# Microlasers Inside Live Cells

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**Abstract:** Here we show, for the first time to our knowledge, stand-alone cell lasers with both gain medium and cavity inside cells. Cells have natural tendency to engulf micro beads made of polystyrene or glass, and we use these microspheres to generate whispering-galley-mode (WGM) lasing inside cytoplasm. The gain was provided by fluorescent dye molecules embedded in the microspheres or in the cytosol. Upon optical pumping, the output emission from the cells show characteristic WGM resonance. By analyzing the wavelengths of the oscillation modes we can determine the bead size with a precision of 50 pm. Using the mode diameter as a unique identifier, one may distinguish more than thousands of cells. Furthermore, we demonstrate real-time sensing of the intracellular refractive index changes.

**OCIS codes:** (140.3945) Microcavities, (280.1415) Biological sensing and sensors

Lasers integrated into the living biological system have a potential to enable novel applications including sensing and imaging. This perspective[1] has motivated recent efforts of developing bio-lasers that are made, in part or in entirety, of biological or biocompatible materials. Cell laser is perhaps the most exciting possibility. Attempts made to date have used some sort of external cavities; for example, cells or bacteria producing green fluorescent proteins were placed between bulk mirrors[2] or encapsulated in water droplets[3]. Semiconductor photonic crystal cavity has been introduced into a live cell[4], however lasing has not been achieved. Here, we employ spherical dielectric cavities into cells, along with dye gain medium, to generate whispering-gallery mode[5] (WGM) lasing, demonstrating stand-alone cell lasers. WGM microresonators have been well known for their applications in temperature[6] and force[7] measurements, label-free chemical sensing down to single molecule level[8, 9] and tagging[10]. We show that much of these capabilities can now be achieved inside cells for various applications including cell tagging and intracellular sensing.

Beads made of polystyrene (n=1.59), glass (n=1.52) or $BaTiO_3$ (n=1.9) were supplied to the cells, which readily internalized the beads by endocytosis (Fig. 1a and b). We have observed that both macrophages[11] and non-macrophage[12] cells, such as HeLa and NIH3T3 cells, engulf beads up to 20 μm in diameter. The gain medium can be inside the sphere, in the cytosol, or only at the bead-cytosol interface (Fig. 1c). In the case where the dye is located in the cytosol, functional fluorescent stains can be used for probing the cells in the same way as in fluorescent imaging but with improved signal strengths due to laser amplification. When the cells containing the beads were pumped with an external Q-switched laser at the absorption maximum of the dye, typical lasing modes were observed (Fig. 1d). Dye doped polystyrene beads larger than 11 μm and $BaTiO_3$ beads larger than 8 μm showed lasing inside cells. WGM spectral peaks were also observed below laser threshold and especially with $BaTiO_3$ beads coated with a fluorescent dye. Even below threshold, sharp spectral peaks corresponding to a Q factor > 700 were observed down to 3.5-μm diameter beads.

To demonstrate tagging capability, we obtained confocal hyperspectral images of the cells containing beads (Fig. 1e and f). The spatial map of the intensity of the spectral peaks shows typical ring shape corresponding to light circulating in the spheres. The spectrum emitted from the beads was used to determine the exact bead diameter in each pixel of the image, with the measured diameter varying only couple nanometers within the same sphere. The precision of the average diameter of a single sphere is ~50 pm. Since the diameter of the beads can be determined by such precision, it can be used as a barcode to tag and track individual cells. For a sample with polydispersed beads with different diameters in the range from 8 μm to 12 μm and a bin size of 2 nm, we should be able to distinguish 2,000 individual beads. More cells can be tagged in principle by using multiple beads different dyes per cell.

The resonant wavelengths of the WGM modes are dependent on the refractive index outside the beads through evanescent coupling. Therefore, this dependence can be used as sensors for the concentration of various compounds near the surface of the beads. As a proof of concept we acquired the laser spectra from cells *in vitro* when the cell culture media is supplied with additional 2g/L of sodium chloride. The change in osmolarity reduces

the volume of the cell and therefore increases the concentration of the molecules in the cytoplasm increasing the refractive index by $1.0\times10^{-2}$. A clear jump in the position of a WGM mode is observed (Fig. 1g).

In conclusion, we have achieved intracellular lasing using WGM micro beads and shown its potential applications to the tagging of a large number of cells and intracellular sensing.

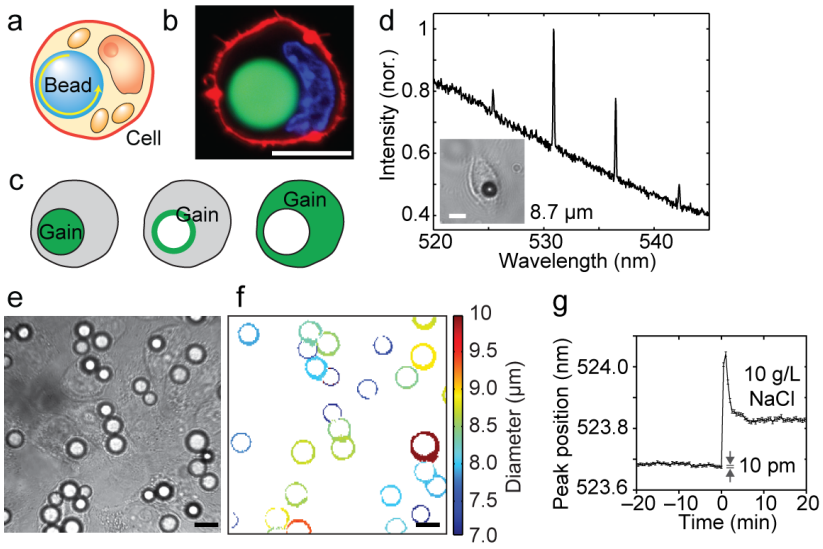


Fig. 1. (a) Configuration of the cell laser. (b) Confocal image of a polystyrene bead embedded in a HeLa cell. (c) Three locations of laser gain used in the experiments. (d) Laser emission from a BaTiO3 bead embedded in a cell containing CMFDA dye in its cytoplasm. (e) Bright field image of multiple cells containing fluorescent polystyrene beads. (f) Confocal hyperspectral image and subsequential analysis of the modes from the beads in (e) reveals precise bead diameters. (g) Spectral shift of a single WGM mode when the cell containing the bead was exposed to increased sodium chloride concentration.

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