

Random lasing in bone tissue

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Owing to the low-loss and high refractive index variations derived from the basic building block of bone structure, we, for the first time to our knowledge, demonstrate coherent random lasing action originated from the bone structure infiltrated with laser dye, revealing that bone tissue is an ideal biological material for random lasing. Our numerical simulation shows that random lasers are extremely sensitive to subtle structural changes even at nanoscales and can potentially be an excellent tool for probing nanoscale structural alterations in real time as a novel spectroscopic modality. © 2010 Optical Society of America
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Random lasers have been the object of intensive investigations, in particular, in strongly scattering materials [1–5]. Conventional lasers consist of an optical gain material and an optical cavity for the system to lase. The optical cavity determines the mode of a laser (i.e., directionality and frequency). In a random laser, the cavity is replaced with closed-loop random cavities due to multiple scattering and the directionality is not maintained in the emitted light [5]. Since light diffusion with optical gain was theoretically studied for random laser action [1], it has been experimentally tested by varying the scattering power through changing the density of microspheres [2]. In addition, since light localization for lasing action was theoretically predicted [3], several experimental studies have been conducted to understand the origin of emission spectra of random lasers. Indeed, random lasing has been widely studied in many types of material systems ranging from strongly scattering regimes to weakly scattering regimes, such as ZnO powders [4], organic–inorganic materials [6], polymers [7–10], and microsphere suspensions [11]. Furthermore, diffusive random laser action in biological tissue was observed by Siddique *et al.* [12], and random lasing action with coherent feedback was also demonstrated in cancerous tissue by Polson and Vardeny [13]. A recent study has also demonstrated that localized and extended random lasing modes can be formed together in ZnO nanoparticle powders, supporting the robustness of random lasing [14].

Because random cavities are strongly related to the structural properties of random media, the emission spectra can also be used to extract structural information of the samples. Thus an excellent and intriguing application of random lasers is to probe the structural properties and characteristics of bone tissue. Bone is a nanocomposite of a mineral phase (e.g., hydroxyapatite crystals) and an organic matrix (e.g., mainly collagen protein). This nanocomposite provides the structural basis for the mineralized collagen fibrils, which serve as the basic building block of bone, while bone's entire structure is highly complex and hierarchical, containing multiscale features

from the nanoscale to the macroscales [15]. The properties of bone at the microscale have been intensively studied for better understanding of the deformation and fractures in terms of plasticity and toughness. However, prefailure damage and deformation mechanisms in bone still remain relatively unexplored, in part, due to current technical limitations for nondestructively studying its structural properties at nanoscales. Light propagation in bone tissue can be strongly influenced by multiple scattering and may potentially result in some degree of light confinement. Thus, emission spectra of a random laser can be extremely sensitive to subtle changes in nanostructures or refractive index fluctuations in the self-formed resonant cavities. As the first step to test this feasibility for a sensitive means for bone or biomaterial characterizations, in this Letter, we demonstrate the random lasing action in bone tissue infiltrated with a laser dye and the feasibility that the narrow laser peaks can potentially be used as a sensitive detector for structural changes at the nanoscale.

We used cortical bone from bovine femurs and prepared the specimens using a precision saw, a polishing paper, and a sonicator. The dimension of the specimen was approximately 10 mm × 5 mm with the thickness of 200 μm–5 mm. We immersed the specimen in a common laser (or fluorescence) dye solution for a few hours [i.e., laser dye: Rhodamine 800, solvents: ethanol or dimethyl sulfoxide (DMSO), and weight ratio: 0.3%]. Both sides of the specimen were covered both with microscope slides and mounted it on a translation stage. As the size of the dye molecule is below 1 nm, the dye was expected to be uniformly distributed inside the bone tissue.

In lasing measurements, we optically pumped the sample using a tunable pulse laser (an optical parametric amplifier pumped with a Ti:sapphire regenerative amplifier). The wavelength of the pump laser was 690 nm. The pulse width was 100 fs, and the repetition rate was 1 kHz. The pump beam was focused normally onto the sample through a cylindrical lens to form a narrow strip with a width of 100 μm, covering a length of 1–3 mm. The emission light was

collected by a fiber bundle through a lens and coupled to a spectrometer with a resolution of ~ 0.2 nm. A bandpass filter of a 20 nm width was used to block the pump laser illumination. The length of the pumping strip was varied, and the minimum illumination length for generating narrow peaks was about 1 mm. The inset in Fig. 1(d) is a representative scanning electron microscopy (SEM) image of the bone specimen. This clearly shows that the mineralized collagen fibrils are the building blocks of the bone structure.

We first tested the emission from the dye solution at the pump power of 20 mW. No lasing spikes have been observed, and the spectral shape merely followed the spontaneous emission through the bandpass filter in our experimental setup as shown in Fig. 1(a). The solid line in Fig. 1(b) shows the emission spectra from the bone specimen infiltrated with the dye solution. At the same pump power as in Fig. 1(a), discrete narrow peaks can be observed in the spectrum. The linewidths of these peaks were 100 times narrower than the spontaneous emission spectrum. These are originated from the bone structure, which consists mainly of the mineralized collagen fibrils (~ 100 nm in diameter). Thus, light is strongly scattered at the lasing wavelength range. To exclude the possibility of Fabry–Perot cavity resonance resulted from the top and bottom surfaces of the specimen, we also measured random laser emission from a relatively thick bone specimen without polished parallel surfaces. As shown in Fig. 1(c), discrete spikes can still be observed.

To further confirm the lasing action, we plotted the output emission intensity over the pump power as shown in Fig. 1(d). Figure 1(d) depicts a clear threshold behavior at ~ 15 mW. During the increase in the

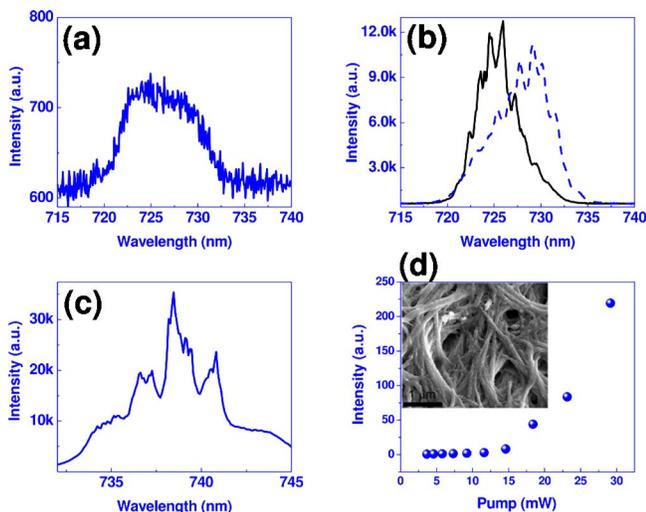


Fig. 1. (Color online) (a) Emission spectrum of the dye solution (Rhodamine 800 in ethanol) without the bone specimen. (b) Emission spectra of random lasers from the bone tissue (thickness = $200 \mu\text{m}$) infiltrated with Rhodamine 800 at different positions. (c) Emission spectrum of random lasers obtained from a thick bone specimen (thickness = 5 mm) infused with Rhodamine 800 in DMSO. (d) Dependence of the output laser intensity on the pump power. Inset: SEM image of the bone tissue. The scale bar is $1 \mu\text{m}$.

pump power, the emission spectra changed from a broad spontaneous emission peak to multiple sharp peaks. Meanwhile, similarly to the previous report [4], the number of narrow peaks also changed with the pump power. The dashed line in Fig. 1(b) shows the spectrum obtained from different positions on the same bone sample as a solid line. But the lasing peaks are totally different. These differences were caused by the nonuniform structures of the bone tissue and also indicate the sensitivity of random lasers on subtle structures in bone tissue.

We further conducted numerical stimulations to understand light confinement in the bone tissue. We simplified the bone structure to a quasi-one-dimensional structure in the following reasons: (i) The minimum pumping area = $1 \text{ mm} \times 100 \mu\text{m}$. (ii) Because multiple scattering events along the depth quickly decrease the pumping intensity below a lasing threshold, laser actions can only be occurred in the internal structure of the superficial layer. (iii) The mineralized collagen fibrils of ~ 100 nm in diameter are the basic building blocks of the bone as shown in Fig. 1(a). Our quasi-one-dimensional sample consisted of 400 layers, and the thickness of each layer was randomly varied from 60 to 120 nm to mimic the size of the mineralized collagen fibrils and the separation matrix between the fibrils. We randomly tilted each layer in a small range of 0.5° to mimic the nonuniform diameter and alignment of the mineralized collagen fibrils as shown in Fig. 2(a). We simulated the system with a finite-element method (Comsol Multiphysics 3.5a). The refractive index of each layer was alternated between $n=1.4$ and 1.6. The refractive index outside the sample was set to be 1.

The calculated eigenvalues inside the system and are shown in Fig. 2(b). Except for several high Q

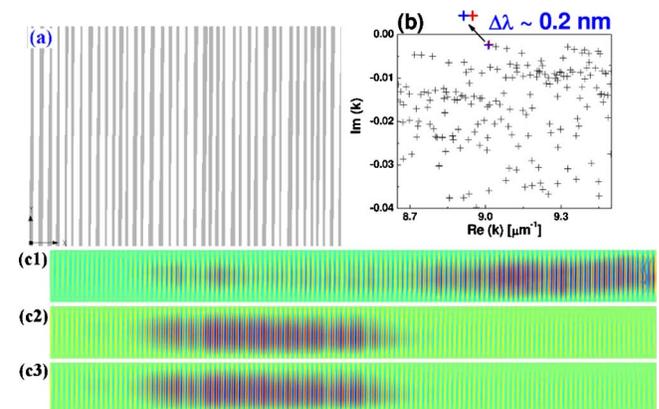


Fig. 2. (Color online) (a) Schematic picture of a representative area of the simulation structure. (b) Eigenvalues in the quasi-one-dimensional random structures. (c1) The field distribution of a randomly selected high Q resonant mode at $\kappa = 9.1378 - i \cdot 0.0099 [\mu\text{m}^{-1}]$. (c2) The field distribution of the highest Q resonant mode at $\kappa = 9.0139 - i \cdot 0.0023 [\mu\text{m}^{-1}]$. (c3) After slightly increasing the thickness of one single layer by 10 nm while keeping other layers the same, the field distribution of the highest Q resonant mode at $\kappa = 9.0115 - i \cdot 0.0024 [\mu\text{m}^{-1}]$. Although its field pattern is almost the same as in (c2), surprisingly, the resonant wavelength was significantly shifted by ~ 0.2 nm.

modes, most of the resonant modes had relative low Q factors [$Q = -\text{Re}(\kappa)/2/\text{Im}(\kappa)$]. Considering the simple relationship between Q factors and laser thresholds, it is obvious that more lasing peaks can be observed at a higher pump power. Figures 2(c1) and 2(c2) show the spatial intensity distribution of a randomly selected high Q mode at $\kappa = 9.1378 - i \cdot 0.0099 [\mu\text{m}^{-1}]$ and that of the highest Q mode at $\kappa = 9.0139 - i \cdot 0.0023 [\mu\text{m}^{-1}]$, respectively. As shown in the two modes, the light was well confined inside the random structures, and the different eigenvalues were localized in the different spatial positions. This is also consistent with the experimental observation of the position dependent laser spectra. Our numerical simulation clearly shows that the light is confined in a relatively large area. The random lasing modes should also be formed by a relatively large volume of the bone specimen. Therefore, the sensitivity of random lasers to subtle structural alterations in bone tissue can potentially be achieved in a relatively large volume.

We further tested the sensitivity of random resonance (i.e., random lasers if gain is applied) on to a structure change. We randomly selected a single layer among the 400 layers in the previous sample and slightly increased its optical thickness by 10 nm while keeping the thicknesses of other layers the same. When we visualized the spatial intensity of the highest Q mode as shown in Fig. 2(c3), the confined mode pattern was almost exactly the same as that of the highest Q mode in the previous random structured sample. Surprisingly, its eigenvalue κ , however, changed from $9.0139 - i \cdot 0.0023 [\mu\text{m}^{-1}]$ to $9.0115 - i \cdot 0.0024 [\mu\text{m}^{-1}]$, corresponding to a wavelength difference of ~ 0.2 nm [Fig. 2(b)]. Such a wavelength shift can be easily resolved using a common spectrograph. This implies that even though the transport-mean-free paths are almost the same, the local difference of scattering properties can also generate a dramatic difference in random lasing spectra, given that in the quasi-one-dimensional system, the resonant modes are dominantly localized in large areas. Thus, our results strongly support the idea that random lasing emission spectra can be extremely sensitive to subtle nanoscale structural changes in a relatively large volume of bone and biomaterials. We also tested the sensitivity of extended modes in a two-dimensional system and observed a similar sensitivity.

In conclusion, we experimentally demonstrated random lasing action originated from the bone struc-

tures infused with a common laser dye or a fluorescence dye. Discrete peaks and threshold behavior were successfully obtained from the optical excitation experiments to confirm the random lasing action. Because the random lasing modes are closely correlated with the structural properties of the random media, lasing spectral properties can potentially be used to probe subtle structural alterations even at nanoscales. Thus, our finding serves as a first step to use random lasing for potentially studying material damage and deformation at nanoscales. For example, during *in situ* mechanical testing, we will be able to monitor structural deformations to study nanoscale bone properties and characteristics. We further envision that random lasing can potentially be established as a novel spectroscopic modality for investigating structural properties in various types of biomaterials and biological tissue.

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