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INPUTS FOR DOSE CALCULATIONS FROM COMPARTMENTAL MODELS

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A concise method to obtain cumulated radioactivities from multicompartmental models with time delays is described. No differential equation solutions are required; the model and a solution to a set of linear algebraic equations is all that is necessary to obtain the inputs for dosimetric calculations. The method is illustrated by providing cumulated radioactivities for isotope distribution represented by a model with a flow loop and time delay.

Loevinger and Berman (*1*) mention the necessity of utilizing a model of radionuclide distribution and kinetics to calculate the absorbed radiation dose (*2*). In this note the cumulated activity is described and calculated for each compartment of a linear time-invariant multicompartment model. Linearity is usually satisfied with tracer doses of the radionuclide. The time-invariance hypothesis requires that the physiologic system must not change its function appreciably over the length of time required for most of the radioactivity to either decay or flow out of the system. If appreciable changes occur in this time interval, more detailed calculations than those given here are necessary.

The equations describing the model need not be integrated to obtain the individual cumulated activities. In other approaches, individual activities are integrated to yield the cumulated activities (*3*). The present formulation which avoids the necessity of solution of the model equations and the subsequent integration of the solutions results in a considerable saving of computer time and code.

RESULTS

Mathematical method. Assume that the tracer distribution in the body may be represented by an N-compartment model described by

$$\frac{d}{dt} q_i(t) = - \sum_{j=1}^{N} a_{ij} q_j(t) - \sum_{m=1}^{M} \sum_{j=1}^{N} b_{mij} q_j(t - \tau_m) + u_i(t) - \sum_{m=1}^{M} \sum_{j=1}^{N} c_{mij} u_j(t - \tau_m) \quad (1)$$

for $i = 1, 2, \cdots, N$. The value of $q_i(t)$ is the amount of tracer (or the radioactivity referenced for physical decay to time, $t = 0$) in compartment i at time t. The individual q_i are examples of the distribution function defined by Loevinger and Berman (*3*). Appropriate choice of the coefficients, a_{ij}, b_{mij}, and c_{mij}, allows for arbitrary intercompartment connection. For example, a_{ii} is the rate coefficient for flow from compartment i; $-a_{ij}$, with $i \neq j$, is the rate coefficient for flow from compartment j into compartment i. Similarly, b_{mij}, with $i \neq j$, can be described as the rate coefficient for flow from compartment j out of the m-th time delay which has contents q_i. Compartments which model tracer transit time delays are included via the double sums on the right of Eq. 1. The individual time delays have value $\tau_m \geqq 0$; a total of M of these delays is present in the model. Tracer is introduced into the i-th compartment at a rate $u_i(t)$; the units of u_i are radioactivity per unit time with correction for physical decay to time, $t = 0$.

We define the total cumulated activity, r_i, in the i-th compartment by

$$r_i = \int_0^\infty q_i(t) e^{-\lambda t} dt \quad (2)$$

for $i = 1, 2, \cdots, N$. The physical decay constant of the simply decaying radionuclide is λ. If the radionuclide has a complex branching decay scheme,

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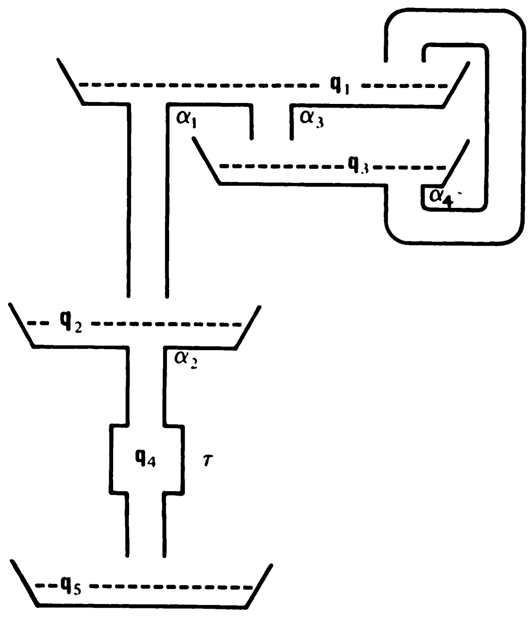

FIG. 1. Model of orthoiodohippurate distribution with kidneys combined into one-nephron representation.

modifications of the results given here are required to obtain the appropriate cumulated activities. These modifications, which will not be included in this note, are direct extensions of the results given here.

Assume that $u_i(t) = q_i(t) = 0$ for $t < 0$ and that $\tau_m \geqq 0$. Also, assume that both $u_i(t)$ and $q_i(t)$ are bounded for $t \geqq 0$; then, multiplication of both sides of Eq. 1 by $e^{-\lambda t}$, integrating, and using Eq. 2, the value of the cumulated activity, r_i, in the i-th compartment may be found by solving the set of linear algebraic equations

$$\lambda r_i + \sum_{j=1}^{N} [a_{ij} + \sum_{m=1}^{M} b_{mij} e^{-\lambda \tau_m}] r_j = q_i(0) + v_i - \sum_{j=1}^{N} \sum_{m=1}^{M} c_{mij} e^{-\lambda \tau_m} v_j \qquad (3)$$

where $i = 1, 2, \cdots, N$. The value of $q_i(0)$ is the amount of tracer in compartment number i at $t = 0$; $q_i(0) = 0$ for those values of i for which q_i represents the amount of tracer in a time-delay compartment.

The value of v_i given by Eq. 4 is the total amount of radionuclide injected into the i-th compartment

$$v_i = \int_0^\infty u_i(t) e^{-\lambda t} dt \qquad (4)$$

Observe that instead of requiring the solution of the set of differential-difference Eq. 1 to obtain the $q_i(t)$ for Eq. 2, one need merely solve the set of linear algebraic Eqs. 3 to obtain the cumulated activity, r_i, for the i-th compartment. This observation has proven to provide considerable saving of computational effort when calculating the inputs required for dose calculations.

Sample calculation. A possible model (*4*) of the renal system for orthoiodohippurate distribution is shown in Fig. 1. In the model each of the kidneys, which are assumed identical, are combined into a common nephron model.

The compartment number/physiologic pool relations are: (A) blood plasma, (B) renal proximal tubular cells, (C) red blood cells and extravascular pools, (D) renal tubular lumen, and (E) urinary bladder. Using dots to represent time derivatives, the defining differential equations are:

$$\begin{aligned} \dot{q}_1(t) &= -(\alpha_1 + \alpha_3) q_1(t) + \alpha_4 q_3(t) \\ \dot{q}_2(t) &= \alpha_1 q_1(t) - \alpha_2 q_2(t) \\ \dot{q}_3(t) &= \alpha_3 q_1(t) - \alpha_4 q_3(t) \\ \dot{q}_4(t) &= \alpha_2 q_2(t) - \alpha_2 q_2(t - \tau) \\ \dot{q}_5(t) &= \alpha_2 q_2(t - \tau) \end{aligned} \qquad (5)$$

The initial conditions associated with these equations are

$$\begin{aligned} q_1(0) &= (1 - f_1 - f_2) A \\ q_2(0) &= f_1 A \\ q_3(0) &= f_2 A \\ q_4(0) &= 0 \\ q_5(0) &= 0 \end{aligned} \qquad (6)$$

where A is the total injected radioactivity at $t = 0$ and the f_1 and f_2 are fractions of the injected radioactivity initially deposited in Compartments 2 and 3.

Comparing Eqs. 1 and 5 one obtains $M = 1$, and $N = 5$; the corresponding values of the rate coefficients are

$$\begin{array}{lll} a_{11} = \alpha_1 + \alpha_3 & a_{22} = \alpha_2 & a_{42} = -\alpha_2 \\ a_{13} = -\alpha_4 & a_{31} = -\alpha_3 & b_{142} = \alpha_2 \\ a_{21} = -\alpha_1 & a_{33} = \alpha_4 & b_{152} = -\alpha_2 \end{array} \qquad (7)$$

The time delay is given by $\tau_1 = \tau$ with the u_i, and the remaining a_{ij}, b_{mij}, and c_{mij}, all equal to zero. Substituting these relationships into Eqs. 3 and 4 yields

$$\begin{aligned} (\lambda + \alpha_1 + \alpha_3) r_1 - \alpha_4 r_3 &= (1 - f_1 - f_2) A \\ -\alpha_1 r_1 + (\lambda + \alpha_2) r_2 &= f_1 A \\ -\alpha_3 r_1 + (\lambda + \alpha_4) r_3 &= f_2 A \\ -\alpha_2 (1 - e^{-\lambda \tau}) r_2 + \lambda r_4 &= 0 \\ -\alpha_2 e^{-\lambda \tau} r_2 + \lambda r_5 &= 0 \end{aligned} \qquad (8)$$

Values of the α_k, f_1, f_2, A, and λ allow solution of this set of equations.

Several sample solutions to the set of Eqs. 8 are given in Table 1. Actual determinations of the parameters of a more detailed model (*4*) have provided the model parameters given in Table 1. For sim-

TABLE 1. CUMULATED RADIOACTIVITIES FOR ^{123}I OR ^{131}I FOR ORTHOIODOHIPPURATE AND UNIT-INJECTED RADIOACTIVITY

Clinical diagnosis	Model parameters f_1	f_2	α_1 /min	α_2 /min	α_3 /min	α_4 /min	τ min	Isotope	Cumulated radioactivity r_1 min	r_2 min	r_3 min	r_4 min	r_5 min	$\hat{r}_5$ min
Normal	0.193	0.110	0.284	0.236	0.183	0.0784	1.81	^{131}I	2.84	4.24	8.05	1.81	16748.3	235.1
								^{123}I	2.81	4.19	7.90	1.78	1131.7	173.9
Ureteral obstruction	0.181	0.070	0.162	0.0360	0.0753	0.0306	12.45	^{131}I	5.05	27.76	14.69	12.40	16705.3	234.7
								^{123}I	4.96	26.73	14.08	11.88	1090.7	169.2
Glomerulonephritis	0.369	0.151	0.269	0.0414	0.187	0.0510	3.22	^{131}I	2.34	24.11	11.48	3.21	16724.1	234.5
								^{123}I	2.30	23.39	11.15	3.11	1108.4	170.3
Low perfusion and hypertension	0.124	0.019	0.0762	0.342	0.0254	0.0031	5.59	^{131}I	11.40	2.90	99.63	5.55	16645.7	233.0
								^{123}I	10.53	2.70	73.43	5.15	1056.6	162.4
Transplant acute tubular necrosis	0.140	0.071	0.0843	0.198	0.0639	0.0634	1.47	^{131}I	10.19	5.05	11.34	1.47	16737.2	234.9
								^{123}I	9.98	4.94	10.99	1.44	1121.0	172.0
Transplant immunologic rejection	0.075	0.180	0.138	0.0958	0.246	0.0458	6.66	^{131}I	6.69	10.41	39.81	6.63	16701.7	234.3
								^{123}I	6.43	9.95	37.76	6.32	1087.9	167.6
Transplant normal	0.144	0.164	0.187	0.266	0.152	0.0461	3.22	^{131}I	4.57	3.77	18.54	3.22	16735.1	235.6
								^{123}I	4.47	3.69	17.91	3.15	1119.2	172.6

plicity, only one of the kidneys has been included in the model. The cumulated radioactivities per unit initial radioactivity are given in minutes, e.g., microcurie-minutes per microcurie of injected radionuclide. Since the model compartment representing the bladder has no outlet (a quite unrealistic assumption in most circumstances), the volume of cumulated radioactivity for a transit time through the bladder of 4 hr has also been calculated and is reported as $\hat{r}_5$. The value of $\hat{r}_5$ may be a more realistic value of the cumulated radioactivity in the bladder.

Dose estimates based on the values of cumulated activity obtained above may be calculated by the method outlined in Loevinger and Berman (*1*); other MIRD data (*5,6*), and tabulations of Lederer, et al (*7*) may be used for the nuclear parameters and decay schemes to obtain the absorbed fractions given by Snyder, et al (*8*).

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