Quantum dot optofluidic lasers and their prospects for biochemical sensing

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ABSTRACT

We achieved four types of laser emissions with quantum dots (QDs) using the same high-Q-factor optofluidic ring resonator (OFRR) platform. In the first type, 2 μM QDs dissolved in toluene that filled the entire OFRR cavity volume were employed as the gain medium. The lasing threshold was 15-22 $\mu\text{J}/\text{mm}^2$. In the second type, 2 μM aqueous QDs were in bulk buffer solution that filled the entire OFRR cavity volume. The lasing threshold was 0.1 $\mu\text{J}/\text{mm}^2$, over 3 orders of magnitude lower than the state-of-the-art. In the third type, the aqueous QDs were immobilized as a single layer on the interface between the OFRR inner wall and buffer solution with a surface density as low as $3 \times 10^9 - 10^{10} \text{cm}^{-2}$. The lasing threshold of 60 $\mu\text{J}/\text{mm}^2$ was achieved. In the fourth type, we achieved optofluidic FRET lasing using aqueous QDs as FRET donors and Cy5 dye molecules as acceptors. We observed lasing from Cy5 emission band in QD-Cy5 pair when excited at QD absorption band, far away from Cy5 absorption maximum. We also report a comprehensive theoretical analysis of optofluidic FRET lasers that was performed based on a Fabry-Perot microcavity using a rate equation model. By comparing FRET lasing-based sensors with conventional sensors using FRET signals obtained by spontaneous fluorescence emission, we show that for optimal pump fluence and FRET pair concentration, FRET lasing can lead to more than 20-fold enhancement in detection sensitivities of conformation changes for linker lengths in the Förster radius range.

Keywords: Quantum dot lasers, optofluidic ring resonator, fluorescence resonance energy transfer, FRET lasers, rate equation model, optofluidic lasers, biosensors, quantum dots

1. INTRODUCTION

High sensitivity of stimulated emission to small perturbations in the laser cavity and gain medium enables optofluidic lasers to be exquisite new tools for biosensing applications.^{1,2} Recently, optofluidic laser biosensors have been applied to DNAs,³ proteins,⁴ cells,⁵ and tissues⁶ to reveal sub-nanometer conformational changes in biomolecules,⁷ distinguish small thermal dynamic difference between two biomolecules,³ analyze structures and morphologies of cells and tissues,⁶ and detect biomarkers at extremely low concentrations ($\sim 1 \text{ fg/mL}$),⁸ all of which cannot easily be achieved with standard fluorescence techniques based on spontaneous light emission. Analogous to their counterparts used in traditional fluorescence detection, gain medium in both bulk solution^{3,5,7} and on solid/liquid interfaces⁹ have been realized with optofluidic lasers.

Despite the fact that they are suffering from photobleaching, to date, organic dyes have been the most commonly used gain medium for optofluidic lasers. Organic dyes are also sensitive to solvent conditions (such as pH, polarity, and ionic strength), making it less attractive when used in different biological systems. In contrast, semiconductor quantum dots (QDs) come together with unique advantages over organic dyes. Core/shell structured QDs can be engineered with optimized passivation layers to achieve monodisperse sizes while possessing high resistance to photobleaching and high quantum yields in the presence of water and other harsh solvents (high acidity, basicity, and salt concentration, etc.)¹⁰ In addition, QDs have high absorption cross sections,¹¹

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Figure 1. Illustrations of aqueous QDs (A) in solution inside an OFRR, (B) immobilized as a single layer on the inner surface of an OFRR. (C) Illustration of QDs dissolved in toluene solution inside an OFRR. Qualitative sketches of radial dependence of WGM intensity are also shown (A), (B), and (C). (D) Illustration of the experimental setup using confocal geometry. (E) Representative TEM image of Qdot[®] 655 QDs used in this study. Average dimensions are estimated to be 8x15 nm.

which is critical for lasing with low pump intensities. Furthermore, QDs have broad absorption bands and their emission wavelength can be tuned by simply changing their size or composition; different colors of fluorescence can be obtained using the same excitation source. Therefore, QDs have increasingly been used as alternatives to organic dyes for biosensing, imaging, and ion detection applications.^{12–14}

Here, we demonstrate low-threshold lasing emission from QDs when they are in bulk aqueous or toluene solutions or immobilized as a single layer on the interface between a solid substrate and aqueous solution. Due to the excellent Q-factor of the optical cavity and the high fluorescence quality of the QDs, lasing thresholds on the order of $0.1 \mu\text{J}/\text{mm}^2$ was obtained for QDs in bulk aqueous solution with a concentration as low as $2 \mu\text{M}$, 3 orders of magnitude lower than the state-of-the-art with the similar QD concentration.¹⁵ For QDs immobilized as a single layer with a surface density as low as $6 \times 10^9 \text{ cm}^{-2}$, the lasing threshold was approximately $60 \mu\text{J}/\text{mm}^2$. In all cases, the QD lasing persisted even under uninterrupted pulsed pumping 7 times the lasing threshold for 10 minutes, showing significantly higher resistance to photobleaching than organic dyes that were almost completely photobleached within a few minutes of laser operation under similar pumping conditions. We also demonstrate fluorescence resonance energy transfer (FRET) lasing from Cy5 emission band in QD-Cy5 FRET pairs when excited at QD absorption band, far away from Cy5 absorption maximum.¹⁶ Finally, we use a rate equation model to compare the performance of FRET lasing-based sensors with conventional sensors using FRET signals obtained by spontaneous fluorescence emission.¹⁷ We show that for optimal pump fluence and FRET pair concentration, FRET lasing can lead to more than 20-fold enhancement in detection sensitivities of conformation changes for linker lengths in the Förster radius range.

2. EXPERIMENTAL

The laser cavity used in our work was an optofluidic ring resonator (OFRR) based on a thin-walled fused silica capillary. The fabrication and characteristics of the OFRR have been well studied in the past few years.¹⁸ Briefly, the OFRR with an inner diameter of 70-90 μm and a wall thickness of 1-2 μm was obtained by rapidly stretching a fused silica pre-form under CO_2 laser illumination. The circular cross section of the capillary forms the ring resonator that supports the high Q ($\sim 10^7$) whispering gallery modes (WGMs). The OFRR is a very versatile cavity that can accommodate liquids with various refractive indices.^{19,20} When the gain medium is in liquid having a refractive index lower than that of glass, the WGM is mainly confined within the capillary wall, but has an evanescent field present inside the capillary to provide optical feedback for the gain medium

Figure 2. Pump intensity dependence of the spectral intensities recorded from lasing and non-lasing spectral regions in the emission of orange (A) and red (B) emitting QDs dissolved in toluence. Spectral integration takes place in the range of 593-598 nm (642-647 nm) for lasing and 575-580 nm (620-625 nm) for fluorescence of orange (red) emitting QDs, respectively. Insets show spectra recorded at varying pump fluences. Lasing thresholds are $15 \mu\text{J}/\text{mm}^2$ and $22 \mu\text{J}/\text{mm}^2$ per pulse for orange and red emitting QDs, respectively. (C) Normalized lasing intensity integrated between 595-598 nm from $2 \mu\text{M}$ orange emitting QDs dissolved in toluene over a duration of 9 minutes under 20 Hz pumping at an intensity of 3.5X threshold ($55 \mu\text{J}/\text{mm}^2$ per pulse). Error bars are obtained with 3 measurements. (D) Lasing spectra recorded from orange emitting QDs dissolved in toluene at $t=0$ min and $t=9$ min show negligible photo-bleaching. (E) Normalized lasing intensity integrated between 642-647 nm from $2 \mu\text{M}$ red emitting QDs dissolved in toluene over a duration of 10 minutes under 20 Hz pumping at an intensity of 1.4X threshold ($30 \mu\text{J}/\text{mm}^2$ per pulse). Error bars are obtained with 3 measurements. (F) Lasing spectra recorded from red emitting QDs dissolved in toluene at $t=0$ min and $t=10$ min show negligible photobleaching.

to lase (Fig. 1(A)). On the other hand, when the liquid has a higher refractive index, the WGM exists mainly in the liquid, which also provides optical feedback for lasing (Fig. 1(B)). Furthermore, the WGM can interact with a single molecular layer of gain molecules at the solid/liquid interface (Fig. 1(C)).⁹ For QD lasing in the aqueous environment (water refractive index = 1.33 at visible wavelengths), we utilize the OFRRs first and third property described in Fig. 1(A) and (C). We also demonstrate QD lasing in toluene (refractive index=1.496 nm at visible wavelengths) using the OFRRs second property described in Fig. 1(B).

Commercially available QD solutions in aqueous buffer (Invitrogen Qdot[®] 655; CdSe/ZnS quantum dots; $2 \mu\text{M}$ in borate buffer; 8x15 nm average QD dimensions²¹ (Fig. 1(E))) and in toluene (Sigma; CdSeS/ZnS alloyed quantum dots; $2 \mu\text{M}$ in toluene; 6 nm average QD diameter) were used in the experiments. Amine-to-amine cross-linking was used for surface immobilization of the Qdot[®] 655 QDs on the inner surface of the OFRRs. For optofluidic QD FRET laser experiments, the covalent immobilization method was used to link Cy5 dye molecules to the surface of Qdot[®] 655 QDs. Optical experiments were performed using a confocal setup exciting OFRRs with the output of a pulsed optical parametric oscillator (OPO) (repetition rate: 20 Hz, pulse width: 5 ns) (Fig. 1(D)). Excitation wavelength of 433 nm was used in all the QD experiments. A 25 mm focal distance planoconvex lens was used for focusing the excitation beam at a 0.8 mm spot on the OFRRs and collecting the OFRR laser emission. A spectrometer (Horiba 550) and a CCD camera were used for spectral detection of the OFRR laser emission signals. All measurements reported in this paper were performed in the absence of liquid flow, when the gain medium was kept still inside the OFRR.

Figure 3. Spectrally integrated intensity as a function of pump intensity for laser emission (squares) and fluorescence (circles) for 21.6 μM aqueous QDs in borate buffer solution. Spectral integration takes place in the range of 660-665 nm for lasing and 650-655 nm for fluorescence. The lasing threshold is 0.1 $\mu\text{J}/\text{mm}^2$ per pulse. Insets show the examples of emission below and above the respective lasing threshold. Error bars are obtained with 3 measurements. (B) Normalized lasing intensity integrated between 660-670 nm from 2 μM aqueous QDs over duration of 10 minutes under 20 Hz pumping at an intensity of around 10X threshold (1.06 $\mu\text{J}/\text{mm}^2$ per pulse). Error bars are obtained with 3 measurements. (C) QD lasing spectra recorded at $t=0$ min and $t=10$ min show negligible photobleaching. (D) Spectrally integrated intensity as a function of pump intensity for laser emission (squares) and fluorescence (circles) from a single layer of QDs immobilized on the inner surface of the ring resonator filled with PBS buffer solution. Spectral integration takes place in the range of 653-658 nm for lasing and 644-649 nm for fluorescence, respectively. The lasing threshold is 60 $\mu\text{J}/\text{mm}^2$ per pulse. Error bars are obtained with 3 measurements. Insets show the examples of laser emission just and well above the lasing threshold. (E) Normalized lasing intensity integrated between 650-660 nm over duration of 10 minutes under 20 Hz pumping at an intensity of 3.5X threshold (199 $\mu\text{J}/\text{mm}^2$ per pulse) from a single layer of aqueous QDs immobilized on the inner surface of an OFRR. Error bars are obtained with 3 measurements. (F) QD lasing spectra recorded at $t=0$ min and $t=5$ min.

3. LASING WITH QUANTUM DOTS DISSOLVED IN TOLUENE

Fig. 2 summarizes the results of the lasing experiments we have performed with QDs dissolved in toluene, kept in OFRRs. Threshold pump intensities of 15 and 22 $\mu\text{J}/\text{mm}^2$ were observed for orange (Fig. 2(A)) and red (Fig. 2(B)) emitting QDs dissolved in toluene, respectively. The observed lasing threshold pump intensities were much smaller than those reported in the other comparable study in the literature ($\sim 250 \mu\text{J}/\text{mm}^2$) due to the superior properties of the OFRR as an optical cavity.²² In both cases, negligible photobleaching was observed during QD lasing for durations over ~ 10 min using optical pumping intensities 1.4-3.5 higher than the corresponding threshold pump intensities (Fig. 2(C) and (D)).

4. LASING WITH AQUEOUS QUANTUM DOTS

Fig. 3(A) shows the QD emission spectra recorded at various pump intensities together with spectrally integrated intensities. At low pump intensities, only spontaneous emission is observed. With the increased pump intensity, multiple lasing peaks emerge at the red side of the QD emission band. An analysis of the power dependent spectral intensity for the lasing region between 660 nm and 665 nm plotted in Fig. 2 reveals a lasing threshold of 0.1 $\mu\text{J}/\text{mm}^2$. In contrast, the non-lasing part (650-655 nm) of the QD emission spectrum increases sub-linearly and saturation is observed at increased pump intensities. The observed lasing threshold is over 3 orders of magnitude lower than for the previously reported optofluidic laser (440-530 $\mu\text{J}/\text{mm}^2$) using aqueous microdroplet resonators that contained similar QD concentrations (1.3-2.6 μM).²³ Such significant improvement is due to the excellent Q-factor of the OFRR ($\sim 10^7$).¹⁸ The observed lasing threshold is also much lower than lasing threshold values reported in OFRR laser demonstrations using organic dyes and green fluorescent proteins of the similar concentration (2-10 μM) (20-100 $\mu\text{J}/\text{mm}^2$).¹⁹ The high absorption cross section at the pump wavelength of the QDs contribute to the significant reduction in the lasing threshold in the QD laser over the dye or fluorescent protein based laser. Figs. 3(B) and (C) show the photostability of lasing intensity obtained from aqueous QDs at 2 μM concentration during 10 min, under a constant pump fluence of 0.7 $\mu\text{J}/\text{mm}^2$ (7X the lasing threshold). Spectra recorded during this time show fluctuations of up to 30% in QD lasing intensity, but no clear sign of photobleaching.

Figure 4. Emission spectra of QD-Cy5 and Cy5 when pumped at 450 nm. Spectra are vertically shifted for clarity.

Figure 5. The sensitivity enhancement factor for (a) donor and (b) acceptor as a function of linker length (R) at different Φ_P values. In all simulations, excitation pulse width was set to $\Delta t = 5$ ns and the cavity Q-factor was 10^6 . Förster radius was assumed to be 6.1 nm.

We performed surface immobilization biochemistry and attached a single layer of aqueous QDs on the inner surface of the OFRRs. OFRRs were subsequently filled with DI water. Upon optical pumping, photostable QD lasing was also observed for this case as demonstrated in Fig. 3(D)-(F). As compared to the results presented in Fig. 3(A)-(C) 2 and 3 using aqueous QD solutions, in this case lasing threshold fluence is larger ($\sim 50 \mu\text{J}/\text{mm}^2$) and the average lasing wavelength (~ 655 nm) is smaller. Both of these observations stem from the much smaller number of QDs coupled to the WGMs²⁴ [48, 49]. However, despite the high pumping intensity conditions, a good photostability was still observed over the duration of 10 min for the case of lasing with a single QD layer (Fig. 3(E) and (F)).

Fig.4 shows the main results of the optofluidic QD FRET laser experiments. In these experiments an aqueous solution containing Qdot® 655 QD-Cy5 dye molecules FRET pairs is used as the gain medium. The gain medium is pumped at 450 nm where considerable QD absorption exists while Cy5 absorption is very low. QD-Cy5 pairs revealed Cy5 lasing at a threshold pump intensity of around $12 \mu\text{J}/\text{mm}^2$ when the concentration of Cy5 molecules was measured to be 30 μM from absorption measurements. In contrast, no lasing was observed from an aqueous solution of 30 μM Cy5 molecules for pump powers up to $176 \mu\text{J}/\text{mm}^2$. These show that for the case of QD-Cy5 pairs, FRET served as the mechanism pumping the Cy5 acceptor molecules.

5. PROSPECTS OF OPTOFLUIDIC LASERS FOR BIOCHEMICAL SENSING

We carried out a comprehensive analysis of optofluidic FRET lasers using the framework of rate equations for the excited state populations of the donor and acceptor molecules and the corresponding donor and acceptor photon densities. Our rate equations are based on those developed previously for a dye laser consisting of a single-dye gain medium.²⁵ These equations have been expanded to account for the presence of a saturable absorber dye acting as an energy acceptor which is radiatively coupled to the donor dye.^{26,27} Moreover, additional terms describing FRET-based non-radiative energy transfer between the donor and acceptor molecules have been included.²⁸

Fig. 5 shows some key results of our analysis. In this figure the donor and acceptor sensitivity enhancement factors Π_D and Π_A are plotted as a function of the donor-acceptor linker length (R). Π_D and Π_A quantify the enhancements observed in donor and acceptor emission intensities to R for the case of an optofluidic laser as compared to the case of regular fluorescence. We define the sensitivity enhancement factor Π as the ratio of lasing FRET sensitivity to the regular fluorescence FRET sensitivity, $\Pi = \Omega_{\text{lasing}}(R)/\Omega_{\text{fluorescence}}(R)$. Here, $\Omega_{\text{lasing}}(R) = |(100 \times dE_{\text{out}})/(E_{\text{out}}dR)|$ is the sensitivity of the output energy of stimulated emission from the donor or acceptor placed inside a high-Q cavity to changes in R characterizing the gain medium whereas $\Omega_{\text{fluorescence}}(R)$ is the corresponding sensitivity of the output energy of regular (non-amplified) fluorescence from the donor or acceptor placed inside a cavity with $Q = 1$. $E_{D\text{out}}$ and $E_{A\text{out}}$ represent the donor or acceptor emission energies. As illustrated by Fig. 5(a) and (b), maximal enhancement factors of ~ 20 for donor and ~ 25 for acceptor sensitivities are observed for a relatively broad range of R at different pump fluences Φ_P . The results of our calculations are in good agreement with the experiments reported in Ref.⁷ where optofluidic lasers were shown to be 16 times more sensitive to Mg^{2+} concentration in DNA Holliday junctions.

6. CONCLUSION

By combining the excellent fluorescent properties of the state-of-the-art core/shell QDs with the unique properties of the OFRR as an optical cavity, we demonstrated optofluidic QD lasing using aqueous solutions and toluene as the solvent. We also demonstrated capability of QDs as donors in FRET lasers. These results greatly improve the versatility for optofluidic laser operation due to the broad and large absorption cross-section of QDs in the blue and UV range. Free from limitations posed by photobleaching, such optofluidic QD lasers are directly applicable to numerous applications in bioanalysis, where optofluidic dye lasers have already proven their superiority over spontaneous fluorescent emission-based measurements. Finally, we have presented a comprehensive theoretical analysis of optofluidic lasers with gain media formed by a FRET pair of donor and acceptor dyes and showed that FRET lasing can lead to more than 20-fold enhancement in detection sensitivities of conformation changes for linker lengths in the Förster radius range.

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