

Nuclear and related analytical techniques for life sciences

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Abstract Place and role of nuclear analytical techniques (NATs) in life sciences is discussed. Examples of radioanalytical investigations at the IBR-2 pulsed fast reactor in Dubna illustrate the environmental, biomedical, geochemical and industrial applications of instrumental neutron activation analysis.

Keywords: analytics, nuclear and related analytical techniques, radioactivity, neutron activation analysis

1. Introduction

The environment is steadily affected by anthropogenic activities such as energy generation and use, production and use of materials and consumer goods, waste disposal, motorized traffic, *etc.* Many of these activities have negative or even devastating effects on the quality of the environment. Thus, the deterioration of the environment by all kinds of human activities should be a very important and urgent topic of research. In the meantime it has become clear that new approaches are necessary to find an acceptable balance between accommodating mankind on the globe, on one hand, and protection the environment, on the other.

Before any action can be undertaken as to the protection of the environment, knowledge should be gathered on our ecosystem itself, for instance in monitoring changes in the environment, in identifying and analyzing problems, in designing and developing solutions, in testing and improving materials. Thus, a large share of all analytical work to be done in the future lies in the area of environment and related fields nowadays classifies as Life Sciences. This is, of course, a challenge for the entire spectrum of analytical methods, covering both nuclear and non-nuclear analytical methods.

For the purpose of this review we define nuclear analytical techniques (NATs) as those that use nuclear reactions, radioactive decay, or nuclear instrumentation to investigate properties of matter.

This definition extends from the well-established radiochemistry, neutron activation analysis (NAA), and prompt-gamma activation analysis (PGAA) to advanced methods at the limits of science and technology, and includes the applications of these techniques to the determination of composition and structure of matter for science and technology.

NATs are playing a significant role in the three "new epidemics" (WHO 2000) of cancer, cardiovascular disease, and diabetes. NATs have a unique role to aid in understanding the mechanism of brain-gut interactions related to satiety and obesity, which appear to be related to the new epidemics, and are in other ways an important health issue in rapidly developing countries. It is noted that a few investigations have commenced involving NATs in the determination of the composition of biological tissues in connection with HIV incidence in sub-Saharan Africa. According with the recommendations of the international and European pharmacopoeia, the quality assurance/control (QA/QC) of labelled compounds and radiopharmaceuticals for human and animal investigations is required making use of sophisticated and sometimes unusual radiochemical and radioanalytical methods of analysis and NATs.

The development of rapid methods of analysis and visualization of radioactive specimens would give a substantial improvement to these technologies. The stability with time of the labelled species and the evaluation of the expiration time is of paramount relevance for the performances of

labelled species. Artificially produced radioactive tracers, characterized by short half-life and high specific activity, are finding several applications in the Life Sciences, in particular in occupational and environmental toxicology, in metallobiochemistry (metalloproteomics) and nanotoxicology as well as in living organisms (cell cultures, plants, animals, and fishes).

The goal of the paper is to highlight the advantageous and strong points of NATs as a valuable and indispensable supplement of the non-nuclear analytical techniques and to demonstrate applications of most powerful NAT neutron activation analysis – at the IBR-2 reactor in JINR, Dubna, Russia.

2. General considerations

In order to explain the role of NATs, it is necessary to answer to the following questions. To what kind of analytical information may be required:

- quantitative analysis;
- speciation (analysis of the chemical forms);
- distributive analysis (depth and lateral resolution);
- structural analysis (including defects);
- analysis of kinetics;
- analysis of reaction mechanisms.

The next question is what means the word “nuclear”? In non-nuclear analytical methods the electrons play the dominant role. The nucleus only serves to keep the electrons together and to provide mass to the atom. However, in nuclear analytical methods the nuclear properties are the basis for analysis. Some important characteristic nuclear properties are listed below:

- spin and magnetic moment;
- mass;
- excited states and related parameters;
- probability for nuclear reactions;
- neutron scattering/diffraction properties;
- half-life, types and energy of emitted radiation (for radionuclides only).

One should realize that here is no sharp borderline between non-nuclear and nuclear methods. Some methods are based on both nuclear and electronic properties, within one single method,

like nuclear magnetic resonance and Mössbauer spectrometry.

Some other analytical methods are just a hyphenation of nuclear and non-nuclear methods, like modern chemical separations coupled with mass spectrometry or radioactivity detection.

Mass spectrometry and magnetic resonance spectrometry and to a lesser extent Mössbauer spectrometry, are not always considered as nuclear analytical methods. They are widespread and not specifically available in nuclear research institutes.

On the other hand, particle-induced-X-ray emission is a non-nuclear analytical method, since it deals with excitation of electron shells. However, this analytical method requires equipment normally available in nuclear research institutes.

Thus, practically it is included in the category of nuclear analytical methods.

The various nuclear analytical methods could be grouped into the following categories:

- mass spectrometry;
- nuclear magnetic resonance spectrometry;
- Mössbauer spectrometry;
- ion beam analysis (including PIXE);
- activation analysis (prompt and delayed; instrumental and radiochemical);
- neutron diffraction/scattering methods;
- isotope dilution analysis and related methods;
- tracer methods (stable and radioactive isotopes);
- radioactivity determinations.

The categories listed may give different types of analytical information. Mass spectrometry oriented methods give information on amounts, and sometimes also on depth or lateral distribution. Nuclear magnetic resonance provides information on amounts, chemical form, and type of binding. Mössbauer spectrometry gives somewhat similar information; however, it is limited to a small number of elements.

Activation analysis gives information on amounts, neutron diffraction/scattering gives structural information and dynamics, isotope dilution analysis information on amounts, tracer methods information on kinetics and distribution, and on reaction mechanisms, direct radioactivity measurements on amounts of radioactive elements.

There are also several nuclear analytical tools which have only scarcely been used as analytical tool and considered as “not-established” so far. For

instance, analysis *via* positronium chemistry and muon spin resonance.

The typical features of nuclear analytical methods may be grouped into four categories:

- 1) physical basis for analysis differs from those of non-nuclear analytical methods;
- 2) isotopic rather than elemental determination;
- 3) insensitive to electrons and molecular structures;
- 4) penetration character of nuclear radiation.

These features may be distinguished, but cannot always be separated or considered isolated. In principle, each of the nuclear analytical methods listed displays one more of these features.

Feature 1: the nuclear analytical methods have a totally different physical basis for analysis. This implies that nuclear analytical methods create an interesting supplementation of other analytical methods. Moreover, the weak and strong points of nuclear analytical methods are distributed over the Periodical Table in a different way compared to the chemical properties. For instance, hydrogen is well visible with neutrons and lead hardly, in contrary to X-rays analysis, where the situation is opposite.

In case nuclear analytical methods provide the same information as other methods, the nuclear analytical methods may serve as independent methods of reference. For instance, neutron activation analysis, and isotope dilution mass spectrometry are often used in certification of environmental reference materials.

Nuclear analytical methods may also act as pioneer. They may disclose analytically new fields of interest. Once the importance of the new fields are recognized, efforts will be spent to get access to the new field by developing non-nuclear analytical methods as well.

Feature 2: the isotopic rather than elemental character enables a physical distinguishing ability between isotopes, behaving chemically identically. This is the basis for much tracer work, with either stable or radioactive isotopes, and is also the basis for isotope dilution and associated methods.

Feature 3: insensitivity to electrons and molecular structure implies that the signal is not disturbed by electronic and molecular structures: this is a substantial advantage, but at the same times also a drawback. Therefore a variety of hyphenated techniques have been developed, consisting of a

chemical basis for selectivity as to chemical form, and a nuclear basis for detection.

Feature 4: in most nuclear analytical methods the excitation and de-excitation signals penetrate through matter, thereby enabling non-invasive measurements, without disturbing the matrix and/or the processes to be studied.

This feature enables non-destructive measurement, large sample analysis, spatial resolution and /or *in-vivo* measurement.

Many NATs deal with ionizing radiation and/or radionuclides, and they are concentrated in nuclear research institutes with cyclotrons, linear accelerators, and/or nuclear reactors.

For successful applications of nuclear analytical methods at least three factors are important. The first is **the environment and related fields**, the second factor is **the group of non-nuclear analytical methods** with a variety of possibilities, and the third factor is **the group of NATs**. The guidelines on the mutual interaction between these factors given below may be of particular interest to nuclear scientists working in large centralized nuclear research institutes and dealing with NATs.

First guideline, apply NATs in a meaningful way to realistic problems, thus to problems where nuclear analytical methods really yield valuable or unique information which cannot be obtained via non-nuclear methods. Thus, balance as much as possible the NATs *versus* other analytical methods. If necessary, combine nuclear analytical methods with other analytical methods.

Second guideline, nuclear physicists dealing with nuclear analytical methods should also develop interest **in** and knowledge **about** the environmental and related fields for proper and meaningful applications of their methods. This inevitably calls for an interdisciplinary international cooperation. Further, modern aspects of analytical quality management should be included.

3. New developments in analytical techniques and applications

Over 200 small and medium charged-particle accelerators are in use in many countries for PIXE and other ion beam analysis techniques. Their applications in materials and life sciences are expanding, especially with micro beam facilities

which allow imaging in two or three dimensions (more than 40 operational μ -beam facilities available at this moment).

Charged-particle activation analysis (with or without radiochemistry) can be a complementary technique to NAA for the determination of particular elements in different matrices (biological, environmental, and certain technologically advanced materials). In the version of TLA (thin layer activation) this technique is effective for wear and corrosion studies on moving mechanical equipments for industrial applications and the assessment of the performances with time of human prostheses as well. There is a remarkable growth in the number and availability of particle accelerators related to the rapid expansion of diagnostic and therapeutic nuclear medicine procedures, notably positron emission tomography (PET), single-photon emission tomography (SPET), (including hybrid systems with CT or MRI), functional diagnosis, molecular imaging, and metabolic radionuclide therapy. For example, more than ten million tests are made with ^{99m}Tc annually in North America alone. The number of qualified and experienced professional nuclear scientists and engineers, in particular radiochemists and radiopharmacists, has not kept pace with this increase, leading to greater risks in these procedures. Analytical techniques based on synchrotron radiation are emerging which can provide qualitative and quantitative information on *in-vivo* elemental composition, structure, and molecular imaging. As many as ten of the new large facilities are dedicated to the biomedical sciences.

4. Examples of radioanalytical investigations at the IBR-2 pulsed fast reactor in Dubna

NAA in particular is in regular use worldwide to perform elemental analysis of as many as forty elements in a variety of materials important to industrial process development and control, human health, environmental protection, and cultural heritage. NAA is especially valuable in the case of large samples, complex matrices, solid materials that are difficult to dissolve, and QA/QC. Although NAA is mature, several developing extensions to the method promise greater applicability to the analysis of large ultra pure solids and extremely heterogeneous samples. There is an urgent demand

for the determination of ultra-fine particles in environmental studies and an understanding of their health impact. NAT's are and will continue to be applied in studies of atmospheric particulates and the developing field of engineered nanoparticles. The broad elemental coverage and high throughput of NAA have made the technique a dominant one in archaeometry.

The pulsed fast reactor IBR-2 provides activation with the whole fission spectrum: thermal, epithermal and fast neutrons. Thermal instrumental neutron activation analysis (INAA) takes advantage of the high intensity of neutrons available from the thermalization of fission neutrons and the large thermal neutron cross sections for most isotopes. The detection limits that can be achieved by INAA depend strongly on the chemical composition of the sample in question. Most often one or more of the matrix elements give rise to activities strongly interfering with the analysis by providing a high background in the γ -spectrometry measurements. In cases where the major interfering radionuclides have shorter half-lives than those of interest in the analysis, the problem can partly be overcome by appropriate delay of the measurements.

Another approach providing very significant improvement in the INAA determination of trace elements is selective activation analysis with the epithermal neutron spectrum in the reactor, using a suitable filter to shield the thermal neutron component. This variant, which has become known as epithermal neutron activation analysis (ENAA), is widely used for radioanalytical investigations at the reactor IBR-2.

The thermal neutrons can be efficiently removed by means of a filter consisting of cadmium or some other material with very high thermal neutron absorption cross-section, allowing selective activation with the epithermal neutron flux in the reactor (resonance + fast neutrons).

The practical «cut-off» of the thermal neutron filter depends on the character and thickness of the filter material. For a 1 mm cadmium foil, in our case, the effective «cut-off» value is 0.55 eV. Epithermal neutrons have energies from the Cd «cut-off» of 0.55 eV up to approximately 1 MeV. Most nuclear reactions with thermal and resonance neutrons leading to radioactive products are (n, γ) reactions.

The neutron activation cross-section as a function of energy however shows great variation among different stable nuclides. In the thermal neutron region the activation cross-section of most nuclides follows the $1/v$ law (inversely proportional to the neutron velocity). Some nuclides continue to follow the $1/v$ law in the epithermal region, while other show strong resonances in their excitation function in that region. Therefore the ratio of thermal to epithermal activation shows large variation between different target nuclides, a fact which may be conveniently illustrated by looking at the ratio of resonance activation integral/thermal neutron cross-section (I_0/σ_0) for the nuclides concerned. While this ratio is of the order of 0.5 for nuclides following $1/v$ law in the epithermal region, it may approach 100 for others.

Many trace elements and rare earth elements in particular have large activation cross-section (resonance integrals) at specific energies in the epithermal energy region [1]. This means that the radionuclide distribution originating from epithermal activation may deviate strongly from that apparent when the whole reactor neutron spectrum is employed. That forms basis of ENAA. The following advantages are evident: (i) improved detection limits by INAA, *e.g.*, for As, Br, Rb, Sr, Cd, Sb, I, Tb, Hf, Ta, Th, U; (ii) reduction of high matrix activity, *e.g.*, from ^{28}Al , ^{56}Mn , ^{24}Na , ^{140}La , ^{46}Sc , ^{60}Co ; and (iii) reduction of fission product interference from ^{235}U fission, which has shown to be essential, *e.g.*, in the case of Mo determination.

The experimental setup named REGATA for INAA consists of four irradiation channels, two of which are connected with the pneumatic system, and four gamma-spectrometers. Its layout and the main parameters of irradiation channels are explicitly described in [2]. New advanced software for recording gamma spectra and their processing was implemented [3]. The advantages of activation with epithermal neutrons at low temperature (70–90 °C) in irradiation channels of the IBR-2 reactor are favorably used for elemental analysis of environmental and biological samples.

4.1. Biomonitoring of air pollution with terrestrial moss (passive biomonitoring)

Moss has become popular as an integrator of air pollutants and is used as a biomonitor in the

European moss surveys since the late 1970s. The data from the moss surveys allow both spatial and temporal trends in heavy metal concentration/deposition to be examined, and the areas where there is high deposition of heavy metals from long-range transport to be identified [4].

Since 1995 Department of NAA FLNP JINR is involved in the European programme «Atmospheric Heavy Metal Deposition in Europe: – *estimations based on moss analysis*» reporting results to the European Atlas from the moss survey 1995/1996 [5], 2000/2001 [6] and 2005/2006 [7].

A combination of instrumental epithermal activation analysis (ENAA) using radioanalytical complex REGATA at the reactor IBR-2, FLNP JINR in Dubna and atomic absorption spectrometry (AAS) in participating countries provides data for concentrations of about 40 chemical elements (**Al**, **As**, Au, Ba, Br, Ca, **Cd**, Ce, Cl, Co, **Cr**, Cs, **Cu**, Dy, Eu, **Fe**, Hf, **Hg**, I, In, La, Lu, Mg, Mn, Na, Nd, **Ni**, **Pb**, Rb, **Sb**, Sc, Se, Sm, Ta, Tb, Th, **V**, W, Yb, **Zn**) that substantially exceeds the requested number of elements (marked as bold) normally presented in the European Atlas.

Not all these trace elements are strictly relevant as air pollutants, but they come from the multi-elemental analyses with insignificant extra costs, and most of them can be used as air-mass tracers.

By applying multivariate statistical analysis to the datasets, it is possible to uncover the character and the origin of pollution sources within an area under investigation, as well as those sources affecting this area through long-range atmospheric transport.

These results obtained in the Department of NAA of FLNP JINR cover Central Russia, South Urals, Bulgaria, Poland, Slovakia, Romania, Northern Serbia, Macedonia, and Western Ukraine [8-22]. Similar biomonitoring projects were initiated in Mongolia, Vietnam, Turkey, China and South Korea [23-27].

4.2. Air pollution studies with moss-bags technique (active biomonitoring)

Alternative to the biomonitoring with terrestrial moss for air pollution studies is the moss-bags technique, when moss (*Sphagnum* predominantly) collected in pristine areas is exposed over territories

under investigation for a fixed period of time.

These studies allow assessing air pollution levels where terrestrial moss vanished due to intense technogenic impact at such areas as large cities and other industrially affected territories or arid areas where moss cannot be found at all. Our experience obtained in Romania, Bulgaria, and Poland [28-30] was successfully extended to assessing air pollution at the territories adjacent to a refinery in Athens possibly affecting nearby olive plantations.

4.3. Analysis of halogens in moss and soil

ENAA is known to be a powerful technique for the simultaneous study of chlorine, bromine, and iodine. This was used to elucidate marine gradients of these elements in moss and soil samples collected at distances of 0–300 km from the coastline in Norway. All three elements decrease exponentially as a function of distance from the ocean in the moss samples, strongly indicating that atmospheric supply from the marine environment is the dominant source of these elements to the terrestrial ecosystem [31]. These results are compared with similar data for surface soils along the same gradients [32]. It is suggested that environmental studies of halogens in general and iodine in particular is a promising future area of application for ENAA. Assessment of halogens behavior was investigated also along transect from the Adriatic to the Black Seas through Macedonia, Serbia and Bulgaria. The results obtained for the South Korea (influence of the Yellow Sea) evidences for the similar exponential decrease of halogen concentrations with the distance from the sea in different climatic areas: North and South of Europe and South-East Asia.

4.4. Food quality and safety

The other newly developing trend of applying NAA in life sciences at FLNP JINR is food quality and safety in the framework of IAEA Technical Cooperation «Investigation of health effects on children from the consumption of food grown in industrially contaminated areas of Central Russia, the South Urals and Siberia, using NAA and AAS» (2003-2005) and IAEA Co-ordinated Research Programme on use of nuclear and related analytical techniques in studying human exposure to toxic elements consumed through foodstuffs

contaminated by industrial activities (2002-2005) [33, 34].

4.5. Workplace monitoring and health-related studies

ENAA at the reactor IBR-2 in combination with AAS and XRF enable relationships to be established between the concentrations of elemental pollutants (Cr, Ni, Cu, Zn, As, Se, Sr, Mo, Ag, Cd, Sb, Pb, (REE), Th, U, and others) in raw material, by-products (phosphogypsum), humans and the workplace of phosphate fertilizer plants. These studies were carried out in the framework of the IAEA coordinated research program on workplace monitoring and occupational health (1997-2001) [35] and the 5th Frame Programme of EU (Copernicus) «Workplace monitoring and health-related studies at fertilizer plants in Russia, Poland, Romania, and Uzbekistan» (2002-2004). The goal of both projects was to determine how man's biosubstrates can be used to follow the rate of pathological changes in the organism when exposed to intense technogenic environments.

Along with biosubstrates of the occupational staff and local residents (hair, nails and teeth), the assessment of general environmental situation was done in the vicinity of the plants based on the analysis of soil, water, air filters, vegetation – crops and foodstuffs [36–38]. At present ENAA at FLNP JINR is used for assessing exposure to toxic/potentially toxic elements (Hg, Pb, As, Mn, etc) in women of fertile age with different nutritional status in Russia in the framework of the IAEA co-ordinated research programme «Exposure to toxic and potentially toxic elements in women of childbearing age» [39].

4.6. NAA for assessment of hazardous impact of toxic trace elements on soil, bottom sediments and aquatic biota

NAA showed itself best in studying scattered elements in soil and vegetation of the boreal forests of the European Russia [40, 41]. Trace elements profiles in Al-Fe humus podzolic soils subjected to aerial pollution from the copper-nickel production industry in conditions of varying lithogenic background of the Kola peninsular was investigated for the first time [42, 43]. Experience obtained in studying anthropogenic scattering of toxic heavy

metals and anionic elements was extended on determination of their amounts in subsoil waters of the European Russia [44].

Water, bottom sediments and biota were analyzed to assess anthropogenic impact of the River Sister, a tribute of the Volga River, in the vicinity of the town of Klin (Moscow Region, RF) [45]. Similar studies were carried out for the Danube delta [46] aimed at intercomparison for trace elements between neutron activation analysis laboratories of Dubna and Bucharest (Magurele). Distribution of trace elements in freshwater ecosystem compartments of man-made Rybinsk Reservoir (Central Russia) using epithermal neutron activation analysis was undertaken in [47].

4.7. Biotechnology: development of new pharmaceuticals and sorbents of toxic elements

Since 1999 NAA was efficiently applied in the collaborative studies with the biophysicists from the Republic of Georgia on experimental substantiation of the possibility of developing selenium-, iodine- and chromium-containing pharmaceuticals [48, 49] and sorbents of toxic elements (mercury [50], uranium, *etc*) based on blue-green microalga *Spirulina platensis*. These investigations resulted in two patents of RF [51], the necessary prerequisites for production of *Spirulina* derivatives for food, perfume and medical needs. Besides *Spirulina platensis*, another simple organism – Cr(VI)-reducer basalt-inhabiting bacteria – was examined using NAA [52]. It was shown that indigenous bacteria can be successfully used to either detoxify or immobilize toxic substances.

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