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KINETIC MODELS FOR ABSORBED DOSE CALCULATIONS

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FOREWORD

The Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine is charged with the responsibility of providing the nuclear medicine community with guidance on how to calculate the radiation dose from radionuclides and with useful information for calculating the radiation dose as well as preparing dose estimates for radiopharmaceuticals.

This pamphlet on kinetics in dosimetry is a first attempt by MIRD to fuse biological modeling with dosimetry calculations into a common continuous framework. Some of the concepts presented are new and some are a restatement of well-established ones. Because the purpose of this pamphlet is to emphasize basic concepts, little effort is made to develop the topics in detail. As a consequence, they may not be readily understood by some. When finally grasped, however, the concepts will provide a valuable tool in understanding the importance of kinetics in estimating the radiation dose to a patient. We anticipate that this is but the first of several pamphlets that will deal with kinetics in dose calculations.

As in the past, the MIRD Committee has played an active role in the preparation and review of this pamphlet. In particular, Drs. R. Loevinger, M. T. Hays, and R. E. Johnston have reviewed this pamphlet in detail. Dr. Loevinger has also made a number of valuable suggestions related to material that was incorporated earlier into *MIRD Pamphlet No. 1, Revised.* But, as always, the Committee welcomes comments. The Committee would especially appreciate receiving suggestions regarding how to make the information more useful to the nuclear medicine community.

The work of the MIRD Committee is made possible by the continued encouragement and support of the Society of Nuclear Medicine and the Bureau of Radiological Health, Food and Drug Administration, Department of Health, Education, and Welfare.

ROGER J. CLOUTIER, Chairman
EDWARD M. SMITH, Executive Director
MIRD Committee

This publication is available from the Society of Nuclear Medicine for $6.75 per copy including the loose-leaf binder. Copies are also available without the loose-leaf binder for $4.50 per copy. Check made payable to the Society of Nuclear Medicine or a purchase order must accompany all orders.

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GLOSSARY OF SYMBOLS

$\dot{}$	dot over symbol indicates a time derivative
$\sim$	tilde over symbol indicates a time integral
*	star superscript indicates radioactivity
$\circledast$	convolution operator
$\bar{D}$	absorbed dose averaged over a region
S	mean absorbed dose per unit cumulated activity
$A(t)$	activity
$\tilde{A}(t_1, t_2)$	cumulated activity (time integral of activity)
A_0	total administered activity in a bolus
$q(t)$	source distribution function (activity corrected for physical decay)
λ	physical decay constant of nuclide
λ_i	biological disappearance constant
$F_i(t)$	tracee amount in compartment i; compartment i function for tracee
$f_i(t)$	tracer amount in compartment i; compartment i function for tracer
$f_i^*(t)$	radioactive tracer amount (activity) in compartment i
$\tilde{f}_i^*(t_1, t_2)$	cumulated tracer amount (time integral of activity) in compartment i
$\gamma_i(t)$	fractional compartment i function for unit impulse input
$\alpha_h(t)$	fractional distribution function in region h for unit impulse input
τ	residence time
g_{ij}	tracee apparent rate constant, usually a function of t and the $F_k(t)$
k_{ij}	tracer rate constant
$U(t)$	input function into system (or model)
$u_i(t)$	input function into the i-th compartment
b_i	fraction of total input that enters compartment i
$R(t)$	response function
C_i	fraction of compartment i seen in a response
$Y(t)$	output function
a_{hi}	identification coefficient (fraction of compartment i identified with region h)
t	time

1. INTRODUCTION

The general equations for dose calculations from internally distributed radionuclides, given in *MIRD Pamphlet 1, Revised* (Ref. 1, Eqs. 2 and 4), can be combined to yield

$$\bar{\dot{D}}(r_k) = \sum_h A_h S(r_k \leftarrow r_h), \qquad (1)$$

where $\bar{\dot{D}}(r_k)$ is the average dose rate over a region k from sources in regions h having activities A_h. $S(r_k \leftarrow r_h)$ is the mean absorbed dose in region k per unit cumulated activity in region h.

The average dose $\bar{D}(r_k)$ in a region k for the time interval t_1 to t_2 is given by (Ref. 1, Eq. 6)

$$\bar{D}(r_k) = \sum_h \tilde{A}_h(t_1, t_2) S(r_k \leftarrow r_h), \qquad (2)$$

where

$$\tilde{A}_h(t_1, t_2) \equiv \int_{t_1}^{t_2} A_h(t)\,dt.$$

A distribution function $q_h(t)$ is defined through the relation (Ref. 1, Eq. 25)

$$A_h(t) = q_h(t) e^{-\lambda t} \qquad (3)$$

to give the activity of a source in a region h, corrected for physical decay of the radionuclide.

A number of MIRD reports deal with the quantities that relate to the $S(r_k \leftarrow r_h)$. Tables of S values for various radionuclides are given in *MIRD Pamphlet No. 11 (2)*. The present report is devoted entirely to quantities that relate to the source distribution functions $q_h(t)$, the activities $A_h(t)$, and the cumulated activities $\tilde{A}_h(t_1, t_2)$. To generate a broader base through which the functions $q_h(t)$ and $A_h(t)$ may be derived, two additional functions are introduced: $f_i(t)$, describing tracer amounts in a compartmental model, and $\tau_h(\lambda)$, the residence time of an administered substance in a region.

In view of the use of labeled substances in a variety of forms under various physiological conditions and

modes of administration, it becomes impractical to generate tables of information describing the kinetics for each of the many combinations that may arise. It is therefore desirable to introduce a more general framework and format for the presentation of kinetic data which may serve as a basis for a wide range of applications. This report attempts to construct such a framework. It involves the use of mathematical models to describe in vivo kinetic patterns and processes. In such models a common set of differential equations describes dynamic systems in the steady and nonsteady states, as well as small (e.g., tracer) and large (e.g., tracee*) perturbations about these states. Changes in physiological states due to abnormalities, drug action, and radiation damage can be incorporated in the models through appropriate changes in parameter values. Thus, a model proposed for the prediction of the behavior of a tracer may be based on and supported by information derived from a variety of sources.

A substance introduced into a biological system undergoes changes of state due to transport and chemical reactions. Since detailed knowledge of the factors affecting these processes is seldom available, the observed kinetics are frequently modeled by simplified constructs which lump the biological details into a relatively small number of discrete states with transitions between them. These constructs are referred to as Compartmental Models, each compartment representing an apparent state of the substance. Given a mathematical description for the model, one can calculate the amount of substance in each of its compartments as a function of time for an arbitrary input. When physiological processes can be correlated with the model parameters, changes in these processes can be represented by corresponding changes in model parameter values, and predictions can be made as to how such changes will affect the amounts of the substance in the compartments. For an arbitrary compartment i, these quantities are designated as $f_i(t)$ for the tracer and $F_i(t)$ for substances in nontracer (tracee) amounts.

Since the compartments are lumped representations of composite biological mechanisms (as viewed from the kinetic behavior of a substance), a direct one-to-one correspondence between compartments and anatomical regions usually does not exist. Most commonly a compartment is spread over a number of anatomical regions. Since for the purpose of dosimetry it is necessary to know the amounts of substance in body regions, an identification must be established between compartments of a model and their anatomic whereabouts. Hence, *identification coefficients* a_{hi} are introduced to relate a compartment i to a region h. Using such identification coefficients one can derive from a model the distribution functions $q_h(t)$ and activity functions $A_h(t)$.

In the sections that follow, a mathematical description of compartmental models is presented first from a general point of view dealing with the tracee in steady and nonsteady states. These equations are then reduced for the special but common cases of tracers in steady- and nonsteady-state systems.

For the case of tracers in steady-state biological systems, mathematical simplification and increased predictive power can be gained by special transformations, such as convolution. These permit the derivation of new solutions from solutions previously derived under different conditions, and the generation of universal response curves for substances having similar distribution functions $q_h(t)$.

When direct observations of $q_h(t)$ or $A_h(t)$ are available, dose calculations can be made without the use of kinetic models. Even in these situations, however, some corrective factors are usually necessary. Use of a model to conceptualize such systems will set the framework for the incorporation of new information and allow predictions for a wider range of applications.

2. COMPARTMENTAL MODELS

2.1 General nonlinear model. A compartmental model, as used here, is a mathematical construct that describes the kinetics of a substance in terms of hypothetical states (called compartments) and laws that govern transition of the substance between the states. In general, for a tracee substance such models can be described by sets of ordinary nonlinear differential equations (*3–5*). For n compartments they can take the form

$$\begin{aligned}
\frac{dF_1(t)}{dt} &= -g_{11}F_1(t) + g_{12}F_2(t) + \cdots + g_{1n}F_n(t) + u_1(t) \\
&\cdots \\
\frac{dF_i(t)}{dt} &= g_{i1}F_1(t) + g_{i2}F_2(t) + \cdots - g_{ii}F_i(t) \\
&\qquad + \cdots + g_{in}F_n(t) + u_i(t) \qquad (4) \\
&\cdots \\
\frac{dF_n(t)}{dt} &= g_{n1}F_1(t) + g_{n2}F_2(t) + \cdots - g_{nn}F_n(t) + u_n(t).
\end{aligned}$$

Where

$F_i(t)$ is the amount of substance in compartment i at time t (grams, moles, fraction of administered quantity, etc.). It is the solution of the differential equations for compartment i and is referred to as the *compartment function.*

g_{ij} is the fraction of substance in compartment j transferred to compartment i per unit time, the

* Tracee is a substance being traced (*3*).

apparent rate constant. In general, g_{ij} *may be a function of time t, and of the* $F_i(t)$.

g_{ii} is the total fractional loss from compartment i, and by definition, $g_{ii} \equiv \sum_{\substack{j=0 \\ j\neq i}}^{n} g_{ji}$, where g_{0i} is the fractional loss to outside of the system.

$u_i(t)$ is the rate of input of substance to compartment i from outside of the system.

When the g_{ij} are functions of the solutions $F_i(t)$, the differential equations are nonlinear, and so are the models they describe. When the g_{ij} are functions of t, the differential equations are linear and describe linear, time-dependent models. In the special case when all g_{ij} are constant, as for tracers in steady-state systems, the differential equations are known as linear-constant-coefficient, and they describe time-invariant or constant-parameter models.

When the input functions $u_i(t)$ are impulses at $t = 0$, they correspond to the initial conditions for the differential equations. In general, the input functions may be a combination of impulses and time-dependent functions.

In practice, the solutions $F_i(t)$ of the general set of differential equations 4 can only be given numerically (or graphically) with the aid of computers. For special cases, when the g_{ij} are constant and the number of compartments is small, analytic solutions (e.g., sums of exponentials, power series, etc.) may be derived. Numerical solutions may frequently be approximated by analytic functions.

2.2 Tracer in steady-state systems. A tracer introduced into a steady-state biological system follows linear kinetics with time-invariant parameters (*4*). In terms of a compartmental model, this can be described by a set of ordinary linear differential equations with constant coefficients k_{ij}:

$$\frac{df_i(t)}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}f_j(t) - k_{ii}f_i(t) + u_i(t), \qquad i = 1, \cdots, n, \quad (5)$$

where $f_i(t)$ is the amount of tracer in compartment i, and the k_{ij} are the *rate constants*. k_{ii} is defined as the total fractional loss from compartment i. When there is a corresponding tracee $F_i(t)$ for the tracer, the k_{ij} depend on the values of the g_{ij} and the levels of the tracee in the steady state.

For the case when the $u_i(t)$ are impulses or constants, the solutions of the above set of differential equations are most commonly sums of exponentials:

$$f_i(t) = \sum_{j=1}^{n} f_{ij}e^{-\lambda_j t}, \quad (6)$$

where the λ_j are the biological disappearance constants and the f_{ij} are constant coefficients. Solutions involving powers of t and sine functions are also possible when the matrix of the k_{ij} has certain properties (multiple and/or complex eigenvalues).

For a radioactive tracer, Eqs. 5 can be written in terms of activity by adding a physical decay term to each of the equations:

$$\frac{df_i^*(t)}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}f_j^*(t) - k_{ii}f_i^*(t) - \lambda f_i^*(t) + u_i^*(t), \qquad i = 1, \cdots, n. \quad (7)$$

Here the asterisk denotes the radioactive tracer, $u_i^*(t)$ is its input function in terms of activity, and λ is the physical decay constant for the nuclide. While the differential equations 7 can be solved directly for the $f_i^*(t)$, it can be shown that for $u_i^*(t) = u_i(t)e^{-\lambda t}$ the solution for a radioactive tracer can be expressed in terms of the nonradioactive tracer solution:

$$f_i^*(t) = f_i(t)e^{-\lambda t}. \quad (8)$$

Equations 7 can also be used to obtain cumulated activities $\tilde{f}_i^*(t_1, t_2)$ in any compartment i. For example, multiplying through by dt, integrating over infinite time, and rearranging terms, we get

$$(k_{ii} + \lambda)\tilde{f}_i^*(0, \infty) - \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}\tilde{f}_j^*(0, \infty) = \tilde{u}_i^*(0, \infty) + f_i^*(0), \qquad i = 1, \cdots, n, \quad (9)$$

where $\tilde{f}_i^*(0, \infty) \equiv \int_0^\infty f_i^*(t)dt$, $\tilde{u}_i^*(0, \infty) \equiv \int_0^\infty u_i^*(t)dt$, and $f_i^*(0)$ is the initial condition for compartment i $[f_i^*(\infty) = 0]$.

Equations 9 are a set of n linear algebraic equations which, when solved, yield the cumulated activities for each of the compartments over infinite time.

2.3 Tracer in nonsteady-state systems. When the biological system is not in a steady state, a tracer still follows linear kinetics but with time-dependent parameters. Nonsteady states may occur when a biological system undergoes changes due to external factors (e.g., diet), pathological factors, the administration of drugs, or the administration of excess carrier levels of the tracee substance. The compartmental models for such systems can be described by the set of differential equations

$$\frac{df_i(t)}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}(t)f_j(t) - k_{ii}(t)f_i(t) + u_i(t), \qquad i = 1, \cdots, n, \quad (10)$$

where the $k_{ij}(t)$ are time-dependent rate constants. In the presence of tracee, the $k_{ij}(t)$ are functions of the g_{ij} and $F_j(t)$ of the tracee as given by Eq. 4.

Except for special cases, there is no analytic solution

for this set of equations. Solutions can, however, readily be obtained numerically with the aid of computers.

For a radioactive tracer, a solution in terms of activity may be obtained by introducing the radioactive decay of the nuclide directly in the differential equations

$$\frac{df_i^*(t)}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}(t)f_j^*(t) - k_{ii}(t)f_i^*(t) - \lambda f_i^*(t) + u_i^*(t). \quad (11)$$

It can be shown that for $u_i^*(t) = u_i(t)e^{-\lambda t}$ the solution for a radioactive tracer can be expressed in terms of the nonradioactive tracer solution

$$f_i^*(t) = f_i(t)e^{-\lambda t}. \quad (12)$$

2.4 Nonlinear kinetics of radioactive substances. Radioactivity sufficiently high to cause biological damage can affect the kinetics of the labeled substance (e.g., therapy levels of radioiodide). This results in nonlinear kinetics and nonlinear differential equations. In this case the physical decay of the radionuclide and the damage function due to radiation must be included in the differential equations directly. The equations can take the form

$$\frac{df_i^*(t)}{dt} = \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}(t, \bar{D})f_j^*(t) - k_{ii}(t, \bar{D})f_i^*(t) - \lambda f_i^*(t) + u_i^*(t), \qquad i = 1, \cdots, n, \quad (13)$$

where the $k_{ij}(t, \bar{D})$ are functions of time (as for the nonsteady-state tracer case) and the mean doses $\bar{D}$ in the regions of the anatomical model. Damage functions to relate the k_{ij} to the mean doses $\bar{D}$ would have to be established.

2.5 Definitions and schematics. In dealing with kinetic models several terms are in frequent use. We define these as follows:

An *input function* U(t) to a compartmental model is defined as the sum of all the inputs to the individual compartments:

$$U(t) = \sum_i u_i(t). \quad (14)$$

When all $u_i(t)$ are constant relative to each other for all values of t, each input $u_i(t)$ may be expressed as a fraction of the total input

$$u_i(t) = b_iU(t), \quad (15)$$

where

$$\sum_i b_i = 1. \quad (16)$$

The input to a compartmental model, when characterized by a set of values for the b_i, is equivalent to a mode of administration in the physiological system being modeled.

The *response function* R(t) of a compartmental model is defined as a linear combination of the compartmental functions. For the tracee

$$R(t) = \sum_i C_iF_i(t)$$

and for the tracer

$$R(t) = \sum_i C_if_i(t), \quad (17)$$

where the C_i are the fractions of the compartments contained in the response. An experimental observation is a particular response, and under standardized conditions it implies a particular set of fixed C_i values.

The *output function* Y(t) of a compartmental model is defined as the function describing irreversible loss of substance from the model to the outside. For the tracee

$$Y(t) = \sum_i g_{0i}F_i(t)$$

and for the tracer

$$Y(t) = \sum_i k_{0i}f_i(t). \quad (18)$$

We use the following conventions for the schematic representation of a compartmental model. A circle represents a compartment. An arrow between compartments represents unidirectional transition from one compartment to another and corresponds to a g_{ij} or k_{ij}. An arrow without a designated ending or without a designated starting point corresponds to a loss path g_{0j} or k_{0j}, or to an input $u_j(t)$, respectively. Initial conditions are specified by an input arrow designated $f_i(0)$. Thus, the tracer model shown in Fig. 1 generates the differential equations for compartments j and i:

$$\frac{df_j(t)}{dt} = -k_{ij}f_j(t) + k_{ji}f_i(t) + u_j(t),$$

$$\frac{df_i(t)}{dt} = k_{ij}f_j(t) - k_{0i}f_i(t) - k_{ji}f_i(t). \quad (19)$$

When time-dependent or nonlinear kinetics are involved, the functional dependence of the k_{ij} or the g_{ij} may be specified along the arrows, or separately.

3. MODEL IDENTIFICATION COEFFICIENTS

To relate the amount of substance in a compartment

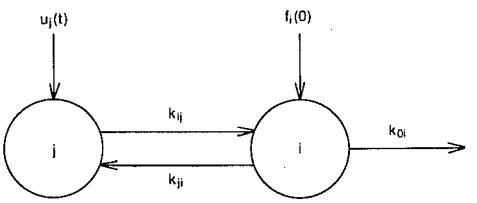

FIG. 1. Compartmental model.

to the amount of substance in an anatomical region requires that a complete identification between the two be established. Since the amount of substance predicted for a compartment of a model must be located in one or more anatomical regions, we can define an *identification* coefficient a_{hi} as the fraction of the amount of substance in compartment i that is localized in the anatomical region h. Thus, for a radioactive tracer, the activity function can be given by

$$A_h(t) = \sum_i a_{hi} f_i^*(t). \qquad (20)$$

To account fully for the contents of each compartment, it is necessary that

$$\sum_h a_{hi} = 1, \qquad \text{for all i.} \qquad (21)$$

Depending on available information various models may be proposed for the kinetics of a substance. For each model there may be a different set of identification coefficients a_{hi}. For a particular model, however, the same set of identification coefficients applies to both the tracer and tracee and holds for all modes of input and all parameter perturbations. Ideally, if the a_{hi} are properly assigned, all models generated from a set of data should—within the precision and resolution of the data—yield the same values for $A_h(t)$.

Similarly, for a radioactive tracer corrected for its physical decay, the distribution function $q_h(t)$ can be given by

$$q_h(t) = \sum_i a_{hi} f_i(t), \qquad (22)$$

where $f_i(t)$ is expressed in activity units, but corrected for physical decay of the nuclide. This suggests that the meaning of $q_h(t)$ can be extended to include nonradioactive tracers, in which case the units of $q_h(t)$ are the same as those of $f_i(t)$.

4. RESIDENCE TIME

We define *residence time* τ_h in a region h as the mean time that an administered substance spends in that region. It can be shown (*6*) that for a constant-parameter model or system the residence time is given by

$$\tau_h = \frac{\int_0^\infty q_h(t)\,dt}{\int_0^\infty U(t)\,dt} = \frac{\tilde{q}_h(0,\infty)}{\tilde{U}(0,\infty)}, \qquad (23)$$

where $U(t)$ is the rate of input of material into the system and $q_h(t)$ is the amount of material in region h as a function of time due to the input $U(t)$.

We define, as was done in *MIRD Pamphlet 1, Revised* (*1*), a *fractional distribution function* $\alpha_h(t)$ as the distribution function resulting from a unit bolus input. Hence, using Eq. 23 we get

$$\tau_h = \int_0^\infty \alpha_h(t)\,dt = \tilde{\alpha}_h(0,\infty). \qquad (24)$$

One can similarly define the residence time for a radioactive nuclide in terms of the mean time of its activity in a region. Since in addition to biological disappearance there is also physical decay, the residence time for activity is a function of the physical decay constant λ as well, and can be written as

$$\tau_h(\lambda) = \frac{\int_0^\infty A_h(t)\,dt}{\int_0^\infty U^*(t)\,dt} = \frac{\int_0^\infty q_h(t)e^{-\lambda t}dt}{\int_0^\infty U(t)e^{-\lambda t}dt} = \frac{\tilde{A}_h(0,\infty)}{\tilde{U}^*(0,\infty)}, \qquad (25)$$

where $U^*(t)$ is the rate of administration of activity and $\tilde{U}^*(0,\infty)$ is the total administered activity.† Note that for $\lambda = 0$ Eq. 25 reduces to Eq. 23.

The residence time in region h is thus the cumulated activity for infinite time in that region per unit administered activity, and

$$\tilde{A}_h(0,\infty) = \tau_h(\lambda)\cdot\tilde{U}^*(0,\infty) \qquad (26)$$
$$[= \tau_h(\lambda)\cdot A_0].$$

If we define $\alpha_h^*(t)$ as the activity in region h per unit activity administered as a bolus at time $t = 0$, we can rewrite Eq. 25 as

$$\tau_h(\lambda) = \int_0^\infty \alpha_h(t)e^{-\lambda t}dt = \int_0^\infty \alpha_h^*(t)\,dt = \tilde{\alpha}_h^*(0,\infty). \qquad (27)$$

Using Eqs. 12, 22, and 27, the residence time can also be given in terms of the compartment functions:

$$\tau_h(\lambda) = \frac{1}{\tilde{U}^*(0,\infty)} \sum_i a_{hi}\tilde{f}_i^*(0,\infty). \qquad (28)$$

In general, the residence time depends on the mode of entry of the substance (oral, intravenous, etc.), and on the physical decay of the nuclide. For a linear, constant-parameter system every administered particle has a priori the same expected residence time in a region, regardless of when it enters the system. $\tau_h(\lambda)$ is thus independent of the total administered activity $\tilde{U}^*(0,\infty)$ or the time course of administration, and is a continuous function of λ. Hence, a plot of $\tau_h(\lambda)$ vs. λ can serve as a universal curve for substances having similar biological responses $q_h(t)$, but labeled with different nuclides.

† When activity is administered in a bolus, $\tilde{U}^*(0,\infty)$ is equivalent to the A_0 used in *MIRD Pamphlet 1, Revised* (*1*).

The relations given above for residence times do *not* apply to linear time-dependent or to nonlinear models or systems.

Using Eqs. 2 and 26, the dose to a region k for infinite time can be given as

$$\bar{D}(r_k) = \tilde{U}^*(0, \infty) \sum_h \tau_h(\lambda) \cdot S(r_k \leftarrow r_h). \quad (29)$$

5. CONVOLUTION

It is a property of a linear, constant-parameter system that given the response $w(t)$ to a unit impulse, the response $R(t)$ to any arbitrary input $U(t)$ administered in the same mode can be derived by use of the convolution integral (*6*):

$$R(t) = \int_0^t U(\theta)w(t-\theta)d\theta = \int_0^t U(t-\theta)w(\theta)d\theta, \quad (30)$$

where θ is a dummy variable of integration. This is frequently abbreviated as

$$R(t) = U(t) \circledast w(t) = w(t) \circledast U(t)$$

to mean the convolution of $U(t)$ with $w(t)$, or $w(t)$ with $U(t)$. Convolution is commutative and distributive:

$$X \circledast Y = Y \circledast X,$$
$$X \circledast (Y + Z) = X \circledast Y + X \circledast Z. \quad (31)$$

Some useful relations can readily be derived using the convolution integral. For example, the response to a constant input U_c is proportional to the area under the unit response curve:

$$R(t) = U_c \int_0^t w(\theta)d\theta; \quad (32)$$

or the response to an exponential input Ce^{-kt} is

$$R(t) = C \int_0^t e^{-k\theta}w(t-\theta)d\theta. \quad (33)$$

For $w(t) = e^{-\beta t}$, the response to an input $U(t) = Ce^{-kt}$ is

$$R(t) = e^{-\beta t} \circledast Ce^{-kt} = C \int_0^t e^{-\beta\theta}e^{-k(t-\theta)}d\theta = C\frac{e^{-\beta t} - e^{-kt}}{k - \beta}. \quad (34)$$

It can be shown that the convolution integral applies to the model functions $f_i(t)$, the distribution functions $q_h(t)$, the activity functions $A_h(t)$, and the cumulated activities $\tilde{A}_h(t_1, t_2)$. Given any of the above response functions for a unit impulse input, the corresponding functions for any other input can be calculated. Knowledge of the model structure is not required to apply the convolution technique. For example, let $\gamma_i(t)$ be the i-th compartment response function to a unit impulse input to the system. The compartment solution $f_i(t)$ due to an input $U(t)$ is then

$$f_i(t) = U(t) \circledast \gamma_i(t) \quad (35)$$

and

$$q_h(t) = \sum_i a_{hi}f_i(t) = U(t) \circledast \sum_i [a_{hi}\gamma_i(t)] = U(t) \circledast \alpha_h(t), \quad (36)$$

where $\alpha_h(t) = \sum_i a_{hi}\gamma_i(t)$ is the fractional distribution function resulting from the unit impulse input into the system.

Convolution is a powerful tool for predicting responses of subsystems when coupled to each other provided their individual responses are known. This is particularly useful when a tracer nuclide of one metabolite enters metabolic pathways of another as a result of catabolism. For example, iodinated albumin eventually loses its iodine as a result of catabolism and the iodine then enters the iodide metabolic system. Knowledge of the albumin and iodide subsystems individually permits a prediction of their responses when coupled. It is therefore useful to build up knowledge of small subsystems for potential integration into larger coupled systems.

It is important to recognize that the convolution technique applies to inputs that follow identical entry pathways, or modes of administration; i.e., there is a common set of b_i (Eq. 15) for all inputs. To predict responses for different input pathways it is best to revert to the model and to the differential equations describing it.

The convolution integral does not apply to linear systems with time-dependent parameters or to nonlinear systems. In these cases it is necessary to deal with the differential equations directly.

6. SIMPLIFICATIONS

When the model is complex, time dependent, or nonlinear, an exact, simple analytic description of the compartment functions $f_i(t)$, the distribution functions $q_h(t)$, and activities $A_h(t)$ is impossible. These functions can be approximated, however, by simple analytic functions, provided one is willing to accept some inaccuracies in the doses to be calculated. For example, one can approximate numerical solutions to within a desired precision by some minimal number of exponentials. Critical in this approximation is the extrapolative precision of the approximating function so that

integration over any time interval including $t = 0$ and $t \rightarrow \infty$ will remain within the desired precision.

Another approach to simplification is the reduction of a complex model to a simpler form by deleting or combining compartments without significantly changing the responses or distribution functions of interest. The simplified model can be simulated and the differences from the original model evaluated. An example of this is the 4-compartment iodine kinetics model shown in Appendix B, which is an approximation to a 13-compartment model discussed in the references of the Appendix.

7. SUMMARY

There are a number of ways to present information about radionuclide distributions in source regions.

1. Activity functions $A_h(t)$ for each radionuclide directly.
2. Metabolite or substance distribution functions $q_h(t)$ (no physical decay).
3. Compartment functions $f_i(t)$ (with or without physical decay of nuclide) with corresponding identification coefficients a_{hi}.
4. Differential equations for a substance with identification coefficients a_{hi} (with or without physical decay of nuclide).

In practice, the activity in a source region may have to be estimated for a variety of conditions.

1. Various radionuclide input functions.
2. Various input modes (pathways).
3. Use of substances with various labels.
4. Changes in system parameters due to abnormalities.
5. Perturbations in system parameters due to drugs or other treatments.
6. Use of radionuclides under nonsteady-state conditions, to include large amounts of carrier.
7. Use of radionuclides for therapy.

To provide the information necessary to estimate radioactivity in source regions for the variety of conditions cited and in a most compact form, the differential equation description is the most general. This implies a model and requires a set of identification coefficients to relate compartments to anatomical source regions. If the differential equation solutions are complex functions, approximations may be introduced. For each model the functions describing each of the loss pathways and their identification as to the metabolite or substance lost and the anatomical site where it takes place should be described. This permits the coupling or convolution of subsystems.

Most useful are probably the residence-time functions $\tau_h(\lambda)$ for source regions since they permit easy calculation of total absorbed doses for different input functions and for various radioisotopes of an element by simple integration.

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Appendix A. Example for Substance X

In this example we use a model for a very simple case in which source organs are measured directly and the compartments of the model correspond directly to the source organs. Because of this, a number of the calculated functions are repetitious. The example is for 1 μCi administered. Since the model is linear, the derived distribution and activity functions are directly proportional to the number of microcuries administered.

Assume that 1 μCi of a labeled substance X is introduced into plasma, and let the fraction retained in plasma, R_P, corrected for physical decay, be

$$R_P = e^{-4.8t}, \qquad (A1)$$

where t is in days.

Assume also that the fraction of the administered activity in the liver R_L corrected for physical decay is a sum of two exponentials

$$R_L = -1.33e^{-4.8t} + 1.33e^{-1.2t} \qquad (A2)$$

and that fecal collections account for about two-thirds of the injected material. R_P and R_L are also plasma and liver response functions, respectively.

The above data are compatible with the interpretation that X is initially contained in plasma, that it is cleared by liver with a rate constant of 4.8/d, and that

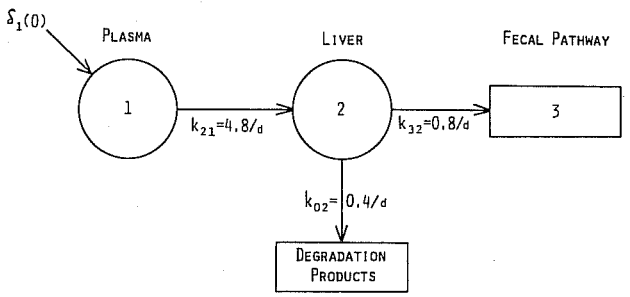

FIG. A-1. Model describing kinetic compartments for substance X and corresponding anatomical identifications.

X in the liver turns over at a rate of 1.2/d. Since two-thirds of X appears in feces, it suggests that $2/3 \times 1.2 = 0.8$/d is cleared by the bile and that $1/3 \times 1.2 = 0.4$/d is degraded and the products (no longer substance X) are released back to plasma.

The model of Fig. A-1 incorporates these interpretations and is quantitatively compatible with the data. These are described by the set of differential equations

$$\frac{df_1(t)}{dt} = -k_{21}f_1(t), \quad f_1(0) = 1,$$

$$\frac{df_2(t)}{dt} = k_{21}f_1(t) - (k_{32} + k_{02})f_2(t),$$

with output functions

$$Y_1(t) = k_{32}f_2(t),$$

$$Y_2(t) = k_{02}f_2(t).$$

$\delta_1(0)$ in Fig. A-1 represents a unit impulse input function at time t = 0. The compartment functions $f_1(t)$ and $f_2(t)$ are the solution of the above differential equations:

$$f_1(t) = e^{-4.8t}, \tag{A3}$$

$$f_2(t) = -1.33e^{-4.8t} + 1.33e^{-1.2t}. \tag{A4}$$

In this example the anatomic regions were measured directly and the model compartment functions are the distribution functions. Hence, the identification coefficients a_{hi} are either unity or zero, as shown in Table A-1. This assignment of coefficients implies a "liver" organ exclusive of its vascular contents, which are considered part of the "plasma" organ.

The fractional distribution functions for plasma, $\alpha_P(t)$, and liver, $\alpha_L(t)$, are

$$\alpha_P(t) = a_{P1}f_1(t) + a_{P2}f_2(t) = e^{-4.8t}, \tag{A5}$$

$$\alpha_L(t) = -1.33e^{-4.8t} + 1.33e^{-1.2t}. \tag{A6}$$

The activity functions (Eq. 3) for a label having a physical decay λ are

$$A_P(t) = e^{-(4.8+\lambda)t}, \tag{A7}$$

$$A_L(t) = -1.33e^{-(4.8+\lambda)t} + 1.33e^{-(1.2+\lambda)t}. \tag{A8}$$

TABLE A-1. COMPARTMENT IDENTIFICATION COEFFICIENTS (a_{hi}), IN FRACTION

Organ h \ Compartment i	1	2
Plasma	1.	0
Liver	0	1.

The residence times (Eq. 27) are

$$\tau_P(\lambda) = \int_0^\infty e^{-(4.8+\lambda)t}dt = \frac{1}{4.8+\lambda} \text{ days}, \tag{A9}$$

$$\tau_L(\lambda) = \frac{-1.33}{4.8+\lambda} + \frac{1.33}{1.2+\lambda} \text{ days}. \tag{A10}$$

The residence time curves for plasma and liver as a function of halftime of the nuclide are shown in Fig. A-2.

To account for all the activity of a label, one must include its fate after being lost from substance X. The rate of loss of activity from the liver to the fecal path is

$$Y_1(t)\cdot e^{-\lambda t} = k_{32}f_2(t)e^{-\lambda t} = -1.07e^{-(4.8+\lambda)t} + 1.07e^{-(1.2+\lambda)t}, \tag{A11}$$

and the loss to the plasma as degradation products is

$$Y_2(t)\cdot e^{-\lambda t} = k_{02}f_2(t)e^{-\lambda t} = -0.53e^{-(4.8+\lambda)t} + 0.53e^{-(1.2+\lambda)t}. \tag{A12}$$

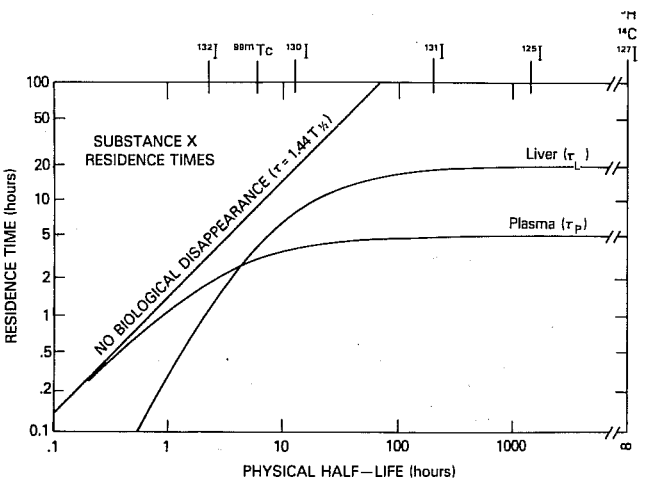

FIG. A-2. Residence times for substance X in liver and plasma organs following bolus injection into plasma. "No biological disappearance" curve corresponds to extreme case for which only physical decay is involved.

We chose to neglect here the function related to the fecal pathway $Y_1(t)$, and deal with the degradation pathway $Y_2(t)$ in Appendix C.

Since $\tilde{A}_h(0, \infty) = r(\lambda) \cdot \tilde{U}^*(0, \infty)$, the value of $\tilde{A}_h(0, \infty)$ for a total administered activity $\tilde{U}^*(0, \infty) =$ 1 μCi of labeled X can be obtained directly from Fig. A-2. For example, for ^{131}I ($T_{1/2}$ = 8.1 days = 194 h):

$$\tilde{A}_P(0, \infty) = r_P \cdot 1 = 4.8\ \mu\text{Ci} \cdot \text{h},$$

$$\tilde{A}_L(0, \infty) = r_L \cdot 1 = 18\ \mu\text{Ci} \cdot \text{h}.$$

Appendix B. Iodine Kinetics

The iodine kinetics model for normal man presented here is based on a model containing 13 compartments (*B1–B3*). The latter is approximated by a four-compartment model which yields distribution functions within about 5% of the original model predictions. The simplification included the deletion of some compartments and pathways with appropriate modification of the values of some parameters.

This example only serves to demonstrate concepts and is not to be taken as an actual report on iodine kinetics.

The model is shown in Fig. B-1. Compartment 1 is extrathyroidal iodide, having a plasma equivalent volume (PEV) of about 25 l. Compartment 3 is extrathyroidal T_3 (triiodothyronine) with PEV = 35 l. Compartment 4 is extrathyroidal T_4 (thyroxine) with PEV = 10 l. Compartment 2 is thyroidal iodine, mostly in organic form.

Notes

1. k_{21} = 0.1144/d was chosen to yield about a 5% peak thyroid uptake value after an iodide injection. For 15% peak uptake k_{21} = 0.385/d; for 25% peak uptake k_{21} = 0.727/d.

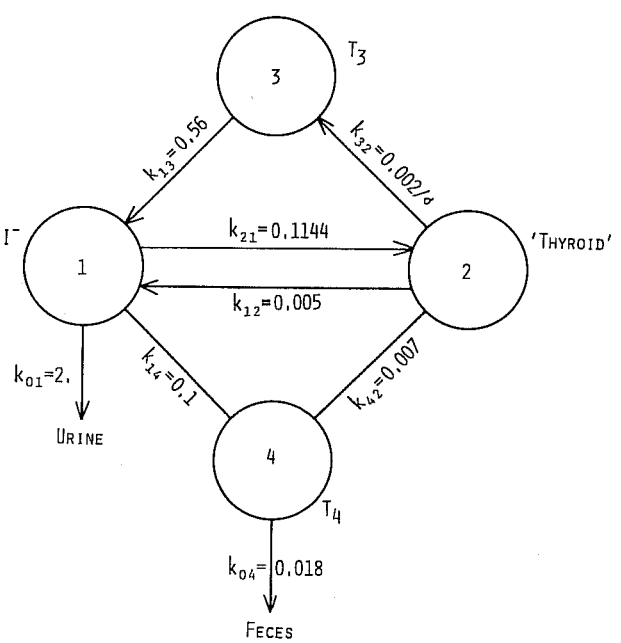

FIG. B-1. Iodine model.

2. For hyperthyroids and for normals on low iodine diets the value for k_{21} can increase by as much as a factor of 150. k_{14} and k_{13} increase by a factor of about 1.7 in hyperthyroids.
3. In nephrotics k_{01} usually decreases.
4. Methimazole reduces the value of k_{21} nearly to zero, and increases k_{12} by a factor of about 3.
5. Perchlorate reduces the value of k_{21} nearly to zero.

From the above data and from literature informa-

TABLE B-1. COMPARTMENT IDENTIFICATION COEFFICIENTS (a_{hi})

	Compartment i			
Source region h	1	2	3	4
RBC	0.045		0.0126	
Salivary glands	0.05			
Plasma	0.099		0.0612	0.245
Stomach	0.15			
GI	0.17			
ECEV	0.423		0.826	0.336
Thyroid		1.00		
Liver	0.063		0.100	0.419

1. The identification coefficients for compartment 1 (iodide) were obtained from the MIRD task group report on iodine kinetics (in preparation).
2. The source region 'liver' as defined here includes its blood content, estimated as 10% of total body plasma and red cells; 10% of total body extracellular, extravascular (ECEV) activity are also assigned to it.
3. The source regions 'RBC' (red blood cells), 'plasma,' and 'ECEV' (extracellular, extravascular) are defined here as estimates for total body, less the amount assigned to the region 'liver.'
4. 'GI' includes iodide contribution only. The contribution from T_4 in the GI contents is not considered in this example.

TABLE B-2. IDENTIFICATION OF LOSS PATHWAYS

Loss pathway	Metabolite form	Anatomical route	Fraction of pathway	Function describing loss
k_{01}	Iodide	Bladder	1.	$k_{01}f_1(t)$
k_{04}	T_4	GI contents	1.	$k_{04}f_4(t)$

TABLE B-3. COMPARTMENT FUNCTIONS (t IN DAYS)

	$e^{-2.11t}$	$e^{-0.56t}$	$e^{-0.118t}$	$e^{-0.0132t}$
Solutions				
$f_1(t)$	1.0	-0.97×10^{-4}	-0.19×10^{-3}	0.354×10^{-3}
$f_2(t)$	−0.054		0.20×10^{-3}	0.054
$f_3(t)$	0.70×10^{-4}	-0.269×10^{-3}		0.198×10^{-3}
$f_4(t)$	0.19×10^{-3}		-0.381×10^{-2}	0.362×10^{-2}
Losses				
$k_{01}f_1(t)$	2.0	-1.94×10^{-4}	-0.38×10^{-3}	0.708×10^{-3}
$k_{04}f_4(t)$	3.42×10^{-6}		-0.69×10^{-6}	0.65×10^{-6}

Example for the use of Table B-3:

$$f_1(t) = 1.0\, e^{-2.11t} - 0.97 \times 10^{-4}\, e^{-0.56t} - 0.19 \times 10^{-3}\, e^{-0.118t} + 0.354 \times 10^{-3}\, e^{-0.0132t}$$

tion, the compartments of the model are identified with source regions as shown in Table B-1. The loss pathways are identified in Table B-2.

Table B-3 is a summary for the compartment functions derived by the solution of the differential equations describing the model for unit injection of iodide into plasma. The entries are the coefficients (f_{ij}) for the exponential components describing the compartment functions.

The distribution functions $q_h(t)$ can be derived from the compartment functions $f_i(t)$ by use of Eq. 22. Using the values for a_{hi} and $f_i(t)$ given in Tables B-1 and B-3, respectively, one can approximate the $q_h(t)$ function by the exponentials and coefficients given in Table B-4.

Residence times are calculated from values given in Table B-4 by the use of Eq. 25. These are given in Table B-5 for some nuclides of iodine. Residence times as a continuous function of λ are given in Fig. B-2.

The values for $\tilde{A}_h(0, \infty)$ for a total administered

TABLE B-4. METABOLITE DISTRIBUTION FUNCTIONS $q_h(t)$ (t IN DAYS)

Source region h	$e^{-2.11t}$	$e^{-0.118t}$	$e^{-0.0132t}$
RBC	0.445×10^{-1}	-0.933×10^{-5}	0.183×10^{-4}
Salivary glands	0.50×10^{-1}	-0.100×10^{-4}	0.178×10^{-4}
Plasma	0.99×10^{-1}	-0.957×10^{-3}	0.935×10^{-3}
Stomach	0.150	-0.302×10^{-4}	0.533×10^{-4}
GI	0.170	-0.342×10^{-4}	0.604×10^{-4}
ECEV	0.423	-0.141×10^{-2}	0.153×10^{-2}
Thyroid	-0.543×10^{-1}		0.543×10^{-1}
Liver	0.63×10^{-1}	-0.162×10^{-2}	0.156×10^{-2}
Total body	0.945		0.55×10^{-1}
Losses (rate)			
I^- to bladder	2.0	-0.38×10^{-3}	0.708×10^{-3}
T_4 to GI contents	0.342×10^{-6}	-0.690×10^{-4}	0.650×10^{-4}

1. The distribution functions presented in this table are approximations (within ±3%) of the values derived from the model functions $f_i(t)$ and the identification coefficients.
2. 'Total body' as a source region is the sum of all other sources listed in the table and is thus redundant.
3. Example for use of Table B-4:

$$q_{GI}(t) = 0.170\, e^{-2.11t} - 0.342 \times 10^{-4}\, e^{-0.118t} + 0.604 \times 10^{-4}\, e^{-0.0132t}$$

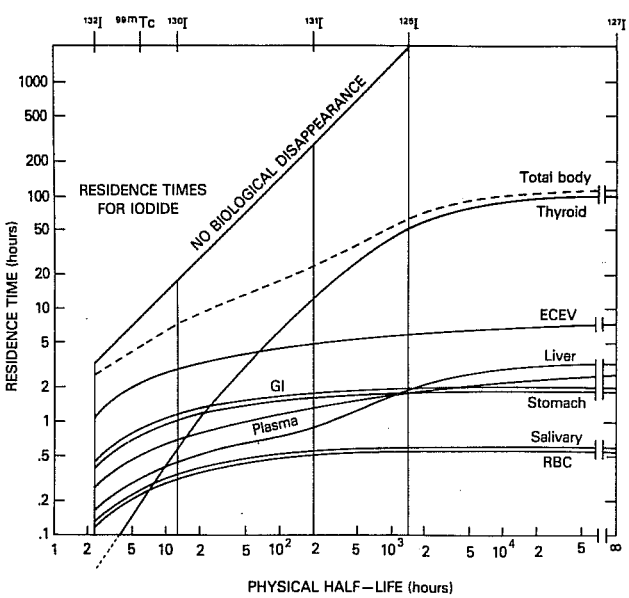

FIG. B-2. Residence times for iodine in various source organs, following bolus injection into plasma.

TABLE B-5. RESIDENCE TIMES (HOURS)

Nuclide→	^{132}I	^{130}I	^{131}I	^{125}I	^{127}I
$T_{1/2}$ →	2.3 h	12.4 h	193.2 h	1440 h	∞
λ →	0.301 h^{-1}	0.0559 h^{-1}	0.00359 h^{-1}	0.000481 h^{-1}	0
RBC	0.114	0.309	0.486	0.521	0.537
Salivary glands	0.129	0.347	0.549	0.581	0.599
Plasma	0.255	0.689	1.195	1.85	2.63
Stomach	0.386	1.043	1.645	1.74	1.80
GI	0.437	1.182	1.865	1.98	2.036
ECEV	1.088	2.95	4.83	6.00	7.31
Thyroid	0.040	0.584	12.52	52.1	98.1
Liver	0.162	0.439	0.875	1.93	3.22
Total body	2.61	7.55	23.9	64.0	110.7
Cumulated losses (fraction of injected activity)					
To bladder	0.214	0.578	0.914	0.966	0.995
To GI contents					0.005

1. 'Total body' as a source region is the sum of all other sources listed in the table and is thus redundant.

activity $\tilde{U}^*(0, \infty)$ can be obtained by the use of Eq. 26:

$$\tilde{A}_h(0, \infty) = \tau_h(\lambda) \cdot \tilde{U}^*(0, \infty).$$

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Appendix C. Example for Iodinated Substance X

When substance X (see Appendix A) is labeled with iodine, the kinetics of the iodine are identical to those of substance X until the latter is degraded. Assuming that iodide is released as X is degraded, the rate of iodide release into plasma, according to Eq. A12, for $\lambda = 0$, is

$$Y_2(t) = k_{02} f_2(t) = -0.53\, e^{-4.8t} + 0.53\, e^{-1.2t}.$$

The distribution functions for the various organs of interest due to this input alone can be obtained by the convolution of $Y_2(t)$ with the distribution functions obtained for a unit impulse of iodide as given in Table B-4. For example, the generated distribution function for the thyroid, $q_{th}(t)$, due to the input $Y_2(t)$ is

$$\begin{aligned} q_{th}(t) &= (-0.53\, e^{-4.8t} + 0.53\, e^{-1.2t}) \\ &\quad \circledast (-0.054\, e^{-2.11t} + 0.054\, e^{-0.0132t}) \\ &= 0.0289(-e^{-4.8t} + e^{-1.2t}) \\ &\quad \circledast (-e^{-2.11t} + e^{-0.0132t}). \end{aligned} \quad \text{(C1)}$$

Using Eqs. 31 and 34, the results of the convolution are

$$\begin{aligned} q_{th}(t) &= 0.0289 \left(\frac{e^{-2.11t} - e^{-4.8t}}{4.8 - 2.11} - \frac{e^{-0.0132t} - e^{-4.8t}}{4.8 - 0.0132} \right. \\ &\quad \left. - \frac{e^{-1.2t} - e^{-2.11t}}{2.11 - 1.2} + \frac{e^{-0.0132t} - e^{-1.2t}}{1.2 - 0.0132} \right) \\ &= -0.00471e^{-4.8t} + 0.0425e^{-2.11t} \\ &\quad - 0.0561e^{-1.2t} + 0.0182e^{-0.0132t}. \end{aligned} \quad \text{(C2)}$$

The derived distribution function for the thyroid is plotted in Fig. C-1. To within a 5% accuracy this function can be approximated by a smaller number of exponentials:

$$q_{th}(t) \approx 0.0133e^{-3.0t} - 0.0315e^{-0.99t} + 0.0182e^{-0.0132t}. \quad \text{(C3)}$$

The total distribution functions for plasma and liver due to labeled X are a combination of those due di-

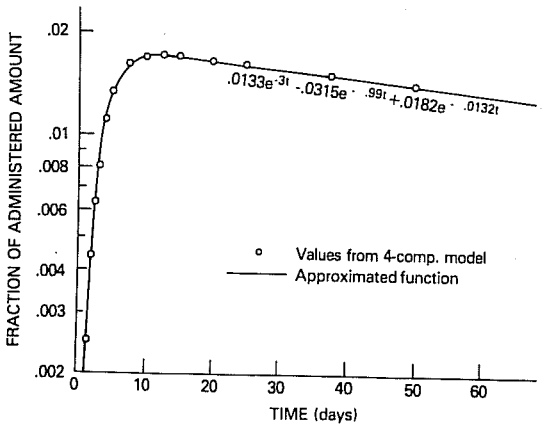

FIG. C-1. Iodine uptake by thyroid due to degradation of iodinated substance X.

rectly to the substance X (X_P and X_L) and those generated from the released iodide. For example, the total distribution function for the liver is

$$q_L(t) = (-1.33e^{-4.8t} + 1.33e^{-1.2t}) + [(-0.53e^{-4.8t} + 0.53e^{-1.2t}) \circledast (0.063e^{-2.11t} - 0.00162e^{-0.118t} + 0.00156e^{-0.0132t})]. \quad (C4)$$

The solution for the above is shown in Fig. C-2 by the dotted circles and can be approximated by three exponentials:

$$q_L(t) \approx -1.45e^{-4.8t} + 1.45e^{-1.26t} + 0.000527e^{-0.0132t}. \quad (C5)$$

The activity function for the liver, using Eq. 3, is

$$A_L(t) \approx -1.45e^{-(4.8+\lambda)t} + 1.45e^{-(1.26+\lambda)t} + 0.000527e^{-(0.0132+\lambda)t}, \quad (C6)$$

and the residence time τ_L from Eq. 25 is

$$\tau_L(\lambda) = -\frac{1.45}{4.8+\lambda} + \frac{1.45}{1.26+\lambda} + \frac{0.000527}{0.0132+\lambda}. \quad (C7)$$

The function for $\tau_L(\lambda)$ could also have been obtained

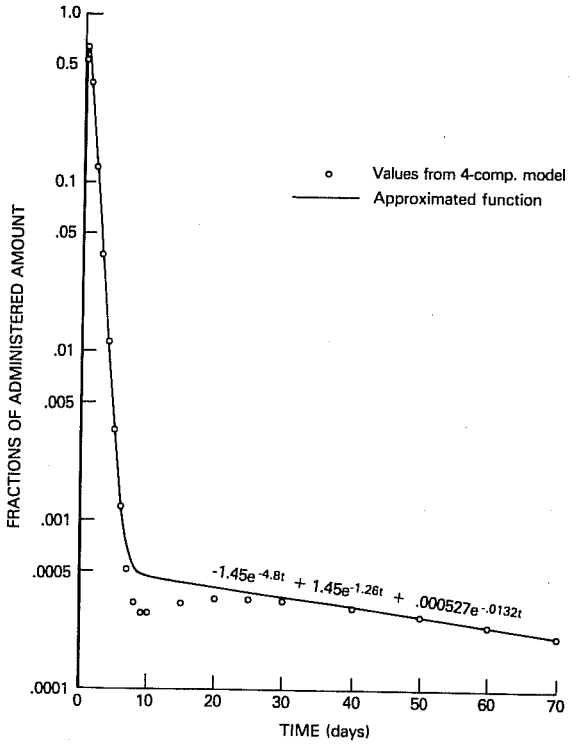

FIG. C-2. Total iodine in liver (q_L) due to iodinated substance X and its degradation products.

by the addition of contributions to the residence time from the substance X directly and from its released iodide. (Convolution leads directly to such a superposition.) The total activity of iodide released by substance X can be obtained by integrating Eq. A12:

$$\int_0^\infty Y_2(t)e^{-\lambda t}dt = -\frac{0.53}{4.8+\lambda} + \frac{0.53}{1.2+\lambda}. \quad (C8)$$

Letting $\tau_L^X(\lambda)$ be the liver residence time for substance X and $\tau_L^I(\lambda)$ the liver residence time for injected iodide, we get

$$\tau_L(\lambda) = \tau_L^X(\lambda) + \left(\frac{-0.53}{4.8+\lambda} + \frac{0.53}{1.2+\lambda}\right)\cdot\tau_L^I(\lambda). \quad (C9)$$

When $\tilde{U}^*(0, \infty)$ is not unity, the value $\tilde{A}_L(0, \infty)$ can be derived directly from $\tau_L(\lambda)$ by use of Eq. 26.