312 (1885) cited in McGucken p. 125
9. Balmer's work appears as "Notiz über die Spectrallinien der Wasserstoffs" in the obscure Verhandlungen der Naturforschenden Gesellschaft in Basel 7 pp. 548-60, 750-2 1883), but mre accessible is the shorter one in Annallen der Physik 25 pp. 80-7 (1885). Also of importance is the note by A. Hagenbach in Die Naturwissenschaften 9 pp. 451-3 (1921) by the son of Balmer's collaborator, Professor Jacob Eduard Hagenbach-Bischoff
10. Hentschel, pp. 298-9

Research Report

Probing the fractal organization of biological tissue with light

Martin Hunter and Maxim Kalashnikov
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Fractal geometry was conceived and developed by Benoit Mandelbrot [1] to describe the inherent complexity of many natural systems. In the broadest sense, a fractal object is one that possesses scale invariance i.e., it appears unchanged when observed under different magnification (self-similarity). A classic example is the Cantor set, shown in Fig. 1. A corollary of this invariance is the lack of a characteristic length-scale; mathematically speaking, this translates into fractals having power spectra and autocorrelation functions that follow an inverse power law behavior.

Figure 1: The Cantor set, a self-similar fractal constructed by repeatedly removing the middle thirds of line segments (first six steps shown).

Fractals are also characterized by the peculiar property of having non-integral dimensions (which, was Mandelbrot's original definition of a fractal). The Cantor set, for example, has a fractal dimension of D=ln(2)/ln(3)=0.63, implying its measured length vanishes as the resolving power of the measuring ruler is increased! Conversely, fractal lines with D>1 (e.g., coastlines) have divergent lengths as a function of measurement resolution.

The variety of systems for which fractal geometry applies is astounding, ranging from the spatial distribution of galaxies to the Earth's relief and coastlines, turbulent flow, Brownian motion and fluctuations in the stock market. In some natural objects, such as fern leaves or Romanescu broccoli, the structural organization can be remarkably close to that of an ideal, self-similar fractal (Fig. 2). More often, however, fractality is expressed only in a statistical sense. As you zoom in on the Florida coastline, for example, you will not observe increasingly miniaturized "panhandles"; however, autocorrelation analysis will still reveal a coastline dimension D>1 and an inverse power law correlation function over many orders of magnitude of length scale.

Spectroscopy has played an important role in the study of fractals. In particular, elastic light scattering spectroscopy (LSS) has been widely used for characterizing the spatial correlations in various fractal systems, such as in speckle analysis of material surfaces or X-ray scattering from diffusion-limited aggregates [2,3]. Fractal behavior can also be exploited as a tool to enhance spectroscopic modalities, such as in the giant signal enhancements observed in surface-enhanced Raman spectroscopy (SERS) when using fractal metallic substrates [4].

Figure 2: Self similarity in a broccoli head.

At the G.R. Harrison Spectroscopy Laboratory, we are developing an LSS system to study the fractal properties of biological cells and tissue. Previous LSS studies looking at the angular and spectral dependence of backscattered light from human epithelial tissues have been successful in characterizing cell nuclear sizes (d=5-20μm), and determining how these change with the onset of dysplasia (pre-cancer) [5,6]. Changes in the sub-micron organization of biological tissue, however, are also known to correlate with pre-cancer development [7,8]. We have thus been interested in extending the applicability of LSS to non-invasive characterization of tissue morphology at the sub-micron scale.

Several studies using traditional microscopy have indicated a fractal organization of the sub-micron features in biological cells and tissues. Sedivy *et al*. observed self-similarity in the nuclear boundaries of human cervical epithelium cells, with fractal dimensions changing significantly with dysplasia [7]. Einstein *et al*. analyzed the two-dimensional spatial correlations in chromatin density of normal and malignant breast epithelial cell nuclei, and also found these to be fractal and sensitive to the onset of pre-cancer [8]. In their case, however, the fractal correlations were self-affine rather than self-similar, much like the Earth's surface topology as first noticed by Mandelbrot. Self-affinity is related to self-similarity, but requires an asymmetric scaling of magnification axes to preserve scale invariance, e.g., in Einstein's data, the chromatin density along any one direction, *n*(x), would appear statistically invariant under the transformation $n(x) \rightarrow b^{-H} n(bx)$, where b is a scaling constant and 0<H<1 is the Hurst parameter, related to the fractal dimension. Self-affinity of sub-micron features has also been observed in various human and mouse tissues by phase contrast microscopy, with power law spatial correlations over the range 200nm<r<2μm [9].

Elastic light scattering from biological samples often shows a scale-invariant (inverse power law) spectral component in the reduced scattering coefficient, $\mu_s'(\lambda) \sim \lambda^{-\gamma}$. This has broadly been interpreted as arising from submicron particles or inhomogeneities in cells and tissue, but the precise source of this power law scattering remains in dispute. A narrow Gaussian size distribution of sub-micron spheres has sometimes been qualitatively invoked to account for this effect [10]. Other researchers have assumed instead a broad (nm to μm range) inverse power law size distribution of Mie spheres to account for similar observations [11,12]. The broad distribution Mie approach provides excellent fits to the data, but it does rely on the assumption of spherical scattering objects and scatterer refractive index independent of particle size.

We have recently developed a more realistic model for elastic light scattering from tissue to account for inverse power law LSS spectra. The model combines the Born approximation (weak scattering regime) with a fractal (self-affine) model for the 3-dimensional continuous refractive index fluctuations of sub-cellular features. The weak scattering assumption is valid for LSS singly-backscattered light from micron-sized (or smaller) cellular and tissue components, given their low relative refractive index contrast (typically, n=1.03-1.07) [9,13]. Self-affinity, as noted above, has been reported in the sub-nuclear and sub-micron morphology of various human and animal cells and tissues [8,9]. This self-affinity can be described analytically by a von Karman correlation function [2,12,14]:

$$C(\mathbf{r}) \propto \left(\frac{\mathbf{r}}{L}\right)^{H} K_{H}\left(\frac{\mathbf{r}}{L}\right) \qquad (1)$$

with r the autocorrelation distance, H the Hurst parameter, L the fractal upper scale and K_H a modified Bessel function of the second kind of order H (the Hurst parameter is limited to the range 0<H<1). von Karman spectral analysis has been previously applied to systems with self-affine fractal correlations with an upper scale limiting the range of that behavior, e.g., atmospheric refractive index inhomogeneities describing classical Kolmogorov atmospheric turbulence [12,14].

In our LSS experiments on cells and tissue, we measure a residually polarized LSS backscattering spectrum, ΔI(λ) = $I_{\|}(\lambda) - I_{\perp}(\lambda)$, where ∥ and ⊥ refer to polarization states parallel and perpendicular to the incident light polarization. As shown in Ref. [5], ΔI(λ) discriminates against light diffusely scattered from tissue and is dominated by singly-scattered photons from the topmost (epithelial) tissue layer (optical density τ < 1). In the Born approximation, ΔI(λ) is related to the Fourier transform of the scatterer refractive index correlations:

$$\Delta I(\lambda) \propto \lambda^{-4} \int C(\mathbf{r}) \exp(i\mathbf{q}\cdot\mathbf{r}) d^3\mathbf{r} \qquad (2)$$

$$C(\mathbf{r}) = \frac{k^2}{4\pi} \int [n^2(\mathbf{r'}) - 1][n^2(\mathbf{r'}+\mathbf{r}) - 1] d^3\mathbf{r'}$$, with **r** the vector correlation distance; n(**r**) the tissue refractive index; k=2π/λ; **q** the scattering vector with modulus q=2ksin(θ/2), and θ the polar scattering angle (θ=180° in our case). By combining Eqs. (1) and (2) we can thus predict the functional form of LSS spectra from self-affine, weakly scattering systems (such as cells and tissue):

$$\Delta I(\lambda) \propto \lambda^{-4} \frac{1}{\left[1 + (4\pi L/\lambda)^2\right]^{\alpha}} \qquad (3)$$

In the limit where there is no upper bound on the fractal range of correlation lengths (L–>∞), the above expression shows power law behavior, $\Delta I(\lambda) \sim \lambda^{2\alpha-4}$. In the other extreme, where there exists an upper scale L << λ, the LSS spectrum converges to the Rayleigh limit, $\Delta I(\lambda) \sim \lambda^{-4}$ For intermediate values (L ~ λ), there exists a transition zone where ΔI(λ) will deviate from power law behavior and show curvature on log-log plots of ΔI(λ) vs λ.

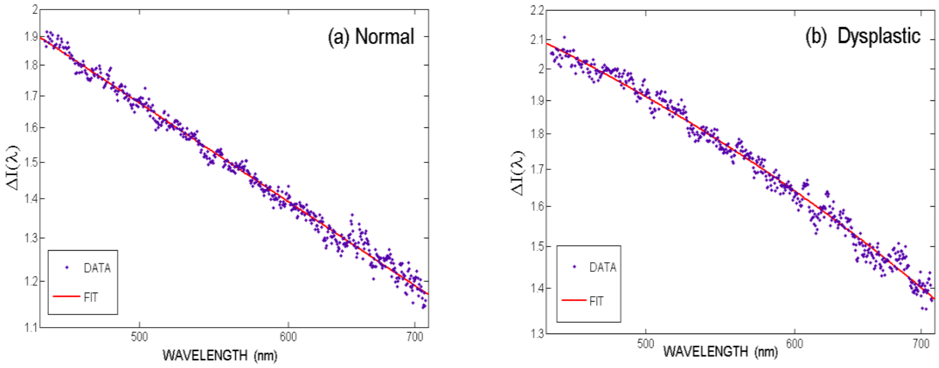

Figure 3: LSS spectra from rat esophagus: (a) normal, and; (b) dysplastic. Solid red line is fit to von Karman/Born tissue scattering model.

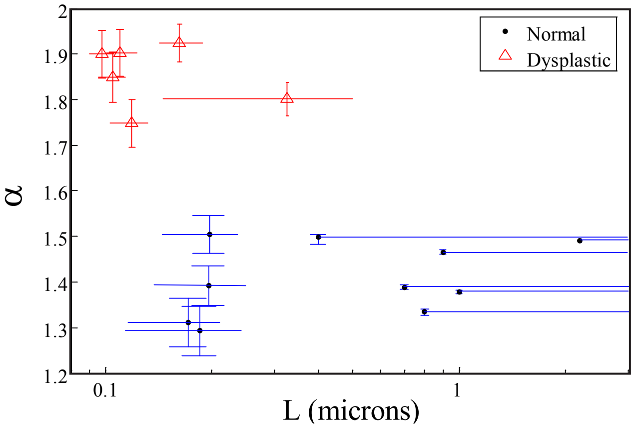

Figure 4: (below) Plot of von Karman/Born parameters α and L for 10 normal and 6 dysplastic sites in rat esophagus LSS study. L values for L>0.4µm are all lower bounds (shown as one-sided abscissal error bars).

We have used this new model to re-analyze the LSS spectra obtained in our rat esophagus animal cancer study. That study was presented in an earlier Spectrograph issue (Spring 2004); briefly, it involved ex vivo LSS studies of normal and carcinogen-treated rat esophagi, and correlation of LSS spectral parameters to histopathological assignment of dysplasia (pre-cancer) in the tissues. Our new, von Karman/Born model fits the experimental data with even greater precision than with the previous, exact power law approach, and provides vastly improved discrimination between normal and dysplastic sites (100% sensitivity and specificity using the exponent α; p < 0.00025 by t-test analysis). Figure 3 shows representative LSS backscattering spectra from two rat esophagus samples (one normal and one dysplastic), with the von Karman/Born model fits overlaid. The spectrum from the normal esophagus appears linear on the log-log scale, while the LSS spectrum from the dysplastic site shows a small but discernible curvature. This increased curvature is accounted for in the von Karman/Born model by a reduction in the upper scale (Fig. 4), thus yielding further information about morphological changes associated with neoplastic progression. In this case, our analysis indicates that the fractal upper scale falls form an average value $\langle L_{normal} \rangle$ = 0.7±0.6µm for normal rat esophagi, to an average of $\langle L_{dysplastic} \rangle$ = 0.15±0.09µm in dysplastic sites. A t-test with Gaussian distribution assumption yields p<0.05, indicating the von Karman/Born parameter L also provides significant diagnostic potential for precancer detection.

Future work using an angular-resolved LSS technique, in which angular- as well wavelength-sensitive differential scattering cross-sections are measured simultaneously, is expected to provide additional diagnostic potential and further clarification of submicron tissue morphology. Optical sectioning light scattering experiments could also identify the dominant tissue components (e.g., top keratinous layer vs. basal epithelial layer) contributing to power law LSS spectra. Finally, electron microscopy studies will be conducted to extend the range of correlation lengths studied, and to explore the inner scale of fractal behavior in tissue organization at nanometer scales. These studies will be conducted on human cell lines and epithelial tissues to establish the clinical diagnostic potential of the von Karman/Born parameters presented here, α and L, for early cancer detection in humans. ✳

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Understanding Free Radical Chemistry through Computer Modeling and Laser Flash Kinetic Spectroscopy

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Our incomplete understanding of the ubiquitous reactions of oxygen with carbon-containing materials hinders progress in the development of cleaner energy alternatives and new materials. These oxidation reactions are thought to occur through a series of short-lived reactive free radicals R (molecules with an odd number of electrons), most of which have never been observed. In order to advance the technology, we need accurate models of the chemistry of these intermediates, which can predict how proposed systems will behave under a range of conditions; these predictive models would greatly facilitate design of improved processes and materials.

Laser techniques make it possible to observe many of these transient intermediates, but it is often difficult to interpret the data observed, and even more challenging to extrapolate from the experimental measurements to predict the oxidation chemistry under different conditions. But the laser experiments can provide a very valuable check on the accuracy of the chemical kinetic models.

We have recently measured the kinetics of two very different R + O_2 reactions using laser flash photolysis techniques, and have interpreted the rather complex transient absorptions observed using chemical kinetic models based on quantum chemistry calculations.

Cyclohexadienyl Radical + O_2

In collaboration with Professor Robert Field's group at MIT, we measured the oxidation of cyclohexadienyl radical (C_6H_7; benzene with an extra H atom on one of the carbons), a resonance-stabilized radical typical of those formed in the low temperature oxidation of aromatics (e.g. in smog or the environment). This radical was known from prior work in the literature to have a strong ultraviolet absorption around 316 nm; we were able to demonstrate that it also has an absorption in the visible (~532 nm).

Although there were prior measurements of C_6H_7 + O_2 kinetics, the literature appeared to be contradictory. Several groups had reported that the reaction was very fast, diffusion-limited, in polar solvents, but a recent gas phase measurement had suggested that the reaction was very slow, suggesting it might have a barrier. However, the reported C_6H_7 gas-phase decays were almost temperature independent – but if there were no barrier, why was the reaction so slow?

We measured the kinetics in nonpolar solvents, where the reaction appeared to be very fast, perhaps diffusion limited. However, a closer look at the transient decays of cyclohexadienyl revealed that they are peculiar multi-exponentials, indicating that the chemistry is more complex that than the simple irreversible elementary-step reaction

$$C_6H_7 + O_2 \rightarrow \text{products}$$

that everyone had assumed.

Quantum mechanical calculations suggested that it might be possible to form several $C_6H_7O_2$ isomers, in addition to very exothermic, essentially irreversible channel forming HO_2 + benzene. If one or more of these $C_6H_7O_2$ species reacted back to form C_6H_7, then the transient spectrum would be expected to have a complicated time-dependence (and the decays would have an unusual temperature dependence). In its simplest form, the proposed chemistry works like this:

$$(C_6H_7O_2 \text{ isomer 1}) = C_6H_7 + O_2 =$$
$$(C_6H_7O_2 \text{ isomer 2}) \rightarrow HO_2 + \text{benzene}$$

Additional isomers and additional reactions connecting all the species are possible, though the rate constants for these reactions are highly uncertain. This $C_6H_7O_2$-intermediate hypothesis could also resolve the discrepancy between the (fast time resolution) solution phase measurements and the (poor time resolution) gas-phase measurements: by this hypothesis, the gas-phase experiments are probing the system after the equilibria are established, but the experiments done using liquid phase samples were measuring the fast primary reactions before the equilibria are established.

The quantum chemical calculations are unfortunately not accurate enough for us to be sure which if any of the $C_6H_7O_2$ isomers were affecting the observed transients, nor the relative importance of the HO_2+benzene channel. We need to discriminate between the possibilities using experimental data.

The candidate kinetic models were nonlinear systems of differential equations with a half-dozen adjustable parameters. There is no way that we could extract all of these parameters from our observations of the time-dependence of the absorption of a single species (C_6H_7). However, if we could not find any choice of the parameters that would make one of the models fall within the error-bars of the experimental data, then we could conclude that the experimental data disproved that particular model. The problem is that we must prove that there is no choice of the parameters that makes the model fit the data. It is possible to recast this as a global optimization problem, on a surface with many local minima. Very recently, Singer & Barton developed the first algorithm guaranteed to find the global optimum for this type of problem; we collaborated with them in the first application of the new mathematical method to kinetic spectroscopy. [Singer et al., J. Phys. Chem. A (2006) in press]

The value of the new approach is illustrated in Fig. 1 and Fig. 2. Fig. 1 displays the time-dependence of the transient absorption of C_6H_7 resulting from photolyzing a 298 K mixture of peroxide, C_6H_8, and O_2 in cyclohexane solvent. The solid lines are the predictions of a chemical kinetic model with three adjustable parameters. Conventional least-squares programs tend to converge to local minima yielding very poor fits, suggesting that the model is inconsistent with the data. However, this is incorrect: the global optimization finds parameters that give an excellent fit (the red line in Fig. 1).

Figure 2 reports data measured under similar conditions to Fig. 1, except at a somewhat higher temperature (323 K). The conventional least-squares fits to the three-parameter model don't look so bad for this case, and one might conclude that these data are consistent with the model. However, the fit is not significantly improved by using global optimization, and a careful statistical analysis concludes that it is very unlikely that a correct model could be this far off: i.e, in this case the data really do disprove the model!

Neo-pentyl radical + O_2

Like cyclohexadienyl, most radicals can react with O2 in multiple ways, making it rather difficult to understand what is going on. Most commonly, R+O_2 leads to formation of HO_2 plus an unsaturated hydrocarbon; the unsaturated hydrocar-

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Seminar on

MODERN OPTICS AND SPECTROSCOPY

Spring 2006

February 28	David Pratt, University of Pittsburgh **Molecular secrets from high resolution gas phase laser spectroscopy**
March 14	Wei-Chuan Shih, MIT **Quantitative biological Raman spectroscopy**
March 21	Richard Van Duyne, Northwestern University **Molecular plasmonics for surface-enhanced sensing and spectroscopy**
April 4	Peter Eklund, Pennsylvania State University **Raman scattering studies of nanofilaments: Phonon confinement vs antenna phenomena**
April 11	Wilton Virgo, MIT **Transition metal diatomic chemical intermediates in electric and magnetic fields**
April 25	Hoi Sung Chung, MIT **Nonlinear infrared spectroscopy to probe thermal unfolding of proteins**
May 2	***15th Annual Richard C. Lord Lecture:*** John Hall, JILA **Optical clocks, combs and coherence: Defining and measuring optical frequency**
May 9	Justin Hodgkiss, MIT **Proton-coupled electron transfer in model systems**

Tuesdays, 12:00 - 1:00 p.m., Grier Room (34-401)

Refreshments served following the seminar

Sponsored by the George R. Harrison Spectroscopy Laboratory, Department of Electrical Engineering and Computer Science and School of Science, MIT.

Lester Wolfe Workshop in Laser Biomedicine

Femtosecond Microscopy and Microsurgery: Make It Fast!

Tuesday, April 18, 2006, 4:00-6:00 PM
Wellman I Conference Room
Wellman Center for Photomedicine
Massachusetts General Hospital
55 Blossom Street, Boston

Modern developments in laser technology have provided the ability to deliver very short pulses of light, in the femtosecond range. This technology has led to novel applications in tissue imaging such as multiphoton fluorescence microscopy and second harmonic generation microscopy. Ultrashort laser pulses also allow unprecedented control of surgery on a sub-cellular scale. This workshop will explore these and related issues.

Subcellular Surgery and Nanosurgery
Eric Mazur, Harvard University

***In Vivo* Brain Imaging Using One- and Two-Photon Fluorescence Microendoscopy**
Mark Schnitzer, Stanford University

New Techniques in Confocal Microscopy
Jerome Mertz, Boston University

Refreshments served at 3:30 pm

Sponsored by the GR 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

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Chemistry, continued from page 8

bons react to form resonantly-stabilized radicals, which are relatively inert. Overall, these steps tend to slow down the oxidation overall. However, it has been hypothesized that a small fraction of the R's undergo a chain-branching sequence

$$R + O_2 = RO_2 = QOOH$$

$$QOOH + O_2 \text{ –>–>–> } 2\,OH + QO_2$$

that converts one radical R into three radicals, two of which are very reactive OH radicals. By amplifying the concentration of reactive free radicals, a relatively small fraction of R's reacting this way could very significantly alter the overall oxidation rate.

Because the competing R+O_2 –> HO_2 channels are usually so dominant, only a tiny amount of QOOH is formed, and it

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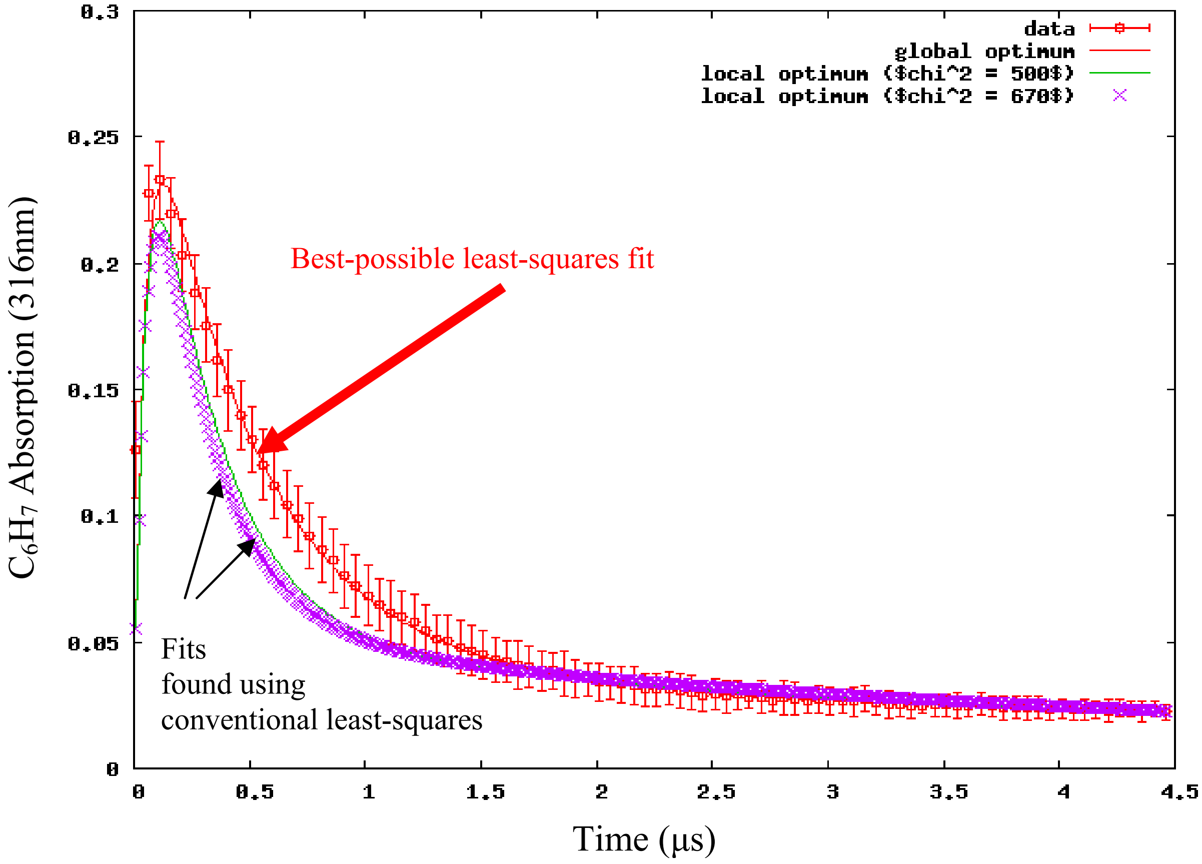
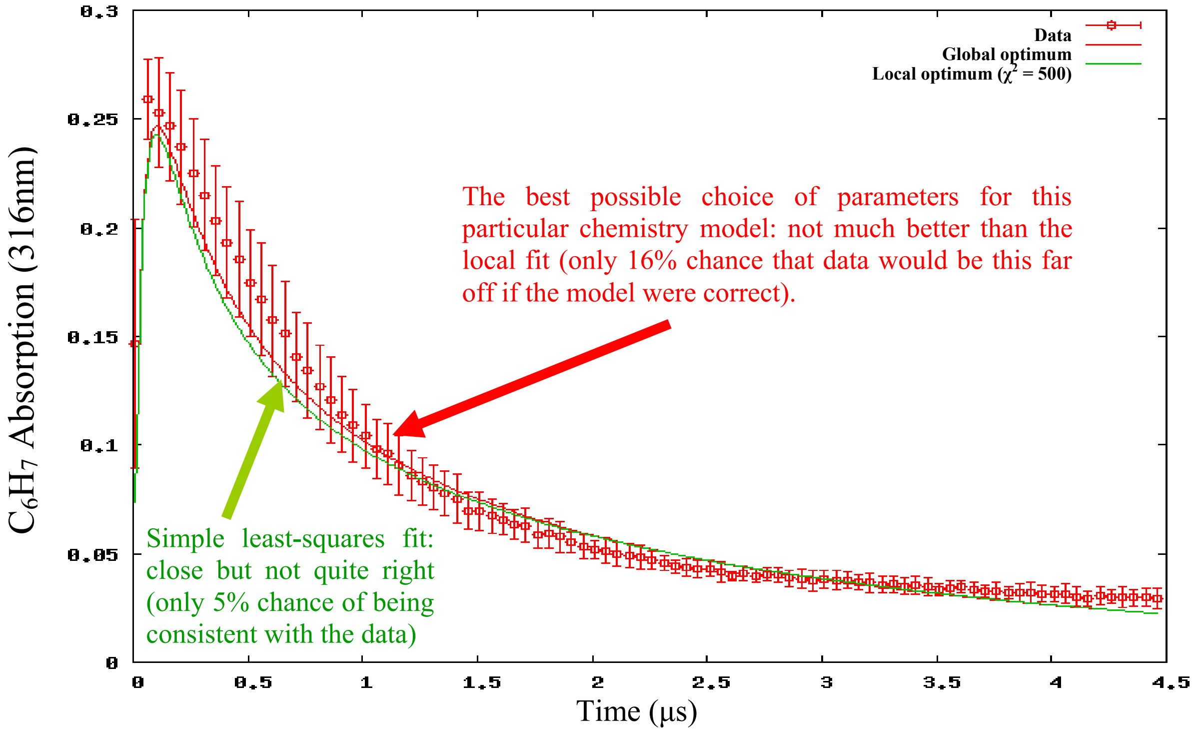


Best-possible least-squares fit

Fits
found using
conventional least-squares

Figure 1: Experimental measurements on C_6H_7 decay at 293 K due to reaction with O_2 (points with error bars) versus chemical kinetic model fits. The fits in green and purple were found using conventional (local) least-squares; these suggested that the data disproved the model. The fit in red is the best-possible fit, found using the new guaranteed-global-optimum algorithm; it shows that the model and the data actually agree perfectly.



The best possible choice of parameters for this particular chemistry model: not much better than the local fit (only 16% chance that data would be this far off if the model were correct).

Simple least-squares fit: close but not quite right (only 5% chance of being consistent with the data)

Figure 2: Experimental data for $C_6H_7 + O_2$ at 323 K. In this case, both the conventional least-squares fits and the global-optimum fit look "pretty good", but statistical tests show that they are very unlikely to be consistent with the data. Since even the best possible fit is inconsistent with the data, we can conclude that the data disproves this model.

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has not been possible to probe the hypothesized QOOH + O_2 reactions. However, there are certain R's whose structures do not allow them to form HO_2 directly; the simplest example is the neo-pentyl radical $(CH_3)3CCH_2$. Taatjes and co-workers have performed a series of laser kinetic spectroscopy experiments measuring the OH and HO_2 formed from R+O_2 reactions using various radicals R. Huzeifa Ismail from the Harrison Spectroscopy Laboratory collaborated with Taatjes to measure these yields for R=neo-pentyl radical formed from laser flash photolysis of neopentyl iodide. Unexpectedly, a large amount of HO_2 is formed from neo-pentyl oxidation, along with a small amount of OH. The HO_2 arises from complicated secondary chemistry after a noticeable time lag, but most of the OH is formed immediately, as a primary product from R + O_2 (not the hypothesized QOOH + O_2 reaction sequence).

Quantum chemical calculations by Sun and Bozzelli indicate that the important direct OH-forming reaction is $(CH_3)3CCH_2$.+ O_2 -> OH + 2,2-dimethyl oxetane, a four-membered-ring cyclic ether. We are currently constructing a chemical kinetic model to aid in the interpretation of the measured spectroscopic transients. By adding some of the expected side reactions, and slightly adjusting the quantum chemical barrier heights, MIT graduate student Sally Petway has brought the model into reasonable agreement with experimental data, Fig. 3. Now that we have a consistent model, we are using it to extract as much information as possible from the measured transient spectra. We are also currently constructing a new kinetic spectrometer capable of probing larger species than OH and HO_2; we believe the complementary data obtained using the new kinetic spectrometer will greatly reduce the number of ambiguities which make interpreting these data so difficult. We ultimately plan to use our improved understanding of this chemistry to design an experiment where one could probe QOOH and directly measure QOOH + O_2, to allow a quantitative assessment of whether or not these species are actually important in ignition and oxidation.

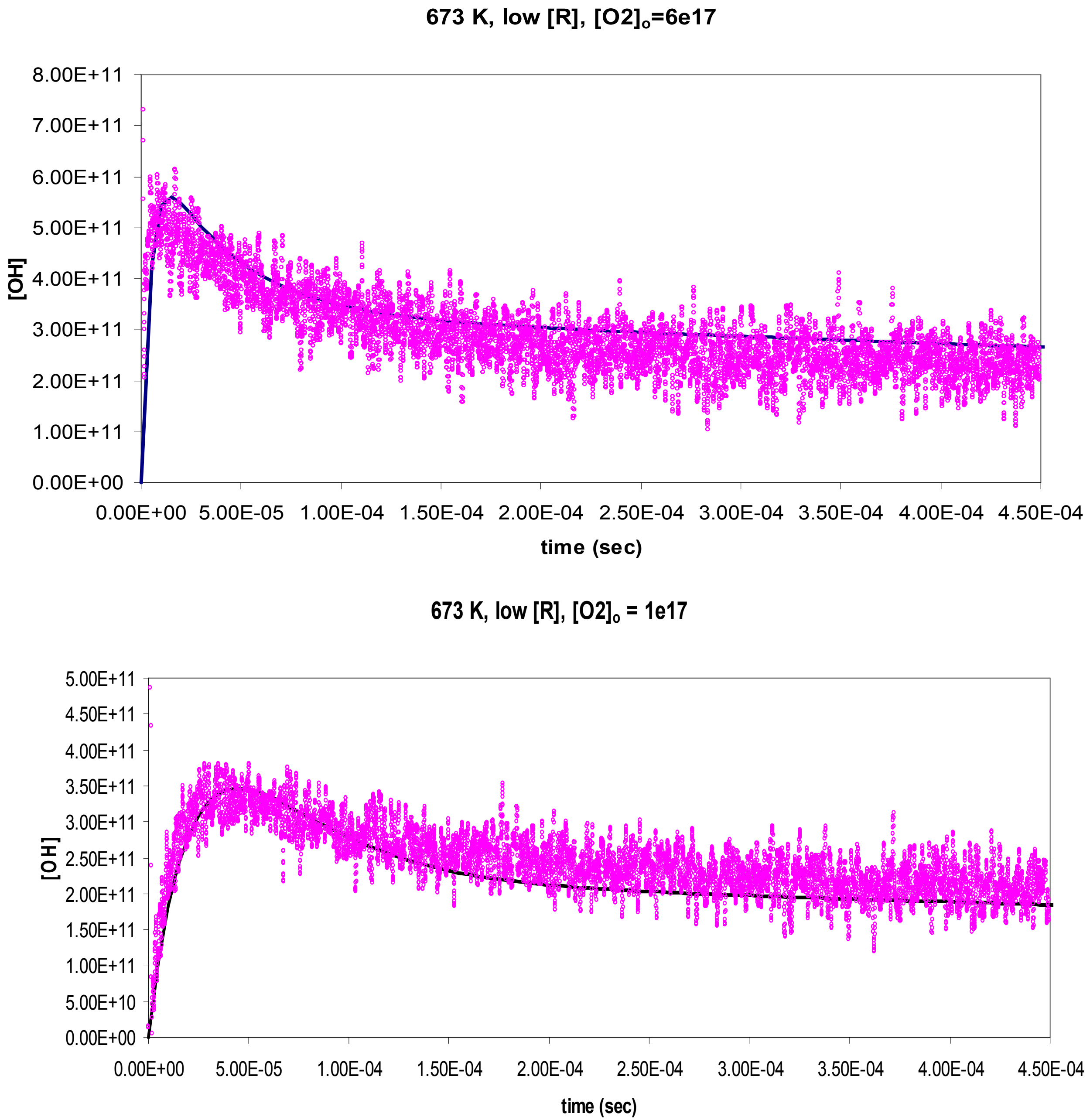

Figure 3: (a) Transient absorption of OH at 308 nm, following photolysis of neopentyl iodide at 673 K (a) in the presence of 6e17 molecules/cc of O_2. (b) in the presence of 1e17 molecules/cc of O_2.

Spectroscopy Laboratory Published Articles, 2005

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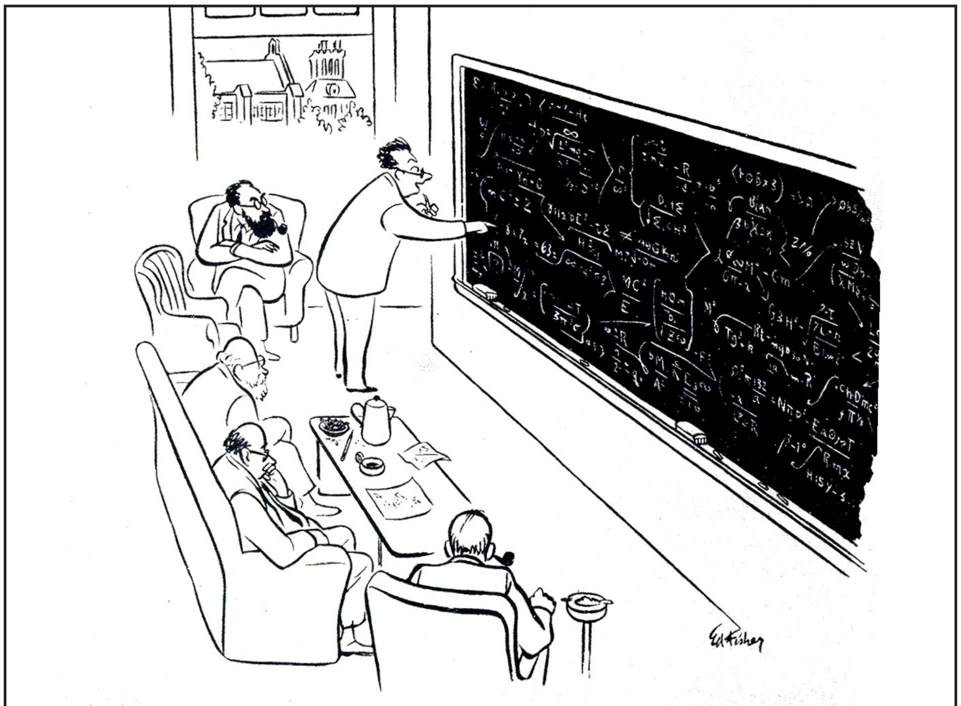
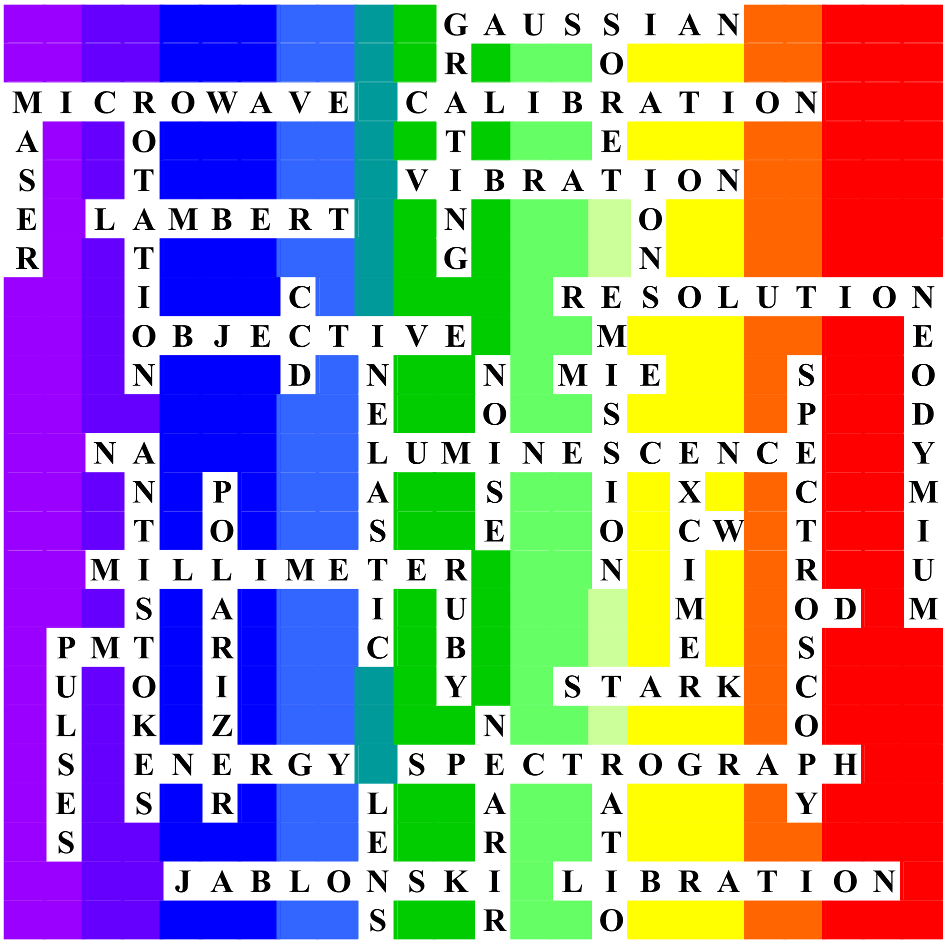


"Say, I think I see where we went off. Isn't eight times seven fifty-six?"

Answers to the previous issue's crossword puzzle:



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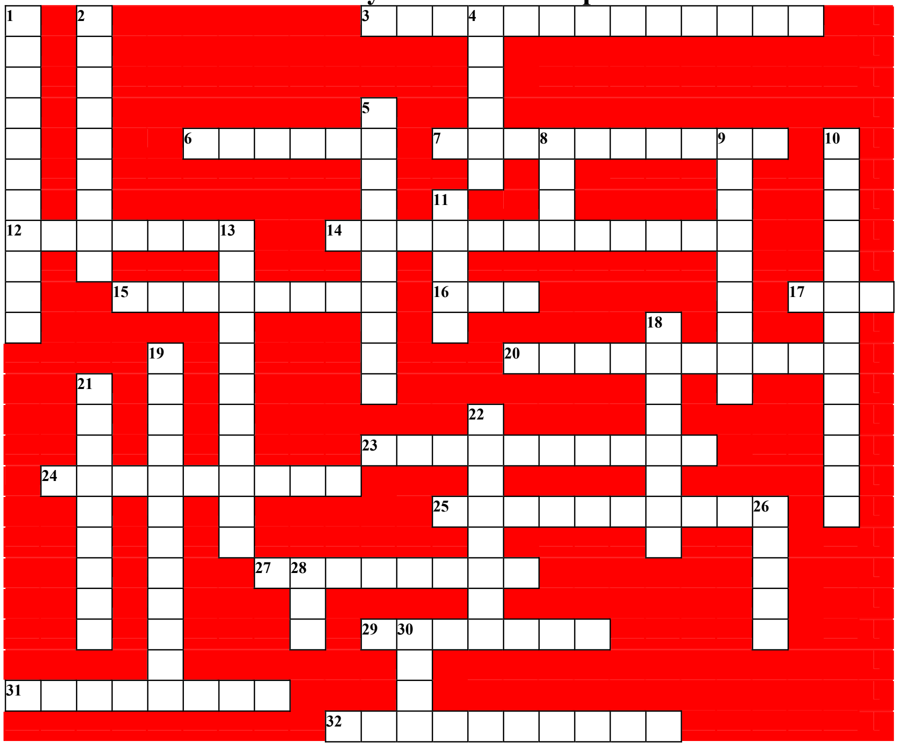
Please send your solution of this issue's crossword puzzle on page 20 to Gabi Popescu (gpopescu@mit.edu). The winner and solutions will be published in the next issue.

✳ The Back Page ✳

History of the Microscope



Across

3. Zernike’s idea (2 words)
6. eye-piece
7. without it, samples are transparent
12. homeland of early microscopes
14. Abbe described the microscope image as “____ effect of a diffraction phenomenon”
15. with the same focus
16. scanning electron microscopy
17. atomic force microscopy
20. doesn’t care about color
23. resolving power
24. gives sub-wavelength resolution (2 words)
25. it shortens in water
27. the higher the better in an image
29. made the first telescope famous and also the first focusing device
31. dyeing
32. eye glasses

Down

1. father of cell biology
2. background-free microscopy (2 words)
4. first reporter of magnifying glasses (Roman, 1st century A.D.)
5. cell organs
8. lens after the objective
9. this aperture limits your resolution
10. how big you see vs. how big it is
11. first company to produce Zernike’s microscope
13. blurs your image
18. microscopes and insect eyes are like that
19. induced in your sample
21. goal
22. DIC
26. wrote spring law and invented the iris
28. high-resolution OCT
30. famous for the “sine condition”

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