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Letter to editor

Calculations in nuclear medicine — application of free online software

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Abstract

Modern nuclear medicine frequently needs to be supported by software for calculations. A self-designed free-accessible online tool named "Calculator" is presented. It can be used from the web-site www.nuk.bieganski.org, option "Calculator". The programs offer: calculations of quantity of a radionuclide after a time (equation of simple radioactive decay), quantity of the second and third nuclide in the decay chain (successive radioactive decay, computation with Bateman equations and their limits), converting of activity units as well as of activity of a radioactive substance into its mass and vice versa, and calculations related to radionuclide therapy (radionuclide uptake, effective half time and activity needed for therapy). Mathematical and historical backgrounds of the algorithms used are shortly discussed in this work.
KEY words: simple decay, successive decay, Bateman equation, effective half time, delivered radiation dose, radionuclide therapy, computation

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Introduction

Nuclear medicine belongs to the most dynamically developing branches of medicine. Optimization of diagnostics and therapy with radionuclides by deploying recent achievements requires application of software for performing calculations. A self-designed tool for such calculations, named "Calculator", is presented. From known, commercially accessible tools designed for similar purposes, it differs that, among others, it is online- and free-accessible.

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To access the "Calculator", one has to go to the web-site of our Department (http://www.nuk.bieganski.org/) first. Unless your language is Polish, you have to choose English; the programs are accessible in these two languages. Then you can choose the option "Calculator" from the menu (green buttons, left side). The "Calculator" is accompanied by short manuals and examples of its use.

Simple radioactive decay

The activity of a nuclide 1, i.e., the rate of the radioactive decay (A_1), is directly proportional to the amount (number of atoms) of the nuclide and its decay constant (λ_1):

$$A = \lambda_1 N$$

The simple decay equation, i.e., the equation determining the number of atoms of the nuclide 1 after time t ($N_{t(1)}$), when the number of atoms at the beginning (t=0) is known ($N_{0(1)}$), is:

$$N_{t(1)} = N_{0(1)} e^{-\lambda_1 t}$$

A similar equation can be applied for calculation of the activity of the nuclide 1:

$$A_{t(1)} = A_{0(1)} e^{-\lambda_1 t}$$

If the time t in the formulas is completed with a negative number, it will be possible to calculate the number of atoms or activity, respectively, before the time, in which the number or activity is known. In this way, one can calculate, for example, the activity of iodine capsule before the time of calibration.

Because the half times of the nuclides ($T_{1/2(1)}$, time, after which the amount of the radioactive nuclide diminishes two-fold) are more useful than the decay constants, the equations can be written as:

$$N_{t(1)} = N_{0(1)} 2^{-t/T_{1/2(1)}}$$

and

$$A_{t(1)} = A_{0(1)} 2^{-t/T_{1/2(1)}}$$

Time, after which the nuclide would have decayed totally, if the decay process had have constant rate (if the activity had been the same as at the beginning throughout the entire time), is called

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mean lifetime (τ). The relation between the mean lifetime, decay constant and half time is:

$$\tau_1 = \frac{1}{\lambda_1} = \frac{T_{1/2(1)}}{\ln 2} \approx 1.442695 \cdot T_{1/2(1)}$$

Successive radioactive decay

The term "Successive radioactive decay" describes a decay of a nuclide 1, which gives rise to nuclide 2, which is also radioactive (and decays further to 3). The reaction equation is as follows:

nuclide 1 → nuclide 2 → nuclide 3 → ... .

The problem of quantity of the second and further daughter-nuclides in the radioactive chain was solved first by an English mathematician Harry Bateman (1882–1946) in 1910 [1]. The formulas describing the quantities are called Bateman-equations. Such a formula can be derived for any member of the chain given [2]. The complexity of the algebraic functions limits their use almost exclusively to computers.

The general equation for derivation of the formula for the number of atoms of the i-th nuclide is:

$$N_{t(i)} = N_{0(1)} \cdot \left(\prod_{l=1}^{i-1} \lambda_l \right) \cdot \left(\prod_{g=1}^{i-1} f_{(g \to g+1)} \right) \cdot \sum_{j=1}^{i} \frac{e^{-\lambda_j t}}{\prod_{k=1, k \neq j}^{i} (\lambda_k - \lambda_j)}$$

where

$f_{(g \to g+1)}$ — branching ratio of the g-th nuclide (i.e., the ratio of the g-th nuclide, which gives rise to the (g+1)-th nuclide; the remainder decays in a different way). It is also assumed that the amounts of all the nuclides in the chain (except for the nuclide 1) are zero at the beginning.

The general equation for the activity of the i-th nuclide is:

$$A_{t(i)} = A_{0(1)} \cdot \left(\prod_{l=2}^{i} \lambda_l \right) \cdot \left(\prod_{g=1}^{i-1} f_{(g \to g+1)} \right) \cdot \sum_{j=1}^{i} \frac{e^{-\lambda_j t}}{\prod_{k=1, k \neq j}^{i} (\lambda_k - \lambda_j)}$$

It should be emphasized, however, that all the nuclides in the chain must have different decay constants (i.e., different half times). Otherwise, the derived formula becomes incalculable because of zero in the denominator.

The derivation of the formula for the number of atoms of the second nuclide in the function of time is:

$$N_{t(2)} = N_{0(1)} f_{(1 \to 2)} \frac{\lambda_1}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

If the number of atoms of the second nuclide is higher than zero at the beginning, one must add to the above formula the number of atoms, which remains after decay of this amount of the second nuclide after the given time:

$$N_{t(2)} = N_{0(1)} f_{(1 \to 2)} \frac{\lambda_1}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t}) + N_{0(2)} e^{-\lambda_2 t}$$

Analogously, the derivation of the formula for the activity of the second nuclide is:

$$A_{t(2)} = A_{0(1)} f_{(1 \to 2)} \frac{\lambda_2}{\lambda_2 - \lambda_1} (e^{-\lambda_1 t} - e^{-\lambda_2 t})$$

For the situation, in what $N_{0(2)}=0$, the time, after which the amount of the second nuclide reaches its maximum ($t_{max(2)}$), can be additionally calculated as the zero-point of the derivative of the above function:

$$t_{\max(2)} = \frac{\ln(\lambda_2 / \lambda_1)}{\lambda_2 - \lambda_1}$$

For another situation ($N_{0(2)}>0$), the appropriate derivative becomes a multistep exponential equation, which cannot be solved for time by use of analytical methods. Therefore, the time of maximum for such a case, as well as for a further nuclide in a chain, can be approached only by use of a successive approximation (iterative) method.

In theoretical cases, in which the decay constants of all the nuclides in the chain are the same, the general equation is:

$$N_{t(i)} = N_{0(1)} \frac{1}{(i-1)!} \left(\prod_{g=1}^{i-1} f_{(g \to g+1)} \right) \lambda^{i-1} t^{i-1} e^{-\lambda t}$$

The maximal amounts of the nuclides are reached after the time $t_{max(i)}$:

$$t_{\max(i)} = \frac{i-1}{\lambda}$$

(on condition that there is present only nuclide 1 at the beginning).

The derivation of the formulas for the number of atoms and activity of the second nuclide in such a case is:

$$N_{t(2)} = N_{0(1)} f_{(1 \to 2)} \lambda t e^{-\lambda t}$$

and

$$A_{t(2)} = A_{0(1)} f_{(1 \to 2)} \lambda t e^{-\lambda t}$$

respectively.

The derivation of the formulas for the third nuclide in all possible cases of the lambdas is more complicated. The formulas are given in Table 1.

Similar equations can be used for purposes other than radioactive decay, as pharmacokinetic models [3]. Quantities (concentrations, activities) of a radiopharmaceutical in an organ can also be approached by similar formulas, as described below.

Calculation of (radio)nuclide uptake

The determination of uptake of a radiopharmaceutical belongs to the most important and, sometimes, very challenging tasks of quantitative nuclear medicine. To get the value of the radionuclide uptake, one needs to know the quantity (practically: measure-value) of the radionuclide before its administration (the "100%-value") and the quantity (measure) of the nuclide in the patient; obviously, both measures must be performed using the same technique. Especially the measure of the patient should be background-corrected; otherwise, the result will be overestimated. There are several techniques for estimation of the background, especially in planar imaging. One of them is to create the first region of interest (ROI) over the organ measured and the second in a close vicinity of the organ. To get the background-corrected value of the radionuclide uptake, one should subtract the (ROI-area-corrected) value of the background from the organ value and divide the result by the radionuclide value:

Table 1. The Bateman equations and their limits for the number of atoms ($N_{3(t)}$) and activity ($A_{3(t)}$) of the third nuclide in the decay chain after time t, when all three half times are the same, or two of the three half times are the same and the third is different, or all three half times are different. It is assumed that the amounts of the second and third nuclides at the beginning are equal to zero

Assumptions	Number of atoms (N)	Activity (A)
$\lambda_1 = \lambda_2 = \lambda_3$ $\lambda_1 = \lambda$	$N_{t(3)} = N_{0(1)} \frac{1}{2} f_{(1\to2)} f_{(2\to3)} \lambda^2 t^2 e^{-\lambda t}$	$A_{t(3)} = A_{0(1)} \frac{1}{2} f_{(1\to2)} f_{(2\to3)} \lambda^2 t^2 e^{-\lambda t}$
$\lambda_1 = \lambda_2 = \lambda_{12}$ $\lambda_{12} \neq \lambda_3$	$N_{t(3)} = N_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_{12}^2 \left(\frac{(\lambda_3 t - \lambda_{12} t - 1) e^{-\lambda_{12} t}}{(\lambda_3 - \lambda_{12})^2} + \frac{e^{-\lambda_3 t}}{(\lambda_{12} - \lambda_3)^2} \right)$	$A_{t(3)} = A_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_{12} \lambda_3 \left(\frac{(\lambda_3 t - \lambda_{12} t - 1) e^{-\lambda_{12} t}}{(\lambda_3 - \lambda_{12})^2} + \frac{e^{-\lambda_3 t}}{(\lambda_{12} - \lambda_3)^2} \right)$
$\lambda_2 = \lambda_3 = \lambda_{23}$ $\lambda_{23} \neq \lambda_1$	$N_{t(3)} = N_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_1 \lambda_{23} \left(\frac{e^{-\lambda_1 t}}{(\lambda_{23} - \lambda_1)^2} + \frac{(\lambda_1 t - \lambda_{23} t - 1) e^{-\lambda_{23} t}}{(\lambda_1 - \lambda_{23})^2} \right)$	$A_{t(3)} = A_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_{23}^2 \left(\frac{e^{-\lambda_1 t}}{(\lambda_{23} - \lambda_1)^2} + \frac{(\lambda_1 t - \lambda_{23} t - 1) e^{-\lambda_{23} t}}{(\lambda_1 - \lambda_{23})^2} \right)$
$\lambda_1 = \lambda_3 = \lambda_{13}$ $\lambda_{13} \neq \lambda_2$	$N_{t(3)} = N_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_{13} \lambda_2 \left(\frac{(\lambda_2 t - \lambda_{13} t - 1) e^{-\lambda_{13} t}}{(\lambda_2 - \lambda_{13})^2} + \frac{e^{-\lambda_2 t}}{(\lambda_{13} - \lambda_2)^2} \right)$	$A_{t(3)} = A_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_{13} \lambda_2 \left(\frac{(\lambda_2 t - \lambda_{13} t - 1) e^{-\lambda_{13} t}}{(\lambda_2 - \lambda_{13})^2} + \frac{e^{-\lambda_2 t}}{(\lambda_{13} - \lambda_2)^2} \right)$
$\lambda_1 \neq \lambda_2$ $\lambda_1 \neq \lambda_3$ $\lambda_2 \neq \lambda_3$	$N_{t(3)} = N_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_1 \lambda_2 \left(\frac{e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} \right)$	$A_{t(3)} = A_{0(1)} f_{(1\to2)} f_{(2\to3)} \lambda_2 \lambda_3 \left(\frac{e^{-\lambda_1 t}}{(\lambda_2 - \lambda_1)(\lambda_3 - \lambda_1)} + \frac{e^{-\lambda_2 t}}{(\lambda_1 - \lambda_2)(\lambda_3 - \lambda_2)} + \frac{e^{-\lambda_3 t}}{(\lambda_1 - \lambda_3)(\lambda_2 - \lambda_3)} \right)$

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$$Uptake = \frac{patient - background}{nuclide - background}(\cdot 100\%)$$

The background can have diverse sources. For example, in planar imaging of the thyroid with iodine-131, it can result from circulating iodide (especially during a few hours after iodine-application) or from circulating radioactive thyroid hormones (especially after a few days following the administration). The background-value, in our own experience, can exceed 10% of the organ-value after one effective half time.

By substitution of the value $N_{0(1)}$ in the simple decay equation with 1 and the *t* with the time interval between the radionuclide and the patient measures, one obtains the decay factor (the fraction of the nuclide what remains after its physical decay). After division of the radionuclide uptake by the decay factor, one obtains the "nuclide uptake" (how high would be the uptake of the nuclide, if it did not undergo radioactive decay), which corresponds to the pure pharmacological processes of the (radio)pharmaceutical in the organ.

Therapy with radionuclides

Radionuclide therapy dates back to the ravine of 1930's and 1940's, when John Hundale Lawrence (1904–1991) (brother of Ernest Orlando Lawrence — 1901–1958 — the inventor of cyclotron) applied phosphorus-32 for treatment of leukemia [4]. The concept of radiotracer developed by György von Hevesy (1885–1966) paved the way for therapy with open radioactive sources [5]. The first radioiodine therapies of the thyroid were performed by the groups of Robley Dunglison Evans (1907–1995) [6–8] and Earl R. Miller (1907–1995) [9–12]. Primarily, a cyclotron-derived nuclide I-130 (half-time 12.36 h, mean beta-energy: 268 keV, gammas: 536, 669 and 740 keV) was applied for this purpose. Later, cheaper and longer-living I-131 (half-time: 8.02 days, mean beta-energy: 181.9 keV, gammas: mainly 364.5 keV) from reactor got the dominant position. Shortly thereafter, calcium and strontium nuclides (mainly Sr-89) were introduced for palliation of bone metastatic disease [13] (instead of highly myelotoxic P-32); the today popular radiolabeled (mainly with Sm-153) diphosphonates became known in 1980's [14, 15]. At present time, there are many dynamically developing possibilities of therapy with radionuclides, including peptide receptor radionuclide therapy [16] and many others.

Parallel to the radionuclide therapies, methods of its optimization were developed. The goal was to make the therapy successful by delivering of optimal radiation dose to the target organ (node, tumor, etc.) and to limit side effects caused by irradiation of normal tissues. Several strategies for calculation of the radiation doses to the target tissues as well as to non-pathologically changed organs have been proposed. The most precise method of calculation of internal radiation dose is based on the amount of energy released by particles in a given mass of target tissue; it is assumed that the range of the particles is negligible small in comparison with the diameters of the target organ (node). It can be described by the following formula:

$$D = \frac{E_{mean}}{m}\int_0^\infty A(t)dt$$

where:

D — focal radiation dose (amount of energy delivered per mass unit)
E_{mean} — mean energy of particle(s) per radioactive disintegration
m — target mass of the tissue (node)
A(t) — activity of the radionuclide in the target organ as a function of time. The integral of the function is equal to the total number of radioactive disintegrations ("cumulative activity"), what take place in the organ.

The activity of a radionuclide in an organ as a function of time can be approached by the Bateman equations, as mentioned above. Radioiodine therapy of thyroid is the most popular example of radionuclide therapy. If the iodine-131 is injected i.v. as bolus, the function of activity of the radioiodine over the thyroid can be approached by the Bateman equation for the second nuclide. If the iodine-131 is administered orally, the function is more complex and is similar to the equation for the third or a further nuclide. This function consists of an ascending branch (influx of the iodide into the organ), a peak, and a descending branch (efflux — mainly hormone — and physical decay). In further considerations, it is assumed that area under the ascending part of the curve is negligibly small in comparison with the area under the descending branch. The descending branch reflects the effective half time of the nuclide in the organ. In this way, one can derive a general formula for calculation of the necessary activity of iodine-131 (expressed in MBq) for treatment of thyroid diseases:

$$A\,[MBq] \approx \frac{24.67 \cdot D[Gy] \cdot m[g]}{U[\%] \cdot T_{(1/2)ef}[d]}$$

where:

D — focal radiation dose, which should be delivered to the tissue, expressed in greys
m — target mass, expressed in grams (since the density of the majority of tissues, including thyroid, is close to 1 g/ml, the target mass expressed in grams is almost equal to its volume expressed in ml)
U — maximal measured radioiodine uptake expressed in percent (the "peak")
$T_{(1/2)ef}$ — effective half-time of the iodine-131 in the thyroid (node) expressed in days.

This formula was first proposed by Leonidas Marinelli (1906–1974) [17, 18]. For nuclides different from iodine-131, a correction for mean kinetic energies of the emitted particles must be made. Apart from this, the "Calculator" offers also a possibility to perform a next correction related to taking into consideration of the area under the ascending branch of the time-activity curve.

The focal radiation doses for several thyroid disorders are suggested in numerous guidelines [19, 20] (and listed in the programs). The target volume must be determined by imaging techniques, preferably by ultrasonography in case of thyroid. The maximal uptake can be directly measured or extrapolated from the time-uptake curve. The effective half time will be discussed below.

Effective half time

The descending branch of the curve of the nuclide activity over the organ is almost exponential; more precisely: the longer time interval after the peak, the more exponential is the curve. On a semi-logarithmic scale, the descending branch is almost

a straight line. This simplifies the calculation of the effective half time, if many measures have been made: it can be performed using the least square method. The "Calculator" makes possible to choose these points, which are placed on or near a straight line and not to choose these, what are far from it (they result most probably from erroneous measures). It is important to remember that results placed near or, especially, before the peak should not be taken into consideration for calculation of the effective half time; otherwise, the time would be overestimated.

There is a relation of the effective half time to the physical half time of the nuclide and to the biological half time (related to pure biochemical/pharmacological processes of a radiopharmaceutical in an organ): the reciprocal of the effective half-time $T_{(1/2)ef}$ equals to the sum of reciprocals of times: physical $T_{(1/2)phys}$, and biological $T_{(1/2)biol}$:

$$\frac{1}{T_{(1/2)ef}} = \frac{1}{T_{(1/2)phys}} + \frac{1}{T_{(1/2)biol}}$$

On the basis of this equation and the calculated effective half time, one can calculate the biological half time as well as the effective half time of another nuclide in the organ. However, one should remember that the method has its limitations. If a nuclide with shorter physical half time is used to determine the effective half time of a nuclide with much longer physical half time in an organ with relatively long biological half time of the pharmaceutical (for example: iodine-123 for determination of the effective half time of iodine-131 in thyroid), the procedure can result in an unacceptably high error.

The process of calculation of the effective half time may seem engaging and time-consuming because of multiple patient-measures. There exist publications on the half times of iodine-131 in the thyroid (nodes) in various pathological states [21]. However, the published half times are only mean values. For example, typical effective half time of iodine-131 in the thyroid of a Graves-Basedow patient slightly exceeds 4 days. In the author's experience, however, there is known a female patient suffering from this disease with the measured effective half time of less than one day. If a "standard effective half time" had been used for the calculation of the administered radioiodine activity, the method would have underestimated this activity more than four-fold.

It is noteworthy that the effective half time and maximal uptake are not constant values of a subject. They can be influenced by the course of the disease itself, but also by some drugs. For example, there are known data about lengthening of the effective half time of radioiodine in the thyroid with discontinuation of antithyroid therapy, administration of lithium salts as well as of non-radioactive iodine (after administration of the radioiodine) [22]. The uptake of radioiodine by thyroid cancer cells can also be enhanced with retinoids, glycerin tributyrate [23, 24] and glitazones [25]. In cases of therapy of the thyroid and its tumors, it is of course very important to keep in mind that pre-therapeutic contamination with (non-radioactive) iodine leads to diminished uptake of the radioiodine not only by competitive inhibition of the iodine transporter (similarly to a blockade of a receptor), but also through a specific arrest of thyreocytes (phenomenon referred to as Wolff-Chaikoff-effect) [26]. An issue of changing the maximal uptake and/or effective half time by irradiation of the target tissue (even during the dosimetry measures) is controversial, but also exists [27–29]. These observations may lead to avoiding errors in radionuclide therapy and to its further optimization.

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