Talanta 177 (2018) 104–121

Contents lists available at ScienceDirect

Talanta

journal homepage: www.elsevier.com/locate/talanta

Analytical Nanoscience and Nanotechnology: Where we are and where we are heading☆

María Laura Soriano[a], Mohammed Zougagh[b,c], Miguel Valcárcel[d,*], Ángel Ríos[e,*]

[a] Department of Analytical Chemistry, Marie Curie Building, Campus de Rabanales, University of Córdoba, E-14071 Córdoba, Spain
[b] Regional Institute for Applied Chemistry Research (IRICA), 13004 Ciudad Real, Spain
[c] Castilla-La Mancha Science and Technology Park, 20006 Albacete, Spain
[d] Spanish Royal Academy of Sciences, Valverde 24, E-28071 Madrid, Spain
[e] Department of Analytical Chemistry and Food Technology, University of Castilla-La Mancha Ciudad Real, Spain

ARTICLE INFO

Keywords:
Nanoscience
Nanotechnology
Analytical Chemistry
Trends
Future challenges

ABSTRACT

The main aim of this paper is to offer an objective and critical overview of the situation and trends in Analytical Nanoscience and Nanotechnology (AN & N), which is an important break point in the evolution of Analytical Chemistry in the XXI century as they were computers and instruments in the second half of XX century. The first part of this overview is devoted to provide a general approach to AN & N by describing the state of the art of this recent topic, being the importance of it also emphasized. Secondly, particular but very relevant trends in this topic are outlined: the analysis of the nanoworld, the so "third way" in AN & N, the growing importance of bioanalysis, the evaluation of both nanosensors and nanosorbents, the impact of AN & N in bioimaging and in nanotoxicological studies, as well as the crucial importance of reliability of the nanotechnological processes and results for solving real analytical problems in the frame of Social Responsibility (SR) of science and technology. Several reflections are included at the end of this overview written as a bird's eye view, which is not an easy task for experts in AN & N.

1. Introduction

As in many other areas, Nanoscience and Nanotechnology (N & N) have had a deep impact in Analytical Chemistry. The revolutionary and transformer character of them was predicted in 2005 in an editorial of the science journal [1] and confirmed 10 years later. AN & N [2,3] can be defined from different points of view as can be seen in Fig. 1. On the one hand, analytical chemists welcome the challenge and opportunities that N & N offer in this area because of both the powerful nanotools to improve analytical properties of results of analytical processes and analysis of the nanoworld. On the other hand, the basic (Nanoscience) and applied (Nanotechnology) developments and achievements need information from the nanoworld to fulfil their respective objectives and to make founded and timely decisions. The mixed approach shown in Fig. 1 is, in fact, the correct definition of AN & N because both points of view are combined.

The impact of instrumentation (e.g., pH-meters, potentiometric and voltammetric electrodes, photometers, fluorimeters, gas and liquid chromatographs, X-Ray spectrometers among many others) from the middle of XXI century was undeniable because of their great possibilities as regards titrimetries and gravimetries and classical methods of qualitative analysis. The second break point in the evolution of Analytical Science in the transition between XX and XXI centuries was the use of computers to improve the analytical processes by supporting automation, miniaturization, simplification, and implementation of quality systems, as well as the data treatment. Nowadays, research or routine analytical laboratories are unimaginable without the support of computers. This is the situation of many areas (e.g. air transportation or train managements, hospitals, universities, etc.). The irruption in the XXI century of AN & N can also be considered a break point in the global evolution of Analytical Chemistry, taking into account its mixed definition depicted in Fig. 1. A great range of possibilities has been opened up to initiate analytical research lines and to solve a great variety of analytical problems that cannot be solved without the involvement of N & N. It is interesting to point out that at the end of the XX century many analytical chemists described nanotools in papers of reputed journals without mentioning the word "nanotechnology". Such is the case of the use of fullerene as sorbent for preconcentration of traces of

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☆ Dedicated to Prof. Gary Christian, master, guide and friend of several generations of scientists in general and analytical chemists in particular all over the word, for his devotion to research and teaching Analytical Chemistry. Thanks Gary for your professional example and human values.

* Corresponding authors.

E-mail addresses: qa1vacam@uco.es (M. Valcárcel), angel.rios@uclm.es (Á. Ríos).

http://dx.doi.org/10.1016/j.talanta.2017.09.012
Received 30 June 2017; Received in revised form 31 August 2017; Accepted 2 September 2017

Nomenclature

AC	Analytical Chemistry
AChE	acetylcholinesterase
Al_2O_3 NPs	alumina nanoparticles
AN&N	Analytical Nanoscience and Nanotechnology
AF4	asymmetric field-flow fractionation
AFM	atomic force microscopy
AgNPs	silver nanoparticles
AuNPs	gold nanoparticles
BET	Brunauer, Emmett and Teller particle analysis
CARS	coherent anti-Stokes Raman
CE	capillary electrophoresis
CM	confocal microscopes
CNDs	carbon nanodots
CNTs	carbon nanotubes
CQD	carbon quantum dot
DCS	differential centrifugal sedimentation
DLS	dynamic light scattering
DMA	dynamic mechanical analysis
DSC	differential scanning calorimetry
EDS	energy-dispersive X ray spectrometry
EELS	electron energy loss spectroscopy
ELSD	evaporating light scattering detectors
ESEM	environmental scanning electron microscopy
FFF	field-flow fractionation
FIA	flow injection analysis
FL	fluorescence spectroscopy
FTIR	Fourier transform infrared spectroscopy
GC	gas chromatography
GO	graphene oxide
GQDs	graphene quantum dots
HDC	hydrodynamic chromatography
ICP-MS	inductively coupled plasma mass spectrometry.
ICP-OES	inductively coupled plasma optical emission spectrometry
LC	liquid chromatography
LIPS	laser induced plasma spectroscopy
MALS	multiangle light scattering
MNPs	magnetic nanoparticles
MOF	metal organic framework
MWCNT	multiwalled carbon nanotube
NC	nanocellulose
NIR	near-infrared
N&N	Nanoscience and Nanotechnology
NP	nanoparticle
NTA	nanoparticle tracking analysis
PIXE	particle-induced X-ray emission
QCM	quartz crystal microbalances
SAED	selected area electron diffraction
SEC	size exclusion chromatography
SEM	scanning electron microscopes
SERS	surface-enhanced Raman scattering
SiO_2NPs	silica nanoparticles
SLS	static light scattering
SQDs	semiconductor quantum dots
spICP-MS	single particle inductively coupled plasma mass spectrometry
SPR	surface plasmon resonance
SPME	solid-phase microextraction
SR	social responsibility
SWCNTs	single walled carbon nanotubes
TEM	transmission electron microscopes
TGA	thermogravimetric analysis
TiO_2NPs	titanium dioxide nanoparticles
TERS	tip-enhanced Raman scattering
UV	ultraviolet
0D	zero dimensions
1D	one dimensions
2D	two dimensions
3D	three dimensions

metal ions [4,5].

Between XX and XXI centuries there are other more unusual, but also very relevant analytical advances. For example, bioanalysis, sustainable methods of analysis, imaging, quality-Social Responsibility binomial, automation, miniaturization, simplification, instruments based on new physic-chemical principles, among others. Each specialist in analytical research can introduce his/her keywords in Fig. 2. As can be seen in the Fig. 3A and B, the growing of AN & N articles is impressive during the last few years. But this spectacular increment will diminish in the next few years to achieve a plateau where AN & N will be a consolidated presence in many sub-areas of Analytical Sciences. From a scientific point of view, it will be very difficult to find out real innovative research topics. By now, the prefix “nano” is a key to open many “doors” but in an immediate future, in papers dealing with nanotechnology, this word will slowly disappear from the title, summary,

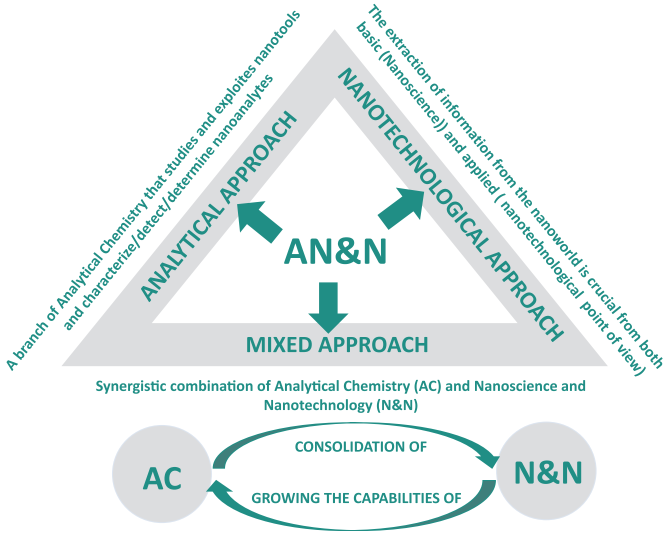


Fig. 1. Complementary definitions of Analytical Nanoscience & Nanotechnology according to three points of view and two way relationships between analytical chemistry (AC) and Nanoscience & Nanotechnology (N & N).

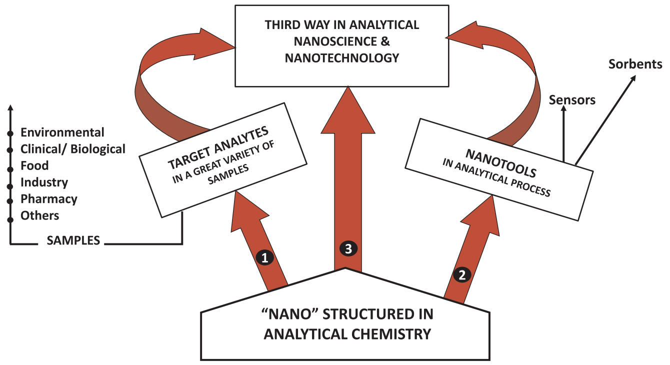


Fig. 2. The three main roles of “nano” structured materials in analytical processes: (1) as analytes in a great variety of samples; (2) as analytical tools; and (3) as tools and analytes in the same analytical process in the so called “third way in AN & N” which is the combination of the two previous ones.

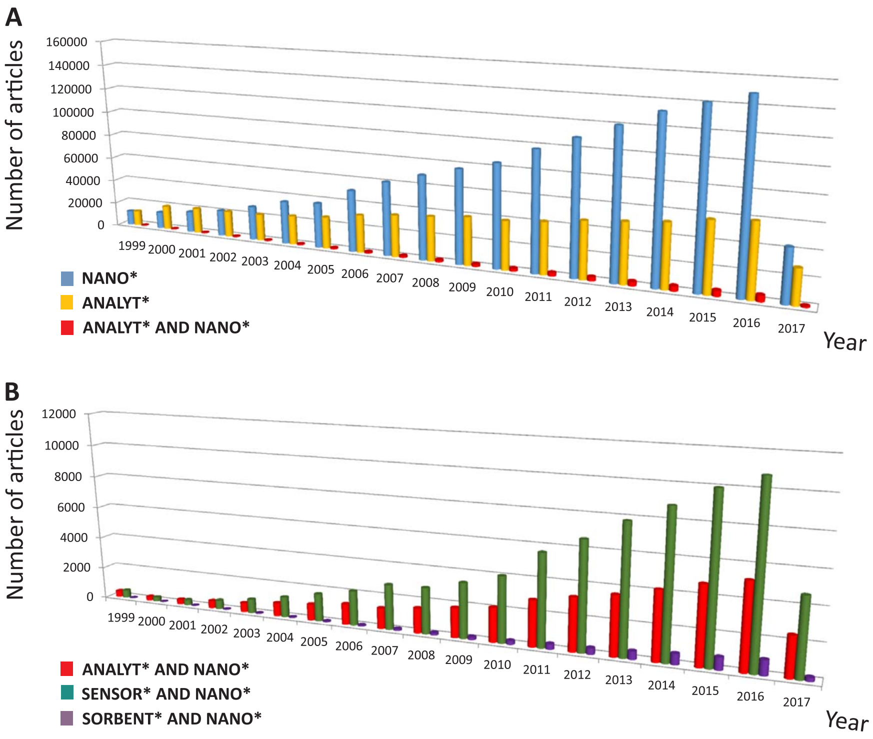


Fig. 3. Evolution of published articles containing the prefix *Nano** and *Analyt** individually or combined during this century (A). Comparison of published papers of *Sorbent, Sensor**and *Analyt** combined with the term *Nano** (B). All data was obtained as a result of the WOS database (1.300.751 papers with the term *Nano**, 664.718 containing the term *Analyt**, 38.737 with *Analyt** & *Nano**, 75.180 with *Sensor** & *Nano** and 4.726 containing *Sorbent** & *Nano**). (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

keywords and even the text. This is the case experienced by Flow Injection Analysis (FIA) [6] which was a very relevant research line in the two-three last decades of XX century. Nowadays, a continuous configuration is used in analytical research and commercially available instrumentation without any mention of FIA.

Undoubtedly, nanotechnological developments should be theoretically supported by the achievements of Nanoscience. Unfortunately, this rational approach is massively circumvented in practice for economic reasons. The transfer of nanotechnological products to the marked now involves billions of dollars, but it will be multiplied by factors from 2 to 5 in the forthcoming years. According to Einstein [7] in critical situations (e.g., how to extract information from the nanoworld?) the simple knowledge is not enough; it is necessary to open the mind-sets looking for imagination by forgetting the current paradigms in the line of Kuhn [8] as well as breaking the static frontiers of knowledge looking for interdisciplinary interfaces. Thus, AN & N is an interdisciplinary science and technology. AN & N advances were not and will be not possible exclusively from the analytical or chemical point of view. The participation of physicists, engineers, biologists, medical doctors, etc., in AN & N is essential in this multidiscipline because the types of information from the nanoworld are very different: physical (e.g., dimensions, physical properties, surface topography, etc.); chemical (e.g., chemical composition, chirality, reactivity, bonds, etc); biological features mainly based on chemical reactivity (e.g., toxicity, membrane diffusion, bio-transformations, interaction with cells and microorganisms, etc.); and the final physic-chemical structure.

This great variety of information required from the nanoworld is, simultaneously, a challenge and an opportunity for AN & N that should be immersed in the interdisciplinary. In this way, Analytical Chemistry is clearly enriched.

The main aim of this article is to offer to specialists and mainly no specialists a panoramic view of the impact of Nanoscience and Nanotechnology in Analytical Chemistry, describing the main developments to date, as well as devising the foreseeable trends of AN & N.

2. Nanostructured matter in analytical chemistry

Not all materials reaching the nanometric scale have the same behaviour. A conventional material simple reduces drastically its specific surface from macro-micro-nanosize and it is more soluble and its sorption capabilities grow considerably. On the other hand, there are materials with a "tendency" to be nanostructured (e.g., carbon, gold, silver, etc.) in such a way than when they cross the micro-to-nano barrier a great change of their physic-chemical properties occurs. These two types of materials are essential in AN & N because its developments can be based on the exploitation of the exceptional properties of nanomaterials, the nanosize or both of them. The parallelism with the microfluidic systems is very narrow, from the macroscale and microscale to the microfluidic, with Reynolds numbers below 1, it is not only a reduction in size but a radical change in the forces that govern processes such as mixing, separation and detection in analytical processes. Thus, it is possible to distinguish between three AN & N types, namely: (a) nanotechnological analytical systems are those that exploit the exceptional physicochemical properties of nanomaterials accounting for the most current uses of analytical nanotechnology; (b) Nanometric analytical systems, which are exclusively based on the nanosize of the devices involved, and they are exemplified by nanopipette or levitated nanodrops as analytical containers and nano-chip liquid chromatography systems exploiting the advantages of working at flow rates as low as few nanolitres per minute; and (c) analytical nanosystems successfully integrate the two previous types of systems, exploiting both the nanosize and nanomaterials properties (e.g., individual carbon nanotubes (CNTs)) for use as electrodes or tips in atomic force microscopy (AFM). This last type represents the ideal situation.

The impact of the nanostructured material in Analytical Sciences in the last two decades is indisputable. In this context, it is necessary to establish a clear-cut distinction between nanomaterials (e.g., gold nanoparticles (AuNPs)) as analytes and tools [9] and nanostructured material (e.g., CNTs dispersed in a monolithic chromatographic column [10]). This is well reflected in the two classifications using dimensionality as criteria. The first classification [11] takes into account the number of dimensions in the nanoscale (1–100 nm), and thus, it is mainly referred to nanoparticle (NP). Examples of one dimension (1D) are surfaces with nanometric thickness such as graphene sheets. Carbon or metallic nanotubes, nanowires, etc. are representative examples of two dimensions (2D), whereas AuNPs or silver NPs (AgNPs), quantum dots, fullerenes, dendrimers etc, are examples of the three-dimension type (3D). A nanostructured or nanoporous material can be considered to have zero dimensions (0D) in this classification. The second classification [12] is more focused to the nanostructured material because it is based on dimensions higher than 100 nm. Thus, metallic NPs, quantum dots, fullerenes, etc. have 0D. CNTs, nanowires, DNA, etc., have 1D (generally their length exceed 100 nm). Nanocoatings have 2D, whereas nanoporous material and NPs dispersed materials are representative examples of 3D in this classification.

It is curious to state the difficulty to use both classifications because it can lead to confusion. For example, carbon nanotubes are 2D in the first classification and 0D in the second one. Fig. 3 depicts the different roles that nanostructured material can play in analytical processes. On the one hand, the nanostructured material can be the target analyte (e.g., spatial characterization of titanium dioxide NPs (TiO_2NPs) dispersed in the concrete of a building for cleaning purposes [13], determination of fullerenes and derivatives in polluted waters [14]); it is quite frequent to name this approach as “analysis of the nanoworld”. On the other hand, nanostructured material can be nanotools in a great variety of analytical processes, where they can act as sorbents, sensors, among other functions (e.g., use of derivatized fullerenes as sorbents for concentration of metal traces in environmental samples [1]; use of semiconductor quantum dots (SQDs) as nanosensors in bioanalysis [15]). These options (1 and 2 in Fig. 2) are the most frequent in AN & N. In recent years, Valcárcel and López-Lorente, have proposed [16] another option called “the third way of AN & N” (3 in Fig. 2) which consists of the use of nanotools to characterize/detect/determine NPs, that is, the combination of the previous two options as the arrows shown in Fig. 2 (e.g., determination of TiO_2NPs in suns creams using a modified Graphene Quantum Dots (GQDs) as nanosensor [17]). This third option will be commented on in detail in Section 5 of this paper.

3. Generic evolution of AN & N

After the period of changes occurred in the analytical science by the emerging N & N, leading to the development of the conceptual triangle “simplification-automatization-nanotechnology” [18], it is important to address the evolution of AN & N. Thus, after those revolutionary years (from 1999 to 2017), a bibliometric study about the current trends of the analytical science based on different topics within it by introducing general and trending terms (e.g., root words like “analyt*”, “nano*”, “sorbent*” and “sensor*”) and string of them together (e.g., “analyt* and nano”, and so on)is essential to give ideas and new insights about how to push the AN & N over the top of science avoiding its stagnation. Herein, an accurate view of the evolution of the AN & N in the last years according to the ISI Web of Science database is shown. On the one hand, it is important to highlight the exponential growth of number of papers related to the term “nano*” if compared to the more stagnant but gradually growing research tendency involving the analytical field containing the term “analyt*” (Fig. 3A). It is undeniable that the impact of nanoscience and nanotechnology is similar to those revolutions occurred by steam engine along XVIII century or informatics in the beginning of the XX century. In contrast, the combination of both keywords “analyt* and nano*” (red bars in Fig. 3A) is rather small if compared to the other mentioned tendencies, but it is noteworthy its exponential growing tendency (see red bars in Fig. 3B). Thus, nanotechnology has begun to have a serious impact on analytical science this decade whereby in the first stage of this century (5 years) was indeed low.

Although the analysis of nanomatter did not grow as quick as the creation of nanotools before 2007 (one third of papers), nowadays it has increased considerably (almost one half of papers) for its importance; it is evident that novel universal instrumentations compatible with a variety of nanosizes, shapes and compositions is emerging fast for the challenging characterization of nanomatter, whereby other conventional ones have been modified and improved taking into account their weaknesses towards the nanomatter (see Section 4). They involved trendy separations approaches such as asymmetric field-flow fractionation (AF4) [19,20], reliable particle counting and sizing (Zetasizer, Nanoparticle Tracking Analysis, Resonant Mass Measurements), as well as the use of other conventional characterization instruments adapted for such nanomatter analyses (dynamic light scattering (DLS) [21], Zeta potential, nuclear magnetic resonance, RAMAN, amongst others). One should keep in mind that field–flow fractionation(FFF) is very versatile technique and has a large impact on the separation and size characterization of a large variety of nanomaterials with different compositions, sizes and shapes, reaching a number of publications over 230 in the last two years (1508 of total publications related to “nano*”). However, this is an expensive and large instrumentation; thus, huge efforts are, in fact, dedicated to the creation of faster and portable inspection tools with low costs for the policy security and quality control of NPs and products containing nanomaterials in spot checks within the industry sector and market, which is a hot topic. However, the combination of nanotechnological tools for the analysis of the nanoworld, which has been described as the Third approach of AN & N [16], is gaining more and more importance in the last years, although it is still represented in a minority percentage. In fact, this third facet is difficult to bibliographic monitoring without the use of their main keywords (three facets of AN & N) and, at present, a few reviews compile this information [22–24]. Most works within the Third facet of AN & N deals with the toxicological feature of such nanomaterials, which is still mooted; more information will be given in Section 10. This is an indicative of a potential trending topic, which must be an eagerness to explore within this direction. The analytical interest in the last years is devoted to create ecofriendly analytical nanotools (sorbents, sensors, substrates, etc.) for the detection, determination and identification of hazardous nanostructures. At present, confidence in analytical methods containing such nanocomponents is needed to be considered as standardized products directed to the nanosafety of consumers and environment. In a near future the creation of standardized nanotools for understanding and controlling the nanoworld will drive those nanotechnological tools or devices to the market.

On the other hand, there is an important interest in fabricating devices and tools based on nanotechnology. Thus, it is important to follow the different evolutionary growing rates of the analytical nanotools (e.g., sorbents and sensors) involved in the AN & N over the past last 17 years (see Fig. 3B). Despite the exponential growing of the papers dealing with “analyt*” & “nano*” (red bars) as commented before, the combined “sensor*” & “nano*” increases drastically faster even if it should be considered within the analytical field. It is important to note that “analyt*” & “nano*” and “sensor*” & “nano*” terms were comparable at the beginning of the XXI century and after a few years the second term involving sensors experienced a large increment, as depicted in Fig. 3B. This is an indicative of the important influence of the keyword sensor for publication along the last decade which entails smart products although they also imply advanced analytics. These sensors represented in green bars in Fig. 3B did not only act as nanotools in an analytical process, but also as micro- or macro-tools for the analysis of nanostructured matter or nanomaterials. This overview only deals with the first case just mentioned, in which sensors may contain nanostructured features or nanometric dimensions (see Section 7). This increased growth happened after chemists observed and followed the nature´s secrets for taking advantage in obtaining better sensors. We still need to gain ground on this subject by introducing analytical features in these sensing systems for their wide application instead of mere publication ends. It is noteworthy that the 48% of the publications are within the chemistry research area, followed by material science (31%), physics (26%), engineering (16%), instrumentation (13%) and biotechnology applied microbiology (over 3%), amongst others. These data corroborate the importance of chemistry.

Sorbents composed of NPs or nanostructures (e.g., nanopores, nanocavities) are outlined in Section 8. The purple bars in Fig. 3B illustrate the small growing of sorbents if compared to sensors. Although this tendency is increasing, it does grow slowly. It is important to understand that the market put all its efforts for new technologies directed to intelligent digital products (mobile phones, television, advanced machine learning and security, textiles, patches and lenses with therapeutics, amongst many others) which involved sensors for monitoring different stimuli, either chemical or physics parameters.

4. Trend A: increasing interest for the analysis of the nanoworld

The need for analysis of nanoworld has been exploded in recent years due the increasing use of engineered nanoparticles (ENPs) in various industries and the subsequent studies that investigate environmental and consumer risks. At the nanoscale, analytical measurement challenges are noteworthy and the ability to measure the elemental concentration of a nanoparticle as the only metric to assess the material does not provide all the information needed. Consequently, to complete analysis of nanoworld it is necessary to know a multitude of chemical and physical parameters, including particle size and shape, surface features and the presence of any surface coating or impurities. Fig. 4 represents the eight features commonly measured and the current analytical technologies that can be applied in each case. Analytical methods of sizing and quantification used to explore the nanoworld can be divided into three groups: fractionation, counting and ensemble methods. In the fractionation group, the most applied technique is probably AF4coupled with multiangle light scattering (MALS) and inductively coupled plasma mass (ICP-MS) for sizing and quantification of metal and metal oxide NPs. Further details can be found in a recent review article [25]. Other separation techniques are size exclusion chromatography (SEC), hydrodynamic chromatography (HDC) and capillary electrophoresis (CE) which have been combined with ultraviolet (UV) and ICP-MS detectors [25]. The combination of a separation technique with ICP-MS is a configuration often used, especially for metal and metal oxide NMs [26]. Another less used fractionation method is differential centrifugal sedimentation (DCS).

The counting group are there based on electron microscopy widely used to characterize NPs by using scanning electron microscopes (SEM), AFM, transmission electron microscopes (TEM), and confocal microscopes (CM) for examination of surface area, porosity, particle shape and aggregation respectively. Single particle ICP-MS (spICP-MS) is another extremely sensitive counting technique for mass (commonly in $\mathrm{ng\,L^{-1}}$) [27]. The third group assembles techniques by which a large number of NMs are measured simultaneously. These techniques are DLS, particle-induced X-ray emission (PIXE), surface plasmon resonance (SPR) and coherent anti-Stokes Raman (CARS). Looking at the variety of these analytical techniques, AF4 is by far the most widely used FFF technique for analysis of nanoworld due to the possibility to couple it with different detectors (UV–vis, MALs, DLS, ICP-MS, etc.). Size and particle distributions are usually in agreement with those obtained using counting and ensemble techniques, although comparison of techniques is not straightforward because different parameters are measured. However, despite its broad applicability, several aspects must be improved and further investigated to make AF4 more robust. Membrane technology should be implemented to reduce particle–membrane interactions, which cause shifts in retention time or, in the case of an irreversible adsorption, even sample loss. The particle–membrane interactions also limit the choice of the standards necessary to produce accurate qualitative and quantitative particle distribution. Analysis time and solvent consumption could be reduced if miniaturized separation cartridges were available.

Some of the current applications of analysis of nanoworld in food and environmental fields are reported in Table 1. While this table is not intended to be exhaustive, it does show how wide the application range is. The analysis of NPs in these samples strongly depends on sample preparation and optimal instrumentation settings. Important variables, often underestimated during sample preparation, include dispersant solution, dispersion technique (mechanical stirring or ultrasound) and instrumental conditions (time, temperature, energy supplied). Expensive detectors are not always necessary. Sometimes, low-cost and universal evaporating light scattering detectors (ELSD) can be also useful. An example is the characterization and quantification of silica nanoparticles (SiO_2NPs) by size (from 20 to 100 nm) using a combination between CE and ELSD [28]. The optimal instrumentation configuration was proved to be a powerful separation tool to determine

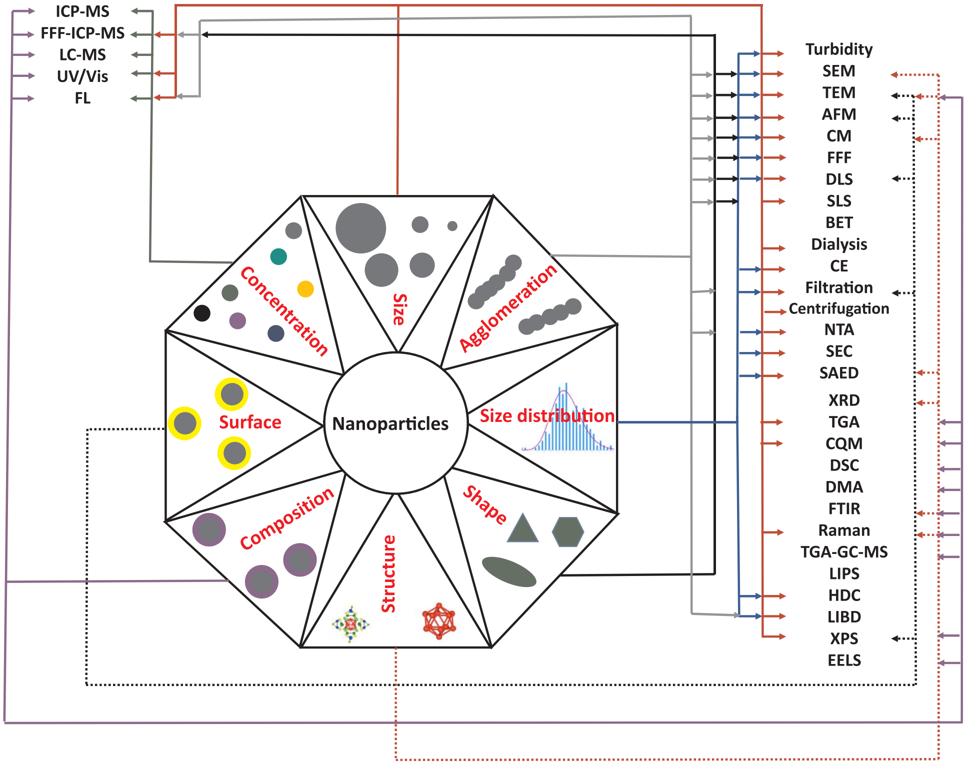


Fig. 4. Chemical and physical parameters (concentration, size, agglomeration, size distribution, shape, structure, composition and surface) used to explore the nanoworld and analytical methods used for sizing and quantification in each case.

Table 1
Selected relevant examples relating nanoworld analysis methods in environmental and food fields.

Field	Type of NM	Technique	Highlights	Ref.
Food field	S_iO_2NPs	TEM CE-ELSD ICP-MS	First online hyphenation of CE and ELSD for characterization and quantification of S_iO_2NPs in salt samples and comparison of results by ICP-MS	[28]
	AgNPs	TEM AF4-ICP-MS Sp-ICP-MS	First time of coupling the AF_4 and ICP-MS in conventional and single nanoparticles mode for AgNPs separation in chicken meat	[29]
	AgNPs	TEM, SEM, EDS and ICP-OES	Combination of TEM, SEM, EDS and ICP-OES techniques to detect contamination of pears by AgNPs	[30]
	T_iO_2NPs	AF4-DAD-DLS-MALS	Determination of particle shape and particle size distribution of S_iO_2NPs in food and feed samples.	[31]
	AuNPs, CeO_2, ZnO	TEM, ESEM/EDS, ICP-MS	Confirmation of the presence of the NP in fish. Characterization of size, particle shape/ morphology and qualitative aggregation by TEM and ESEM/EDS	[32]
	S_iO_2NPs	AF4-MALS-ICP-MS	Simultaneous size determination and quantification of s S_iO_2NPs in food samples	[33]
	T_iO_2NPs	DLS, SEM	This study quantifies the amount of titanium in common food products, derives estimates of human exposure to dietary (nano-) TiO_2, and discusses the impact of the nanoscale fraction of TiO_2 entering the environment	[34]
Environmental field	ZnO NPs	SpICP-MS	Use of ion-exchange resin for preconcentration, characterization and quantification of ZnO NPs at ng L^{-1} in surface and effluent wastewaters.	[27]
	CNTs	Microwave induced heating	Determination the degree of potential CNT contamination in the environmental matrices (sand, soil and sludge) by microwave induced heating	[35]
	AgNPs	HDC, AF4-ICPMS, SpICP-MS	Comparison of three analytical methods to measure the size of AgNPs in real environmental water and wastewater samples. HDC and SpICP-MS techniques are most accurate than AF_4-ICPMS at determining NP sizes in aquatic environments.	[36]
	AgNPs	SERS	Detection of AgNPs in environmental water by using surface-enhanced Raman scattering based on ferric dimethyl-dithiocarbamate.	[37]
	nano-Fe_3O_4	SEC-UV-ICP-MS	Investigation of nanoparticle fate and behaviour in environmental samples by online steric exclusion chromatography UV- ICP-MS	[26]
	AuNPs	TEM and CE-ELSD	Separation and characterization of AuNPs in water samples by online hyphenation of CE and ELSD. Comparison of characterization results by TEM.	[38]
	SWCNTs	SERS	Determination of carboxylic SWCNTs in river water by microextraction inionic liquid (IL) and determination by Raman spectroscopy	[39]
	Inorganic nanoparticles	AF4-ICP-MS	Simultaneous quantification of releasable pharmaceutical relevant inorganic nanoparticles in tap water and domestic waste water	[40]

particles with such small sizes, which produce peaks very close to each other, with short analysis time and good resolution. The biggest advantage is reliability, as well as simplicity of the interface used in the separation/detection configuration, which is based on commercially available devices, and the inexpensive nature of the methodology.

In the food field, NPs are used throughout the agricultural-food sector from crop treatment to food storage and delivery. In some cases, the NPs are short-lived and degrade quite easily. In other cases, consumers may be exposed to the NPs (hard NPs), requiring a risk assessment. Awareness of this new exposure route has focused the attention of the EC on materials traditionally used as additives in food or food supplements, including SiO_2NPs, TiO_2NPs, AgNPs and black carbon. In the environmental field, the atmosphere, hydrosphere, lithosphere and even biosphere have always contained NPs as a result of chemical, photochemical, mechanical, thermal and biological processes. These NPs also include those formed spontaneously as a result of human activity (mining, industrial processes and production of waste water and waste). When the NPs are extracted from the environmental matrix, it is extremely important to consider the ionic composition and pH [26,27,33–35] of the extracting solutions. This is required to maintain NPs in their native state, preserving their natural particle size distribution and their elemental chemical composition, and to avoid altering the interactions of the NPs with trace metals.

5. Trend B: insisting on the “third way” of AN & N

The third way of AN & N is the result of combining the use of analytical nanotools for the analysis of nanoworld [16] as can be seen in Fig. 2; thus, nanomaterials are involved in the analytical process within two different roles, to be the target analyte and the analytical tool. Taking into account the lack of nanoparticle references and the unknown interaction between NPs of equal or different nature, this third approach is considered as a net progress in the tough analysis of nanoworld taking advantage of the improved nanotools. Few are the applications of NPs used as sorbents capable of targeting other nano-objects. The first reported is the use of CNTs in sampling and separation by virtue of their peculiar π- π stacking interactions, so their potential in the Third way is fundamental for cases of targeting nanomaterials composed of aromatic systems; such is the case of multiwalled carbon nanotubes (MWCNTs) immobilized on filters for extracting and preconcentrating oxidized single walled carbon nanotubes (SWCNTs) [41,42] Other case is the use of barium hexaferrite ($BaFe_{12}O_{19}$) nanofibers packed into a column for retaining only nanometric magnetite (Fe_3O_4NPs), in contrast to non-magnetic oxide NPs like TiO_2, due to magnetic interactions [43]. In other cases, chemical modification of the NP surface seems to be an excellent alternative for achieving methods capable of targeting nano-objects. On account of this, the unique hierarchically structure of eco-friendly nanocellulose (NC) is getting more interest as sorbent material of metallic NPs, as those AgNPs previously reported via dispersive microsolid-phase extraction (SPE) [44]. In this particular example, sulfonate groups onto their large surface allow NC efficiently extracting and preconcentrating AgNPs from food products by virtue of the high affinity of sulphur towards metals.

On the other hand, the main contributions of NPs in sensing deal with their unique optical properties, being the most relevant tendencies within the third way described below.

(a) The *intriguing surface plasmon properties* (unique absorbance, scattering, coupling features) of plasmonic NPs (e.g., AuNPs, AgNPs). It is important to emphasize the use of AuNPs and AgNPs in the detection of a variety of carbon nanomaterials (e.g., fullerenes, CNTs, graphene derivatives) for their implications in surface-enhanced Raman scattering (SERS) [16]. For instance, it is notably the improvement of the SERS activity of AuNPs supported into a filter paper when C60/C70 are well-dispersed in organic solvents like pyridine [45]. Furthermore, AuNPs serves as energy transfer channel, as previously pointed out by Zhao [46], in which the emission peaks of fullerene can be enhanced or quenched depending on the influence of the radiation decay channel effect of C60 (enhanced local field effect is strong or weak, respectively). In the case of using C60 dissolved in pyridine (fullerene structure is distorted in such solvent) the reduction of symmetry allows observing a significant enhancement and reduction of fluorescence peaks at 700 and 450 nm, respectively, being the ratio of both intensities dependent on the concentration of the target fullerene.

(b) The *excellent fluorescence properties* of noble metal clusters and semiconductor nanodots and carbonaceous NPs [22]. Currently, fluorescent nanocrystals [47] and nanodots [48] are widely used as sensing probes in replacement of common organic fluorophores in a variety of applications including those belonging to the third way. On the one hand, a few authors reported sensors based on clusters composed of noble metals, which lack of apparent SPR absorption in contrast to their larger analogues NPs but exhibit excellent luminescence. Thus, Zhong [47] demonstrated the use of fluorescent copper nanocrystals coated with thiol-based β-cyclodextrin as excellent sensor of graphene oxide (GO). In this case, the fluorescence properties of this type of cluster are really stable at different pH values (4–10) and in presence of a variety of ions but it does strongly quench by the influence of GO concentration, being a suitable method for detecting this nanoobject in environmental waters. Interestingly, they demonstrated that a dynamic quenching mechanism was involved. On the other hand, two families of nanodots are involved in sensing nanoobjects. The first one is the so called SQDs where the first one discovered and more explored for its narrow emission band, mainly governed by the quantum confinement effects, being its maximum emission wavelength strongly dependent on size. The second one is the more recent discover that carbon-based nanodots are characterized for wider emission bands, divided into the spherical carbon nanodots (CNDs), and carbon quantum dots (CQDs), and planar GQDs with quantum confinements. In this respect, accordingly to the type of composition, the use of surface modification is getting more important, especially in those nanodots made by toxic heavy metals (see Section 10). Examples of the determination of C60 fullerenes are accomplished by host-guest interactions of both SQDs and CQDs properly functionalized with suitable cavitands (calixarene and cyclodextrin) with the target in different media (i.e., organic solvents and aqueous solutions) [14,49]. CQDs have also been used in the determination of noble metal NPs (AuNPs and AgNPs). Firstly, the CQD surface was modified with thiol groups to bind AuNPs, resulting in the quenching of their emission [50]. Secondly, CQDs coated with free amine groups are suitable to detect citrated AgNPs as a result of fluorescence quenching of CQDs via filter inner effect mechanism [51]. A relevant application of CNDs in sensing relates to the detection of oxidized MWCNTs in environmental waters [52]. It is important to mention that mainly hydrogen bond interactions between both NPs are responsible of the quenching in the emission of CNDs, being able to detect and quantitatively determine the MWCNT concentration. Another interesting case is the determination of graphene oxide (GO), which was achieved so far using two fluorescent nanosensors, GQDs and CNDs [53,54]. In both cases the detection processes in environmental waters involve the formation

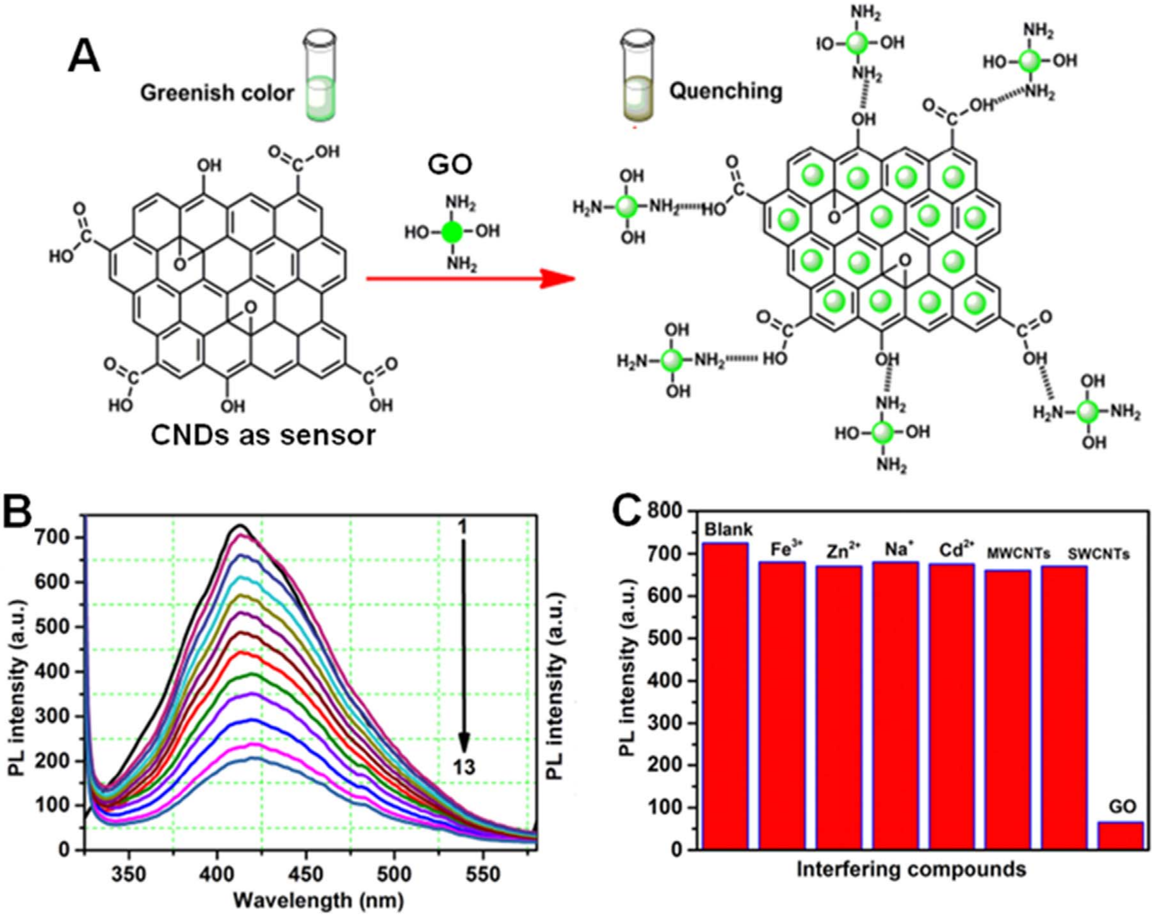


Fig. 5. Illustration of the method proposed for determining graphene oxide (GO) using fluorescent carbon nanodots (CNDs) acting as analytical nanotool and their binding mechanism (A). Gradual drop in intensity of CND emission versus increasing concentrations of graphene oxide (B). Interference study of the method versus different metal ions and π-conjugated carbonaceous nanomaterials (C), as described in Ref. [54] (adapted with permission of American Chemical Society).

of nanohybrids via static quenching mechanisms based on π-π stacking interactions between GQDs-GO [53] or by binding interactions between functional groups of both CNDs-GO, as reported by Patra (Fig. 5) [54]. In the last case, the strong selectivity of the CND sensor (Fig. 5C) resulted in very good recoveries when the method was applied to urine and human blood, opening a new path for medical applications. Lastly, GO has also been used as fluorophore, being its emission sensitive to the presence of AuNPs coated by thin silica layers [55]. In fact, a metal-enhancement of the low emission of GO was observed when this AuNPs were adsorbed onto this GO nanosheet, via a surface plasmon resonance. The same mechanism occurred for the metal-enhanced fluorescence of negatively charged CNDs in presence of AgNPs coating with a positively charged layer of SiO2 stem from the electrostatic interaction between them [56].

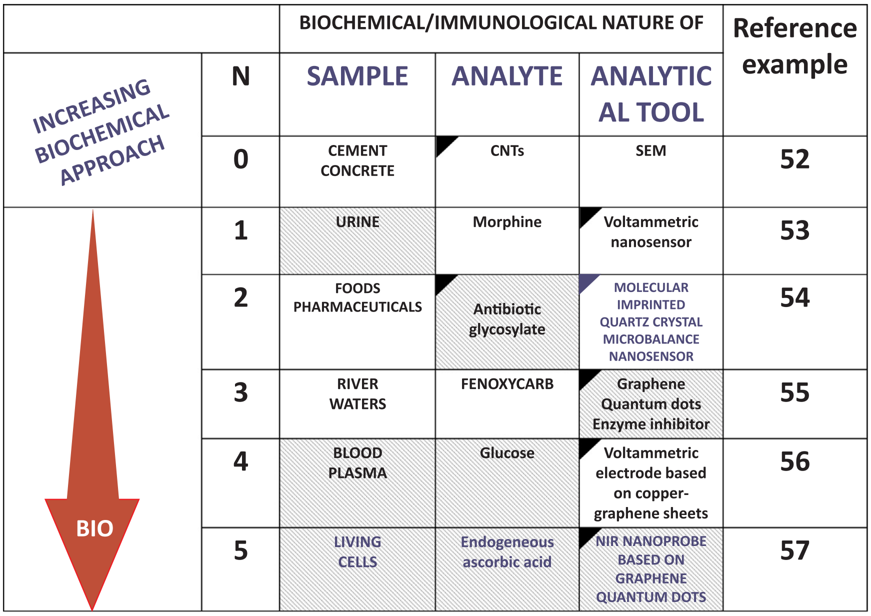
(c) In minority, *optical transparency* of well-dispersed nanofibers is also of great interest in the fabrication of novel platforms with sensing properties; thus, optically transparent NC, characterized with multiple surface groups and rheological properties, were recently used as sensing hydrogels when combined with fluorophores. Ruiz-Palomero [57] reported the use of fluorescent NC hydrogels as sensing platforms for the determination of AgNPs. In this example, simply mixing NC (acting as gelator) and Ru(bipyridyl)-complex (acting as fluorophore) lead to gel formation which resulted in a fluorescent enhancement of the Ru(II) complex immersed and stabilized in such hydrogel of NC. These systems are ideally suited for analytical and biomedical applications [23]. Thus, more efforts are needed to develop new sensorial materials based on NC gels, using a large variety of fluorophores embedded, for its potential application within the third way of AN & N.

6. Trend C: triple biochemical approach

It is difficult to define precisely the word "bioanalysis", because there are different conceptions of it. On the one hand, it can be a subdiscipline of Analytical Chemistry, Biology or Biomedicine according to the professionals that define the term; these divergences are not relevant. On the other hand, the most important contradictions arise from what aspect of the analytical process is of biochemical or biological nature: sample, analyte(s) or analytical tools involved in the process. Broadly speaking, bioanalysis covers the qualitative/quantitative measurement of xenobiotics (drugs, metabolites and small biological molecules) in unnatural concentrations or locations, and biotics (macromolecules, proteins, DNA, RNA, etc.) in biological systems [58]. The most ordinary approach [59] is to consider a bioanalytical process when the analyte is of biochemical nature (e.g., enzymes) which is, generally, a component of a sample matrix of biochemical or biological nature (e.g., human fluids), but in this conception are also included the determinations of drugs/metabolites of organic nature in biological samples.

One of the most relevant trends in Analytical Chemistry consists of the increment of the so-called "biochemical approach", probably because the increasing in quality and quantity of bio-information requirements. The key aspect of this evolution is the development of reliable both sample treatments systems and new adapted instrumentation for such a purpose. AN & N cannot be out of this generic trend. In fact, the number of AN & N developments in the context of bioanalysis grows considerably in the last five years. Fig. 6 depicts a scheme-table showing how grows the biochemical approach in AN & N takes into account the biological/biochemical feature of sample, analyte and analytical(s) tools involved in the analytical process. All the six options (from 0 to 5) have been materialized in specific examples from no biological/biochemical character of the three key aspects (samples, analytes and analytical tools) to the triple "bio" approach (no. 5). The nanotechnological character is marked by a red drop in each instance.

Many AN & N processes have no "bio" connotations (Fig. 6, N = 0). Such is the case of the characterization of CNTs-reinforced cement or concrete by SEM [60]. In this case the nanotechnological aspect is the nanostructured material. There are also many AN & N developments where the only "bio" connotation is the sample (Fig. 6, N = 1). The determination of morphine in presence of diclofenac in urine using a voltammetric nanosensor (NiO/CNTs/IL paste electrode) is a representative example of this situation [61]. In this case, the analytical tool is the frame of N & N. The third option (Fig. 6, N = 2) occurs when the analyte is a biochemical specie. Such is the case of the determination of an amino-glycosylated antibiotic (trobacyn) in pharmaceuticals and foods using a molecular imprinted nanosensor [62]. In this particular case both the analyte and the analytical tool have nanotechnological character. The analytical tool has biochemical character (Fig. 6, N = 3) in AN & N. A simple, rapid and reproducible sensing approach for determination of fenoxycarb pesticide in river water based on the combined use of nitrogen-doped GQDs dots (N-GQDs) and acetylcholinesterase (AChE) enzyme as biorecognition element; nanoparticles were used as fluorescent probes, while AChE was employed for inhibitor screening. In this particular example [63], the analytical tool



		BIOCHEMICAL/IMMUNOLOGICAL NATURE OF			Reference example
INCREASING BIOCHEMICAL APPROACH	N	SAMPLE	ANALYTE	ANALYTICAL TOOL	
	0	CEMENT CONCRETE	◤ CNTs	SEM	52
BIO	1	URINE	Morphine	◤ Voltammetric nanosensor	53
	2	FOODS PHARMACEUTICALS	◤ Antibiotic glycosylate	◤ MOLECULAR IMPRINTED QUARTZ CRYSTAL MICROBALANCE NANOSENSOR	54
	3	RIVER WATERS	FENOXYCARB	◤ Graphene Quantum dots Enzyme inhibitor	55
	4	BLOOD PLASMA	Glucose	◤ Voltammetric electrode based on copper-graphene sheets	56
	5	LIVING CELLS	Endogeneous ascorbic acid	◤ NIR NANOPROBE BASED ON GRAPHENE QUANTUM DOTS	57

Fig. 6. Schematic diagram of the growing biochemical approach to AN & N by considering the combined nature of samples, analytes and tools involved in the analytical processes. An example of each possibility is included in the scheme. The triangle in some boxes means nanotechnological character. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

has a dual nanotechnological feature. It is quite usual that the sample-analyte(s) binomial has a dual biochemical character (Fig. 6, N = 4). Such is the case of the determination of glucose in blood and plasma samples using a non-enzymatic glucose sensor based on a copper-graphene sheets electrode and cyclic voltammetry [64]. In this particular case, the nanotechnological connotation is the nanoelectrode. The full approach of an AN & N process occurs when the three key aspects of it are of biological/biochemical nature (Fig. 6, N = 5). A recent representative example is the use of a near-infrared (NIR) two photon nanoprobe based on GQDs for direct bioimaging of endogenous ascorbic acid in living cells [65]. In this case, the nanotechnological approach is the nanoprobe for bioimaging.

7. Trend D: evolution of nanosensors

According to the relative number of papers published in the framework of AN & N in different fields (see Section 3) as well as taking into account the economic impact, there is no doubt to confirm that nano-(bio)-sensors are the most important branch of AN & N. The impact in Nanomedicine and Biotechnology could be one of the reasons of the importance of the topic. It should be recognized that the concept/definition of “sensor” is in a permanent moving sand situation. Since its impact in the last decade of XX Century, many authors have used profusely this word in papers without common criteria because of considering it as a keyword to open many doors. In the present situation (2016–2017), we can find in the literature many contradictory papers about what, when and where the word “sensor” is applied. It can be also called as “probe”, “marker”, “label”, among others (e.g., sensing platform). There are many classifications of the sensors using different but complementary criteria. Some of the most relevant are briefly commented on, here: (a) the nature of the sensor, which can be simply sensor or biosensor; (b) the associated instrument and, in this way, sensors can be optical, electrochemical, mass (crystal balance) among others; (c) the measurand can be physical, chemical and biological; (d) the existence of a solid support for it (e.g., an electrode), or the dissolution or dispersion of it in the sample (e.g., reprivatized SQDs in blood); (e) the size of the device: macro-, micro- and nano-sensors.

A variety of active biochemical species are the foundation of many “sensors” of nanometric size (e.g., DNA, immunoreagents, proteins, etc.) which are exploited by many authors to called them nanosensors or nanobiosensors, being even so a micrometric-size sensing platform. It is difficult to qualify as correct or incorrect this assignation. In conclusion. A proper definition of a nanosensor is very hard to get. From a practical point of view, the real importance is that this nanosensing devices produce reliable results (see Section 9) better that the classical macro- and micro- sensors. The most convenient distinction among nanosensors is based on its nature: nanosensors and nano-bio-sensors. There are thousands of those described in literature in a great variety of analytical and general journals. A description of the representative types is out of the scope of the present overview which is devoted to the trends in AN & N in general and in particular in the field of nanosensors. According to the nanotechnological facet exploited, there are three types of nanosensors, namely: (a) nanometric sensors, based on the size of the sensor. Such is the case of nanoelectrode for pH measurements inside cells [66]; (b) nanotechnological sensors, are those exploiting the exceptional properties of the nanostructured matter, as the case of using CNTs as sensors for a variety of gases [67]; and (c) nanosensors, properly said, which combined both the nanosize and the exceptional properties in the nanoscale. Such is the case of the DNA thermometer [68] based on the folding and unfolding reconfiguration of DNA strands containing a fluorescent marker. However, this classification is not frequently used, being all of them called as “nanosensors”. Some of the most relevant tendencies to achieve better nanosensors are briefly described below.

(a) The increment of reliability of the results they provide is the first trend in nanosensors (see Section 9). Derivatization of nanoparticle-based sensors boosts the reliability of the results because increases stability, biocompatibility, sensitivity and selectivity. The surface modification of SQDs with macrocycles allows the selective detection of fullerene C60 in water [49]. AgNPs are not able to detect phosphates; the use of AgNPs with macrocyclic polyammonium cations led to the formation of a sensitive and selective sensor towards the so called “phosphate family of species” [69].

(b) The substitution of toxic or potential toxic sensors for others particularly less hazardous is the second trend in the evolution of nanosensors, setting up a framework of green methods of analysis [70]. Toxicity can affect both the technicians operating sensors (e.g., radiometric nanosensors [71]) or the patients in which the nanosensors are introduced. Such is the case of using CQDs [72] instead of the well-known SQDs [73] as fluorescent nanomarkers in human fluids for oncologic monitoring via bioimaging (see Section 11). The core of SQDs is composed of metals such as selenium, cadmium, zinc, etc.; some of them consisting on heavy metals are very toxic and there is a reasonable doubt about their long-term toxicity because of the metals release from the outer covering layers. CQDs are non-toxic due to a lack of metals (see Section 10 of this paper). A systematic comparison of both types of nanosensors has been recently published [48].

(c) The dual relationships of nanosensors with nature is the third trending evolution. They are based on the adaptation of natural organisms to survive, and thus, this fact allows them to continuously develop and improve a special sensibility for physical, chemical and biological stimuli. The smell of dogs, the capability of differentiating closely related antigens, the sensitivity of the dolphin skin is some of the most relevant examples amongst many others. In addition, raw data treatment from nanosensors could be improved using natural models such as neural networks and genetic

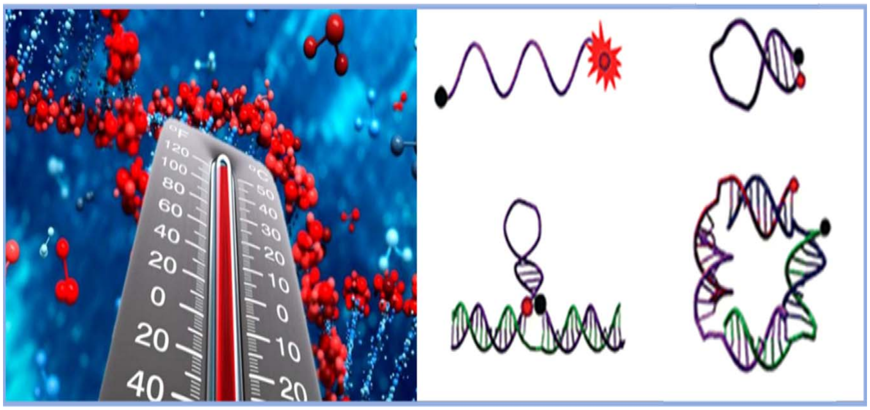


Fig. 7. Schematic presentation of ultrasensitive nanothermometers based on DNA thermoswitches capable to produce fluorescence changes within small temperature variations with a fast response time, from Ref. [68] (Adapted with permission from American Chemical Society).

algorithms. There are two main possibilities of exploiting these natural sensing capabilities. The first one is the biological nanosensors, which implies the direct use of natural systems, such as the antibodies used as capturing agents in the fabrication of nano-biosensors [74], neural networks for multiplexing analysis [75], tissues of natural materials as components for electrodes as a way to immobilize enzymes of nanometric size (e.g., a "banana tissue carbon paste electrode" reinforced with CNTs [76]), immobilized enzymes in solid supports such as controlled-pore-glass [77], among others. The main problem of these biological nanosensors is the scarce durability and the low batch-to-bath reproducibility of the preparation of the nanosensor. Unfortunately, there are many described biological nanosensors of this type without taking into account these practical aspects. Therefore, they are very interesting but useless from a practical point of view, with very few exceptions. Quality assurance is mandatory in all these approaches. The second one is artificial nanobiosensors, which is built by simply mimicking a natural sensor. Nature learns scientists, technologists, engineers, etc., to introduce innovations in many fields in a very elegant manner [78]. Such is the case of those architects who built buildings inspired by natural structures (e.g., Gaudí in the Holy Family church in Barcelona). Indeed, in the field of nanobiosensors [79,80] there are many mimicking approaches as well, being the majority designed for physical measurands such as temperature (e.g., DNA-based thermometer [68], see Fig. 7), presence of fire (e.g., insect –inspired biomimetic infrared sensors) [81], strain (e.g., Campaniform sensillum is a kind of strain sensor commonly found in insects used as a gyroscope for fly´s flight stabilization) [82], among others. A curious example of the association of living spinach plants and nanosensors is presented this year by Wong et al. to pre-concentrate/detect/determine nitroaromatic compounds in ambient groundwater [83]. The infrared spectroscopy is used to monitor contaminant nitroaromatics in left tissues introduced from roots. Contaminants are accumulating in the mesophyll, and the detectable emission intensity changes are sent to a smartphone. Two nanosensors are introduced in living spinaches. The nitroaromatic nanosensor is composed of SWCNTs conjugated to the peptide Bombolitin II. The second nanosensor is a reference for measurements (blank), for such a purpose polyvinyl-alcohol functionalized SWCNTs were used.

(d) The progressive substitution of "hard" nanosensors by "soft" ones is the fourth trend in the improvement of nanosensors. In many areas where N & N have positively impacted during almost 20 years, it is possible to advise a tendency to progressively substitute typical hard NPs (e.g. AgNPs, AuNPs, SQDs, SWCNTs and MWCNTs) by soft ones such as micelles, dendrimers, nanoporous polymers, encapsulated hard NPs within hydrogels [84], etc., to reinforce the trend to substitute toxic to non-toxic substances; this is of potential interest in areas such as medicine (looking for the renal clearance) [85] or in the nanofood sector, this tendency being definitively consolidated [86]. Hydrogels-based nanosensors [52] are based on the structural combination of a polymer hydrogel network with a nanoparticle (metals, non-metals, metal oxides, and polymeric moieties). This combination resulted in a synergistic enhancement of the characteristic properties of both components. For example, the mechanical strength of the hydrogel is reinforced whereby the nanoparticle aggregation is minimized or even avoided. Among diverse fields of application (e.g. drug delivery, electronics, catalysis, environmental remediation), nanosensing is one of the most appealing. A gel matrix of NC (acting as gelator) can host both fluorescent complexes and nanomaterials, giving rise to a new class of nanosensors with a variety of properties. Fig. 8 depicts several NC hydrogel-based nanosensors for the determination of a variety of analytes in different samples. The inclusion of a luminescent bipyridinium-ruthenium complex in the NC-hydrogel resulted in an excellent nanosensor for AgNPs which were successfully determined in deodorants and socks [52]; this example is in the framework of the Third Way of AN & N commented on in Section 5 of this article. On the other hand, the inclusion of GQDs into the NC hydrogel originates a suitable nanosensor able to determine trichlorophenol in waters [87] and laccase in shampoos [88]. Luminescent CQD hydrogels are formed by using a low molecular weight hydrogelator mixed with CQDs with different superficial moieties (carboxylic acids, thiols and amines); the resulting hydrogels are excellent nanosensors for the determination of traces of metals such as silver ions in river waters with excellent selectivity and sensitivity [89]. NC,which is obtained from abundant natural resources, is the last "star" of the series of carbon NPs described in the last three decades: fullerenes (1986), CNTs (1991), graphene and carbon-based nanodots (2004) and NC (2006). It represents one of the most "soft" NPs used in the last years in a great variety of areas [23]. It is important to mention the unique properties of NC, a rod-like nanoparticle: natural, non-toxic, lightness, large superficial area, chemical reactivity and stiffness, inherent hydrophilicity, chirality, easy functionalization, etc. The net contribution of NC to develop nanosensors (this section) and nanosorbents (see Section 8) come to the conclusion that NC and its derivatives have an increasing importance in AN & N.

(e) The change of the placement of nanosensors is the fifth evolution of nanosensors: from the classical locations (e.g., laboratory, on-site nanosensing platforms) to the so called dynamic approach (e.g., in nanotheragnostics, the use of nanomotors as sensing devices). Optical and electroanalytical nanosensors are used extensively in the analytical laboratory were the samples arrived. The majority of references in this topic are representative examples of them. Also, nanosensors can be used in situ, such as the case of the pH nanoelectrode [66] which is used inside living cells. The so called "dynamic approach" to nanosensors is an exciting topic just initiated but that will have a great impact in the near future, especially in the promising Nanomedicine field. It consists of the use of dynamic nanosensors that differ from the conventional ones in the fact that they are travelling through the object (e.g., living body) searching for a target place (e.g., a tumor) where they are concentrated thanks to antigen-antibody links. This type of dynamic nanosensor can be considered among the AN & N imaging (see Section 11). The dynamic nanosensor travels with a therapeutical agent, as it is the case of theragnostics. Other dynamic alternative is the use of nanomotors for analytical purposes. Theragnosis (also called as "theranostics") is a promising branch of Medicine devoted to the combination of therapies (chemical by dugs, physical by radiation, or both) and diagnoses (covering structural (physical)

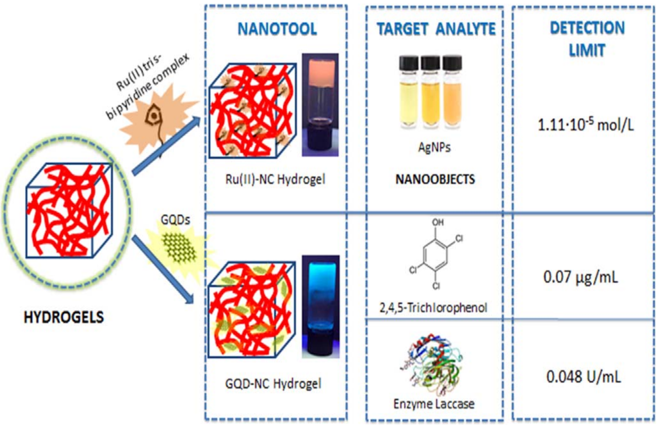


Fig. 8. Analytical applications of nanocellulose hydrogels as fluorescent sensors of a variety of target analytes, such as silver nanoparticles, trichlorophenols or enzymes, as function of the type and proportion of luminophore added. For more details see Ref. [23] (reproduced with permission of Elsevier).

and functional (chemical) imaging, surgery assisting delineation, and in this case monitoring of therapy). The impact of AN & N in theragnostics is undeniable [90]. No doubt, the R & D & T (research, development and transference) in this topic must be in the framework of interdisciplinary. The called "nanotheragnostics" open up impressive future avenues in Nanomedicine. Theragnostics [91] can be defined as the use of hybrid multifunctional or multicarrier NPs (sometimes called as "reporter nanoparticle") to implement almost at the same time and at the same place of the human body both therapy and diagnosis. According to when the analytical diagnoses happens, it is possible to distinguish two types of nanotheragnostics which are commented in Fig. 9 using representative examples related to very relevant diseases such as diabetes and cancer. Nanotheragnosis can be applied in two different ways. In the first case nanotheragnosis is based on the diagnosis after therapy. The main objective is to know the effectiveness of the therapy in situ. Thus, Sangupta et al. described in 2016 [91] a polymeric reporter nanoparticle, which are internalized in cancer cells acting as a carrier containing two components: the chemo/immunotherapy agent and a luminescent nanosensor of the enzyme laccase used as indicator of apoptosis of cancer cells. The nanosensor indicates in few minutes the efficiency of the therapeutic drug through the skin of the living body, in such a way that the "sensitive tumors" (those where the therapy is effective) showed a great luminescence through the skin, whereas the resistant tumors of this specific nanotherapy displayed a small luminescence. This procedure is particularly applied when the selection of the most efficient therapeutic agent is necessary. The mechanism with and without apoptosis is shown in Fig. 9A. In the second case, nanotheragnosis is based on the diagnosis before therapy. In this case, therapy starts when the result of diagnosis requires action. Such is the case of the monitoring/control of glucose in diabetes disease [92]. The nanocapsules involved have a dual function. Their cover is the nanosensor for glucose and the core is full of insulin. As it can be seen in Fig. 9B, there are two mechanisms of delivering internal insulin when the response of the cover reported a high level of glucose: swelling and degradation. The main objective is to mimic the response of the healthy pancreas when the glucose level increases. This is an elegant way to circumvent the daily use of insulin injections. The role of the cover nanosensor is essential.

Nanomotors as nanosensors are another promising area of AN & N. Motion-based sensing using nanomotors belongs to the "dynamic nanosensors approach". Jurado-Sanchez and Escarpa [93] recently pointed out the impact of milli-, micro- and nano-sensors in the realm of Analytical Chemistry. For example, trace silver ions are based on the enhanced motion of hybrid gold/platinum nanowires in the presence of the analyte, which is attributed to underpotential deposition of silver ions onto the platinum segment. This motion is tracked using an optical microscope.

8. Trend E: evolution of nanosorbents

According to the relative number of papers found on the ISI Web of Science database (see Section 3), there is no doubt that nanosorbents have attracted considerable attention as a sample-preparation tool. Fig. 3B shows the number of papers published every year over the period 1999–2017. As seen, the use of nanosorbents rose rapidly in its early years, and the number of publications grew steadily from 1999 to 2016. This increase in the productivity is mainly due to the previous discovery of fullerenes in 1985 [94] and their production on a preparative scale in 1990 [95]. As early as 1994, Gallego et al. [4] first reported an article on the analytical use of C_{60} fullerenes as sorbent materials for the preconcentration of metal traces through the formation of neutral chelates. The authors determined the adsorption isotherms of Pb at low concentrations, and found that C_{60} had a greater adsorption capacity than C18-bonded silica and activated carbon, which were tested as sorbents under similar conditions, indicating that the van der Waals interactions between the ligand (chelate) and fullerene, which are stronger than those with other sorbents. Since then, hundreds of papers have appeared in scientific journals describing various types of nanosorbents and applications in various fields, and many articles reviewing the use of nanosorbents in sample treatment can be found in literature [96–101] as well. Since these reviews give a thorough description of preparation and use of nanosorbents as well as comparison with other conventional or non-conventional materials, to avoid useless redundancy, the intention is to present a brief reminiscence of 32 years on the use of nanosorbents in sample treatments. In this part, we classified nanoadsorbents mainly used in analytical applications for adsorption into two groups based on their role, which is dependent on their innate surface property and further external functionalization: (a) carbon nanomaterials including fullerenes, CNTs,

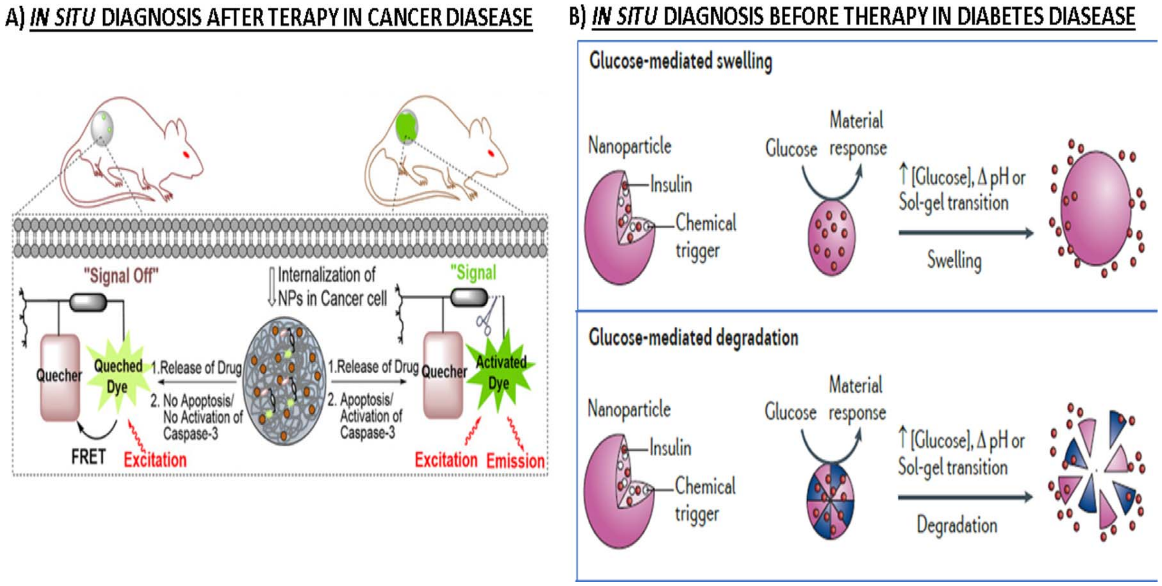


Fig. 9. The two types of nanotheragnostics. (A) In-situ diagnosis by nanosensors after therapy; from Ref. [91]; and (B) in situ diagnosis by nanosensors before therapy, from Ref. [92]. For details, see text. (Reproduced with permissions of National Academy of Sciences and Springer Nature, respectively).

graphene and NC; and (b) metallic nanomaterials including SiO_2NPs, alumina NPs (Al_2O_3NPs), magnetic NPs (MNPs) and metal organic framework NPs (MOFs).

Nanosorbents are very different from most “traditional” sorbents, because they are built from nanosized molecules with exceptional properties attracting a great interest among material scientists. The Web of Science historical search showed that nanosorbents used in sample treatments have accumulated 5411 publications from 1985 to 2017, out of which 41% (2220 publications) were identified using carbon nanomaterials, and 13% (690 publications) using metallic nanomaterials, as Fig. 10 shows. In the case of carbon nanomaterials sorbents,1575 publications were found using CNTs, 535 for graphene, 85 for fullerenes and 25 for NC. Interestingly, the total number of publications on CNTs accounts for 70.9%, graphene 24.1%, fullerene 3.8% whilst NC just means 1.1% of the carbon nanomaterials used as nanosorbents. CNTs [99], graphene [100] and fullerenes [94,95] have been exhaustively used as nanosorbents since their discovery due to their unique physic–chemical properties, which make them promising for their use as sorbent materials, with elevated affinity, capacity and selectivity. They have gained wide attention as sorbents in several analytical techniques, such as solid-phase microextraction (SPME), fibers covered with carbon nanomaterials, solid-phase membrane tip extraction (SPMTE), SPE, or as stationary phase in gas chromatography (GC) and liquid chromatography (LC) [102]. Upper material features, such as high surface-to-volume ratios, high thermal stability, formation of non-covalent interactions with organic molecules, resulted in a steadily increasing application of these carbon nanomaterials in analytical chemistry [102]. π-π electron donor-acceptor and hydrogen bond interactions are the relevant non-covalent interactions, which result in strong sorption affinity of carbon nanomaterials [102]. NC [23,103] as new nanosorbent material is considered to be an effective choice for extraction/clean-up, and preconcentration techniques, by virtue of its excellent sorbent properties, due to the hydrophilicity of their surfaces favoring the formation of strong intermolecular and intramolecular hydrogen bonds. This exploitation of their properties contributes to develop innovative analytical strategies or to improve of the conventional ones, in order to meet the required analytical properties (accuracy, precision, sensitivity, selectivity, speed and cost).

In the case of nanoscopic sorbents, 447 publications were found using MNPs, 129 for MOFs, 101 for SiO_2NPs and 13 for AlO_2NPs. Interestingly, the total number of publications on MNPs accounts for 64.8%, 18.7% MOFs, 14.6% SiO_2NPs when Al_2O_3NPs just mean1.9% of the metallic nanomaterials used as nanosorbents. SiO_2NPs [104] and Al_2O_3NPs [105], have been widely used as nanosorbents for the extraction and separation of toxic metal ions and organic compounds [101]. They show unique properties, such as high thermal, mechanical and chemical stability, as well as large specific surface area, high adsorption capacity and low temperature modification ability, meeting the requirements for sorbents. The incorporation of magnetism to these nanosorbents is a good alternative, because the easy collection of nanosorbents by an external magnetic field and the elimination of the time-consuming for filtration steps. Silica-coated magnetic material is the most metallic nanomaterials used as nanosorbent in sample treatment, because they exhibit the advantages of easy surface modification and easy control of interparticle interactions. Surface modification of the magnetic core via silanization is a common way for particle functionalization. In order to enable the selective extraction of analytes, the silica coating can be easily formulated by attaching inorganic or organic molecules to its surface. One of the most promising and advanced composite material is MWCNTs-nano$C_{18}SiO_2$ composite, which has a high enrichment ability attributed to the nanosizes and the plentiful C_{18} groups and MWCNTs [106]. MOFs represent a new class of hybrid organic inorganic supramolecular materials comprised of ordered networks formed by organic electron donor linkers and metal cations. They can exhibit extremely high surface areas, as well as tunable pore size and functionality, and can act as hosts for a variety of guest molecules. Since their discovery [107], MOFs have been subjected to extensive exploration, to serve as next-generation nanosorbents materials.

9. Trend F: increasing reliability of nanotools

The great capability to solve analytical problems using new nanotools in AN & N is strongly limited by the reliability of the corresponding methods, which is frequently forgotten by those scientists publishing articles in this field. This fact can be explained by the “research reproducibility” defined by Ioannidis et al. [108], and because

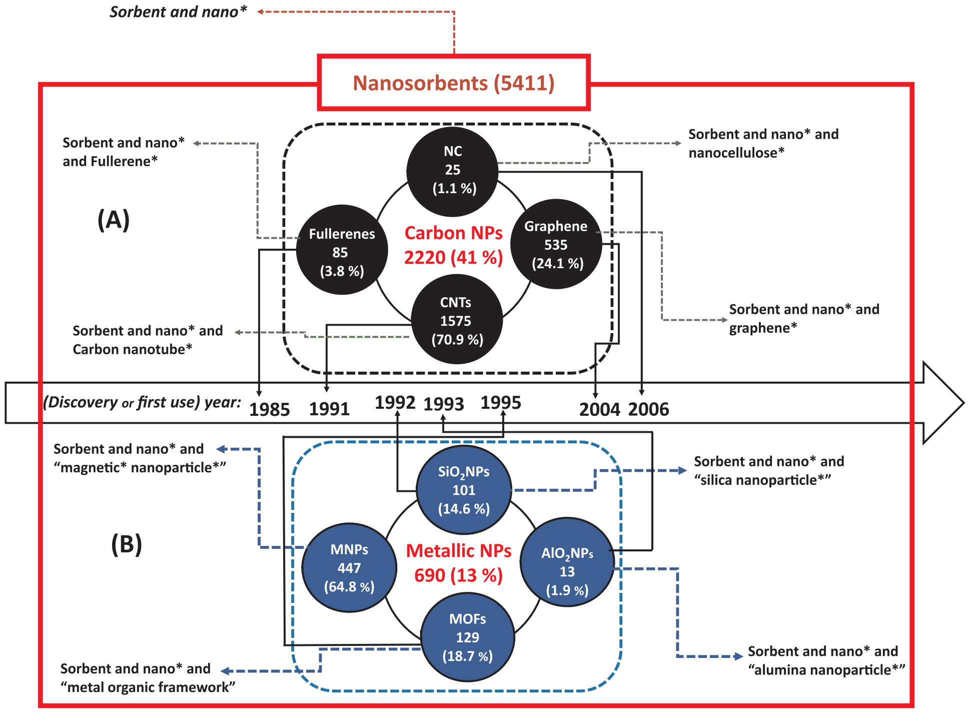


Fig. 10. Evolution of nanosorbents in analytical applications and diagram of publications obtained from crossing the search expression results in the data base of science citation index source, divided in two groups: (A) Carbon nanomaterials Sorbent and nano* and nanocellulose* (25 articles), Sorbent and nano* and Fullerene* (85 articles), Sorbent and nano* and graphene* (535 articles) and Sorbent and nano* and Carbon nanotube* (1575 articles) and (B) Metallic nanomaterials Sorbent and nano* and “alumina nanoparticle*” (13 articles), Sorbent and nano* and “silica nanoparticle*” (101 articles), Sorbent and nano* and “metal organic framework” (129 articles) and Sorbent and nano* and “magnetic* nanoparticle*” (447 articles).

any real validation of the proposed AN & N process is carried out (use of intended samples, and not "easy samples", such as clean waters and spiked samples). This negative fact can be attributed to the misconception of Analytical Chemistry by other scientists. Whitesides in a lightening article [109] about the reinvention of Chemistry, attributes to this discipline a key role; he considered it a bottle-neck for innovation in chemistry in an interdisciplinary approach. Reliability is a very rich concept because its integral character and the fact that it is very easy to be understood for scientists and citizens. The adjective reliable is equivalent to trustworthy, confident, safe, sure, transparent, qualified, Social Responsibility (SR), among other meanings. In the metrological realm, to be reliable means to proven consistency in producing satisfactory primary data, information and knowledge. Reliability in Analytical Chemistry is a "cocktail" of analytical properties such as accuracy (that relies on sensitivity and selectivity), precision, robustness, representativeness, productive characteristics (time, costs risks) in addition to its qualitative connotations. It is, thus, a global indicator that encompasses many specific indicators.

Authors are convinced that "reliable" is an adjective that should be used be used to characterize, AN & N processes and/or the results provided by it. It is the only way to guarantee the quality of the described nanotool. In fact, there are many papers on "nano-(bio)-sensors" without any analytical approach as can be inferred from strategic bibliographic searches in international databases (e.g., WOS and Scopus), as was stated in Section 6, and reading many articles published in specialized journals on sensors of high impact factor. This situation is especially worrying in the field of nanobiosensors (with nice colored figures of the biochemical mechanisms), but the figures of merit, the fitness for purpose of describing the sensing platform, the application to real samples are frequently forgotten. In addition, the impression of an expert is that the research is just "pinned", that is, the "research reproducibility" [108] and results reliability are not relevant for authors, reviewers and editors. This tendency should be avoided if we like to exploit the real potential of these powerful nanotools. In fact, publishing non-reliable nanobiosensors could arise false expectations of scientists and citizens in the frame of SR of Analytical Chemistry [110]. It is necessary to stop the publication of useless AN & N articles, as was proposed by Ioannidis [111] in the field of clinical research. One of the "engines" of this wrong approach is the incorrect evaluation of AN & N scientists, research teams, and research centers mostly based on quantitative data.

10. Trend G: role of AN & N in nanotoxicological studies

The intriguing properties of NPs and their large surface areas per mass makes them very reactive species which can interact with a variety of chemicals in almost any media, affecting biomolecules and cell functions. Thus, as all emerging area, the extensive uses of nanotechnology entail unperceived release of NPs from a mass of consumer products into the environment, and thus, their inevitable future exposure have become a great concern in the last decade. Many factors influence the so-called nanotoxicology originated by such active biologically nanostructures [112,113], being related to the intrinsic features of NPs, the environmental conditions but also the exposure type (time, penetration, concentration, temperature, among others) and other parameters characteristic of living organisms (adsorption rate, distribution, fate), so far. Interestingly, the predisposition to NP exposure is dependent on their morphology (size, shape and crystallinity) and surface features but also on their chemical composition and stability (Fig. 11A) [114,115]. This is the case of fluorescent nanodots, a novel family of spherical NPs [48] of great interest in many areas (analytical, medicine, energy, among others). This family can be classified into SQDs (composed mainly of heavy metals) and spherical carbon based nanodots (CQDs, CNDs). Toxicological studies of the SQDs and CQDs (nanodots with quantum confinement) of identical shape, size and surface functionalities in different cell lines demonstrated the lack of deleterious effect of CQDs if compared to the very toxic SQDs even at very low dose concentration. This has markedly influenced the exponential nanotechnological growth of hazardous SQDs, which resulted to slow down along this decade [48] in concordance with the discovery of non-toxic CQDs; however, because of the great potential of SQDs, it is expected to recover quickly with the latest novel approaches for obtaining safety SQDs, as for instance changing their core-shell composition to non-heavy metals. In the other direction, carbonaceous NPs with fibrillary shape as CNTs resulted to produce~~d~~ higher damage in organisms than spherical carbonaceous NPs like CQDs or nanodiamonds. Apart from the intrinsic properties of NPs, a big handicap is the batch-to-batch reproducibility in their synthesis (involving mixed of different sizes and shapes, and even with impurities), although in the last years a considerably improvement has been achieved as a result of recent developments and synergy of material science and AN & N.

Different legislations in countries are responsible for performing toxicological tests, controlling their release to the environment and avoiding damaging the whole ecosystem including ourselves. However, the nanotoxicological research is still neither conclusive non-reliable. Part of researchers designated the emerging NPs as hazardous materials whereas others insisted in causing many benefits with low or non-toxic effects. In other words, there exist many controversies and ambiguities in this respect. Thus, although the great number of toxicological studies in diverse cell lines and some microorganisms, comprehension of the NP influence in living organisms is fundamental but, unfortunately, it is limited by the wide variety of NPs, being a hot topic [116]. Sophisticated analytical tools for understanding the cellular defense mechanisms or apoptosis against NPs are still under investigation, although many successfully approaches in sensing have been developed so far. Unfortunately, multiple parameters must be taking into account to reach accurate results in such a difficult task that is risk assessment. Standardized method applicable to all type of NPs with same cell lines and culture conditions are needed first to be generalized for all type of NPs. Unfortunately, more formal toxicological kits from the short-term (toxicity in cells, small living organisms, some plants, algae) to long-term (disease, mutagenicity, etc.) risk assessments caused by NPs in the environment (waters, soils, atmosphere) and living organisms must be produced, standardized and used for rapid sensitive screening of NP impact.

From a chemistry perspective, it is essential to tackle and get over this challenging task thanks to its multidisciplinary. As depicted in Fig. 11B, the analytical chemists need to play the following roles: to guarantee high repeatability and reproducibility of the assays;

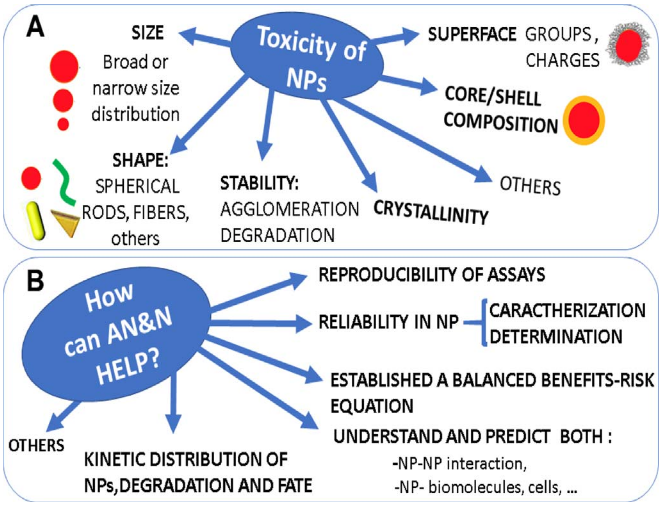


Fig. 11. Toxicity and AN & N binomial. Factors affecting the toxicity of NPs accordingly to their intrinsic properties (A). Fundamental roles of AN & N to be played to improve toxicity assays (B).

reliability in both characterization and determination of NPs; to evaluate the benefits and avoid the negative outcomes from nanotechnology;monitoring the evolution of NP-NP interaction and with other chemicals [117]; and kinetics of NP distribution, degradation/agglomeration and elimination or fate along the living organism [118,119] or environment. In this respect, AN & N is directed to solve or control the NP presence not only in risky commercially products containing NPs (above the established NP concentration by legislation) but also in the environment (coming from industry, transport brakes, heating systems, among others). As shown in this overview, the great potential of AN & N is clear (advances analytical tools) for contributing to the nanotoxicological examination of NPs, control their use in the market and assure our safety. However, more efforts are needed; in fact, it is fundamental to move the benefit balance in a different interest rate; that is, multinationals and governments must dissociate the benefits of Society (toxicological issues hidden) from the financial interests (avoiding that trend marks guide the market by forgetting the most crucial value: protection of consumer´s interests and social developments). Unfortunately, it is still a pending subject hard to be solved in a near future.

11. Trend H: increasing role of AN & N in (bio)imaging

Analytical chemists should be aware of two facts: first, an image can be the result of an analytical process as are qualitative and quantitative results, total indexes, etc.; and second, this type of information is increasingly required in many areas, especially in the biomedical context, to make founded decisions. In this context, it should be distinguished two facets. First, the use of nanotechnological tools to implement (bio) imaging of the macro- or microsample; and second, to visualize images in the nanoscale. The increasing impact of AN & N in (bio)imaging processes is undeniable. In fact, AN & N tools are crucial to support these processes. There are three general strategies with few other possibilities to implement nano-(bio)imaging, that are commented on below.

(a) The first strategy is based on the use of fluorescent NPs [120,121] to label or mark specific places of an animal/human body where the disease has been developed or it is in evolution. The so called up converted fluorescent nanomarkers minimize the problems of the classical down converted NPs (e.g. autofluorescence, low-signal-to-noise ratio, etc.) [122]. The main advantages of up converted NPs for bioimaging excited by NIR radiation are as follows [123]: improving penetration depth; low photobleaching; higher sensitivity; and multiplex up conversion in vivo bioimaging. The paradigmatic image of Nie et al. [124] showing the localization of different types of cancer in a single animal using fluorescent SQDs of different diameters (and, thus, colours) externally derivatized by using different specific antibodies of the different cancer cells. Nanotheragnosis for tumor cells in Fig. 9A [91,92] is also an example of the use of NPs for bioimaging. In addition to SQDs, many types of NPs such as silica core shell, GQDs, derivatized AuNPs, etc., have successfully been used for bioimaging. A detailed description of all of which is out the scope of this overview.

(b) The second strategy can be called “nanospectroscopy” [125] implies the visualization of the nanoworld using spectroscopic techniques. In other words, it means to achieve nanometer spatial resolution in spectroscopy. Abbe diffraction limit implies that is not possible to achieve spatial resolution between two objects lower than 200 nm. There is a great number of optical spectroscopic approaches to monitor phenomena at the nanometric scale (1–100 nm). Undoubtedly, nanotechnology has been crucial in the last years to achieve this goal. Raman spectroscopy and its variants is the most capable of the optic spectroscopic techniques to implement nanospectroscopy, especially the tip-enhanced Raman scattering (TERS) [126] and SERS [127] modes. Both types can be applied to biological or not samples-analytes.

(c) The third strategy is the use of microscopies to visualize objects at the nanoscale. Electron microscopies (e.g., TEM, SEM) have been milestones in the short but intense story of Nanotechnology because discrimination in the nanometric scale is fully possible. Nevertheless, a great limitation is their incompatibility with living organisms because tissue destruction of incident electrons. Ordinarily, optical fluorescence microscopes do not reach the discrimination at the nanoscale. The so-called “nanoscope” (super-resolution fluorescence microscopy) has been awarded with the Nobel Price of Chemistry in 2014, since, for the first time, an optical microscope can produce nanoimages of biological significance as the discrimination of proteins (images) inside the cells [128].

12. Trend I: solving real analytical problems by AN & N

The analytical control of nanomaterials in real samples is a new challenge in Analytical Science. In spite of recognizing the first achievements in the characterization of nanomaterials through the use of microscopic techniques, the analysis of samples containing NPs is at the very beginning infancy. In fact, the classical nanometrology implemented for the characterization must be expanded to a wider concept including the determination of NPs in specific types of samples. Perhaps can it be cold “analytical nanometrology” to this last approach? This view supposes the transit from the “physical nanometrology” to the “chemical nanometrology”. And hence, the inherent difficulties detected at the macro level in the transit from metrology in physic to metrology in chemistry. This is the general framework for planning strategies and developing the new analytical methods for the determination of NPs in specific types of samples.

Therefore, specific strategies must be included in analytical processes addressed to the identification and the determination of nanomaterials in natural or artificial samples. This present challenge, associated to the real world for solving specific analytical problems (thinking in the end users: routine/control analytical laboratories), has clear bottle-necks:

(a) The initial definition of the analytical problem in relationship with the new social problems created by the massive use of NPs (and nanomaterials in general) in almost all fields. More and more the remarked toxicological properties of many NPs with respect the corresponding micro/macroones are a demonstrated evidence [129]. And, more important, maximum tolerated levels of these nano-compounds in the present legislation ~~is~~ are basically referred to micro/macro compounds. This fact is particularly critical in food safety field [130], but also in environmental field [131]. Some specific and representative examples can be consulted in the literature [132]. In consequence, it is must be clear what nano-component(s) in particular types of samples introduce this problem, and at what concentration level the actual tolerance must be fixed (interdisciplinary task).

(b) Sample treatment, especially in the case of complex matrices, is a critical step for preserving the integrity of the original nanomaterials and to contribute to the required selectivity and sensitivity of the analytical method. This problem is not new in analytical science and, perhaps, a close reference is speciation studies. The common alternatives in sample preparation step include the digestion of the sample (acid, alkaline or enzymatic) in order to achieve the dissolution of the sample and the possible degradation of the sample matrix; the centrifugation to isolate the NPs from an aqueous suspension; dialysis and ultrafiltration with nanoporous membranes working as cut-off devices, liquid phase extraction and SPE [133].

(c) Detection/determination of the nanomaterials from the prepared sample (commonly in solution) can follow two different approaches with their corresponding difficulties. The first one is the use of direct detection systems such as single particle ICP-MS or chemical sensors. spICP-MS clearly represent the most useful and reliable alternative, whereas chemical sensors (or sensing systems in general, according a wider definition of 'sensor', as it was discussed in Section 7), can be an interesting alternative in the future but their applicability has been not sufficiently demonstrated for practical purposes so far. In any case, spICP-MS only provide information about the concentration of NPs in the sample and the elemental mass content for the specific nanoparticle. Additional information is needed about the size distribution, in order to ensure the spICP-MS information corresponds to true NPs in the sample. The second approach is the use of (hyphenated) hydrodynamic instrumental separation techniques. In this case, different techniques have already demonstrated their suitability for the separation of nanomaterials/nanoparticles according to properties such as size, surface, density and charge. Thus, liquid chromatography (HDC, mainly), CE, and specially AF4 are very suitable techniques for the separation of nanomaterials. The coupling of these techniques with specific detectors (preferable in on-line arrangements), such as ICP-MS or DLS may be considered as the most serious approach for this type of analysis.

(d) The need of reliable standards for calibration purposes is another metrological problem. A reduced number of standards for nanomaterials are available and, sometime, the quality is not very well reported.This is a major issue from a practical point of view, and it should be a priority for national and international bodies, promoting R & D activities dealing with this objective.

(e) Quality assurance programs also include the validation of the analytical methods to guaranty the traceability. Working standards/references different from those used for calibration are needed. The present situation in analytical nanometrology is not very optimistic in this context: availability of certified reference materials (matrix type)?; reference/primary method for comparison?; or the possibility implementing proficiency testing rounds? (with which sample test?). Probably, the most real, but not the best, alternative could be the use of spiked samples. When the method is applied as a routine method, after the appropriate validation, internal quality control activities must be implemented: with which control sample? Many question marks indicating the need of many metrological tools for analytical nanometrology, and hence for the reliability of the information reported. Some of these challenges have recently been pointed out by Picó [134].

Nanoscience and nanotechnique is a true revolution, with impact in almost all activity fields, and it is needed a radical (re)evolution in the analytical patters to be adapted to the new social problems associated to N & N. Although evolutions have been taken place in analytical science (qualitative, quantitative, structural analysis; inorganic, organic; elemental analysis, molecular information, speciation, enantiomeric analysis; automation-simplification, screening approaches, spot tests; miniaturization-portability), now we have a revolution in charge in the analytical science.

13. Trend J: emphasizing social responsibility of AN & N

Corporate social responsibility was applied in several enterprises at the middle of XX century. Fruit of these efforts, several written standards produced by prestigious international organizations (e.g., ISO 26.000:2014) have been produced and helps to implement SR in bodies and persons. In the XXI century, integral quality cannot be fully understood without the SR component. In the frame of Science and Technology, Krogsgaard-Larsen et al. stated in 2011 [135] that Scientific Social Responsibility - which it is more than ethics- is an urgent issue that should be systematically considered, for supporting the great Humanity challenges defined in the two Declarations of Lund in 2009 [136] and 2015 [137]. Two years after, an integral model SR in N & N combining research centers, production companies and the citizens was proposed [138]. In the dilemma posed by Dyson [139]: Science driven by ideas (Khun) or tools (Galison), there is another alternative: a vision-oriented approach to Science looking for the welfare of all the citizens. SR in Analytical Chemistry has been specifically presented [111] by emphasizing its two related connotations, namely: A) internal: sustainable production of quality (bio)chemical information; and B) external: delivering quality (bio)chemical information to society to make sound and timely decisions. AN & N has a high level of SR owing to the higher potential as regards Analytical Chemistry to satisfy information requirements.

The combination of these three previous approaches allows one to properly define SR in AN & N as the awareness of all stakeholders involved in the impact of their actions, decisions, delivering and reception of (bio)chemical information, in the society and environment. The very relevant foundations of SR in AN & N are: accountability, transparency, ethics (honesty), satisfactions of the interest of almost all stakeholders, respect for the Human Rights and applicable legislation. The internal connotations of SR of AN & N are related to the sustainable production of quality (bio)chemical information. As way of example, the use of CNDs [140] instead of the classical fluorescent nanosensors (semiconductor nanodots, SQDs) allows one to reduce the toxicity affecting both technical people manipulating them and the body under study. The use of nanotools in analytical in AN & N processes allows one to increase the quality of the information delivered; such is the case of detection/determination of graphene in waters around airports by using the fluorescent nanoprobe [14] that offers quality indicators (sensitivity and selectivity) higher that those achieved using traditional analytical techniques.

On the other hand, the external connotations of SR of AN & N, are based on the internal ones. They can be defined as the success in the transmission of the (bio)chemical information between laboratories and "clients" requesting information. This achievement can be materialized in the satisfaction/usefulness of the information received, development of AN & N processes producing non- required information but that can be very necessary in a near future; such is the case of the detection of the virus Zika in saliva using a nanotechnological platform before the Olympic games of Rio de Janeiro [141]. In this context, it should be recognized that there are many causes of failure in this information transmission, the most relevant of which are as follows: 1) The client does not precisely define what is expected from the laboratory; 2) The relevant differences among providing data or information or knowledge, being the best. 3) The scarce technical experience of the receptor of the information, which is a situation quite frequent; and 4) Fraudulent external manipulation of the object or sample to be analysed.

The SR of AN & N that is materialized in the pillars previously mentioned. The most relevant of them is the satisfaction of all the stakeholders involved, but by establishing a priority order: citizens, scientists, technologists, non-governmental organizations, governments, enterprises, among others. SR is crucial in Analytical Chemistry is more relevant in a powerful and enabling context as N & N infers to analytical processes.

14. Final remarks

After the general survey reported in this article on AN & N, a general conclusion can be stated: there are two sides dealing with AN & N, as they are the use of the nano-world as analytical tools, and the measures dealing with the nano-world (determination of nanomaterials in specific samples, mainly). The third way is also an attractive goal (use of nano-tools for the analysis of nanomaterials), as pointed out in Section 2 [16]. As reported in this article there are many analytical achievements in the use of nanomaterials as tools in the development of new analytical processes, with special incidence in sample treatment (extraction of analytes, preconcentration, and clean-up), and in the detection (sensing systems). When the objective is the analysis of nanomaterials in natural or artificial samples (qualitative and quantitative, but also intended to a sample screening), serious problems appear. We introduce the term of 'analytical nanometrology' in this case.

Analytical nanometrology is a present challenge in today's analytical science, and it involves a revolution involving new paradigms. Dyson suggested [139] that science is driven by ideas or by tools; but he forgot that there is another relevant driven "motor": the societal needs. Such is the case of AN & N where the need for information from the nanoworld (e.g., nanoproducts in the market) has propitiated the impressive developments of Nanoscience and Nanotechnology, also thanks to the scientific ideas and the developments of proper tools. In this context, it is necessary to recognize that the detection and determination of nano-components in complex samples (foods, environmental, biological, or industrial) is still very limited, and the systematic validation of the corresponding methods to be incorporated in routine/control laboratories is far from reality today [142]. But, at the same time, and connected to societal needs, governments and international bodies have to produce new regulations about maximum tolerated levels, as well as on control recommendations [143,144]. For this purpose, exposure limits of nanomaterials must be studied and fixed according to the potential risks [145]. Some legal aspects cannot be understood without the recommendations given by the EU about the definition of nanomaterial [146].

(Re)evolution in Chemistry at the beginning of the XXI century has already pointed out by Whitesides, speaking on 'reinventing Chemistry' [109]. In this reinvention, the importance of the (bio)chemical information plays a critical role, and the author remarks that one of the most crucial steps in the beginning of new scientific-technical areas is the development of innovative analytical techniques that make possible relevant measurements. Even more, the development of analytical methodologies and techniques that open new areas of science are needed. Analytical nanoscience is, of course, one of these areas of science. But, in this way, it may be wonder if the present research in Analytical Chemistry is truly useful and addressed to this goal. Ioannidis recently introduce this debate in the field of clinical research [111]. Sometimes, the research only aims to increase the number of publications and fatten the researchers' CVs, or producing benefits for publishers, but scarcely contributing innovation, novelty or scientific impact.

In this way, AN & N needs a change of course to stay on the frontier of knowledge. Thus, more and more it is difficult to introduce innovation or novelty in the use of nanomaterials as analytical tools, whereas the side of considering nanomaterials as target analytes is recognized as a new route in the way of innovation for solving real analytical problems. In this path-way, the reliability of chemical information must be assured. Analytical nanometrology needs clear specific developments for these achievements. State-of-the-art and relevant trends have been reported in this article as potential tools/approaches to connect to the expected (re)evolution in AN & N.

A bottle neck of the positive evolution and consolidation of AN & N is the human factor, that is, the education of young students. It is necessary a global approach starting from the very beginning in the secondary school by introducing nanotechnology as a scientific technical revolution using representative examples. Then, in teaching Analytical Chemistry courses, AN & N should be explained in both classrooms and laboratories. This will be the best way to engage students to look AN & N as a scientific and technical branch of great future.

Acknowledgements

The Spanish Ministry of Economy and Competitiveness (MINECO) and JJCC Castilla-La Mancha are gratefully acknowledged for funding this work with Grants CTQ2016-78793-P, CTQ2014-52939-R, and JCCM PEIC-2014-001-P, respectively. The support given through an "INCRECYT" research contract to M. Zougagh is also acknowledged.

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