Random lasing in human tissues

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A random collection of scatterers in a gain medium can produce coherent laser emission lines dubbed "random lasing." We show that biological tissues, including human tissues, can support coherent random lasing when infiltrated with a concentrated laser dye solution. To extract a typical random resonator size within the tissue we average the power Fourier transform of random laser spectra collected from many excitation locations in the tissue; we verified this procedure by a computer simulation. Surprisingly, we found that malignant tissues show many more laser lines compared to healthy tissues taken from the same organ. Consequently, the obtained typical random resonator was found to be different for healthy and cancerous tissues, and this may lead to a technique for separating malignant from healthy tissues for diagnostic imaging. © *2004 American Institute of Physics*. [DOI: 10.1063/1.1782259]

Most laser actions occur within carefully configured resonant cavities. However, random collections of scatterers in an optical gain medium can also lead to laser action having coherent or noncoherent emission, depending on the optical feedback mechanism.[1] Incoherent random lasing is similar to amplified spontaneous emission in that it dramatically narrows the emission spectrum and transforms the usual linear excitation-emission intensities relation to be highly nonlinear. This type of random lasing has been discussed thoroughly in the literature.[2–7] However, random lasing with *coherent feedback* that leads to a sequence of narrow spectral lines,[8,9] each corresponding to a coherent emission characteristic of laser modes,[10,11] is a fascinating laser action phenomenon, dubbed the "coherent random laser," which lies closer to conventional lasers than to incandescent light sources.[12] Despite the inherent underlying disorder in the optical gain media of this type of random laser, the laser modes in the emission spectra may still be used to extract important information about the optical scattering mechanism in the gain medium.[13,14] In this work we show that laser dyes infiltrated into biological tissues form systems where coherent random lasing is possible. Moreover, by averaging the power Fourier transform (PFT) of the emission spectra across the samples we could distinguish malignant and nonmalignant human tissues with about a 2-mm spatial resolution, which may lead to another type of tissue imaging for cancer diagnostics.

For the laser action measurements we have used an excitation beam from a Nd: YAG regenerative laser amplifier, at a wavelength of 532 nm, with pulses of 100-ps duration, 50-μJ energy/pulse operating at a 100-Hz repetition rate. The excitation beam was focused on the samples through a cylindrical lens to form a narrow stripe of 100 μm$\times$2 mm on the illuminated tissue. The emission light was collected using a fiber and sent to a 0.5-m spectrometer, with an overall spectral resolution of 0.02 nm. PFT was performed for each collected laser spectrum with about 5-μm resolution. The PFT averaging procedure was done by changing the illuminated stripe on the sample; the minimum lateral change of the illuminated stripe that was needed to generate an independent spectrum was about 50 μm. The samples were biological tissues extracted from vegetables (potatoes), animals (chicken meat), and human organs (such as colon and kidney). The various tissues were soaked in the laser dye Rhodamine 6G, which has a strong absorption band in the green spectral range and a fluorescence band in the red spectral range.

Figure 1 shows typical random laser emission spectra from small samples of human colon, with healthy [Figs. 1(a) and 1(b)] and malignant [Figs. 1(c) and 1(d)] tissues, respectively, obtained with an excitation intensity of 200 μJ/cm^2. The overall emission spectrum is much narrower than the dye emission spectrum obtained at low excitation intensity; in fact, it follows the dye gain spectrum as is obtained at relatively high excitation intensities from the R6G concen-

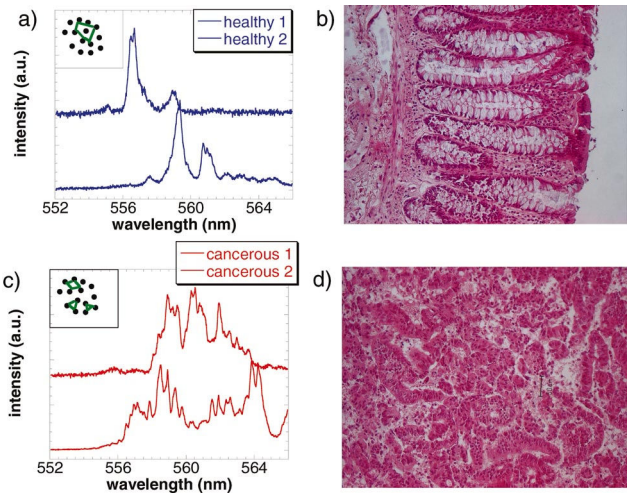

FIG. 1. (Color) Random laser emission spectra of human colon tissues infiltrated with a concentrated laser dye, namely R6G. (a) Two typical random laser emission spectra from a healthy, grossly uninvolved tissue (blue), of which microscopic image is shown in (b). The narrow spectral lines are in fact coherent laser emission modes (Refs. 10 and 11. The inset shows schematically closed random laser resonators formed due to scatterers in the gain medium. (c) and (d), same as in (a) and (b), respectively, but for a malignant colon tissue. There are more lines in the laser emission spectra in (c) (red) that are due to more resonators in the tumor; these are caused by the excess disorder that is apparent in (d).

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trated solution in a cuvette via the amplified spontaneous emission process. The narrow emission lines in these spectra, which are superimposed on the gain profile, were measured to be coherent laser emission modes[10,11] coming from specific resonators[13,14] in the tissue. Similarly, we have also succeeded in obtaining coherent random laser action from many biological tissues infiltrated with concentrated laser dyes. These include various vegetable and animal tissues, as well as human tissues from various organs.

Since a disordered medium has scatterers in random positions that lead to the formation of random resonators,[14] then the consequent laser emission spectrum is strongly dependent on the illuminated spot of the sample with a specific scatterers configuration.[8,9] This is apparent from the different spectra shown in Figs. 1(a) and 1(c) that were collected from different illuminated spots of the healthy and malignant tissues, respectively. It is also seen that *there are more laser lines in the emission spectra of the cancerous tissue* compared to the healthy tissue; this was checked to hold true on the average for 125 different emission spectra. This indicates that there are more laser resonators in the cancerous tissue due to more scatterers and/or excess disorder.

Each random laser emission spectrum is different, because different random cavities are sampled in the various illumination spots. For example, the two random emission spectra from different illumination spots seen in Figs. 1(a) and 1(c) look very different from each other, even though they were measured from the same tissue. A particularly powerful technique to analyze random laser spectra is the PFT. The PFT of the emission spectra in Figs. 1(a) and 1(c) are shown in Fig. 2(a). Each PFT spectrum contains a series of FT components that are related to the specific resonators in the particular illuminated area of the sample, but there is no dominant FT component in any of them. It is apparent, though, that the PFT of the emission spectra from the malignant tissue contain more FT components compared to those from the healthy tissue. This originates from the excess laser emission lines in the laser emission spectra from the tumor. In addition, each PFT spectrum is different, corresponding to the different associated emission spectra.

Unlike the average emission spectrum, which when averaged yields a smooth spectrum proportional to the R6G gain profile, the average PFT reveals distinct harmonics that do not disappear upon further averaging.[13] To obtain the average PFT over the sample we normalized each individual emission PFT at path length $d=0$, and summed up a number of transformed spectra. The buildup of the average PFT spectrum is shown in Fig. 2(b). The average PFT is shown for a total of 100 different illuminated spots, with increments of 25 additional individual PFT spectra. It is apparent that the average PFT does not smooth out with the number of spectra that are averaged. Instead, several sharp features are unraveled; these features actually become clearer with the number of PFT spectra averaged. These features evolve into rather sharp harmonics, revealing the existence of a dominant cavity in the dye-soaked tissue. The harmonics seen in Fig. 2(b) correspond to a dominant resonator in the lasing tissue, and occur at multiples of nL/π, where n is the refraction index and L is the cavity roundtrip length.[15] Assuming $n \approx 1.8$, we obtain from the data in Fig. 2(b) the dominant laser cavity length in the healthy colon tissue to be about 34 μm. Similarly, we discovered in the course of our study the existence of harmonics in the average PFT of random laser spectra

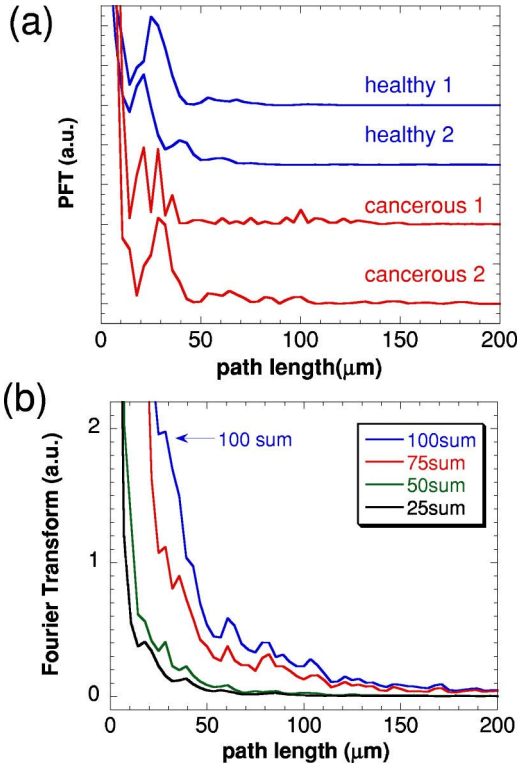

FIG. 2. (a) (Color online) PFT of the random laser emission spectra shown in Figs. 1(a) and 1(c) blue spectra show the healthy colon tissue, whereas red spectra show the malignant tissue. (b) Buildup of the average PFT of laser emission spectra from individual PFT of the healthy colon tissue as in (a) in increments of 25. The sharp features in the PFT spectrum do not average out; instead, they become clearer with the increasing number of PFT spectra that are averaged.

from a variety of dye-soaked human tissues and biological samples, such as chicken meat and vegetables.

The average PFT spectrum technique was used to examine random laser emission spectra from healthy and malignant colon tissues taken from the same patient [Fig. 3(a)]. Because in a healthy tissue the cell sizes and spacing are more regular [Fig. 1(b)], then the average PFT shows more well-resolved harmonics. To emphasize this effect the "background-free" spectrum, where the background FT is removed, is also shown [Fig. 3(a) inset]. In contrast to the healthy tissue, in the average PFT of random laser emission spectra from the malignant tissue, which has a wide range of cell sizes that are less ordered [Fig. 1(d)], no typical resonator size is unraveled; this holds true even in the background-free spectrum [Fig. 3(a) inset]. The average PFT in the cancerous tissue is rather smooth and has many more FT components that correspond to more laser lines; consequently, this increases the background in the spectrum compared to that of the average PFT in the healthy tissue, but otherwise averages out any dominant laser cavity.

A simple simulation was performed to study the underlying mechanism for the difference between the average PFT spectra of healthy and cancerous tissues. The average PFT was calculated from simulated laser emission spectra, each having several longitudinal laser modes that are formed from an ensemble of small cavities, where the probability, $P(L)$, of finding a proper resonator decreases exponentially with the length, L. In one resonator ensemble, $P(L)$ was truncated at a length $L_{\min}$ that corresponds to the typical $L=34$ μm that was obtained from the average PFT of the healthy tissue in

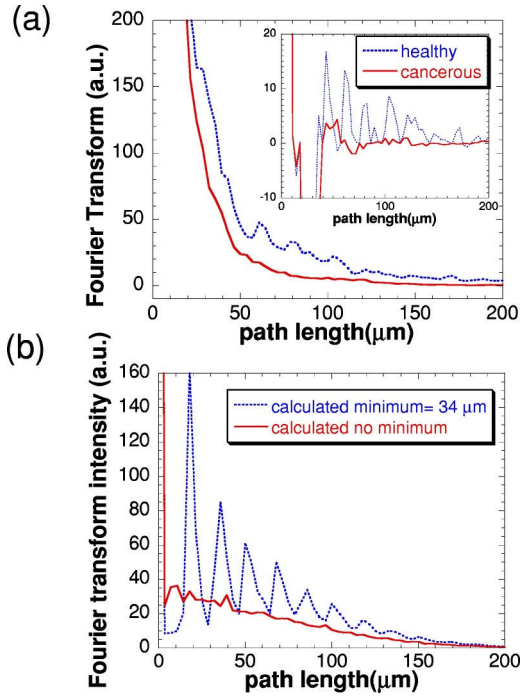

FIG. 3. (Color online) Normalized average PFT of random laser emission spectra. (a) The average PFT spectra of healthy, grossly uninvolved (blue), and cancerous (red) dye-soaked colon tissues; the inset shows the "background-free" PFT of the same spectra, where the background FT was removed. (b) Simulations (see text) of the average PFT spectra from an ensemble of resonators with a minimum length, $L_{min}=34$ μm (blue) that corresponds to the case of healthy colon tissue, and with no L_{min} (red) that demonstrates the case of cancerous colon tissue.

Fig. 3(a), whereas, in the second ensemble there was no minimum resonator in $P(L)$. The results of both simulations, when averaging 1000 PFT spectra, are shown in Fig. 3(b); they are in good agreement with the experimental data, and especially with the "background-free" spectra seen in the inset of Fig. 3(a). This agreement indicates that indeed there is no typical resonator length involved in random lasers from cancerous tissues. The more regular cell size of healthy tissue maps into well-defined L_{min} that gives distinct peaks in the average PFT spectrum.

It is expected that the average PFT for a large number of longitudinal modes would show regular, equally spaced FT components that decrease monotonously.[13] This, however, is not exactly the case in the data [Fig. 3(a)]. Our simulation shows [Fig. 3(b)] that the irregularities in the experimental average PFT spectra are due to the small number of laser modes within the spectral window provided by the gain medium, rather than the lack of averaging. Of the lines in the emission spectrum, most have no correlation to each other. The few lines that are correlated indeed show harmonics, but the average PFT is the result of the competing components of uncorrelated lines from separate resonators and regularly spaced lines from each resonator. The shape of the experimental average PFT is therefore not the result of incomplete averaging; rather, it is due to uncorrelated lines between different resonators that are sampled by the specific gain medium window. In the case of cancerous tissue there are many resonators with small L that contribute only a single line in the gain spectrum. This does not contribute to the harmonic features in the average PFT; however, it may contribute to the PFT background. This explains the large background seen in the average PFT of the malignant tissue.

We have experimented with various healthy and cancerous colon tissues taken from different patients, as well as from other parts of the human body such as the kidney, with very similar results. Thus, the distinction between the average PFT spectrum of healthy and cancerous dye-laser-soaked tissues may be useful for diagnostics imaging. Our measured spatial resolution from which we can distinguish malignant tissues was about 25 spectra, or 2-mm lateral resolution. It is also noteworthy that coherent random lasing has been demonstrated using two-photon fluorescence,[16] where two laser beams are needed to generate the appropriate optical gain for lasing. This demonstration, and the development of very efficient molecules for two-photon fluorescence,[17] may render the random laser diagnostic of cancer tissues to be a truly three-dimensional imaging technique.

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