Theorem on the Apparent Volume of Distribution and the Amount of Drug in the Body at Steady State

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Abstract □ For an N-compartmental system, with irreversible drug loss from the sampled compartment, the equilibrium concentration, $C(\infty)$, obtained with a zero-order drug input is related to the total amount of drug in the system, T, by $C(\infty)V = T$. The scalar V is the volume of distribution of the corresponding closed system. The moment functions of the open system define V, and hence T is directly calculable. The derivation is general in the sense that the topology of the system is not specified and no functional form for $C(t)$ is required.

Keyphrases □ Volume of distribution, apparent—theorem, amount of drug in the body at steady state, topology, moment functions □ Topology—apparent volume of distribution, amount of drug in the body at steady state, moment functions, theorem

The apparent drug distribution volume of an irreducible compartmental system, with a unit impulse drug input into a sampled compartment, is given by the ratio of the first statistical moment to the definite integral of the sampled concentration function (1). This apparent drug distribution volume is identical to the apparent volume of the corresponding closed system if drug elimination occurs exclusively from the sampled compartment (1).

In the present paper a relationship between the apparent volume of distribution of a compartmental system and the total amount of drug in the system, obtained with a zero-order drug input, is derived. The derivation does not require any conditions on (*a*) the eigenvalues of the system, (*b*) the topology of the system, or (*c*) the intercompartmental rate constants. However, it is assumed that drug input is into the sampled compartment and that drug elimination occurs only from the sampled compartment.

THEORETICAL

Consider an arbitrary set of N interconnected compartments in which it is possible for material in compartment j to reach each of i compartments ($i, j \epsilon 1, 2 \ldots N; i \neq j$). Such a compartmental system does not contain any sinks, disjointed sets of compartments, or subsystems. For such a system:

$$\begin{bmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \\ \vdots \\ \dot{X}_N \end{bmatrix} = \begin{bmatrix} -E_1 & k_{21} & k_{31} & \ldots & k_{N1} \\ k_{12} & -E_2 & k_{32} & \ldots & k_{N2} \\ k_{13} & k_{23} & -E_3 & \ldots & k_{N3} \\ & & & & \\ k_{1N} & k_{2N} & k_{3N} & \ldots & -E_N \end{bmatrix} \begin{bmatrix} X_1 \\ X_2 \\ X_3 \\ \vdots \\ X_N \end{bmatrix} \equiv \dot{\mathbf{X}} = \mathbf{AX} \qquad \text{(Eq. 1)}$$

where X_j ($j \epsilon 1,2 \ldots N$) is the amount of drug in compartment j, and $\dot{X}_j$ is the first derivative of X_j with respect to time. The off-diagonal elements of matrix A, k_{ji} and k_{ij}, are intercompartmental rate constants for drug transport from compartment j to compartment i and from compartment i to compartment j, respectively, j and $i \epsilon 1,2 \ldots N$ $i \neq j$. Both k_{ij} and k_{ji} are ≥ 0, and if a particular $k_{ij} = 0$ the status of k_{ji} cannot be inferred. Consequently, matrix **A** has no specified topological arrangement of the compartments. The diagonal elements of matrix **A** are defined by:

$$E_j = k_{j0} + \sum_{\substack{i=1 \\ j \neq i}}^{N} k_{ji} > 0 \qquad \text{(Eq. 2)}$$

$$(j \epsilon 1,2 \ldots N)$$

where k_{j0} ($k_{j0} \geq 0$) is the rate constant for irreversible drug loss from the system *via* compartment j. For an open compartmental system at least one k_{j0} is greater than zero, and for a closed compartmental system all values of k_{j0} are equal to zero.

For an open compartmental system the coefficient matrix **A** is a dominant diagonal matrix with respect to the columns and is an irreducible matrix (2, 3). Since the off-diagonal elements of **A** are non-negative, each $X_j(t)$ is greater than or equal to zero for all values of t for any set of non-negative initial conditions or any non-negative input function (4). Further, since matrix **A** is column dominant it follows from Gerschgorin's eigenvalue theorem (5) that all the characteristic values of **A** have negative real parts. Consequently, $X_j(\infty) = 0$, $j \epsilon 1,2 \ldots N$, for any set of non-negative initial conditions. Combining the non-negativity of $X_j(t)$ and the irreducibility of matrix A no $X_j(t)$ is zero for all values of t when the initial conditions are non-negative and at least one initial condition is >0. The latter conditions guarantee that $\int_0^\infty X_j(t)\,dt$ exists for all values of j and that each integral is greater than zero for any set of non-negative initial conditions with at least one positive initial condition. Theorems concerning the determinant of an irreducible matrix are known (6); thus, $|A| \neq 0$ if at least one $k_{j0} > 0$ and $|A| = 0$ if all $k_{j0} = 0$ for $j \epsilon 1,2 \ldots N$.

A special form of matrix **A** is one in which only one value of k_{j0} is greater than zero. Considering such a system, and without loss of generality, let $k_{10} > 0$ and $k_{j0} = 0$ for $j \epsilon 2,3 \ldots N$. In this case the apparent volume of distribution (V) of the irreducible compartmental system is given by:

$$V = \frac{D \int_0^\infty t\,C(t)\,dt}{\left(\int_0^\infty C(t)\,dt\right)^2} \qquad \text{(Eq. 3)}$$

where D is an impulse drug input into compartment 1 and $C(t)$ is the resulting drug concentration–time function observed in compartment 1 (1). This apparent volume is related to the total amount of drug in the body by the following theorem.

Theorem—For an irreducible compartmental system with irreversible drug loss from one compartment only, *e.g.*, compartment 1, and zero-order drug input K into this compartment, then the limiting concentration, $C_1(\infty)$ in the sampled compartment (compartment 1) is related to the total mass of drug in the system, $T(\infty)$, by:

$$C_1(\infty) \cdot V = T(\infty) \qquad \text{(Eq. 4)}$$

where V is the apparent volume of distribution of the compartmental system as defined by Eq. 3.

Proof—To establish a proof, an expression for the scalar volume ($\overline{V}$) that maps the limiting concentration, $C_1(\infty)$, in compartment 1 to the total mass of drug in the system as $t \to \infty$ is required. If this latter volume can be shown to be identical to V then a proof is established.

Expressions for $T(\infty)$ and $\overline{V}$ can be obtained as follows. By standard Laplace transform theory:

$$x_j(s) = \frac{K}{s} \cdot \frac{(-1)^{j+1}|s\mathbf{I} - \mathbf{M}_{1j}|}{|s\mathbf{I} - \mathbf{A}|} \qquad \text{(Eq. 5)}$$
$$(j \epsilon 1,2, \ldots N)$$

where $x_j(s)$ is the Laplace transform of $X_j(t)$, s the Laplace variable, $\mathbf{M}_{1j}$ the matrix obtained by deleting row 1 and column j from matrix **A**, and **I** is the identity matrix.

Expanding the polynomials in Eq. 5, then:

$$x_j(s) = \frac{K}{s} \cdot \frac{(-1)^{j+1}(s^{N-1} + a_1 s^{N-2} \ldots a_{N-2}s + (-1)^{N-1}|\mathbf{M}_{1j}|)}{(s^N + b_1 s^{N-1} \ldots b_{N-1}s + (-1)^N|\mathbf{A}|)} \qquad \text{(Eq. 6)}$$

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where b_i and a_i are $(-1)^i$ times the sum of the determinants of all the i-squared principle minors of matrix $\mathbf{A}$ and matrix $\mathbf{M}_{1j}$, respectively. The coefficients b_i ($i\epsilon 1,2 \ldots N-1$) and $(-1)^N|\mathbf{A}|$ are greater than zero (1).

Applying the final value theorem of Laplace transforms:

$$\underset{(j\epsilon 1,2 \ldots N)}{X_j(\infty)} = \underset{\text{Lim } s \to 0}{s \cdot x_j(s)} = \frac{K(-1)^{j+1}(-1)^{N-1}|\mathbf{M}_{1j}|}{(-1)^N|\mathbf{A}|} \quad \text{(Eq. 7)}$$

The numerator terms in Eq. 7 are all positive. The latter follows from the fact that $|-\mathbf{A}|$ has all positive cofactors (4), and since $-1^{(N-1)}|\mathbf{M}_{1j}| = |-\mathbf{M}_{1j}|$, the determinants $-1^{(j+1)}|-\mathbf{M}_{1j}|$ are cofactors of $|-A|$. Consequently $X_j(\infty) > 0$ for all values of ($j\epsilon 1,2 \ldots N$) when $K > 0$.

The total amount of drug in the system as $t \to \infty$ is given by $\Sigma_{j=1}^{N} X_j(\infty) = T(\infty)$ and $C_1(\infty) = X_1(\infty)/V_1$ where V_1 is the volume of compartment 1. Consequently, the scalar $\overline{V}$ that maps $C_1(\infty)$ to $T(\infty)$ is given by application of Eq. 7 as:

$$\overline{V} = \frac{\sum_{j=1}^{N}(-1)^{j+1}(-1)^{N-1}|\mathbf{M}_{1j}|}{(-1)^{N-1}|\mathbf{M}_{11}|} \cdot V_1 \quad \text{(Eq. 8)}$$

The latter scalar volume $\overline{V}$ is equivalent to the apparent volume of distribution (V). This identity can be established as follows. Consider the corresponding closed compartmental system ($k_{10} = 0$) with a unit impulse input into compartment 1. In this case, by standard Laplace transform theory:

$$\underset{(j\epsilon 1,2 \ldots N)}{\hat{X}_j(\infty)} = \underset{\text{Lim } s \to 0}{s \cdot \hat{x}_j(s)} = \lim_{s \to 0} \frac{s \cdot (-1)^{j+1}|sI - \mathbf{M}_{1j}|}{|sI - \hat{\mathbf{A}}|}$$

$$= \lim_{s \to 0} \frac{(-1)^{j+1} s\,[s^{N-1} + a_1 s^{N-2} \ldots . a_{N-2}s + (-1)^{N-1}|\mathbf{M}_{1j}|]}{[s^N + \hat{b}_1 s^{N-1} \ldots . \hat{b}_{N-1}s + (-1)^N|\hat{\mathbf{A}}|]} \quad \text{(Eq. 9)}$$

where $\hat{b}_i$ is $(-1)^i$ times the sum of the determinants of all the i-squared principal minors of $\hat{\mathbf{A}}$, $\hat{\mathbf{A}}$ is the coefficient matrix of the closed system (*i.e.*, all $k_{j0} = 0$) and $\hat{X}_j(\infty)$ is the mass of drug in compartment j of the closed system as $t \to \infty$. Since $|\hat{\mathbf{A}}| = 0$, the limits in Eq. 9 are obtained by the L'Hospital rule, and applying Eq. 9:

$$\sum_{j=1}^{N} \hat{X}_j(\infty) = \frac{\sum_{j=1}^{N}(-1)^{j+1}(-1)^{N-1}|\mathbf{M}_{1j}|}{\hat{b}_{N-1}} = 1 \quad \text{(Eq. 10)}$$

Since the system is closed the total amount of drug in the system at any time is unity, this gives the unity identity of Eq. 10.

Substituting Eq. 10 into Eq. 8 gives:

$$\overline{V} = \frac{\hat{b}_{N-1}}{(-1)^{N-1}|\mathbf{M}_{11}|} V_1 \quad \text{(Eq. 11)}$$

The quotient expressed in Eq. 11 has been shown previously (1) to be equivalent to the apparent volume of distribution of a compartmental system, whence $\overline{V} = V$, from which Eq. 4 follows and thus completes the proof.

DISCUSSION

The apparent volume of distribution specified by Eq. 3 does not assume any particular functional form for $C(t)$. After an impulse input (D), V can be calculated by standard numerical methods. Additionally, V can be calculated for any given input function into the central compartment and does not necessitate the use of an intravenous bolus drug dose (1).

As is stated in the given theorem the apparent volume can be used to calculate the total amount of drug in the system at steady state when a constant intravenous infusion is administered: conversely if the amount of drug in the system and $C(\infty)$ are known, then V can be calculated.

The volume of distribution of a compartmental system is the apparent volume of the completely closed system (*i.e.*, when no irreversible drug loss occurs). It is defined as that scalar quantity which maps the equilibrium concentration, in the sampled compartment of the closed system, to the amount of drug in the closed system after a finite drug input (1). For an open system with elimination occurring only from the observed compartment this volume is given by Eq. 3 when an impulse input (D) is used.

Riggs (7) introduced, but without reference to a closed system, the term steady-state distribution volume. This volume of distribution is defined specifically with respect to a two-compartment open model and it is the ratio of the total drug content in the system to the drug concentration in the central compartment, these measurements being taken at a time when the second compartment contains the maximum amount of drug. For a two-compartmental model with drug elimination occurring only from the central compartment the latter definition coincides with the definition based on a closed system. However, in an irreducible open compartmental system with more than two compartments, all of the peripheral compartments will not necessarily be in equilibrium with the central compartment at the same time. Consequently the steady-state distribution volume (7) cannot be arbitrarily extended to include a general N-compartmental system of unknown topology. For a two-compartmental model the use of permeability coefficients for drug transfer (8) or partition coefficients (9) also gives an identical distribution volume to that of the closed system. The concept of permeability and partition coefficients could be extended to larger compartmental models such as mammillary and catenary models. However, the notion of partitioning in systems containing irreversible drug cycles is inappropriate. No such difficulties arise when the closed system is used as the reference.

Since previous analyses are not general it is essential, for a clear understanding of drug distribution volume, to have a general theorem that relates the distribution volume to the total amount of drug in an open system of unknown topology at steady state. It could be argued that it is intuitively obvious that the volume of distribution of a closed system maps the equilibrium concentration of the sampled compartment obtained with a zero-order drug input to the total amount of drug in the system. However, the reverse opinion has been held previously (9, 10) and an erroneous proof has been presented to show that the distribution volume does not have a direct relationship to the total amount of drug in the system at steady state (10).

The derivation of the theorem presented in the text is general in the sense that no knowledge of the topology of the system is required and consequently no constraints on the eigenvalues of the system are required nor are any constraints on intercompartmental rate constants required. However, it is assumed that irreversible drug loss from the system occurs only from the sampled compartment.

Although the term compartment has been used in the derivation, the term is merely a convenience and should not be interpreted literally as a circumscribable region of space. Frequently the term noncompartmental is applied incorrectly to pharmacokinetic theory when topological independence is intended (11, 12).

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