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Radioactivation Analysis in Clinical and Biochemical Analysis

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1. Introduction

Radioactivation analysis is based upon irradiation of nuclei with elementary particles. In many cases the interaction gives rise to radioactive nuclei, which can be detected and identified by the emitted radiation. If we irradiate under identical conditions an unknown quantity of a certain atomic species and a known quantity of the same species, the following relation will exist between the induced radioactivities and the irradiated masses:

$$\frac{\text{Activity standard}}{\text{Activity unknown}} = \frac{\text{Mass satndard}}{\text{Mass unknown}}$$

From this equation the mass of the unknown can be easily calculated. This relativly simple technique (abstract made from the irradiating facility) allows quantitative determination of about 60 elements with a sensibility that most of the time considerably exceeds the sensibility of conventional analysis techniques. General review articles from Gordon[1] and Meinke[2-4] should be consulted for further detail.

2. Nuclear reactions

Radioactivation can only be performed by means of nuclear reactions. These reactions occur when nuclei are bombarded with elementary particles such as protons, deuterons, α-particles, neutrons etc.

The probability for a nuclear reaction increases if the bombarding particle can approach the bombarded nucleus very closely. Due to the repulsive forces bombarding particles should therefore be accelerated to very high energies. Neutrons however, having no charge, can approach the bombarded nucleus very closely and are therefore especially indicated for activation processes. In practice however other bombarding particles can be used, and in some special cases are to be prefered.

2. 1. Nuclear reactions with Neutrons

Most of the activation analyses are performed by neutron bombardment. Different reactions may

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occur with different neutron energy. Neutrons obtained in accelerators and reactors are high-energetic or fast neutrons. By elastic collision with nuclei of a so-called moderator substance their energy is reduced by dissipation, until thermal neutrons are obtained (0.025 ev). These thermal neutrons give rise to reactions of the type (n.γ):

$$\underset{Z}{\overset{A}{X}}+\underset{0}{\overset{1}{n}}\longrightarrow \underset{2}{\overset{A+1}{X}}+\gamma+\Delta E \tag{2}$$

In this type of reaction, the isotope formed is a radioactive isotope formed is a radioactive isotope of the bombarded element. With fast neutrons reactions may occurof the (n,p) or (n,α) type:

$$\underset{Z}{\overset{A}{X}}+\underset{0}{\overset{1}{n}}\longrightarrow \underset{Z-1}{\overset{A}{Y}}+\underset{1}{\overset{1}{H}}+\Delta E \tag{3}$$

$$\underset{Z}{\overset{A}{X}}+\underset{0}{\overset{1}{n}}\longrightarrow \underset{Z-2}{\overset{A-3}{Y}}+\underset{2}{\overset{4}{He}}+\Delta E \tag{4}$$

A rather special case is this of the fission reaction, in which heavy nuclei such as uranium nuclei fall apart into two pieces under the influence of neutron bombardment, liberating at the same time an excess of neutrons.

This neutron excess is of uttermost importance for reactor technology, as it allows the chain reaction to proceed. Attention should be drawn to the fact that in the case of (n,p), (n,α) and (n,f) reactions, transmutation takes place. The radioisotopes thus formed are carrier-free: each atom is radioactive, and the specific activity (activity per unit of weight) is very high.

2. 2. Neutron Sources

It is possible to obtain about 10^7 n.sec^{-1} c^{-1} with radium beryllium sources using the reaction Be^9 (α,n)C^{12}, the α particles being contributed by Ra-226. The high price of radium however makes this procedure rather prohibitive. Antimony-Beryllium sources are less expensive. Sb^{124} produces the photons used in the reaction: $Be^9(\gamma,n)Be^8$.

The neutrons are produced in a ratio of about 3×10^6 neutrons per second and per curie of Sb^{124}. Stronger neutron sources can be obtained with different accelerators, at shown in Table I.

TABLE I.—Accelerators as neutron sources

Neutron Generator	Energy of the obtained neutrons	Intensity of beam	Reaction	No. of neutrons n. sec^{-1} uA^{-1}
Cyclotron	14 MeV	100 μA	$Be^9(d,n)B^{10}$	10^{11}
Van de Graaff Accelerator	2 MeV	50 μA	$Be^9(d,n)B^{10}$	10^7
Cockroft-Walton Accelerator	0.5 MeV	1 mA	$T^3(d,n)He^4$	10^8
Linear Accelerator	30 MeV	10 μA	U(e,f)	10^{12}

The most intense neutron sources are however obtained in nuclear reactors, where neutron fluxes of 10^{12}n.cm^{-2}. sec^{-1} are commonly available, and sometimes fluxes of 10^{15}n.cm^{-2} sec^{-1} and more can be obtained. These neutrons are liberated by the fission process of uranium.

The flux gradient in nuclear reactors is important: the flux increases strongly towards the centre and the ratio of slow neutrons to fast neutrons(the so called cadmium ratio) increases towards the periphery of the reactor. By a judicious choice of the cadmium ratio it is thus more or less possible

to adopt the neutron energy to the specific purpose under consideration.

2. 3. Nuclear reactions with charged particles and photons

Most of the activation analysis work is carried out by neutron irradiation. In some specific cases however, when nuclear data are unfavorable other elementary particles or photons are used.

Irradiation with intense gamma sources for instance was used for the determination of beryllium with the 2.11 MeV γ rays from Sb^{124}:

$$Be^{9}(\gamma,n)_{2}He^{4}$$

The liberated neutrons were counted with a BF_3 detector. In a similar way the following reactions were used in quantitative determination:

$$H^{2}(\gamma,n)H^{1}$$
$$C^{12}(\gamma,n)C^{11}$$
$$N^{14}(\gamma,n)N^{13}$$
$$O^{16}(\gamma,n)O^{15}$$
$$F^{19}(\gamma^{c}n)F^{18}$$

Irradiation with α rays gives rise to reactions as:

$$Be^{9}(\alpha,\alpha\ 2n)Be^{7}$$
$$B^{10}(\alpha,n)N^{13}$$
$$C^{12}(\alpha,\alpha\ 2n)C^{11}\ \text{etc.}$$

With deuterons, some interesting determinations could be made:

$$O^{16}(d,n)F^{17}$$
$$S^{30}(d,p)Si^{31}$$
$$C^{12}(d,p)N^{13}$$

Finally protons and tritons can be used for activation work:

$$N^{17}(p,\alpha)C^{11}$$
$$O^{16}(t,n)F^{18}$$

In this way it was possible to analyse for elements for which neutron irradiation techniques could not give satisfactory results.

2. 4. Quantitative aspect of activation analysis

If a stable nucleus is bombarded with elementary particles, the number of radioactive particles formed per unit of time, can be represented by:

$$\frac{dN^{*}}{dt}=\sigma.\ N.\ f$$

where N=number of inactive nuclei

f=flux of bombarding particles in n.cm.$^{-1}$sec.$^{-1}$.

σ=cross section, expressing the probability for the reaction to go through. unity=10^{-24} cm =barn

The radioisotopes formed start desintegrating immediately:

$$\frac{dN^{*}}{dt}=\sigma.\ N.\ f-\lambda N^{*}$$

where λ=desintegration constant=$\frac{0.693}{T^{1}/_{2}}$

$T1/2$=half life value

After integration for a time the relation becomes:

$$N^* = \frac{f.\sigma.N}{\lambda}\ (1-e^{-\lambda t}) \tag{8}$$

The number of desintegrations, or activity in given by $At = N\lambda$

and:

$$At = f.\sigma.N.(1-e^{-\lambda t}) = f.\sigma.N(1-e^{*\frac{0.693t}{T\,1/2}}) \tag{9}$$

$$= f.\sigma.N.S \tag{10}$$

S=saturation factor

If irradiation is carried out for a time $t = T1/2$, $t = 2T1/2$.....the value of S becomes 0,50; 0,75;.....Little or no activity is thus build up after an irradiation time 2 to 5 times the half life.

For analytical purposes, it is interesting to know results expressed in grams.

If we consider that $\frac{g}{M} = \frac{N}{N_{AV}}$ (11)

g=weight of target material

M=molecular weight of target material

N_A=number of Avogadro=6.02×10^{23}

there:

$$g = \frac{At.\ M}{f.\sigma.N_{AV}.S} \tag{12}$$

A final correction factor θ has to be introduced for the% abundance of the isotope under consideration in the target material:

$$g = \frac{At\ M}{f.\sigma.N_{AV}.\ S.\theta.(e^{-\frac{0.66\,t'}{T^1/_2}})} \tag{13}$$

If t'=time elapsed between the end of irradiation and the begining of the counting. This relation allows calculation of sensibility in grams for different elements, if f,σ,θ, are known and if we suppose that $At=1$ count per second can be detected.

Table II summarizes some calculated detection sensibilities. It appears that for many elements the sensibility is greater by a factor up to 10^3 as compared to conventional analysis procedures.

TABLE Ⅱ.—Sensitivity of activation analysis

Isotope	Half life	Sensitivity limit in g	Isotope	Half life	Sensitivity limit in g
Dy^{165}	2.3 h	10^{-12}	Na^{24}	15 h	10^{-10}
Eu^{152m}	9.2 h	10^{-12}	Cs^{134}	2.3 y	$5x10^{-10}$
Au^{198}	2.7 d	$5x10^{-12}$	Co^{60}	5.3 y	$5x10^{-10}$
In^{116}	57 m	10^{-11}	P^{32}	14.3 d	$5x10^{-10}$
Mn^{56}	2.6 h	10^{-11}	Rb^{86}	18.6 d	$5x10^{-10}$
As^{76}	26.5 h	$5x10^{-11}$	Ba^{139}	85 m	10^{-9}
La^{140}	40 h	$5x10^{-11}$	Hg^{203}	47.d	10^{-9}
W^{187}	24.1 h	$5x10^{-11}$	Cl^{38}	37.3 m	$5x10^{-9}$
Cu^{64}	12.8 h	10^{-10}	Ba^{140}	12.8d	$5x10^{-9}$
Ga^{72}	14.1 h	10^{-10}	Mo^{99}	68.h	10^{-8}
Ta^{182}	111.d	10^{-10}	Ni^{65}	2.6h	10^{-8}

Sr^{89}	50 d	10^{-7}	Cr^{51}	27.8 d	10^{-7}
Ca^{45}	164 d	10^{-7}	S^{35}	87.1 d	$5x10^{-7}$

3. Sample Irradiation

In practive it is very difficult to obtain exact values for σ, f, θ and At. For this reason he relative irradiation technique, as described in the introduction, is prefered. A standard sample of known composition is irradiated under identical conditions as the unknown sample.

After irradiation the weight of the unknown is calculated from the activities ratio. Irradiation takes place in polyethylene or silica vials, depending upon irradiation time or temperature conditions in the irradiation facility.

4. Sample treatment after irradiation

After irradiation the induced activity of the element under consideration must be measured selectively against a heavy background activity from the matrix material. Chemical separation of the element can be carried out after addition of inactive isotopic carrier element. This carrier enables conventional analysis procedures on semi-micro scale.

Techniques must not be quantitative, as a final yield determination allows correction to be made for losses during the purification steps. The final preparation should however be radiochemically pure.

In the non destructive techniques, the element is measured selectively by purely instrumental techniques: composite decay-curve analysis, β-absorption techniques and γ-ray spectrometry.[5]

5. Sources of errors

The activation analysis technique is subject to the errors common to all radiochemical techniques, such as errors caused by the apparatus, counting geometry and statistical character of the desintegration process.

Several other sources of errors are more specifically to be attributed to the activation analysis process:

5. 1. Variations in neutron flux

The neutron flux decreases quickly in function of distance to the reactor core: Experimental setups and changes in fuel element disposition may furthermore create flux inhomogenities. By using a relative irradiation method as described before, these sources of errors can be eliminated.

5. 2. Neutron absorption by the wrapping material

It is advisable to wrap all specimens and standards in the same type of wrapping material, to elimimate preferential neutron absorption.[6]

5. 3. Neutron absorption by the sample: self-shadowing effect

The mean flux absorbed by a sample is sometimes lower than the flux of bombarding particles. This flux attenuation, caused by neutron absorption by the sample itself, can often be neglected in reactor irradiations, as sample size can be kept small due to the high fluxes available.

In the case of material with a high absorption cross section, or in irradiations of large samples,

the neutron shadowing can lead to important errors. This effect can be eliminated by the use of very thin samples, by dilution of the sample with an inert material that does not absorb neutrons, or by the use of the method of the internal standard.[7]

5. 4. Neutron energy: secondary reactions

Thermal neutron irradiation gives rise to (n,γ) reactions. If a mixed flux is used, containing fast neutrons,some (n,p) and (n,α) reactions may occur. These can be sources of serious errors, as shown by the following example. The determination of manganese is based upon the reaction Mn^{55} (n,γ) Mn^{56}.

In a matrix containing large quantities of iron and cobalt, the following reactions give positive errors:

$$Fe^{56}(n,p)Mn^{56}$$
$$Cg^{59}(n,\alpha)Mn^{56}$$

Irradiation should be carried out in a thermal neutron flux.

6. Advantages and Disadvantages of Radioactivation Analysis

6. 1. Advantages

a. Very sensible method for many elements.
b. No contamination problems after irradiation.
c. Addition of carrier allows manipulation by conventional chemical procedures.
d. Selectivity: the isolated element can be identified by chemical and radiochemical means. It is possible to use non-destructive instrumental techniques in many cases.

6. 2. Disadvantages

a. Irradiation facilities are not allways available.
b. Some elements as H,O,C,.....are difficult to determine due to their unfavorable nuclear data.
c. Induced activity in the matrix material may make processing of the samples difficult or impossible.

7. Applications of Activation Analysis in Clinical and Biochemical Analysis

Activation analysis can play an important role in clinical and biochemical chemistry for analysis of inorganic constituents. The sensibility of the method is great for many elements, and sample size can be kept to a minimum. A summary of activation analyses on biological material is given in table III.

TABLE Ⅲ.—Activation analyses on biological material

Element or subject	Matrix material	Author	Reference
General	Drinking water	Blanchard et al.	8
〃	Biochemistry	Benson	9
〃		Borg	10
〃		Bowen et al.	11
〃		Druyan et al.	12
〃	Marine organisms	Fukai	13
〃	Blood	Hutchinson	14

Secondary reaction	Tissue	Kaiser	15
General	Biochemistry	Lenihan	16
〃	Clinical applications	Lenihan et al.	17
〃	Biology	Loveridge	18
〃	Biological material	Tobias et al.	19
Na-K	Biological material	Pijck et al.	20
Na	Bone tissue	Druyan et al.	21
Na	Urine	Odeblad	22
Na-P	Bone marrow	Odeblad et al.	23
Na-K	Nervous tissue	Keynes et al.	24
Na-K-P	Muscle tissue	Reiffel et al.	25
Na-K-P	Biological Material	Bowen	65
Na	Blood	Salmon	22
Na-P	Bone tissue	Sato et al.	27
Na	Serum	Spencer et al.	28
Na-K	Serum	Spencer et al	29
K	Blood	Wahler et al.	30
K	Blood	Pauly	31
Zn	Blood	Banks et al.	32
Zn	Biol, material	Tupper et al	33
Cu	Biol. material	Pijck et al	34
Cu, Cr, Zn, Co	Serum	Pijck et al.	35
Cu, Cr, Zn, Co	Biol. material	Pijck	36
Cu,Zn	Biol. material	Bowen	37
Cu	Blood	Szekely	38
Au	Blood	Purser	39
Au	Biol. material	Gibbons	40
As, Au, Co,	Biol. material	Dale	41
As	Biol. material	Smales et al.	42
As	Biol. material	Smith	43
Mn	Biol. material	Bowen	44
Cl	Muscle tissue	Bergstrom	45
Cl, Br, I	Biol. material	Bowen	46
Ba, Sr	Biol. material	Harrison et al.	47
Sr,	Biol. material	Loveridge et al.	48
Ga	Biol. material	Morris et al.	49
Ga-Mo	Biol. material	Bowen	50
Ti	Biol. material	Kim	51
Tc	Biol. material	Fukai	52
W	Biol. material	Bowen	53
General	Marine organisms	Fukai et al.	54
Au	Biol. material	Müller	55
Co	Biol. material	Tobias et al.	56
Rare earths	Biol. material	Brooksbank et al.	57
As, Hg	Teeth	Nixon	58
I	Proteins	Leddicotte et al	59
Sr	Biol. material	Sowden et al.	60

some of the more recent personal experiments well be treated in detail below.

7. 1. Determination of Na and K in biological material

Na and K occur in rather large concentrations in biological material. If however only very small samples are available (punctions, ear-liquid,.....) a very sensible technique has to be used. A

method was developed, using samples between 1 and to 10 μl.[61] The samples were blood serum and ear liquid of avias.

In a first technique, samples of about 1μl are irradiated in silica capillaries and simultaneously irradiated with standard Na and K solutions.

After irradiation the silica vials are crushed in the counting vial, and Na is determined by γ spectrometry, the bias being set to exclude the K components. K is then separated as tetraphenyl boron salt or as dipicrylaminate and measured through absorbers, calculated to eliminate the Na β-components. The method was controled with standard Na and K samples and proved to be accurate and reproducible.

Results are summarized in Tables IV and V.

TABLE Ⅳ.—Activation analysis of standard Na-K samples. Sample size: μl. Results are mean from 10 experiments and expressed in μg/mg

series No	Na added	Na found	K added	K found
1	2,50	2,43 ±0,19	0,250	0,239±0,040
2	2,50	2,53 ±0,10	2,50	2,51 ±0,08
3	0,250	0,259±0,014	2,50	2,51 ±0,16

TABLE Ⅴ.—Activation analysis of Na and K in blood serum (μg/mg)

serum No	element	Mean value	No of experiments
1	Na^+	3,21±0,14	15
1	K^+	0,27±0,02	9
2	Na^+	3,57±0,17	8
2	K^+	0,25±0,03	6

A second technique uses samples of 5 μl which pipetted together with Na and K standards on Whatman No. 1 paper strips. The strips are irradiated, cut into fragments and analysed.

Sodium is determined γ-spectrometrically by discriminative counting, and potassium is counted under a G. M. counter using absorbers to eliminate the less energetic β rays from Na^{24}. Corrections are made for the paper blancs. This rapid method gives accurate and reproducible results, as shown in table VI.

TABLE Ⅵ.—Analysis of Na^+ and K^+ in blood serum; paper strip technique. Results, in μg/mg are mean values of 10 determinations. Values given as ± are standard deviations.

Sample	Sodium	Potassium
1	3,22±0,04	0,425±0,021
2	3,16±0,12	0,463±0,061
3	3,05±0,13	0,667±0,034
4	3,36±0,23	0,685±0,113
5	3,42±0,21	0,612±0,082
6	3,23±0,25	0,647±0,078

7. 2. Determination of Cu, Cr, Zn and Co in blood serum by activation analysis

The determination of trace quantities of Cu, Cr, Zn and Co in blood serum and other biological material by activation analysis is discussed in recent publications.[35] [34]

After mineralization of the organic matter with a mixture of acids H_2SO_4, $HCeO_4$-HNO_3(1:1:3) copper is selectively extracted with 2-2'-dichinolyl(cuproine).[62] [63] Chromium is distilled under the form of chromylchloride CrO_2Cl_2.[64] Zinc was separated by classical H_2S system analysis, seletively extracted with methyldioctylamine in xylol and finally precipitated as $ZnHg(SCN)_4$. A simplified method was used for the determination of trace zinc in homaeopathic triturations.[66]

Cobalt was determined by extraction with β-nitroso-α-naphtol in citrate medium. Results are summarized in table VII.

TABLE Ⅶ.—Activation Analysis of Cu, Zn, Cr, Co. in Biological Material

Element	Matrix material	Results	No of determinations
Cu	Blood serum	164.0±0.8 μg%(=μg/100 g)	6
Cu	Blood serum	165.0±1.3 μg%	6
Cu	Blood serum	165.0±3.2 μg%	6
Cu	Hair(red brown)	1.69±0.04 μg/mg	6
Cu	Hair(dark brown)	2.18±0.03 μg/mg	6
Cu	Hair(grey black)	2.57±0.05 μg/mg	6
Cu	Hair(ashen)	1.04±0.05 μg/mg	6
Cu	Hair(light brown)	1.08±0.04 μg/mg	6
Cu	Hair(dark bown)	1.80±0.04 μg/mg	6
Cu	Hair(dark brown)	1.62±0.04 μg/mg	6
Cu	Hair(red brown)	1.98±0.05 μg/mg	6
Cu	Plant material	4.18±0.11 μg/100mg	7
Cu	Plant material	4.15±0.03 μg/100mg	5
Cr	Blood serum	20.8±0.6 μg%	6
Zn	Blood serum	226.7±2.3 μg%	7
Co	Blood serum	25.9±0.5 μg%	8

7. 3. Activation Analysis in Dental Science

The role of trace elements in normal tooth growth is considered to be very important. Analysis by conventional methods can only be performed on pooled tooth material, whereas activation anlaysis gave good results on single tooth samples. As and Hg were determined with great accuracy[58] and activation analysis could shed light on the controverse about the toxicity of amalgam fillings. The presence of V, suspected to play a role in tooth grow and decay, could futhermore be substantiated activation analysis.

7. 4. Miscellaneous applications of activation analysis in biology

Very little is known about the biochemical behaviour of the rare earths. These elements have good activation-cross-sections and can be determined with great sensibility by activation analysis. Combined with ion-exchange techniques, Er, Tm and Yb were determined in this way in bone tissue.[57]

In a similar way, interesting data could be obtained about the role of Ni and Al in biological matter.

By means of activation analysis it has been possible to prove an accelerated uptake of cobalt by the nucleus of cancerous cells.

Distribution of radio-gold, given under colloidal form in cancer theraphy, has been controled by activation analysis of tissue particles after complete decay of the injected gold.[55] This enabled

calculation of the irradiation doses received by the patient.

Concluding with table VIII, summarizing some trace element determinations on biological material, it is shown there that sensibility of radioactivation analysis is indeed very great and neatly exeeds the sensibility of conventional analysis.

TABLE VIII.—Activation Analysis of Biological Material

Element	Concentration found (ppm)	Sensibility limit (ppm)
Sb	0.5—1.0	0.005
As	0.005—1	0.001
Br	1—10	0.001
Cd	1—5	0.01
Cs	1—10	0.05
Co	0.1—1	0.05
Cu	0.1—700	0.05
I	1—10	0.05
Ni	0.5—2	0.1
K	100—1000	0.02
Rb	10—100	0.1
Se	0.001—10	0.001
Ag	0.1—1	0.1
Na	10—10000	0.007
Sr	6.5—30	0.5
Te	10—100	0.2
Zn	1—1000	0.02
Zr	1—10	0.2

SUMMARY

The theoretical bases and quantitative aspect of radioactivation analysis are discussed in detail. Sources of errors and application possibilities are shortly commented. The method is highly sensitive and thus particulary indicated for trace analysis or for determinations on very small samples. A few representative examples are treated more in detail. It appears that quantitative and reproducible results can be obtained. Attention is drawn to some biochemical problems which were solved or could be solved by activation analysis techniques.

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