Anal Bioanal Chem (2008) 390:67–69
DOI 10.1007/s00216-007-1613-4

EDITORIAL

Miniaturisation of analytical steps: necessity and snobbism

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Published online: 22 November 2007
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Introduction

Automation and miniaturization were two widespread trends implicitly included in the research priorities of most scientific fields in the last few decades of the twentieth century. One result of the latter trend was the development of microtechnology, which has by now been superseded by nanotechnology by virtue of the advantages of small devices over macroscale systems. Analytical chemistry has also taken advantage of these trends in general and of nanotechnology in particular. The advantages thus gained include accurate spatial control over reagents and samples, increased throughput, automatability—which is absolutely mandatory, the ability to handle picoliter volumes of undiluted reactants—which saves reagents and sample, compatibility with a wide range of detection systems, the availability of a variety of materials for manufacturing at relatively low cost, design flexibility, the ability to perform multiple tasks (e.g. for the simultaneous development of several sample-preparation steps such as dissolution, extraction, or preconcentration) and improvements derived from the reduced dimensions used (e.g. in nanochromatography or chip-based separations). The development of portable miniaturized devices has facilitated the decentralization of analyses, a primary goal for this century, by enabling real time, in situ, on-line, in-vivo monitoring of processes without the need for skilled operators or special equipment [1]. There is no doubt that miniaturization and nanotechnology have contributed enormously to the emergence and development of new research areas which have brought about true revolutions, particularly in bioanalysis.

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Cutting-edge applications of nanotechnology in analytical chemistry

Single-cell-level research is one of the more salient applications of analytical nanotechnology. This is a very challenging task because of the typically small sample volume available, low abundance of the target material, and fragile nature of cells, which entail using preparation procedures causing no stress or damage to cells, in addition to sensitive detection techniques. The growing interest in single-cell physiology is driving the (bio)analytical and medical engineering fields to improving the technology of lab-on-a-chip devices, which are specially suitable for the manipulation and analysis of single cells [2].

Proteomics is one other area of high impact at present where miniaturization and automation have become high-priority topics with a view to scaling-down analysis methods to the micro and nanolevel while ensuring a high throughput and sensitivity. A number of analytical protocols capable of processing nanoliter to picoliter volumes and low femtomole to attomole or even smaller amounts of proteins or peptides are being developed as a result. Biological samples such as tissue biopsies and laser microdissected specimens are frequently available in reduced amounts and can thus also take advantage of analytical nanotechnology [3].

Nanotechnology is playing an innovative role in the manufacturing of nanostructures such as nanotubes, nanopores, nanowires, and nanofibers with a host of important analytical applications (Fig. 1) [4, 5, 6]. Comprehensive research on the imaging of individual small molecules with a characteristic long hydrocarbon chain has recently been

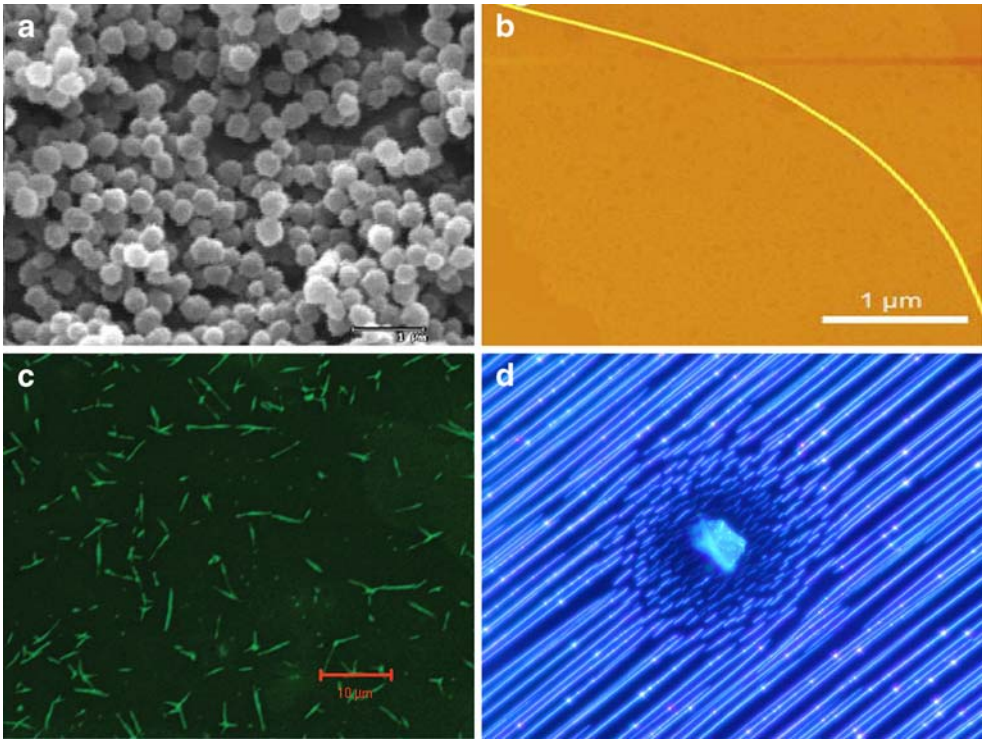

Fig. 1 Nanostructures commonly employed for analytical purposes. (**a**) Nanoparticles, which are the source of continuous innovation in separation sciences [4]. (**b**) AFM phase image of polyaniline-tobaco mosaic virus nanofibers, which have a good processing capability [5]. (**c**) Nanotubes, which provide a useful tool for capillary electrophoresis [6]. (**d**) Nanofibers, which are particularly useful for developing photonic devices. (Courtesy of F. Quochi, Università de Cagliari, Italy)

achieved by trapping the molecules inside single-walled carbon nanotubes. The hydrocarbon chain helps distinguish the head and tail regions of the molecule and also to correlate its motion relative to the nanotube [7]. The analysis of DNA has also benefited from preparation of nanomaterials to construct nanopore arrays, which afford rapid testing of DNA duplexes for sequence specificity using a technique known as "multinanopore force spectroscopy". Also, a lipid bilayer has been obtained by inclusion of α-haemolysin protein molecules which act as nanopores, resulting in a disposable device for rapid clinical detection of polymorphs [8]. Semiconducting nanowires can be used as sensors for low concentrations of species such as microorganisms, small molecules, and proteins with a fast detection response and low detection limits (as low as ~10 fmol L^{-1}) [9]. Also, light-emitting nanofibers, which allow light emission to be confined within nanoscale dimensions, have been produced by electrospinning. Nanofibers are thus attractive for sensing and lab-on-a-chip applications [10].

Drawbacks and the ensuing limits of downscaling analytical methods

Achievements in micro and nano analysis have led a number of analytical chemists to regard them as the panacea and use them unnecessarily, thereby complicating otherwise simple analyses; in fact, miniaturization not only downscales the analytical process, but also introduces additional driving forces for the process which result in the occurrence of new phenomena related to surface, shear, electrical double layer, size, entropy, and molecular structure, among other factors. One especially relevant phenomenon in micro and nanofluidics is the increase in surface-to-volume ratio arising when devices are downscaled to nanometre dimensions. In liquid flows, fluidic phenomena at the micro scale (100 nm–100 μm) can still be described by the continuum theory; however, the decreased length scale makes surface force and electrokinetic effects significant and suppresses the effect of inertial force. Fluidic channel dimensions below 100 nm fall in the region of nanofluidics. Under these conditions, the liquid cannot be considered a continuum proper, but rather as an ensemble of individual molecules. On these scales, the surface-to-volume ratio is very high, non-slip boundary conditions hold incompletely, and fluid constitutive relations are strongly affected by the presence of a boundary [11, 12]. Understanding micro/nanoscale fluid mechanics is mandatory with a view to improving lab-on-a-chip devices, which are arousing great interest as future tools for (bio)chemical analysis. Virtually every step of the analytical process can be incorporated into an integrated lab-on-a-chip device; if the overall analytical process is considered, however, the main hindrances to miniaturization in

lab-on-a-chip and similar devices arises from steps such as sampling (sub-sampling), specific pre-treatments, and tasks such as calibration or validation of the analytical method. The risk of analyte adsorption on walls and at interfaces, and optical interference at the walls of chips, hampering detection, are two additional problems related to the materials used to manufacture the devices. Detection and data-processing equipment have reached a high degree of miniaturization by virtue of the interest of detector manufacturers.

Where are the boundaries between the use of the different analytical scales? When are methods at the nano scale necessary or a matter of snobbism? No doubt the low-millilitre scales are easier to handle than are lower volumes and should be used when the sample is not expensive or rare and the reagents are neither expensive nor toxic. On the other hand, single-cell analysis and proteomic analysis require operation on the micro or nano scale. There are some other areas where micro and nano analysis can be convenient in specific cases and others where their use is not only superfluous, but also counterproductive. Thus, the use of micrototal analysis systems (μ-TAS) such as lab-on-a-chip devices is never justified in applications where the amount of sample is not a limiting factor and the reagents are not expensive (e.g. in the determination of nutrients in foods, or pollutants in soils or waters, except in cases when some immunoreagent or a similarly expensive biochemical reagent is needed). The short analysis times claimed by microchip users can also be obtained—and much more readily—with capillary electrophoresis, ultra-performance liquid chromatography, or ultra-fast gas chromatography.

In short, one of the duties of the analytical chemist is to establish a clear criterion for choosing the most appropriate scale for each task irrespective of the prevailing trend. This requires a sound knowledge of the boundaries between analytical scales, their pros and their cons.

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