The current state-of-the art in Lab-on-a-Chip (LOC) technology provides a paradigm shift for medical diagnostics. In lieu of sending out test samples to laboratories for analysis, healthcare providers could potentially use LOC devices to test patients at point-of-care facilities, thus diminishing analysis time from days to minutes. This diagnostic speed is critically important for time-dependent medical treatments such as diagnosing a viral infection in an elderly immune-compromised patient or pinpointing biological warfare agents from an exposed solid. By condensing a modern chemistry laboratory onto a micro-sized LOC device, diagnostic testing in remote or resource-poor locations is also made possible. The advantages of LOCs are compelling, but designing and fabricating these devices are challenging. LOC technology has been widely researched but still remains rarely commercialized [1,2]. LOC devices are typically comprised of complex networks of channels, valves/pumps, and chambers coupled with biofunctionalized, nanostructured surfaces to detect target analytes from biological serum. The micro fluidic system typically passes the test fluid over a stationary capture/detection region (e.g. arrays of microcantilevers [3], carbon nanotubes [4] or graphene petals [5]) that have been grown or fabricated onto the microchip. Biorecognition agents (e.g. enzymes, antibodies, single-stranded DNA, etc.) chemically/physically attached to the sensor detection region bind with target analyte within the moving media to initiate an electrical/optical signal transduction. These LOC biodetection strategies have yielded promising results, including use of smaller volumes of reagents/samples and high-throughput processing leading to fast turnaround times [6-8]. However current drawbacks to LOC technology include the inability to detect and quantify low concentration levels (submicromolar regime), inability to multiplex, and complex fabrication/biofunctionalization protocols that are costly and difficult to replicate [9]. Most importantly, there is still a significant inability to perform most assays in complex media such as blood or serum which means that most samples must undergo extensive sample purification and cleanup prior to analysis on a chip device. Thus, fundamental design questions regarding LOC design, sample preparation, and signal quantification still need to be addressed before LOCs can be widely commercialized. A new paradigm shift in LOC design is needed to address the current challenges associated with the technology. To address these challenges, researchers are beginning to demonstrate mobile sample preparation and bioagent detection/quantification schemes that interact with and move within the test solution. Self-functionalized, artificial nanomotors offer a unique solution to prepare and analyze biological samples on LOC devices [10]. Receptor-functionalized nanomotors, propelled by catalytic decomposition of hydrogen peroxide, are capable of capturing and isolating biological targets (e.g. E. coli and pancreatic cancer cells) from unprocessed biological media while possessing sufficient power to propel against flowing streams within micro fluidic channels [11-13]. Ultrasound-driven "microbullets", powered by the rapid expansion and vaporization of per fluorocarbon emulsion droplets, can accelerate with sufficient force to penetrate, cleave, and deform cellular tissue while reaching velocities of over 6 m/s [14]. These micro/nanomotors could be placed within micro fluidic compartments to isolate target analyte or cleave cellular tissue from unadulterated biological samples such as a portion of tissue biopsy. If properly implemented, this could certainly simplify processing prior to on-chip analysis. Establishing detection/quantification that interacts with and moves with the test solution will also greatly reduce the fabrication complexity and throughput performance of LOC devices. Incorporating Förster Resonance Energy Transfer (FRET)-based nanosensors may reduce microchip design by eliminating the need for separate nanostructured, biodetection regions grown or immobilized within the structure. DNA hybridization, antibody-antigen binding, and enzyme-substrate interaction would all occur rapidly in solution—eliminating the slow, diffusion-limited kinetics and bound/free reagent separation and washing steps typically associated with heterogeneous biosensing [15]. In particular, the use of luminescent semiconductor Quantum Dots (QDs) may hold the key to an optofluidic, FRET-based biodetection scheme that is capable of highly-sensitive, multiplexed bioanalytical analysis. These nanocrystalline materials possess properties well-suited to optical biosensing including high quantum yields, size-tunable Photoluminescence (PL), resistance to photobleaching and enhanced avidity/sensitivity to biomolecular probes and biosensing [16,17]. Pairing QDs with fluorescent dye-labeled biological probes can yield FRET sensors that are superior to standard sensors in many ways. The FRET efficiency of these QD-dye conjugates can be greatly enhanced when connecting multiple dye-acceptors around the central QD in a centrosymmetrical fashion where the probability of FRET between a QD and dye is significantly enhanced as multiple FRET “lanes” are introduced [16,17]. QD-fluorescent dye bioconjugates can detect a wide range of biomarkers through both increases and decreases in FRET (donor/acceptor) efficiencies. For example QD-dye conjugates are brought within closer proximity when detecting estrogen receptor β, an important diagnostic biomarker for breast cancer, creating an enhancement in FRET efficiency [18], while QD-dye conjugates that monitor botulinum neurotoxins, extremely potent bacterial toxins that contaminate food supplies, monitor a decrease in FRET efficiency via the toxins active proteolytic cleavage of the linker between the fluorophores [19]. Such FRET-based QD-dye conjugates introduced into LOC microfluidic devices could quickly bind to target analyte in solution for a rapid, real-time bioanalytical analysis that is also easily quantifiable. The photophysical characteristics of QDs including their large effective Stokes shifts and size-tunable PL also make them well-suited for multiplexed biosensing. Our recent work has shown that simultaneous five-color imaging could be achieved within a single cell with a single excitation signal—opening the door to multiplexed biosensing [20]. Conjugating both long lifetime luminescent terbium (III) complexes and fluorescent dyes to QDs has permitted us to create...
time-gated FRET relays where the QD acts as both an acceptor and donor at distinct time intervals [21]. These time-gated relays could add another dimension to FRET-based LOC devices to enhance multiplex capabilities while eliminating the effects of background fluorescence as endogenous, fluorescent interferents are quenched long before the FRET sensitization is monitored [21,22]. LOC technology contains the potential to dramatically improve the speed, efficiency, and cost of almost all chemical-based diagnostics. To move this technology to maturation and commercialization, several challenges need to be addressed including low target analyte sensitivity, complex fabrication protocols, and almost non-existent multiplexed capabilities. Recent strides in both self-propelled nanomotors and FRET-based biosensing may provide potential solutions to these challenges by eliminating the need for stationary biodetection regions within LOC devices. Self-propelled nanomotors have been shown to have the force and selectively necessary to swim in microchannels, bind and transport biological agents, and penetrate and cleave cellular tissue for enhanced biodetection and sample preparation strategies. FRET-based sensors would then travel within microfluidic channels of the LOC devices to provide selective and sensitive biodetection that is easily quantifiable. Multiplexed detection capabilities could be enhanced both spatially and temporally by using distinct QD-dye conjugates simultaneously and in time-gated fluorescent sensing modalities. The time-gated nature of these relays would also improve the sensitivity of detection as background interference is eliminated through delayed emission. Both nanomotors and QD-based biosensing would eliminate slow diffusion-limited kinetics and many of the washing steps associated with stationary built-in biodetection regions - thus improving the performance of LOC technology.

References