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Arjun Yodh

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Scattered light detects cancer

From **Arjun Yodh** in the Department of Physics and Astronomy, University of Pennsylvania, US

Experiments based on light spectroscopy and scattering have been extraordinarily useful for analysing a variety of materials, ranging from dilute samples of atoms or molecules to condensed media such as metals, semiconductors and complex fluids. An exciting but elusive goal for scientists working in biomedical optics has been to apply such techniques to perform clinically useful examinations of living human tissues. Research in this area has been stimulated by the possibility of using optical methods to detect cancerous and precancerous tissues, since many cancers are curable if diagnosed at an early stage.

However, light travels in living tissues in a complicated way. Because tissue scatters light strongly, it is difficult to discern what information the tissue has impressed on the light. Now, however, Michael Feld and colleagues at MIT in the US have overcome some of the problems and have developed a light-reflection method that can detect precancerous cells in the oesophagus (*Phys. Rev. Lett.* 1998 **80** 627).

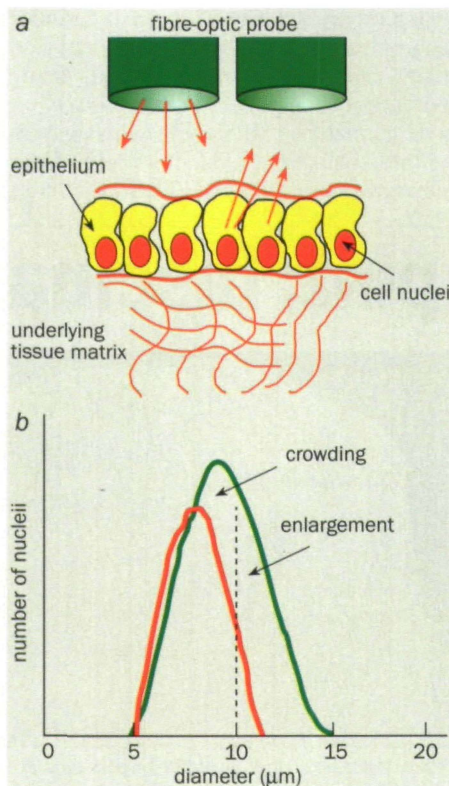
Many cancers originate in the thin surface layer of "epithelial" cells that line the hollow organs of the body. In healthy tissues this epithelium consists of a well organized layer of approximately cylindrical cells 10–20 μm in diameter and 25 μm long (figure *a*). In cancerous and precancerous epithelium, the cells proliferate and their nuclei enlarge.

Currently pathologists look for these changes by removing some of the cells and examining stained tissue sections under the microscope. The aim of the MIT researchers was to obtain information about the size distribution of epithelium nuclei using reflected visible light.

Light reflected from tissue contains a small number of single-scattered photons superimposed on a large background of diffusely scattered light. The single-scattered photons come from cell nuclei very near the tissue surface, and their wavelength and angular distribution depend on the size and position of the scattering particles.

The cell nuclei can be modelled as spherical particles with scattering resonances that are determined by their size and refractive index. These resonances appear as oscillations in the intensity of the spectrum of the singly scattered light. Oscillations of a similar nature have been used as fingerprints of particle size and shape in flow cytometry, a method for separating cells of different sizes. But cytometry does not suffer from a diffuse background.

Unfortunately the diffuse light scattered from underlying tissue masks the signal from



(a) A schematic diagram of cells and cell nuclei in the epithelium. (b) The size distribution of cell nuclei can be deduced from the periodic fine structure. There is a clear difference between normal (red) and cancerous cells (green).

the epithelium, since the diffuse light has travelled a relatively long distance through the tissue. A team of researchers, including Britton Chance and me at the University of Pennsylvania, has modelled the transport of such photons as a diffusion process.

Scattering and absorption introduce a complex spectral structure into the intensity and spatial distribution of the diffuse background. The diffusion model accounts for each of these effects, separating the "random walk" steplength – the distance a photon travels before its initial direction is forgotten – from the absorption length. The random-walk steplength varies with wavelength, which in turn is related in a quantitative way to the size and position of particles, just as for single scattering. But the resonances are weaker than those from single-scattered photons because diffuse light has been scattered many times at different angles. These effects are being extensively explored by Irving Bigio and co-workers at Los Alamos as a way of characterizing diseased tissues (*Appl. Opt.* 1997 **36** 949).

The MIT researchers isolated the single-scattering effects of the near-surface epithelial nuclei by rigorously accounting for the contribution from the diffuse background light. In the experiments they used a 1 mm diameter fibre-optic probe to launch light

into the sample, and six optical fibres located symmetrically about the central source of the probe to detect the backscattered light.

There were three major contributions to reflection in the narrow cone of angles collected by the probe: the single-scattered light that was backscattered by cell nuclei near the surface; an indirect single-scattered component (derived from the diffuse background) that was forward-scattered by tissue just below the surface; and the diffuse background signal due to scattering and absorption in the deeper underlying tissue. The intensity of both elements of single-scattered light oscillates with wavelength, and so these features could be modelled quite accurately with the theory for spherical particles. The rapid oscillations in the reflected intensity, dubbed "periodic fine structure" by the MIT researchers, contrasted strongly with the relatively smoother spectral variation of the diffuse background.

In test experiments, single layers of cancerous and normal epithelial cells were placed on the surface of a non-absorbent diffuse material. The reflected light intensity was recorded as a function of wavelength, and the periodic fine structure was easily observed on top of the diffuse background. By obtaining the Fourier transform of the periodic fine structure, the researchers deduced the size distribution of the nuclei. Regions of cancerous nuclei were clearly separate from normal nuclei, which agreed with observations under the microscope.

The technique is more difficult to apply to human tissues *in vivo* because of haemoglobin absorption, which causes the diffuse background light to vary substantially with wavelength. However, the researchers modelled the background due to the haemoglobin so that it could be subtracted from the total reflected signal.

Using this technique, the periodic fine structure could be extracted from the background even though it represented less than 1% of the total signal. It was then used to determine the size distribution of nuclei at normal and cancerous sites. Moreover, results obtained from *in vivo* measurements on the human oesophagus (figure *b*) agreed with independent pathological assessment. Further work is underway to confirm the predictive power of the technique by testing larger samples of patients.

As well as indicating cancer, measuring the size of nuclei could also provide information about the presence of other types of cells. The MIT researchers suggest, for example, that the technique could be used to study the inflammatory response of biological tissue. The "optical biopsy" is a promising tool for pathologists, and could be more widely applied in the future.

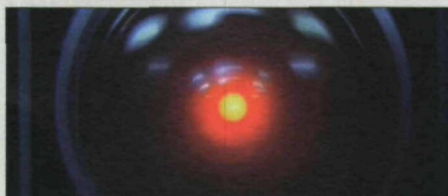
Sensors put words in a computer's mouth

At the heart of many good science fiction films is an omnipresent computer that can respond to the human voice, writes Susan Curtis. But this is still a distant dream for today's computer users, who must continue to rely on their typing skills to produce any useful results.

Fortunately, help may be at hand. John Holzrichter and Lawrence Ng of the Lawrence Livermore National Laboratory in California have been developing a system that can characterize and recognize human speech (US Patent 5729694/1998 03). The system could also be used to synthesize speech, identify particular speakers, and to diagnose and correct speech disorders.

The system works by measuring not only the acoustic signals produced in human speech, but also the electromagnetic waves emitted when a person is talking. The electromagnetic signals provide important information about the size and shape of the resonators in the human vocal system, which play a key role in producing the sounds we hear.

The human vocal system is made up of two main parts. Acoustic pulses are generated deep in the throat as the air flow over the vocal chords is made to pulsate rapidly. These pulses are then transformed into recognizable sounds by the vocal tract.



Read my lips – HAL could be a reality before 2001

In mathematical terms, the acoustic pulses are known as the excitation function. This is convolved with a "transfer function", determined by the physiology of the vocal tract, to produce the speech we hear. The interaction between the excitation and transfer functions means that it is impossible to characterize the elements of human speech, such as individual syllables, from the acoustic output alone. A particular problem is that we cannot determine the physiology of a speaker's vocal tract, except through x-ray imaging or by inserting optical probes into the vocal system. This has limited progress in developing schemes for speech recognition and synthesis.

Holzrichter and Ng have solved the problem by measuring the electromagnetic radiation generated by the vocal system that, they claim, provides direct information about the excitation function. As the acoustic

pulses travel into the vocal tract, some of the energy is reflected back towards the vocal chords. This causes the vocal tissue to vibrate at frequencies ranging from the radiofrequency region to optical frequencies. These vibrations can be measured with an electromagnetic sensor.

By measuring the excitation function in this way and recording the speech output at the same time, conventional signal processing can be used to determine the vocal-tract transfer function. The system can therefore be used to characterize the speech in terms of excitation and transfer functions. This means that different sounds can be "coded" into mathematical language.

This ability to code individual sounds and words makes the system extremely powerful. Algorithms can be designed to match human speech with the coded sounds, allowing the system to recognize individual sounds more reliably than is possible with techniques based only on the acoustic output. And because the sounds are coded in a computer, the speech could be translated to another language. Moreover, the coded sounds can be used to create more realistic synthetic speech, if necessary based on a particular person's voice. The system can also be used to help people with speech disabilities.

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