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Kinetic Modeling in Support of Radionuclide Dose Assessment

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In this review, we trace the origins of mathematical modeling methods and pay particular attention to radiotracer applications. Nuclear medicine has been advanced greatly by the efforts of the Society of Nuclear Medicine's Medical Internal Radiation Dose Committee. Well-developed mathematical methods and tools have been created in support of a wide range of applications. Applications of mathematical modeling extend well beyond biology and medicine and are essential to analysis is a wide range of fields that rely on numerical predictions, eg, weather, economic, and various gaming applications. We start with the discovery of radioactivity and radioactive transformations and illustrate selected applications in biology, physiology, and pharmacology. We discuss compartment models as tools used to frame the context of specific problems. A definition of terms, methods, and examples of particular problems follows. We present models of different applications with varying complexity depending on the features of the particular system and function being analyzed. Commonly used analysis tools and methods are described, followed by established models which describe dosimetry along gastrointestinal and urinary excretory pathways, ending finally with a brief discussion of bone marrow dose. We conclude pointing to more recent, promising methods, not yet widely used in dosimetry applications, which aim at coupling pharmacokinetic data with other patient data to correlate patient outcome (benefits and risk) with the type, amount, kind and timing of the therapy the patient received.

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Introduction

Radioactivity

Within a year of Roentgen's discovery of x-rays, Becquerel discovered naturally occurring radioactivity and Rutherford described the laws that govern the kinetics of radioactive transformations. Human use of radioactivity began immediately, and within a few years undesired radiation effects were noted and the need for measuring and monitoring dose was recognized. The need for guidance on the safe use of radiations led in 1928 to the formation of the International Commission on Radiation Protection (ICRP),[1] which has since coordinated the worldwide development and dissemination of radiation-protection guidelines. The methods and procedures for calculating dose developed more rapidly for externally administered radiations than for internally administered radioactivity, which only later came into increasing use. Internal dosimetry is inherently more complex, as the radioactive source moves between organs, decaying and undergoing changes that influence the local and remote dose distribution.

Tracer Models

Radioactivity provided an important advantage because, when used in minute quantities, it was able to trace the fate of labeled substances in an organism with exquisitely high sensitivity without perturbing the system. In general, a *tracer* is a label attached to a labeled substance (the *tracee*). The label (tracer) follows the labeled substance (tracee) because it has the same mechanical or chemical or biological properties. In short, a tracer must have 3 fundamental properties: (1) it must have the same phenomenological properties of the tracee, (2) it must be added to the tracee in a quantity that does

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not alter its behavior, and (3) it must be easily detected as a separate entity.

In a lighter tone, we mention an early example of the use of tracers. The fictional character Gian Burrasca,[2] well known to all Italian children, suspects that the tasty soup his boarding school serves every Friday, is prepared by rinsing the dirty dishes of the previous week; to make sure of it, he adds a few grains of aniline to each dish he has eaten from in the last few days. Sure enough, the following Friday the soup is bright red! The Hungarian physicist George de Hevesy reported a similar anecdote in which he traced the leftover food at his boarding house to hash served the following day.

More scientifically, in 1913 de Hevesy developed the tracer concept when he used the naturally occurring radioactive element ^{210}Pb (Ra D) as a tracer in chemistry studies, and in 1923 to trace the movement of ^{212}Pb in plants and 1 year later ^{210}Bi in animals.[3] When linked to biologically important molecules by means of innovative radiochemistry, these radioactive isotopes served as tracers leading to new understanding of physiological processes. For Hevesy's pioneering studies, he was awarded a Nobel Prize in 1943. After the discovery of artificially produced radioactivity in 1934 by the Joliot Curies, a wide range of radioactive elements became available from the early cyclotrons, and they were used in many pioneering biologically important investigations.

Tracers are labeled substances that are given in small amount with respect to the native substance being studied. The intent of the tracer experiment can be to learn about the metabolism of the tracee, or to achieve diagnosis. The temporal and spatial distribution of different tracers depends on the nature of the nuclide and its attached compound, how it enters the body, and the nature and state of the subject being studied. In particular for radiotracers, very small amounts of tracer are administered for diagnostic purposes, whereas larger amounts are given for treatment planning, and therapy, the latter given with the intent to change the state of the system for the patient's benefit. A recent review of tracer models is provided in Cobelli and coworkers.[4] In general, one can think of at least the following two classes of models in terms of the applications for which they are to be put.

Biological Kinetic Models

Tracer–tracee models can be considered a special case of biological kinetic models. Generally, biological models are used to simulate and to predict the behavior of a biological system in response to different changes in state: for example, the administration of drugs or other interventions. The biological applications can be very general, and the most common application involves estimation of physiologically significant parameters from limited data. Physiologically based pharmacokinetic models are an example application.[5] In this situation, one continually adjusts the model (based on differential or algebraic equations) until predictions and experimental realizations agree, usually based on some predetermined statistical criterion of goodness of fit and model adequacy. The model is considered useful until discrepancies with additional data are noted, at which point the model can be revised. A model can also be used to simulate, ie, generate synthetic data that can be compared with expectations or otherwise obtained measurements.

Dosimetry Models

Dosimetry models can be construed as a further generalization containing elements of both tracer models and biological models. The goal of models used for dosimetry studies is to achieve statistically adequate agreement between the observed experimental data and model predicted results, with the end result being useful in the calculation of radiation dose estimates to organs of the body. In this case, one identifies and uses the simplest system representation that produces such results. In summary, the principal goal of biokinetic modeling for dosimetry is to obtain the area under the time-activity curve for all organs with measured and significant uptake of the tracer. The time–activity curve would be expected to be different for different organs and different subjects and is the primary source of information about absorbed radiation in individual organs. The area under the time-activity curve, defined as the integral of the time–activity curve over some fixed time (often from zero to infinity), provides the number of disintegrations that have occurred in the measured region over the interval of integration, and is directly proportional to the cumulative dose received there. The actual dose distribution, however, may be more complicated, as the energy deposition patterns of different radiations may need to be taken into account. The integrals of the radioactivity time courses of individual organ are thus a starting point for the dose transport modeling calculations, which provide measures of the absorbed dose. The Medical Internal Radiation Dose (MIRD) Committee of the of Society for Nuclear Medicine was established in 1966 to develop methods for internal dose analysis, for their dissemination and to provide data on practices that influence their appropriate use in patients. Much information on these developments is discussed elsewhere.[6]

Data on new tracers are usually obtained initially from preclinical (ie, animal) experiments, followed by clinical experiments involving human subjects, occasionally supplemented by in vitro experiments that study specific parts of the system. The methods for analyzing biokinetic data are several and vary from the (computationally) very simple to very complex. Simple methods include direct integration of the observed data (which one may argue does not imply a model at all, but this depends on what the calculation is supposed to provide) to linear or nonlinear regression analysis of the data using an assumed functional form. More complex systems use compartment models to represent the (patho) physiology of the system and the related tracer biodistribution. In this case, the data are modeled by the solution to a system of differential equations, possibly nonlinear. Compartmental models are one of the most commonly used means of formulating and analyzing data from nuclear medicine studies. MIRD Pamphlet 12 provides a comprehensive discussion of kinetic models for absorbed dose calculations.[7] It discusses terminology, the general principles involved in

compartment modeling, with a series of examples. The discussions we present here on compartment models will use the terminology promulgated in MIRD 12. Operationally, one seeks a model with as few compartments as are needed to produce results consistent with the data, and our experience is that typically 2 to 3 compartments are sufficient. The model selection decision is often based on some parsimony criterion such as the Akaike Information Criterion[8] or the Bayesian Information Criterion.[9] A noncompartmental approach is also possible, but the outcome of this approach is highly dependent on hypotheses regarding the system under observation, as others have shown. Alternative methods exist, including integral equations methods, which we omit in favor of more computationally tractable compartment models. Next, we focus on historical and practical aspects of creating and analyzing models for use in analysis of radiation tracer dosimetry data.

A Historical Development Methodological Perspective

Radioactive Disintegration

It can be argued that the first application of compartmental models was in physics, specifically to describe radioactive decay. A review of these models is available elsewhere.[10] After the discoveries and experiments by Becquerel,[11,12] Rutherford and Soddy,[13,14] the law of radioactive decay has been formalized as

$$\frac{dX}{dt} = -K \cdot X(t) \qquad (1)$$

where $X(t)$ is the quantity of radioactive substance present at time t. The integral solution of this equation is

$$X(t) = X(t_0)e^{-K(t-t_0)}$$

where $X(t_0)$ is the initial value of $X(t)$ at time t_0.

Thus, radioactive decay is modeled as a first order process, and this has been verified independently by several experimental observations.

Physiology

Benke and coworkers[15] studied the phenomenon of nitrogen absorption by, and elimination from, the various tissues via the lung and circulation. They measured the elimination of nitrogen in human subjects breathing pure oxygen; their results could be represented by the expression

$$Y = A(1 - e^{-kt})$$

where Y is the amount of nitrogen eliminated up to time t, A is the total amount of nitrogen contained in the body at time $t = 0$, when the breathing of pure oxygen began, and k the logarithmic slope of the curve representing Y as a function of time.

Behnke and coworkers observed that the value of k decreases after the first 25 minutes; their explanation was that the nitrogen is eliminated partly from the body fluid and partly from fatty tissues, simultaneously but with different rates; during the first part of the experiment the nitrogen elimination from the body fluids is prevalent, whereas later the elimination from fatty tissues prevails. A better description of the experiment is therefore given by a multiexponential function

$$Y = B(1 - e^{-k_1t}) + C(1 - e^{-k_2t})$$

where B is the total amount of nitrogen contained in water, and C the total amount contained in fatty tissues, with $A = B + C$. In more modern terminology, we would call Y the "sum of two compartments".

Pharmacology

In 1937, Teorell[16,17] reported studies of the in vivo kinetics of drugs after various modes of administration, where the idea of compartment became a useful generalization of a state of a substance characterized by both spatial localization and chemical nature. As it is widely accepted, a multicompartmental model accounts for spatial heterogeneity by postulating the presence of different spatial locations where the substance distributes or is transformed. Teorell's equations for resorption, elimination, tissue uptake, and inactivation were first-order differential equations whose solutions describing the amounts of drug in blood and tissue as function of time are sums of exponential terms with constant coefficients. This is of course not exclusive to compartmental systems: multiexponential decays can also be interpreted as a purely data-based descriptive approach, as others have pointed out in distinguishing between "models of data" and "models of system."[18]

Tracer Kinetics

Teorell's work extended the idea of compartment from the radioactivity problem (where it describes a set of particles all with the same probability of transformation) to the physical and physicochemical problem. In a 1938 paper, Artom and colleagues[19] presented a radioactive tracer study of the formation of phospholipids as affected by dietary fat, in which they gave a more formal analysis than was provided before. Their equations are also linear constant coefficient differential equations, and have been reviewed in detail elsewhere.[10]

In the intervening decades, applications of model-based data analysis have become widespread and far too many to be counted. Our intent here is only to provide a historical perspective on the origin of the related concepts and especially on the initial intent of the pioneering work at the root of so many current efforts in the fields of systems modeling in nuclear medicine, pharmacology, metabolism, etc.

Continuous Distribution

In all examples we have shown so far, the entity under observation, be it a tracer or a tracee, was supposed to be distributed among a number (small or large, but always finite) of compartments, each one of them characterized by a function of time, *extensive* (mass) or *intensive* (concentration). This hypothesis is certainly completely confirmed by the evidence

in the case of radioactive disintegrations, because we know that in a radioactive chain one nuclide is transformed into its immediate successor without any intermediate steps (at least from a macroscopic point of view). In the biological world, the hypothesis of a finite number of compartments leads frequently, as we have shown above, to a reasonable description of the observed events, but there may be cases when this approximation is no longer valid. An obvious example is the distribution of a drug in the plasma after an IV injection: except when the elimination rate is very slow, there will always be a gradient of $c(t)$ from the site of injection to the site (or sites) of elimination.

In general, to account for the nonuniform distribution of a substance in an organ, the pertinent function $c(t)$ should be substituted by a function $c(s,t)$, where s is a spatial coordinate; s can be the one-dimensional coordinate along a narrow vessel, or a three-dimensional coordinate in a large organ. In any case, the differential equations used in the previous sections should be replaced by partial differential equation whose solution and parameter estimation is in general quite difficult, except in some special cases when the contribution of nonexchanging and exchanging vessels can be separated thanks to the available data, eg, from multiple indicator dilution. Illuminating examples are described, for example, in the work by Goresky.[20]

Compartment Models

Definition of Compartment

Formal definitions of "compartment" can be found in Sheppard,[21] Sheppard and Householder,[22] Rescigno and Segre,[23] Hearon,[24] Brownell and coworkers,[25] Berman,[26] Rescigno and Beck,[27] Jacquez,[28] Gùrpide,[29] and Siri.[30] Paraphrasing these authors, a compartment may represent either a physical location where a substance resides or a specific chemical state of the substance under study. Nuclear medicine examples vary greatly in complexity. In positron emission tomography kinetic studies,[31,32] ^{18}F-fluorodeoxyglucose (^{18}F-FDG) and ^{18}F-FDG-6P are different chemical entities which are both physically present in the intracellular space: as such, they are represented as two distinct compartments in kinetic models of ^{18}F-FDG studies. More complex models include the Berman iodine kinetics model[26] which contains thirteen compartments, of which eight comprise the thyroid space submodel. The thyroid space is modeled with a delay chain of six compartments which represent the transition between rapid and slow clearance phases of iodine transport through the thyroid. In the case of the thyroid, these transitions happen to constitute a chemical transformation in time and space.

One-Compartment Model

For practical purposes, in tracer kinetics it is sometimes convenient to use the following operational definition[33]: "A variable $x(t)$ of a system is called a compartment if it is governed by a differential equation of the type

$$\frac{dx}{dt} = -K\,x(t) + r(t), \tag{2}$$

with K constant." The constant K, as we have seen in the previous sections, may be the rate of radioactive disintegration, or the rate of elimination of a drug, or the probability of a particle passing from its present state to other possible states.[10] The equation is formalized starting from observation and is usually confirmed by independent experimental evidence, like we have mentioned above for biological models.[34-36] Of note, K is always constant in tracer systems if the tracee is in a steady state.

In general, moving beyond tracer kinetics, it is possible for the rate K to be time varying, for instance in systems that are characterized by saturative behavior. In this case, the differential equation is nonlinear and has the form

$$\frac{dx}{dt} = -\frac{V_m}{K_m + x(t)}x(t) + r(t). \tag{3}$$

Such nonlinear systems can be handled only through numerical integration. It is noteworthy to repeat that administration of a tracer, by definition, "linearizes" the system, if the tracee is at steady state; in fact if eq 3 is valid for the tracee, the tracer equation is

$$\frac{dx^*}{dt} = -\frac{V_m}{K_m + x(t) + x^*(t)}x^*(t) + r(t) + r^*(t),$$

where $x^*(t)$ is the amount of tracer present and $r^*(t)$ is its rate of recirculation. But

$$\frac{V_m}{K_m + x(t) + x^*(t)} \approx \frac{V_m}{K_m + x(t)}$$

and the right hand side ratio is constant at tracee steady state. Clearly, if a compartment is at steady state the turnover time of the tracee is constant; furthermore, tracer and tracee have the same turnover time by definition.

Eq 2 is a conservation equation (ie, conservation of mass), ie, it states that the temporal variation dx/dt of the quantity $x(t)$ present in the compartment is the difference between its rate of entry $r(t)$ and its rate of exit. This is in addition to the first order hypothesis. When comparing models such as this to data, the amount of substance in an organ cannot be directly measured, however its concentration may be available. Concentration values may be calculated by dividing both sides of eq 2 by an appropriate value for V, the volume of the compartment, providing

$$\frac{dc}{dt} = -K\,c(t) + \frac{r(t)}{V}, \tag{4}$$

where $c(t) = x(t)/V$ is the concentration of the substance in the compartment. Note that eq 4 is not a conservation equation, as has been discussed previously.[37] Volume of distribution can be calculated using the equation

$$V = \frac{D}{c^*(0)} \tag{5}$$

where $c^*(0)$ is the extrapolated value of the concentration time curve at 0, immediately after a pulse dose. However, in this case the initial volume of distribution V is not necessarily the physical volume of the compartment, as has been discussed previously.[37] Thus, the initial volume of distribution, as defined by eq 5, cannot be considered an absolute pharmacokinetic parameter.[38]

If we multiply and divide the first term of the right-hand side of eq 2 by V we get

$$\frac{dx}{dt} = -VK \cdot c(t) + r(t); \tag{6}$$

where the extensive term VK is *clearance*, *Cl*.

Explicit integration of the differential equations to reconstruct $c(t)$ is only possible in very simple cases. However, even if we don't have sufficient data to reconstruct the function $x(t)$ or $c(t)$, we can extract some partial information on the system under study, as we shall show in the next few sections.

In general, suppose that the substance or tracer under study is distributed among n compartments, but only one of them can be sampled, and that its concentration $c_1(t)$, after a bolus administration there at time $t = 0$, can be approximated reasonably well by a sum of exponential functions; then

$$c_1(t) = A_1 e^{-\lambda_1 t} + A_2 e^{-\lambda_2 t} + \cdots + A_n e^{-\lambda_n t}$$

which is also the general solution to some n-compartmental systems characterized by linear kinetics.

Modeling in Support of Radiotracer Dosimetry

Model complexity ranges from early one compartment studies designed to test red blood cell membrane permeability to Na and K ions.[39] Compartment models are adequate descriptors, easily amenable to either analytical or numerical solution for such systems. Modeling of thyroid iodine metabolism requires at least three compartments.[40] Depending on the application and the available data, 13 compartments were needed by Berman to analyze fundamental aspects of thyroid hormone metabolism. When the system being studied is extended to include pregnant females, 22 compartments were needed to include radioiodine kinetics including maternal fetal exchange.[41] Although explicit analytic methods are adequate to calculate the system parameters for 1 to 3 compartment systems, more complex models even for dosimetry usually require use of computer-based analysis tools and numerical analysis, both for calculating model predictions (*simulation*) and estimating model parameters from data (*identification*). Given limited data from individual subjects, patient specific model estimates derived from multicompartment models assume default values for many, if not most of the transport parameters. More recent techniques, such as nonlinear mixed effects models, could in principle help avoid this problem, although they also tend to be quite computer intensive.

Practical guidance on the design and analysis of experiments using modeling approaches was given by Berman in a seminal reference.[42] In it, Berman discusses factors relating to the type and class of models. The choice of models is based on the intended purpose of the model (ie, to describe the data, describe the response of a system to a stimulus, simulate the system, or to characterize changes in the system). The article outlines how computers can be used to obtain best fit solutions to the defining equations. Analysis of plasma clearance or whole body turnover data are used as examples in assessing the number of exponential terms, and hence the number of compartments needed to obtain a good fit to the data. Compartment models are then discussed in terms of model known and model unknown circumstances, with a discussion of the problems relating to the uniqueness of model solutions. Elsewhere, Berman shows how the equivalence of results from properly analyzed compartmental and noncompartmental data are essentially indistinguishable.[43,44] Di Stefano has also discussed elsewhere the properties of compartmental and noncompartmental systems and modes of analysis, and the circumstances where such approaches may give comparable results.[45,46]

Compartmental Model Examples

We will now describe compartmental models of increasing detail to illustrate the range of complexity that has been used in radiation dosimetry in the analysis of medically significant problems from nuclear medicine.

1. A simple 3-compartment model (Fig. 1) was widely used in studies to describe thyroid uptake and turnover.[47]
2. Johansson and coworkers[48] extended the iodine model

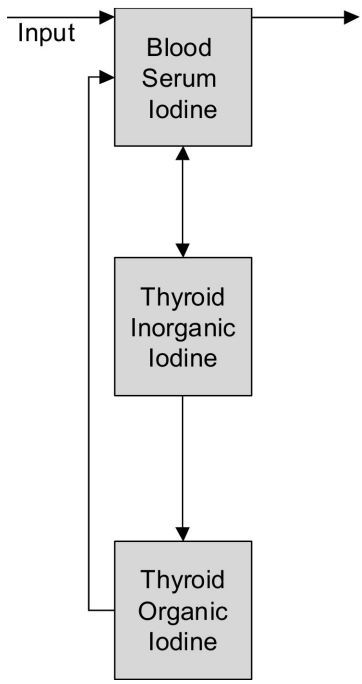

Figure 1 Schematic representation of a 3-compartment model for iodine metabolism.

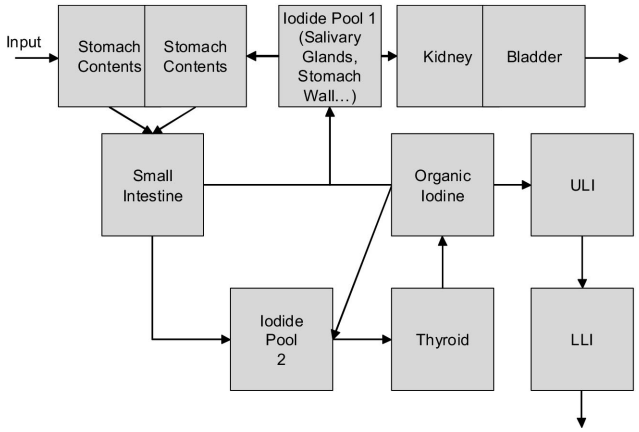

Figure 2 Schematic representation of a biokinetic model for oral intake of iodide.

to calculate dose to other iodine concentrating organs as indicated in Fig. 2. See paper for rate constants and "residence times."

3. The metabolism of the different thyroid hormones was described by Berman using an 11 compartment model (Fig. 3).
4. The need for estimates of radiation dose to the mother and fetus from large environmental releases of radioactive iodine (Chernobyl accident), led Berkovski and ICRP[49] to promulgate a more complex model (Fig. 4). Default values for many rates were chosen based on expected normal values.
5. Iron kinetics processes and dosimetry in patients in a MIRD publication in which a single model was used to represent iron transport in normal and altered disease states (Fig. 5).[50] See reference for rate constants for patients in different disease states.
6. Given interest in tumor dosimetry, a simplified model (Fig. 6), has been adapted from ICRU 67.[51]

Computer software has been of paramount importance in allowing the accurate numerical solution of physiologically realistic models and, at the same time, providing computational and statistical tools to fit such models to observations. The SAAM software has arguably been one of the first contributions in this area. In fact, the original motivation for the SAAM codes was provided by dosimetry studies. The original SAAM codes are still available using both the original command line interface[52] and a Windows-based interface termed WinSAAM.[53] In addition, a completely reengineered program allowing for solution and fitting of nonlinear compartmental models is available and is called the SAAM II project.[54] Such software programs, among others, have allowed the modeling scientists to perform the rapid and accurate calculation of amounts and rates of change in various locations of generally defined multicompartmental models. At the same time, such modeling software provides general-use tools to enforce conservation of mass and radioactivity and evaluate the total amount of radioactivity in groups of compartments and thus peripheral tissues of interest, eg, by summing over multiple compartmental amounts. We will discuss the methodology behind these and other tools in the remainder of this document.

Simple Numerical Tools Used in Routine Practice

It can be argued that the simplest measure of absorbed dose relates to the integrals from zero to infinity of the time-activity curves of a given data set. When researchers obtain preclinical or clinical data, a number of simple tools and methods are often used to obtain those integrals.

Direct Integration

One can directly integrate under the actual measured values by a number of methods. This does not give very much information about the underlying system, but it does allow one to calculate the number of disintegrations rather easily. The most common method used is the Trapezoidal Method, simply approximating the area by a series of trapezoids. An important concern with this method is the calculation of the integrated area under the curve after the last datum. If activity is clearing slowly near the end of the data set, a significant portion of the total decays may be represented by the extrap-

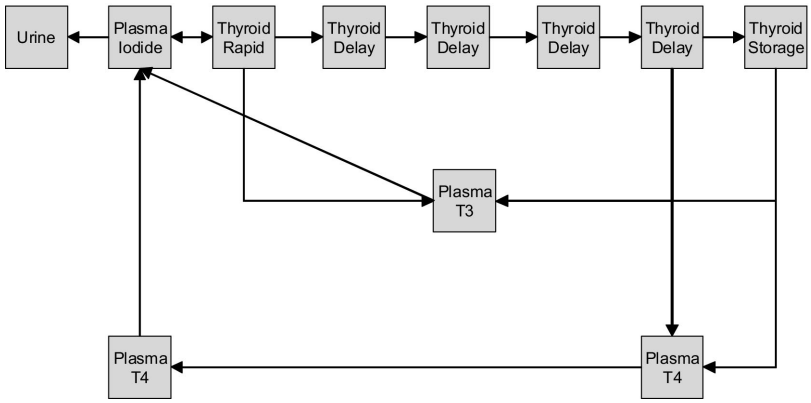

Figure 3 Schematic representation of a compartmental model for thyroid iodine metabolism. Measurements are performed in the urine, plasma iodide, T3, and T4 compartments; in addition, aggregates of the thyroid compartments are also measured.

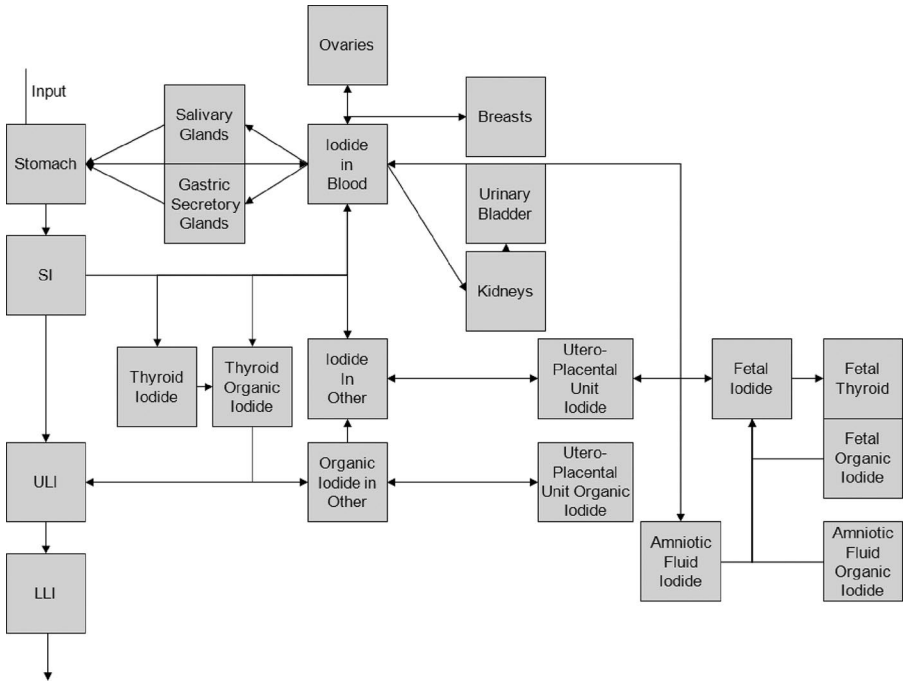

Figure 4 Schematic representation of a maternal-fetal model for iodine metabolism.

olated area under the curve remaining after the last point. A number of approaches may be used to estimate this area. The most conservative is to assume that removal is only by physical decay after the last point; another approach is to calculate the linear or logarithmic slope of the line using the last 2 or 3 points, and assume that this slope continues until the retention curve crosses the time axis. This approach also assumes that the terminal logarithmic slope is unique and relates to the rate constant(s) of the slowest compartment. No single approach is necessarily right or wrong—a number of approaches may be acceptable under different circumstances. It is generally desirable to overestimate the cumulated activity than to underestimate it, as long as the overestimation is not too severe. The important point is to clearly document what was done. A thoughtful discussion of the various possible approaches to this problem was presented by Bass and coworkers.[55]

Least Squares Analysis

An alternative to simple, direct integration of a data set is to attempt to fit smooth curves of a given shape to the data. The curves are represented by mathematical expressions which can then be directly integrated. The most common approach is to attempt to characterize a set of data by a series of exponential terms, as many systems are well represented by this form, and exponential terms are easy to integrate. In general, the approach is to minimize the sum of the squared distance of the data points from the fitted curve. The curve will have the form:

$$A(t) = a_1 e^{-b_1 t} + a_2 e^{-b_2 t} + \cdots$$

A least-squares method looks at the squared difference between each point and the solution of the fitted curve at that point, and minimizes the sum of squared differences by taking the partial derivative of this expression with respect to each of the unknowns a_i and b_i and setting it equal to zero. Once the best-fit estimates of a_i and b_i are obtained, the integral of $A(t)$ from zero to infinity is simply:

$$\int_0^\infty A(t)dt = \frac{a_1}{b_1} + \frac{a_2}{b_2} + \cdots$$

If the coefficients a_i are in units of activity, this integral represents cumulated activity (the units of the b_i are time^{-1}). If

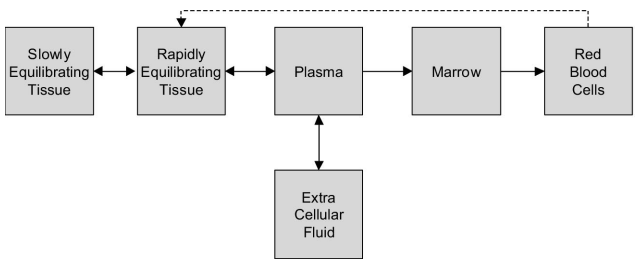

Figure 5 Compartmental model for iron transport.

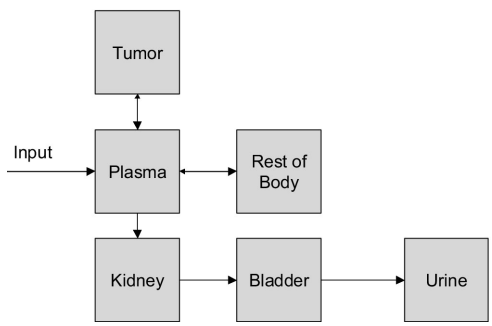

Figure 6 Simplified tumor model.

the coefficients give fractions of the administered activity, then the area represents the normalized cumulated activity (eg, Bq-h/Bq). Many computational kinetic modeling tools have been developed that are in principle useful for computing pharmacokinetic parameters for calculating absorbed dose in different tissues.[56]

More Complex Computational Tools

The main limitation of the approach we have described previously is, as we have mentioned, that no additional information is obtained about the system behavior except for inference directly based on the observations. This may be sufficient when only an estimate of radiation dose to organs in the body is desired. Under these circumstances, the use of mathematical models that summarize what is known about the system behavior can be useful to infer the biodistribution in inaccessible sites exclusively from information available in observable sampling sites. Such inference is an aspect of the engineering inverse problem,[57] and the robustness and reliability of predictions made in such sites can be tested based on statistical and system identification methods and procedures. Others have discussed in detail structural aspects of model identifiability and whether inference on remote compartments can be well posed, conditional on limited knowledge on accessible sites.[58]

Least squares, and especially weighted least squares, have been for many years the tool of choice for fitting multicompartmental models to data.[59] The advantage of weighted least squares is to provide a straightforward and formally accurate way to explicitly incorporate the knowledge (when available) that data points collected over time may be more or less precise. Knowledge of the measurement error then shapes the relative importance of the contribution of every residual (difference between model and data) to the overall weighted sum of squares. In addition, the statistical interpretation of the data weights (proportional to the data measurement error) allows for the accurate calculation of parameter confidence intervals, now available in many modeling packages. Other least squares approaches relax the assumption that the weights are calculated conditional on the measured value. Extended least squares approaches[60] have also a natural interpretation based on maximum likelihood, and use the predicted value, as opposed to the measured value, to calculate the weight for each residual in the weighted sum of squares. This minimizes the impact of noisy and scattered measurements on the calculation of the weights, and smoothes the overall weighting scheme. Extended least squares methods are also available in several modeling packages. Clearly, differing assumptions about the data weights have the potential to return different parameter estimates.[61,62] Thus, inference based on data are always conditional not only on the shape of the curve, but also on the measurement error associated with every data point on the curve.

Another factor that is relevant to the performance of parameter estimation methods is the temporal location of the samples, together with their number. Loosely speaking, the number of samples is related to the number of compartments, or separate exponential terms, while their timing is related to the exponentials' decay rates. Rapidly decaying exponentials, for example, will necessitate frequent and early sampling, while slowly decaying exponentials require fewer and more widely spaced measurements. These topics have been studied extensively elsewhere, in quantitative physiology,[59] pharmacokinetics[63] and nuclear medicine.[51,64]

Population estimates of model rate constants and exposures can be constructed by aggregating individual estimates obtained by repeated experiments in a number of individual subjects. Such aggregation can be performed by calculating arithmetic means or medians, depending on the underlying distribution and the availability of individual data. Individual estimates must be available for this method to work. Another, more recent class of methods that has found extensive application in pharmacokinetics, but not as much so far in radiation dosimetry, is the family of approximate maximum likelihood methods which is usually termed "population pharmacokinetics."[65] This is a class of nonlinear mixed effects models that explicitly represents, in addition to the functional form of the curve to be modeled, the probability distribution of its model parameters in the population of interest. Such an approach allows estimating population features with reasonable reliability, even when individual estimates are not available, or are extremely imprecise.[66]

The model building process uses the parameter estimation tools that we have described to narrow the model space to the most parsimonious, but robust, structure that the data support. This may start with a preliminary investigation of the number of exponentials in the system (for linear systems), which would dictate the number of compartments for initial model exploration. For systems which do not behave like sums of exponentials, numerical integration techniques may be employed to model the sample sites. Competing models are then tested on the basis of the reduction in measurement residual variance that they provide, in addition to parsimony criteria that penalize more complex models in favor of less complex ones. Against this background, physiological plausibility must always be taken into account, and a physiologically plausible model should be considered superior to a parsimonious, but oversimplified, one.

Special Kinetic Models Developed for Radioisotope Dosimetry Analyses

A number of kinetic models have been developed to facilitate dose calculations in several special cases. Often, models have progressed from simple to complex or from less detailed to more detailed, depending on the specific application and their intended use. An example of this is the Berkovski model for iodine kinetics for pregnant women and children who had accidentally been exposed to radiation from the Chernobyl accident and how it incorporates parameters and structures from the basic Berman model. Below we describe a series of example models that have been developed over the years for some general applications.

Urinary Bladder

Short-lived radionuclide labeled small molecules are filtered by the glomerulus and rapidly excreted; thus, kidney and bladder modeling is important to describe the kinetics of these substances. When activity is excreted from the body in the urine, the function that describes it usually consists of one or more exponential terms. Fitting observed activity levels in the urinary bladder is not helpful, because the bladder fills and empties repeatedly, and measurements are too infrequently gathered to characterize this time-activity curve. Material leaving the body is most often governed by first order processes, which mean that the retention (in the body) can be expressed as a function such as $A \cdot \exp(-\lambda t)$. Therefore, the time-activity curve for the bladder takes the form of $A \cdot (1 - \exp(-\lambda t))$, but the curve is periodically interrupted by voiding and goes to zero (or nearly zero) and then begins to accumulate again, as in Figure 7.

What is needed is a characterization of the values A and λ (in real situations there may be more than one term in the equation, but for now, let's just consider one). In a particularly ingenious derivation, Walt Snyder and colleagues[67] showed that the number of disintegrations occurring in the bladder could be given in such cases by a single equation:

$$N = A_0 \sum_i f_i \left[\frac{1 - e^{-\lambda_i T}}{\lambda_i} - \frac{1 - e^{-(\lambda_i + \lambda_p)T}}{\lambda_i + \lambda_p} \right] \left[\frac{1}{1 - e^{-(\lambda_i + \lambda_p)T}} \right]$$

Here, A_0 is the initial activity entering the body, λ_p is the physical decay constant of the radionuclide, λ_i is the biological removal constant for the fraction of activity f_i leaving the body via the urinary pathway, and T is the bladder voiding interval, assumed to be constant. If we have all the activity in the body passing out through the urinary pathway with a 1 hour half-time, for example, our f would be 1.0 and λ would be 0.693/1 hour = 0.693 hour^{-1}. Let's say we have 40% passing out through the gastrointestinal (GI) tract, and 60% through the urinary pathway, with two-thirds of the urinary clearance having a half-time of 1 hour and one-third with a half-time of 10 hours. Then f_1 would be 0.4 and λ_{b1} would be 0.693 hour^{-1}, and f_2 would also be 0.2 and λ_{b2} would be

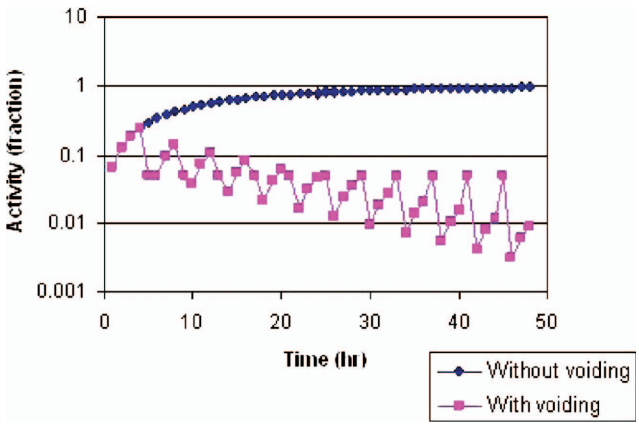

Figure 7 The influence of urinary bladder voiding schedule is shown in comparison with the urinary accumulation curve in the absence of voiding. (Color version of figure is available online.)

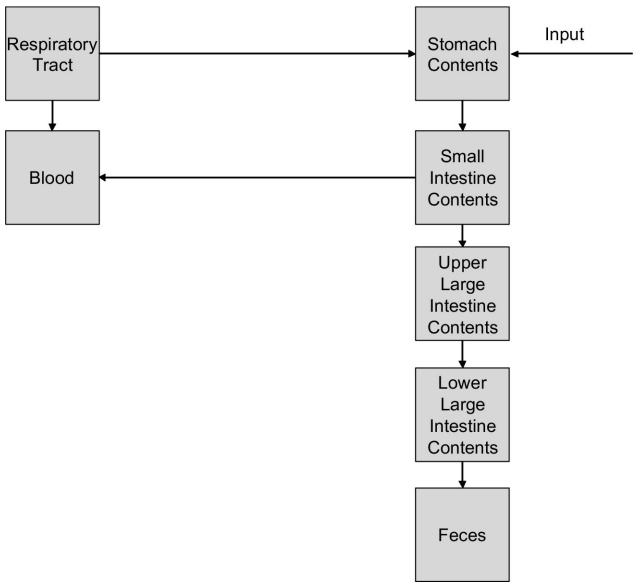

Figure 8 The components defining the pathways influencing the dose to the GI tract in the ICRP 30 model.[69]

0.0693 hour^{-1}. These parameters are not particularly hard to derive - one must either measure the total body retention or the cumulative urinary excretion and fit a function, either of the form $A \cdot \exp(-\lambda t)$ (in the former case) or $A \cdot (1 - \exp(-\lambda t))$ (in the latter case). Again, the equation may have more than one term, depending on the data observed. If there is GI excretion, this complicates the use of whole body retention data, unless intestinal activity is somehow excluded from the images. But in either case, the complication can be overcome by careful data gathering and inspection of the results.

Gastrointestinal Tract

Ingestion is a common means of intake of radioactive material, either through swallowing of material somehow introduced into the mouth or through transfer of material from the various regions of the lung system to the throat and subsequent swallowing. A standardized kinetic model of the GI tract was first proposed by Eve[68] and was adopted by the International Commission on Radiological Protection in ICRP Publication 30.[69] Four sections of the GI tract were defined (Fig. 8), having separate kinetics, with activity in the contents passing through with standard rate constants. The walls of the various sections and were treated as separate target tissues according to the ICRP 30 (Fig. 8) dosimetric system. At that time, they were not assigned any specific weighting factors for calculation of "effective dose" quantities, and were treated, if significant, as 'remainder' tissues in this calculation. In more recent recommendations of the ICRP, however, segments of the GI tract have been assigned specific risk weighting factors. A more detailed and realistic model has been recommended recently by the ICRP, named the Human Alimentary Tract (HAT) model (Fig. 9). This model has more compartments, includes some nonfirst order kinetic components, models age-dependent compartment transfer rates, treats liquid and solid materials differently, and

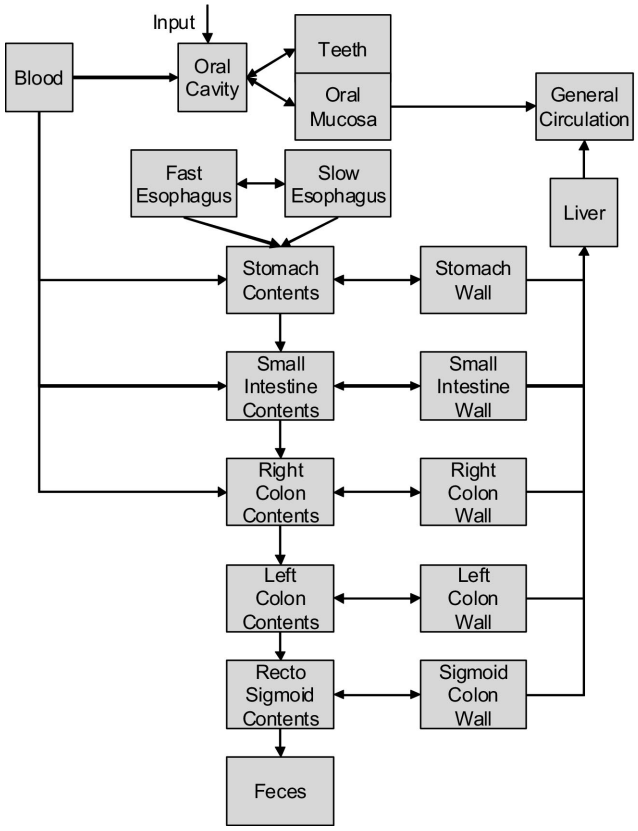

Figure 9 The components defining the pathways influencing the dose to the different segments of the GI tract are defined in the new ICRP Human Alimentary Tract Model (HAT) model.[70]

calculates doses to segments of the HAT not previously considered.[70]

Bone Marrow

Bone marrow is a highly radiosensitive, rapidly turning over hematopoietic organ. The red marrow is distributed throughout the different regions of the skeleton in a fashion that varies with age.[71] When increased uptake of radioactivity is noted in bone marrow-containing regions, different methods have been used to separate the marrow content from superimposed activity in the surrounding bone, adjacent and surrounding blood vessels.[72,73] Given the number and location of vertebrae sampled, one then estimates the fraction of total bone marrow contained in those sites based on reference man distribution values.[71] The need for bone marrow dose estimates derives from interest in estimating risk of stochastic effects (diagnostic exposures) and of deterministic effects (therapeutic exposures). These measures are also important to the physician in planning and evaluating effects of administered therapy. When the tumor-involved marrow site has been invaded by tumor, the dose to these measured regions conveys a desired effect. Lower concentrations of activity in blood which circulates through uninvolved regions convey a lower dose to normal marrow. Given an estimate of the fraction of marrow that is occupied by tumor, the dose to those regions is estimated directly from the measured uptake and the dose to the remaining fraction of the marrow is based on blood contributions. Compartment models can be used to compute marrow dose weighting these two contributions using the modeling tools described earlier, in particular by interrogating and then summing over time the contributions of several compartments in the model, even those that are not directly amenable to measurement.

When uptake is not visualized in the marrow, the most commonly-used method measures the amount of activity in the blood as a function of time, and assumes that the uptake in marrow can be related to the activity in blood:

$$[A_{\text{marrow}}] = [A_{\text{blood}}] \times RMBLR$$

where $[A_{\text{marrow}}]$ is the concentration of compound (assumed in this publication to be a monoclonal antibody) in the marrow, $[A_{\text{blood}}]$ is the concentration of the agent in the blood or serum, and *RMBLR* is the red marrow to blood cumulated activity ratio. One expression of this, used by many was proposed by Sgouros[74]:

$$[A_{\text{marrow}}] = [A_{\text{blood}}] \frac{RMECFF}{(1 - HCT)}$$

Here, *RMECFF* is the vascular and ECF volume in the marrow, and *HCT* is the patient hematocrit. The "working" value for the *RMECFF* was suggested to be 0.19. Other authors[75] have adapted this method to other agents, assuming different values for the *RMECFF*.

Conclusions

In this short, and by necessity incomplete, review of mathematical models that have been used or can be used in dosimetry applications we have attempted to cover ground both on the methodology and the applications. We have tried to briefly review the origins of existing methodology for compartmental modeling and parameter estimation, at the same time attempting to review other, more recent methodological developments that could be useful in future applications of dosimetry. We have also listed example models and calculations, so as to provide the reader with an overview of the breadth of kinetic model applications in dosimetry. It is probably worthwhile to remind the reader that the model building process is only in part facilitated by the ready availability of large computational power and accurate and easy to use modeling software. By and large, the definition and application of these models remains, to a large extent, an art form, whose practitioners remain few and far between. The background of these scientists spans a tremendous range, from physics to biology, and engineering and computer science. The variety of model applications we have listed and the impact these models continue to have on the practice of dosimetry gives testimony to their creativity and ingenuity.

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