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Editorial overview

Andrew J deMello and Adam T Woolley

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Andrew J deMello

Imperial College London, Nanostructured Materials & Devices Group, Exhibition Road, South Kensington, London SW72AZ, United Kingdom
e-mail: a.demello@imperial.ac.uk

Andrew J. deMello is Professor of Chemical Nanosciences and Head of the Nanostructured Materials & Devices Group at Imperial College London. His research group is engaged in a broad range of activities in the fields of microfluidics, nanoscale science and ultra-sensitive optical spectroscopy. He is a Fellow of the Royal Society of Chemistry and was recently awarded the 2009 Clifford Paterson Medal by The Royal Society for contributions to Nanotechnology and the 2009 Corday Morgan Medal by the Royal Society of Chemistry.

Adam T Woolley

Department of Chemistry and Biochemistry, Brigham Young University in Provo, Utah, USA
e-mail: awoolley@chem.byu.edu

Adam T. Woolley is Professor and Associate Chair in the Department of Chemistry and Biochemistry at Brigham Young University in Provo, Utah, USA. His research focuses on microfluidics, bioanalytical chemistry, and biotemplated nanofabrication. He was awarded a 2006 Presidential Early Career Award for Scientists and Engineers and also received the 2007 American Chemical Society-Division of Analytical Chemistry Award for Young Investigators in Separation Science.

Over the past few decades the concept of miniaturization has been earnestly applied to chemical and biological problems. For example, much interest has been focused on the development of lab-on-a-chip or microfluidic technology. Largely, this has been driven by a need to accomplish rapid analysis of the small sample volumes that are typical in genomics, drug discovery, high-throughput screening and medical diagnostics. However, at a basic level, the appeal of microfluidic technology has been motivated by the fact that physical processes can be more easily controlled, accelerated and exploited when instrumental dimensions are reduced to a micron or submicron scale. The idea of miniaturization, pushed to an even greater extreme, has led to the emergence of the field of nanotechnology. Approaching the nanometer scale, bulk properties start to give way to molecular and atomic interactions, often leading to novel phenomena. The past decade has seen enormous growth in our understanding of and ability to characterize objects with nanometer-range dimensions. Importantly, these recent advances in nanoscience now show great promise in a diverse array of endeavors such as drug delivery, electronics, optical detection and sensing. The current issue highlights some of the emerging themes in the fields of micro- and nanotechnology and provides a glimpse of how the concept of miniaturization is beginning to impact chemical and biological sciences.

Hollfelder and co-workers describe recent advances in the emergent field of segmented flow or droplet-based microfluidics. In segmented flow microfluidics droplets are generated by combining two immiscible phases (typically aqueous and oil) in a continuous flow. Importantly, using such an approach allows picoliter-sized droplets to be generated at kHz rates with exquisite control over both droplet size and composition. On the basis of these features droplet-based platforms are well suited to performing biological experiments in ultra-high throughput. Indeed, the authors provide a specific focus on how unit operations achievable within such formats may be integrated to create complex workflows that perform key biological functions such as directed evolution, diagnostics and compound screening.

Over the past half century well in excess of $1 trillion has been invested on cancer research. Concurrent developments in molecular and cellular biology have allowed a better understanding the disease process and enabled the identification of potential therapies. Despite this progress malignancy still remains a surprisingly multifarious disease and survival rates are unacceptably low. To this end researchers desperately require new analytical technologies that will accelerate the study of cancer biology and diagnostics and the search for new effective therapies. Wlodkowic and Cooper present recent developments in the use of microfluidic technologies for elucidating the inherent complexity of cellular systems. Importantly, the authors

focus on how novel microfluidic formats can exploit the enhancements in analytical throughput, exquisite reagent control and ability to process small numbers of derived cells, and be used in pharmacological screening, drug discovery and clinical oncology.

Evolution by natural selection is a process that occurs over a number of generations and can thus be a challenge to study directly and in a controlled manner in a laboratory environment. Integrated microfluidic systems provide a well-suited platform for manipulating and characterizing the evolutionary processes of mutation, selection and amplification. In his manuscript, Paegel details recent progress in the design and implementation of different integrated microfluidic architectures for the *in vitro* study of directed evolutionary processes. Current issues in the field, such as scaling to larger population sizes and developing highly parallel screening protocols, are discussed along with proposed solutions.

Several papers in this issue highlight work involving enclosed channel microfluidic systems, which are the most established and common format for these experiments. Jabrail and Wheeler describe recent research on an emerging but potentially powerful alternative to the enclosed channel platform: digital microfluidics. The digital microfluidics approach entails the controlled and parallel manipulation of multiple droplets on a planar surface. Unlike in channel microfluidics, fluid droplet volumes in digital microfluidics can span a million-fold range. Digital microfluidics protocols are now being used in addressing a host of problems in chemical biology, including cellular assays and detection of targeted biomarkers in clinical specimens.

The emergence of nanometer-sized contrast agents has led to significant improvements in the understanding of biological processes at the molecular level and the development of new diagnostic and therapeutic tools. Typical imaging agents such as compound semiconductor, silica, metal and metal-oxide nanoparticles have proved to be superior to traditional molecular contrast agents but still often exhibit non-ideal chemical stability, insufficient *in vivo* stability and broad optical signatures. To this end, Wolfbeis and co-authors discuss the synthesis and application of upconverting luminescent nanoparticles in bioconjugation and bioimaging. Upconverting nanoparticles luminesce in the visible region of the electromagnetic spectrum after excitation with infra-red or near infra-red radiation. This feature is especially useful for bioimaging applications since auto-fluorescence of background matter is reduced. Moreover, the large anti-Stokes shifts typical of such particles ensure excellent distinction of luminescence from excitation radiation, and the narrow emission bands pave the way for highly multiplexed analysis. The authors describe a range of recent studies incorporating upconverting luminescent nanoparticles which not only suggest a healthy future in tissue imaging, but also highlight the need for more robust and reproducible functionalization strategies to allow for efficient immobilization of appropriate biomolecules.

The controlled bottom-up self-assembly of nucleic acids into designed and complex structures has long been considered as a route for nanofabrication. In recent years, this approach has gained considerable traction and seen remarkable progress with both two- and three-dimensional nanostructures having been formed. This issue has two papers that focus on efforts to utilize the controlled folding of nucleic acids into rationally designed nanometer-scale features. The first manuscript, by Sleiman and co-workers, focuses on the formation of three-dimensional nucleic acid assemblies. Strategies for creating these constructs include the directed use of the DNA double helix in dictating structure, the application of synthesized rigid molecules to form vertices in DNA-based assemblies, and chemical crosslinking of small molecules attached to DNA to generate ordered motifs. These three-dimensional DNA nanostructures have potential for application in encapsulation and delivery of drugs, and the formation of nanowires of controlled dimensions for usage in electronics. A second paper in this issue, authored by Yan *et al.*, details the rapid emergence of scaffolded DNA origami as a powerful technique for the assembly of DNA into targeted nanoscale shapes. This approach entails the controlled folding of a relatively long piece of single-stranded DNA using a number of much shorter and complementary synthesized oligonucleotides. Although the method of scaffolded DNA origami was initially described only in 2006, growth in this field has been enormous. Various two-dimensional nanostructures have now been constructed, including geometric shapes, smiley faces, maps, institutional logos, and alphabetic characters. More recently, the method of DNA origami has been applied in making three-dimensional nanostructures, and in the controlled localization of biological or inorganic features with nanometer precision. Nanoscale assemblies formed by this approach show promise for application in controlling chemical and biological reactions, and the enhancement of conventional lithographic methods in electronics.

Most biomolecules have dimensions in the nanometer range, such that there is keen interest in characterizing biological interactions with things at the nanometer scale. Moreover, the eventual utilization of nanoscale objects in biology will require an understanding of interfaces between biological and nanoscale materials. Park and Hamad-Schifferli discuss the bio-to-nano interface and crucial surrounding issues including non-specific adsorption. Importantly, viewing non-specific adsorption less as a 'bug' and more as a 'feature' enables one to potentially harness this interaction, by using the nanoparticle-to-biomolecule interface in manipulating biology in novel

ways. Potential applications of this approach include controlled release of desired reagents in cells and targeted reaction enhancement.

The final contribution to the issue by Lee and Lee reports on recent developments in nanoplasmonic technologies for on-demand and systematic intracellular gene regulation. Individual cells are hugely complex machines that continually sense and react to their local environment. Thus the ability to understand the functional components and inner workings of single cells lies at the heart of cell biology and systems biology. Specifically, intracellular control of internal connections can provide an unequalled view of cellular machinery, and with recent developments in nanotechnological and plasmonic tools, novel light-sensitive probes are now being directly interfaced with intracellular processes. The authors elegantly highlight that by using these tools the intracellular environment can be probed in an efficient way, which in principle allows the extraction of dynamic information.