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EDITORIAL

Ultrasmall sample biochemical analysis

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Richard Feynman's landmark lecture from 1959 titled "There's Plenty of Room at the Bottom: An Invitation to Enter a New Field of Physics" is widely known for encouraging research into the field we now refer to as nanotechnology. In that same lecture, he also presciently recognized that many fundamental questions in biology could be answered through miniaturization, particularly using microscopy, noting that many knowledge gaps could be readily addressed if we could "just look at the thing!" Indeed, increasing the resolution with which biological systems are investigated, whether it be through cryoelectron microscopy, flow cytometry, or single-cell RNA-Seq, has revolutionized many aspects of biological inquiry. In this themed topical collection of *Analytical and Bioanalytical Chemistry*, we emphasize that there is still "plenty of room at the bottom" when it comes to biochemical analysis. Great strides have been made in biology and medicine as chemical measurements that have historically been applied to bulk tissues are extended to the scale at which the biology is occurring, which is often at the cellular or subcellular level.

One immediate use case for ultrasmall sample biochemical analysis is the spatial mapping of biomolecules in biological systems. Biological tissues exhibit a high degree of phenotypic heterogeneity and plasticity, with tissues often comprising many intermixed populations and subpopulations of cells. Understanding the three-dimensional architecture of healthy and diseased tissues with high spatial resolution and molecular depth will provide a wealth of information that will improve diagnosis and prognosis and lead to far more effective treatments. To this end, the United States National Institutes of Health has recently launched the Human BioMolecular Atlas Program (HuBMAP) (https://commonfund.nih.gov/hubmap) "to explore the relationship between cellular organization and function, as well as the variability in normal tissue organization at the level of individual cells". Similar initiatives include the US National Cancer Institute's Human Tumor Atlas Network (https://www.cancer.gov/research/key-initiatives/moonshot-cancer-initiative/implementation/human-tumor-atlas), which includes the mapping of tumors and precancerous lesions. There are many similar efforts underway across the globe. Of course, sample size decreases as spatial resolution increases, leading to an intrinsic requirement for ultrasmall sample analysis of the nucleic acids, proteins, lipids, and metabolites within these tissues to achieve detailed mapping.

In addition to tissue mapping, many biological systems or phenomena are intrinsically small and tools need to be developed and refined for the study of their chemical makeup. Circulating tumor cells, exosomes, fetal nucleated red blood cells in maternal blood, and many other samples of great interest in biology and medicine all are present at levels that challenge many current bioanalytical techniques. Yet developing effective assays for measuring the biochemical makeup of such trace samples will lead to improved diagnoses and treatments for many diseases.

Extending biochemical analyses from bulk to trace levels involves more than enhancing detection sensitivity. Indeed, every aspect of the workflow must be carefully optimized. This often includes isolating the rare biological material of interest while excluding background materials, efficiently preparing and cleaning up the samples for analysis while minimizing sample losses, adapting separations and detectors for maximum sensitivity and developing innovative methods for

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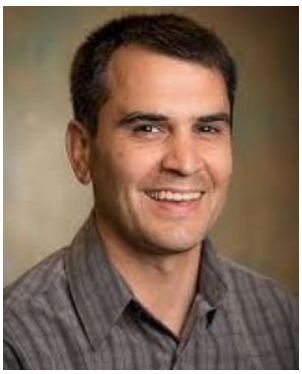
data analysis to extract as much information as possible from sometimes very weak signals. In addition, as one of the objectives of single cell and other trace biochemical analyses is to resolve heterogeneity obscured by bulk measurements, increasing measurement throughput for small samples also facilitates analyzing sufficient numbers of samples for statistically powered studies. As such, the many ongoing efforts to minimize sample requirements span many subdisciplines within the field of bioanalytical chemistry.

This themed topical collection covers many important contributions toward extending biochemical analyses to ultrasmall samples. A review article details the isolation and proteomic analysis of exosomes. An original report describes advances in device fabrication based on 3D printing of microfluidic structures toward the development of integrated sample-to-answer devices for point of care testing of biomarkers for pre-term birth. Another original report optimizes superhydrophobic surface patterning and magnetic actuation of droplets on a surface to perform rapid, low-input fluorescence-based DNA assays. An innovative approach achieves the multiplexed analysis of cell surface proteins from single circulating tumor cells isolated from whole blood of lung adenocarcinoma patients. A simple and low-cost homogenous fluorescence assay was developed for sensitive detection of Pb^{2+} from lake water based on induced DNAzyme cleaving reaction and rolling circle amplification. We describe a two-dimensional separation strategy for nanogram protein digests based on nanoflow liquid chromatography (nanoLC) and ultra high resolution ion mobility spectrometry with the aim of increasing the throughput and peak capacity of proteomic analyses.

We would like to thank all the authors for contributing their innovative work to the topical collection, as well as all the reviewers for providing constructive comments toward the improvement of the manuscripts. We hope the topical collection can provide a glimpse into the current efforts focused on ultrasmall sample biochemical analysis and encourage more scientists to join this exciting field.



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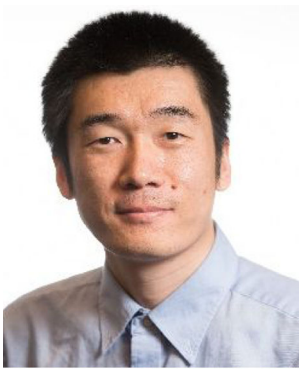

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