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From nano to yocto, and beyond?

My first scientific paper appeared in this journal in 1962 – midway through the experimental work of my PhD thesis – and was concerned with the determination of antimony in lead by instrumental neutron activation analysis [1]. At that time neutron activation analysis was the most sensitive elemental analytical tool for a range of elements with detection limits down to the nanogram *per* gram ($1\,ng\,g^{-1} = 10^{-9}\,g\,g^{-1}$ = 1 ppb, part *per* billion) level for a considerable number of elements. Another elemental analytical technique, based on high resolution spark source mass spectrometry was then being developed for panoramic elemental analysis of solid samples at the lower ppb concentration level [2]. Back in the early 1960s, my colleagues and I were most impressed by the capabilities of such powerful instrumental techniques. Most of analytical chemistry then was wet-chemical. . .and rather tedious.

The importance of spectroscopy in analysis was already clearly apparent then; in fact, it was recognized much earlier. Many elements were discovered in the 19th century with separation tools assisted by spectroscopic measurements. Alfred Whitehead pointed already to the importance of instrumentation and spectroscopy in his treatise "An enquiry concerning the principles of natural knowledge" in 1919 [3]. The following is a quote from this work:

> *The reason we are on a higher imaginative level is not because we have a finer imagination, but because we have better instruments. In science, the most important thing that has happened in the last forty years is the advance in instrumental design. The gain is more than a mere addition; it is a transformation. This advance is partly due to a few men of genius such as Michelson and the German opticians.*

Mentioning Michelson, Whitehead refers to the Michelson–Morley interferometer experiment on the "aether wind" of 1887, an experiment that has been called "the most successful failed experiment in science" but also, the "the kicking-off point for the theoretical aspects of the Second Scientific Revolution". The German opticians referred to are Ernst Abbe, Carl Zeiss, Robert Bunsen and Gustav Kirchhoff.

Let us come back to the last 50 years of analytical science in order to highlight its prominent role in chemistry on the occasion of the International Year of Chemistry of 2011. We can illustrate the impressive progress achieved in analytical performance, taking measurement sensitivity as an example, with the data summarized in Table 1. The table shows schematically the introduction of units for the lower limit of detection in chemical analysis as they appear in the ISI Web of Knowledge. Since the 1960s each new decade gave rise to the introduction of a new range of units each with an improvement of lower limits of detection by three orders of magnitude; this amounts to an impressive 15 orders of magnitude over a time span of 50 years.

By now, the units femtogram and attogram and their use in chemical analysis is commonplace, the zeptogram is used less regularly. The unit yoctogram appeared first in the literature in 2010 [4] in a theoretical study of the intrinsic quality factor of the fundamental flexural vibration in a carbon nanotube.[1] The study reveals design principles for the construction of ultra-sensitive nanotube mass sensors: under tensions close to the elastic limit; it allows for single yoctogram mass resolution at room temperature while cooling might open the possibility of sub-yoctogram mass resolution. We will come back later to the significance of analysis at such a mass sensitivity level.

In what follows we concisely comment the evolution in performance of analytical chemistry with the schematic diagram shown with Fig. 1. Consider it as a (simplified) Greek temple structure with a base, then columns supporting an entablature.

Analytical instrumentation based on spectroscopy and other physical principles and analytical techniques forms the fundamental building base for progress in analytical chemistry. Development was based on two distinct and correlated columns; these are: microelectronics and integrated circuit (IC) technology (left in the figure) and information technology (IT, right). Performance parameters such as detection limits and spatial analytical potential (lateral and depth resolution) consistently kept track with the evolution of IC technology as put forward in Moore's Law [5]. With increasing speed of data generation, various analytical techniques become increasingly dependent on IT infrastructure for instrument operation and, with time, increasingly complex calculations, for data management, spectral data handling, image processing and statistical analysis of increasingly large data sets. IT also completely revolutionized certain well-established concepts. One example among many is the Abbe-Rayleigh diffraction limit which was successfully challenged in different forms of super-resolution microscopy; applications now allow a spatial resolution of a few nm for visible light. Another example concerns X-ray imaging on the basis of phase contrast instead of absorption contrast which

[1] The term yocto- (Greek, from octo-, "eight"; a decimal prefix used in the international metric system for measurements) needs some word of explanation. It was adopted by the Conference Génerale des Poids et Mesures (CGPM) in 1991. The name yocto is derived from octo, suggesting the number eight (the eighth power of 10^3 or 10^{24}). The letter 'y' is added to avoid the use of the letter 'o' as a symbol which would lead to confusion with the number zero.

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Table 1
The introduction of ultimate limits of detection and sensitivity.

Time of introduction	Name	Metric unit (g)	
1960–1970	Nanogram (ng)	10^{-9}	ppb
1970–1979	Picogram (pg)	10^{-12}	ppt
1980–1989	Femtogram (fg)	10^{-15}	ppq
1990–1999	Attogram (ag)	10^{-18}	
2000–2009	Zeptogram (zg)	10^{-21}	1000 Da molecule
2010–2019	Yoctogram (yg)	10^{-24}	1 Da, 1.7 H-atom

allows lens-less 2-dimensional (2D) imaging and 3-dimensional (3D) tomography with unprecedented detail.

As a consequence of all this, there are now many highly sophisticated analytical tools available for the characterization of inorganic and organic materials with a high structural complexity and heterogeneity. Significant is that a number of these techniques have the potential to do 2D and 3D imaging on the sub-microscopic, even on the nanoscopic (<100 nm) level. In chemical analysis at the nano-level a number of spectrometric tools are used that complement information available through physical techniques such as atomic force microscopy, scanning tunneling microscopy and electron microscopy. These techniques are mostly based on the use of spectrometric tools such as Raman spectroscopy, near-field microscopy, laser ablation or secondary ion mass spectrometry, and nano-optical sensing. Beam methods of analysis based on ion, laser and synchrotron X-ray bombardment are being optimized at the nanoscale level and now operate at nanoscale resolution for 2D and 3D analysis at a resolution down to 10–20 nm.

The evaluation of structure and composition provides insight into the chemical and physical properties of complex heterogeneous materials and possibilities for the development of entirely new materials, tools, functions and applications. This brings us now to the top level in Fig. 1 (the architrave and frieze of our temple) which concerns new developments in analytical chemistry at the nanoscale, occurring at present.

Richard Feynman foresaw the potential of manipulating matter at the atomic scale in 1959 in his visionary lecture "There's plenty of room at the bottom" [6]. He postulated the need to improve the performance of instruments such as electron microscopes to observe individual atoms and described the exciting possibilities that would open up if scientists could learn how to control single atoms and molecules. Now, 50 years later both of these objectives have been achieved. It is now possible to observe the position of single atoms with a precision of 50–100 picometer and nanoscale materials can be produced of increasing complexity. While materials at the micron size have bulk properties obeying the laws of classical mechanics, sub-microscopic (mesoscopic) objects are affected by fluctuations around the average and become subject to quantum mechanics. Many exciting new tools and functionalities are opening up in this new technological field.

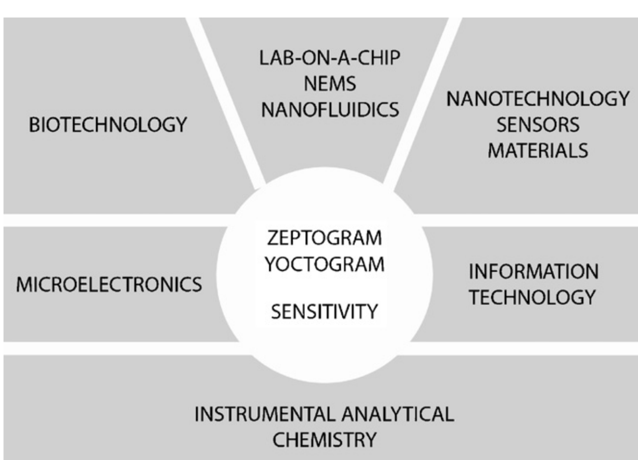

Fig. 1. Contributing factors to the evolution of analytical sensitivity over the last 50 years.

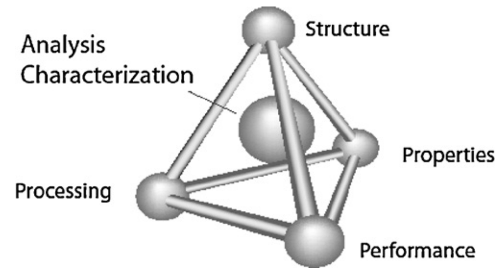

Fig. 2. The relation between analysis and properties and performance for nanomaterials.
Adapted from Ref. [7].

Two complementary approaches to fabrication of nanomaterials and systems can be defined. A top-down physical approach on the basis mainly of traditional microfabrication methods based on optical and electron beam lithography, and bottom-up (chemical) approaches that utilize the concepts of molecular self-assembly and/or molecular recognition. Both approaches require the support of analytical techniques for production and functional control. The intimate relation between characterization and structure on one side and properties and function on the other side for nanomaterials is schematized in Fig. 2 [7]. Physicochemical properties of nanomaterials significantly depend on their 3D morphologies (size, shape, and surface topography) and heterogeneous composition. Systematically and precisely correlating these parameters with the related physicochemical properties of specific materials is a fundamental requirement for the design and fabrication of new materials and the discovery of their novel properties and applications.

Advances in microfabrication have resulted in increasingly sophisticated microfluidic systems that are fulfilling the promise of true "labs-on-a-chip" or "micro total analysis systems" by integrating multiple processing steps on a single device. Furthermore, improved fabrication techniques have resulted in the construction of micro- and nano-electromechanical systems (MEMS, NEMS). MEMS/NEMS is an enabling technology allowing the development of smart products including analytical measurement devices by bringing together silicon-based microelectronics with micromachining technology, making possible the realization of complete systems-on-a-chip. The carbon nanotube used in the measurement device that provided a yoctogram detection limit (Table 1) belongs to the exotic materials developed in nanotechnology. Similar results can be obtained with graphene as a sensor material. With this sensor device for highly sensitive analysis we are well in the realm of nano-analytical chemistry; also, it is not surprising that the detection sensitivity is what it is considering the reduced dimension and mass of the sensing device.

It remains to be explained why the term biotechnology is present (top left) in Fig. 1. The complex interplay between molecules in living systems results in a continuous alteration of these properties at the molecular level. Analytical approaches that provide better insight into these processes are needed. Single analytical methods are usually insufficient when a better understanding of the function of these different biological systems is needed. Challenges to be faced are enormous, for instance there is now a need to study individual cells instead of batches of cells and specific molecules need to be detected in sub-cellular compartments. Use of new materials to make nanometer-scale structures designed to interact with biological systems (BioMEMS and BioNEMS) are opening a new field of nanotechnology that promises advancements in fabrication technology, biological control, medical and analytical applications. One example of new developments that are now taking place, the combination of a NEMS mass sensor that provides detection at the level of single-Dalton level mass sensitivity with the specificity of biological receptor–ligand pair interactions. Large scale integration of such devices could offer the possibility of sensing many different types of molecules simultaneously in biological probes with single-molecule sensitivity and very high specificity [8]. As such 20 years of R&D in nanotechnology becomes combined with 3.8 billion years of biological evolution!

Let me come now to a conclusion. Analytical chemistry has played a major role in the success of chemistry as a central discipline; it contributes fully together with other aspects of chemistry to the well-being of humankind. It matured at a pace concomitant with the needs for science and society and will continue to do so. It fully participates in the nanotechnology and nanoscience revolution that presently changes our world and our society.

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