Theorems on the Apparent Volume of Distribution of a Linear System

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Abstract □ If the concentration of drug in one compartment of a linear N-compartment system, without sinks and loss only from the sampled compartment is sampled, then the total apparent volume of distribution can be determined without knowledge of the topology of the system. This apparent volume is identical to the apparent volume of the corresponding closed system.

Keyphrases □ Volume of distribution—apparent, theorems of a linear system □ Linear system—theorems on the apparent volume of distribution □ Theorems—apparent volume of distribution of a linear system

Oppenheimer and others have derived a noncompartmental drug distribution volume (1). This volume is the ratio of the first statistical moment of the blood drug concentration–time function observed after a unit intravenous drug dose to the integral of the function on $(0,\infty)$. Benet and Galeazzi have re-presented Oppenheimer's derivation (2). In both these texts the derivation is not strictly analytical and relies mainly on unsubstantiated statements. However, this expression for a distribution volume has previously been derived, for an N-compartmental system, in a strict analytical fashion by Bright (3).

Bright's derivation is based on the following assumptions:

(*a*) irreversible drug loss from the compartmental system occurs only from the sampled compartment;

(*b*) the eigenvalues of the coefficient matrix are all real and distinct;

(*c*) if Compartment j is connected to Compartment i (i and $j \in 1,2,\ldots N, i \neq j$) by a rate constant, $k_{ji} > 0$, then compartment i is connected to compartment j by a rate constant $k_{ij} > 0$;

(*d*) $k_{ij} = k_{ji}$.

Conditions *c* and *d* define the coefficient matrix of the N-compartmental system as a symmetric matrix which directly implies condition *b*. Conditions *b* and *c*, but not necessarily condition *d*, are obviously realizable for mammillary and caternary compartmental systems (4, 5). However, condition *b* specifically excludes any compartmental system whose matrix has repeated real eigenvalues or has pairs of complex conjugate eigenvalues. Condition *c* excludes systems with nonreversible cycles involving three or more compartments, regardless of the validity of condition *b*.

Compartment systems, that are based on physiological considerations and include specific compartments for the arterial and venous blood, must contain nonreversible drug circulation cycles involving three or more compartments. Consequently, previous derivations (3) are not applicable to such systems.

In the present report, a relationship between the volume of distribution of a compartmental system and the first moment of the sampled function is derived. This derivation does not require conditions on the eigenvalues of the system, the topology of the system, or the intercompartmental rate constants.

THEORY

Consider an arbitrary set of N interconnected compartments in which it is possible for material in Compartment j to reach all other Compartments $i, i \neq j$. Such a system of compartments does not contain any sinks, disjointed sets of compartments, or subsystems (6). For such a system:

$$\begin{pmatrix} \dot{X}_1 \\ \dot{X}_2 \\ \dot{X}_3 \\ \vdots \\ \dot{X}_n \end{pmatrix} = \begin{pmatrix} -E_1 & k_{21} & k_{31} & \cdots & k_{N1} \\ k_{12} & -E_2 & k_{32} & & k_{N2} \\ k_{13} & k_{23} & -E_3 & & k_{N3} \\ \vdots & \vdots & \vdots & & \vdots \\ k_{1N} & k_{2N} & k_{3N} & & k_{N4} \end{pmatrix} \begin{pmatrix} X_1 \\ X_2 \\ X_3 \\ X_4 \end{pmatrix} \equiv \dot{\boldsymbol{X}} = \boldsymbol{AX} \quad \text{(Eq. 1)}$$

where $X_j (j \in 1,2,\ldots N)$ is the amount of drug in compartment j, and $\dot{X}_j$ is the first derivative with respect to time of X_j. Intercompartmental rate constants, k_{ji} and k_{ij}, are for drug transport from Compartment j to Compartment i and from Compartment i to Compartment j, respectively (j and $i \in 1,2,\ldots N, i \neq j$). Both k_{ij} and k_{ji} are ≥ 0. If a particular k_{ij} is zero, the status of k_{ji} cannot be inferred.

The E_j's are defined as:

$$E_j = k_{jo} + \sum_{\substack{i=1 \\ j \neq i}}^{N} k_{ji} \qquad (j \in 1,2,\ldots N) \quad \text{(Eq. 2)}$$

where $k_{jo} (k_{jo} \geq 0)$ is the rate constant for irreversible drug loss from the system *via* Compartment j.

The coefficient matrix $\boldsymbol{A}$ is a dominant diagonal matrix and, since the compartmental system does not contain any sinks or disjointed subsystems, matrix $\boldsymbol{A}$ cannot be reduced to a matrix of the form:

$$\begin{pmatrix} \boldsymbol{P} & \boldsymbol{O} \\ \boldsymbol{U} & \boldsymbol{Q} \end{pmatrix}$$

by some permutation of the rows and columns where $\boldsymbol{P}$ and $\boldsymbol{Q}$ are square matrixes and $\boldsymbol{O}$ consists of zero elements. These row column permutations are equivalent to a renumbering of the compartmental system (6).

Matrix $\boldsymbol{A}$ is irreducible and theorems have been given (7) for irreducible dominant diagonal matrixes of the form specified by matrix $\boldsymbol{A}$; thus, the determinant of matrix $\boldsymbol{A}$ is bound by $|\boldsymbol{A}| \neq 0$ if at least one $k_{jo} \geq 0$, and $|\boldsymbol{A}| = 0$ if all the $k_{jo} = 0$ for $j \in 1,2,\ldots N$.

A special form of matrix $\boldsymbol{A}$ is one in which only one k_{jo} is greater than zero. Considering such a system, and without loss of generality, let $k_{10} > 0$ and $k_{jo} = 0 (j \in 2,3,\ldots N)$. In this case:

$$|\boldsymbol{A}| = -\left(k_{10} + \sum_{j=2}^{N} k_{1j}\right) |\boldsymbol{M}_{11}| + \sum_{j=2}^{N} (-1)^{(j-1)} k_{j1} |\boldsymbol{M}_{1j}| \neq 0 \quad \text{(Eq. 3)}$$

where $\boldsymbol{M}_{11}$ is the principle minor of matrix $\boldsymbol{A}$ obtained by deleting Row 1 and Column 1, and the $\boldsymbol{M}_{1j}$'s are the minors of $\boldsymbol{A}$ obtained by deleting Row 1 and Column $j (j \in 2,3,\ldots N)$.

The minors, $\boldsymbol{M}_{11}$ and $\boldsymbol{M}_{1j}$ are independent of k_{10}. By setting $k_{10} = 0$ in Eq. 3 and utilizing Taussky's theorem, it follows that:

$$-\sum_{j=2}^{N} k_{1j} |\boldsymbol{M}_{11}| + \sum_{j=2}^{N} (-1)^{(j-1)} k_{j1} |\boldsymbol{M}_{1j}| = 0$$

consequently, Eq. 3 becomes:

$$|\boldsymbol{A}| = -k_{10} |\boldsymbol{M}_{11}| \quad \text{(Eq. 4)}$$

Volume of Distribution—Consider a closed irreducible compart-

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mental system (*i.e.*, $k_{jo} = 0$ for all $j, j\epsilon 1,2,\ldots N$) with a unit drug impulse input, δD, into a particular compartment. Assume the drug concentration–time function, $\hat{C}(t)$, in Compartment 1 is observed. Since the system is closed, the amount of drug in the compartmental system at any time t is D. Also, since the system is irreducible and closed, the system will eventually achieve a state of drug concentration equilibrium. Consequently, the equilibrium drug concentration, $\hat{C}(\infty)$, in Compartment 1 is governed by $\hat{C}(\infty) > 0$. The volume of distribution of the closed system, V, may be defined as the scalar that maps the equilibrium concentration in the sampled compartment to the known amount of drug in the system, where $V = D/\hat{C}(\infty)$.

If the equilibrium concentration in all compartments of the closed system were identical, then V would define the exact volume of the system. However, since the latter condition cannot be assumed to hold for an arbitrarily closed compartmental system, the derived volume must be regarded as an apparent distribution volume. In general, $\hat{C}(\infty)$ will not be constant for all observation points. Consequently, the numerical value of V depends on which particular compartment is sampled.

The apparent volume of an open irreducible compartmental system is the same as the corresponding closed system. When the topology and intercompartmental rate constants of an open system are known, the distribution volume can be calculated readily. However, an analytical method for calculating V, which does not require specified topology or intercompartmental rate constants, would be useful since the calculated V would be model independent.

Theorem 1—For an irreducible compartmental system with irreversible drug loss from one compartment only and sampling from the same compartment, the first moment, $\bar{t}$, of the sample concentration–time function, $C(t)$, after an impulse input, δD, into the sample compartment is related to the apparent volume of distribution, V, of the corresponding closed compartmental system by:

$$\frac{D\bar{t}}{\int_0^\infty C(t)dt} = V$$

where $\bar{t} = \int_0^\infty tC(t)dt / \int_0^\infty C(t)dt$.

Proof—To establish a proof, expressions for $\bar{t}/\int_0^\infty C(t)dt$ of an open compartmental system with sampling and loss from one compartment and the concentration at $t = \infty$ in the corresponding closed system, $\hat{C}(\infty)$, are required. These expressions are derived first and then used to establish the theorem.

Open System—For an impulse input, δD, into Compartment 1, the initial conditions are $X_1(+0) = D$ and $X_j(+0) = 0$ for $j\epsilon 2,3,\ldots N$. With these initial conditions, the Laplace transform $x_1(s)$ of $X_1(t)$ can be expressed by standard methods as:

$$x_1(s) = \frac{D|s\boldsymbol{I} - \boldsymbol{M}_{11}|}{|s\boldsymbol{I} - \boldsymbol{A}|} = \frac{D(s^{N-1} + a_1 s^{N-2} \ldots a_{N-2}s + (-1)^{N-1}|\boldsymbol{M}_{11}|)}{(s^N + b_1 s^{N-1} \ldots b_{N-1}s + (-1)^N|\boldsymbol{A}|)} \quad \text{(Eq. 5)}$$

where b_j and a_j are $(-1)^j$ times the sum of the determinants of all the j-squared principle minors of matrix $\boldsymbol{A}, j\epsilon 1,2,\ldots N-1$, and matrix $\boldsymbol{M}_{11}$, respectively.

Since $\boldsymbol{A}$ and $\boldsymbol{M}_{11}$ are matrixes with real elements, the coefficients a_j and b_j are real. Both $\boldsymbol{A}$ and $\boldsymbol{M}_{11}$ are dominant diagonal matrixes and by the application of Gerschgorins root location theorem (8) both $\boldsymbol{A}$ and $\boldsymbol{M}_{11}$ have eigenvalues with negative real parts. Consequently, the polynomials $|s\boldsymbol{I} - \boldsymbol{A}|$ and $|s\boldsymbol{I} - \boldsymbol{M}_{11}|$ have coefficients that are all of the same sign (9). Since the diagonal elements of $\boldsymbol{A}$ and $\boldsymbol{M}_{11}$ are negative, the coefficients a_1 and b_1 are positive, consequently, $a_j > 0$ and $b_j > 0$ for all $j(j\epsilon 1,2,\ldots N-1)$ and $(-1)^N|\boldsymbol{A}| > 0$ as is $(-1)^{N-1}|\boldsymbol{M}_{11}|$.

By standard Laplace transform theory:

$$-\frac{dx_1(s)}{ds} = \int_0^\infty tX_1(t)dt = \lim_{ts\to 0} \frac{D[b_{N-1}(-1)^{N-1}|\boldsymbol{M}_{11}| - a_{N-2}(-1)^N|\boldsymbol{A}|]}{|\boldsymbol{A}|^2} \quad \text{(Eq. 6)}$$

which on substitution of Eq. 4 into Eq. 6 gives:

$$\int_0^\infty tX_1(t)dt = \frac{D(b_{N-1} - a_{N-2}k_{10})}{(-1)^{N-1}|\boldsymbol{M}_{11}|(k_{10})^2} \quad \text{(Eq. 7)}$$

Also, by standard Laplace transform theory:

$$\lim_{ts\to 0} \frac{x_1(s)}{} = \int_0^\infty X_1(t)dt = \frac{(-1)^{N-1}|\boldsymbol{M}_{11}|D}{(-1)^N|\boldsymbol{A}|} \equiv \frac{D}{k_{10}} \quad \text{(Eq. 8)}$$

The latter identity in Eq. 8 follows from Eq. 4. The limits in Eqs. 6 and 8 are guaranteed by the fact that $X_j, j\epsilon 1,2,\ldots N$, are nonnegative bounded functions such that $X_j(\infty) = 0$(10). The $X_j(t)$ functions are nonnegative since the off diagonal elements of A are ≥ 0 (11), and $X_j(\infty) = 0$ because the eigenvalues of A have negative real parts. Combining Eqs. 7 and 8 and substituting $X_1(t) = V_1C(t)$, where V_1 is the volume of Compartment 1, then:

$$\frac{D\int_0^\infty C(t)dt}{\left(\int_0^\infty C(t)dt\right)^2} = \frac{(b_{N-1} - a_{N-2}k_{10})}{(-1)^{N-1}|\boldsymbol{M}_{11}|}V_1 \quad \text{(Eq. 9)}$$

Closed System—In the arbitrary open system, $k_{10} > 0$ and $k_{jo} = 0$ for $j\epsilon 2,\ldots N$; consequently, the corresponding closed system is obtained by setting $k_{10} = 0$ in $\boldsymbol{A}$. Let the closed system matrix be $\hat{\boldsymbol{A}}$ and let $\hat{\boldsymbol{M}}_{11}$ be the matrix obtained by deleting Row one and Column one from $\hat{\boldsymbol{A}}$; $\hat{\boldsymbol{M}}_{11} = \boldsymbol{M}_{11}$ and from Eq. 4, $|\hat{\boldsymbol{A}}| = 0$. Let $\hat{X}_1(t)$ represent the mass–time function of drug in Compartment 1 after an impulse input, δD, into Compartment 1.

By standard Laplace transform theory:

$$\lim_{ts\to 0} \frac{s\hat{x}_1(s)}{} = X_1(\infty) = \lim_{s\to 0} \frac{ts|s\boldsymbol{I} - \boldsymbol{M}_{11}|}{|s\boldsymbol{I} - \hat{\boldsymbol{A}}|} = \lim_{s\to 0} t\,\frac{Ds(s^{N-1} + a_1 s^{N-2} \ldots a_{N-2}s + (-1)^{N-1}|\boldsymbol{M}_{11}|}{(s^N + \hat{b}_1 s^{N-1} \ldots \hat{b}_{N-1}s + (-1)^N|\hat{\boldsymbol{A}}|)} = \frac{(-1)^{N-1}|\boldsymbol{M}_{11}|D}{\hat{b}_{N-1}} \quad \text{(Eq. 10)}$$

where $\hat{b}_j$ is $(-1)^j$ times the sum of the determinants of all the j-squared principle minors of $\hat{\boldsymbol{A}}$.

Since the volume of distribution, V, is defined by $V = D/\hat{C}(\infty)$, and $V_1\hat{C}(\infty) = \hat{X}_1(\infty)$, then from Eq. 10:

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

The equivalence of Eqs. 9 and 11 is necessary and sufficient for Theorem 1 to hold. Consequently, if:

$$\hat{b}_{N-1} = (b_{N-1} - a_{N-2}k_{10}) \quad \text{(Eq. 12)}$$

then Theorem 1 is established. The latter identity, Eq. 12, can be proved as follows: The coefficients b_{N-1}, $\hat{b}_{N-1}$, and a_{N-2} are given as:

$$b_{N-1} = (-1)^{N-1}\sum_{j=1}^{N}|\hat{\boldsymbol{M}}_{jj}|$$

$$\hat{b}_{N-1} = (-1)^{N-1}\sum_{j=1}^{N}|\hat{\boldsymbol{M}}_{jj}| \quad \text{(Eq. 13)}$$

$$a_{N-2} = (-1)^{N-2}\sum_{j=1}^{N-1}|\hat{\boldsymbol{M}}_{jj}| \quad \text{(Eq. 14)}$$

where M_{jj} and $\hat{M}_{jj}$ are the $(N-1)$ squared principle minors of the N-squared matrixes $\boldsymbol{A}$ and $\hat{\boldsymbol{A}}$, respectively, and the $\overline{M}_{jj}$'s are the $(N-2)$ squared principle minors of the $(N-1)$ squared matrix $\boldsymbol{M}_{11}$. The coefficient b_{N-1} can be expressed as:

$$b_{N-1} = (-1)^{N-1}\left[|\boldsymbol{M}_{11}| + \sum_{j=1}^{N-1}|\boldsymbol{P}_j|\right] \quad \text{(Eq. 15)}$$

where:

$$|\boldsymbol{P}_j| = \begin{vmatrix} -E_1 & \boldsymbol{r}_{j+1} \\ \boldsymbol{c}_{j+1} & \hat{\boldsymbol{M}}_{jj} \end{vmatrix}$$

and where $\boldsymbol{r}_{j+1}(j\epsilon 1,2,\ldots N-1)$ is the row of $N-2$ elements obtained from $(k_{21},k_{31},\ldots k_{N1})$ by striking out the element $k_{j+1,1}$ and $\boldsymbol{c}_{j+1}$ is the column of $N-2$ elements obtained from $(k_{12},k_{13},\ldots k_{1N})^T$ by striking out the element $k_{1,j+1}$. Expanding the determinants $|\boldsymbol{P}_j|(j\epsilon 1,2,\ldots N-1)$ by their first rows, then:

$$b_{N-1} = (-1)^{N-1}\left[|\boldsymbol{M}_{11}| - \left(k_{10} + \sum_{i=2}^{N}k_{1i}\right)\sum_{j=1}^{N-1}|\overline{\boldsymbol{M}}_{jj}| + \sum_{j=1}^{N-1}|Z_j|\right] \quad \text{(Eq. 16)}$$

where $|Z_j|$ is the summation of determinants associated with the expansion of $|\boldsymbol{P}_j|$ along $\boldsymbol{r}_{j+1}$. Since the elimination constant k_{10} does not occur in any $\boldsymbol{r}_{j+1}$ or any $\overline{\boldsymbol{M}}_{jj}$, the determinants $|Z_j|$ are independent of k_{10}. Since $\boldsymbol{M}_{11}$ is also independent of k_{10}, then $\hat{b}_{N-1}$ is directly obtainable from b_{N-1} by setting $k_{10} = 0$ in Eq. 16, thus:

$$\delta_{N-1} = (-1)^{N-1}\left[|\boldsymbol{M}_{11}| - \left[\sum_{i=2}^{N} k_{1i}\right]\sum_{j=1}^{N-1}|\overline{\boldsymbol{M}}_{jj}| + \sum_{j=1}^{N-1}|Z_j|\right] \quad \text{(Eq. 17)}$$

Substitution of Eqs. 16 and 17 into Eq. 12 establishes the identity expressed in Eq. 12 and thus complete the proof of Theorem 1.

Theorem 2—For a known nonnegative and finite drug input function, $\mathrm{In}(t)$, into Compartment 1 of an open irreducible compartmental system, with sample and loss from Compartment 1 only, the volume of distribution of the corresponding closed system, V, is given by:

$$V \equiv \frac{\int_0^\infty tC(t)dt}{\left(\int_0^\infty C(t)dt\right)^2} = \left[\frac{\int_0^\infty t\overline{R}(t)dt}{\int_0^\infty \overline{R}(t)dt} - \frac{\int_0^\infty t\mathrm{In}(t)dt}{\int_0^\infty \mathrm{In}(t)dt}\right]\frac{\int_0^\infty \mathrm{In}(t)dt}{\int_0^\infty \overline{R}(t)dt} \quad \text{(Eq. 18)}$$

where $\overline{R}(t)$ is the observed drug concentration–time function produced by the input function $\mathrm{In}(t)$, and $C(t)$ is the concentration–time function produced by a unit impulse input into Compartment 1. Both $\overline{R}(t)$ and $C(t)$ are observed in Compartment 1.

Proof—By application of standard linear system theory the mass of drug, $R(t)$, in Compartment 1 is:

$$R(t) = \int_0^t \mathrm{In}(\tau)X_1(t-\tau)d\tau \quad \text{(Eq. 19)}$$

where $X_1(t)$ is the mass–time function in Compartment 1 that would result from a unit impulse input into Compartment 1.

By the standard Laplace transform theory:

$$\int_0^\infty tR(t)dt = \frac{dR(s)}{ds} = \operatorname*{Lim}_{ts\to 0} \operatorname*{Lim}_{s\to 0} t\left[-\frac{d\mathrm{In}(s)}{ds}x_1(s) - \frac{dx_1(s)}{ds}\mathrm{In}(s)\right] \quad \text{(Eq. 20)}$$

Since $\mathrm{In}(t)$ is a nonnegative function with $\mathrm{In}(\infty) = 0$ the limit of $\mathrm{In}(s)$ as $s \to 0$ is $\int_0^\infty \mathrm{In}(t)dt$ and the limit of $-d\mathrm{In}(s)/ds$ as $s \to 0$ is $\int_0^\infty t\,\mathrm{In}(t)dt$. Also, since $X_1(t)$ is nonnegative and integrable on $(0,\infty)$ the limit of $x_1(s)$ as $s \to 0$ is $\int_0^\infty X_1(t)dt$, and the limit of $-dx_1(s)/ds$ is $\int_0^\infty tX_1(t)dt$. Applying a known theorem on the limits of products of Laplace transforms (10):

$$\int_0^\infty tR(t)dt = \int_0^\infty t\mathrm{In}(t)dt\int_0^\infty X_1(t)dt + \int_0^\infty tX_1(t)dt\int_0^\infty \mathrm{In}(t)dt \quad \text{(Eq. 21)}$$

Also, applying the known theorem on limits (10) to Eq. 19:

$$\int_0^\infty R(t)dt = \int_0^\infty \mathrm{In}(t)dt\int_0^\infty X_1(t)dt \quad \text{(Eq. 22)}$$

An expression for $\int_0^\infty tX_1(t)dt/\int_0^\infty X_1(t)dt$ is obtainable by a rearranging Eq. 21 and dividing by Eq. 22, which on dividing by $\int_0^\infty X_1(t)dt$ and utilizing Eq. 22 gives:

$$\frac{\int_0^\infty tX_1(t)dt}{\left(\int_0^\infty X_1(t)\right)^2} = \left(\frac{\int_0^\infty tR(t)dt}{\int_0^\infty R(t)dt} - \frac{\int_0^\infty t\mathrm{In}(t)dt}{\int_0^\infty \mathrm{In}(t)dt}\right)\frac{\int_0^\infty \mathrm{In}(t)dt}{\int_0^\infty R(t)dt} \quad \text{(Eq. 23)}$$

Substituting $V_1C(t) = X_1(t)$ and $V_1\overline{R}(t) = R(t)$ into Eq. 23 gives Eq. 18 and completes the proof of Theorem 2.

DISCUSSION

Theorems 1 and 2 state model-independent methods for calculating a drug distribution volume. The expressions are model independent in the sense that no knowledge of the topology of the compartmental system is required. Since no constraints on the topology are applied, then no constraints on either the eigenvalues of the coefficient matrix or on intercompartmental rate constants are applied. Additionally, it is not necessary to specify some functional form (*e.g.*, a summation of exponentials) to apply the equations. However, it is assumed in the derivation that irreversible drug loss from the system occurs only from the sampled compartment. The proofs of Theorems 1 and 2 are strictly analytical and have the advantage of being mainly algebraic. No concepts of clearance or equilibrium elimination are required.

The derived volume is clearly related to the apparent volume of the corresponding closed system.

Although the terms compartments are used in the derivation, their use should not be interpreted literally as circumscribable regions of space where physical translocation of matter takes place. The term is merely a convenience. Matrix $\boldsymbol{A}$ is simply an operator for a stable linear system, and the conditions of nonnegative off-diagonal elements in $\boldsymbol{A}$ are necessary if observations in the system are to be nonnegative functions. Also, the negative diagonal elements are necessary for stability. Consequently, the derivation could have followed equally well the line of considering a stable linear system which would also have yielded Eq. 1 but where the elements of Matrix $\boldsymbol{A}$ would have no meaning in relation to compartmental analysis. These latter concepts have been discussed previously (11).

To apply Theorem 1, it is not necessary to assume any functional form to describe the $C(t)$ data. The numerical values of the required integrals can be obtained by standard numerical methods (2). For Theorem 2, it is necessary to know the functional form of the input function. For example, the input function may be a step input of magnitude k and of duration τ. In this case $\int_0^\infty \mathrm{In}(t)dt = k\tau$ and $\int_0^\infty t\ \mathrm{In}(t)\ dt = k\tau^2/2$. The numerical values of the other integrals in Theorem 2 are obtainable by standard numerical methods.

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