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A Proof of the Occupancy Principle and the Mean-Transit-Time Theorem for Compartmental Models

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Abstract

The occupancy principle and the mean-transit-time theorem are derived for the passage of a tracer through a system that can be described by a general pool model. It is proved, using matrix theory, that if (and only if) tracer entering the system labels equally all tracee fluxes into the system, then the integral of the tracer concentration is the same in all the pools. It is also proved that if, in addition, all flow out of the system is through the observation point, the first moment of the tracer concentration at the observation point can be used to calculate the total amount of trace in the system. The necessity of this condition is analyzed. Examples are given of models in which the occupancy principle and the mean-transit-time theorem hold or do not hold.

INTRODUCTION

In analyzing tracer kinetic data, the total tracee flux through the system is frequently determined from the area under the tracer concentration curve at some point in the system by applying the occupancy principle [1], which requires the area to be the same at all points in the system under certain conditions to be described below. Also, the first moment of the tracer concentration curve is used to determine the total amount of tracee in the system, given knowledge of the steady-state tracee flow through the system.

In this paper, the two results are proved for a general pool model from appropriate assumptions. The results are not new, but it is felt that the proofs are of interest, since they utilize familiar equations for pool models and make clear how the assumptions lead to the conclusions. Hence the new proofs may lead to a better understanding of the assumptions, applicability, and limitations of both the occupancy principle and the mean-transit-time theorem. The study of the converse of the mean-transit-time theorem is thought to be new. The mathematical proofs are followed by a discussion with examples and counterexamples.

Perl et al. [2] have presented proofs, using matrix theory, of basic theorems on flow, system volume, and mean transit time for models that can be described by three interconnected “compartment regions.” Their formulation is somewhat more general than that of a three-pool model, but it is restrictive in that while each region does not have to be a single pool, all the outflow from a region must have the same tracer concentration. In the current paper, a general pool model is considered, and the occupancy principle and the mean-transit-time theorem (relating the tracer mean transit time to the distribution volume of the tracee) are derived from appropriate assumptions.

Orr and Gillespie [1] have stated and proved the occupancy principle for a general linear system. Their proof applies to compartmental models as particular instances of a general linear system. Bergner [3] has also proved the occupancy principle, though the proof is somewhat hard to follow. Hearon [4] has proved an equivalent theorem for experiments in which tracer infusion is at a constant rate.

The mean-transit-time theorem is stated without proof in any number of books and articles. A proof, based on exit-age distributions, has been given by Danckwerts [5].

MATHEMATICAL DESCRIPTION

An arbitrary open, nonsingular, linear, stationary model with n pools is considered. The pools are numbered from 1 to n . The i th pool has a distribution volume M_i , the flow rate or flux from the j th pool to the i th pool is R_{ij} , the flux from outside the system to the i th pool is R_{i0} , and the total flux into or out of the i th pool is R_{ii} :

$$R_{ii} = \sum_{j \neq i} R_{ij} = \sum_{j \neq i} R_{ji}.$$

The volumes and fluxes are for the traced substance, or *tracee*. Tracer enters the system at the rate $z(t)$ at time t ; the fraction entering the i th pool is p_i . The total amount of tracer entering the system is a finite quantity m , equal to $\int_0^\infty z(t) dt$. Initially, at $t = 0$, there is no tracer in any of the pools.

Stationarity implies that volumes, fluxes, and the p_i 's are constant with time; also, the total flux into each pool equals the total flux out of that pool. Linearity implies that linear differential equations can be written for y_i , the tracer concentration in each pool:

$$M_i \frac{dy_i(t)}{dt} = -R_{ii}y_i(t) + \sum_{j \neq i} R_{ij}y_j(t) + p_i z(t), \quad i=1, \dots, n.$$

In matrix notation,

$$\frac{dy}{dt} = Ay + bz, \quad y(0)=0,$$

where

y is a vector with n elements $y_1, y_2, \dots, y_n$,

A is an $n \times n$ matrix with $A_{ii} = -R_{ii}/M_i$, $A_{ij} = R_{ij}/M_i$, and

b is a vector with n elements $p_1/M_1, p_2/M_2, \dots, p_n/M_n$.

If the tracer enters the system as a bolus or impulse, $z(t)$ is $m\delta(t)$, where m is the amount injected and $\delta(t)$ is the Dirac delta function. Alternatively, as is usually done, $z(t)$ can be set equal to zero and $y_i(0)$ set equal to $p_i m/M_i$. The solutions are identical. The development here uses $z(t)$, since more general tracer inputs can be considered.

The system is open, which means that there is at least one flow out of the system. It is nonsingular [4], which means that for every pool, there is a flow path leading out of the system from that pool (directly or through other pools). This term arises from the matrix A being nonsingular. Nonsingularity implies that tracer introduced anywhere will eventually disappear from the system. Mathematically, nonsingularity means that the eigenvalues of A are all negative and so the solutions for y contain only decaying exponentials. Therefore, tracer concentrations asymptotically approach zero in an exponential fashion: $y(t)$, $ty(t)$, etc., go to zero as t goes to ∞ .

The description here is for a general pool model structure. By a particular model is meant that n is specified and that each R_{ij} and p_i ($0 \leq i \leq n$, $0 \leq j \leq n$) is specified to be zero or positive (the connectivity matrix is known). The numerical values of the nonzero R_{ij} and p_i are usually not known. The purpose of the tracer study is to estimate these numerical values. The theorems proved here spell out the conditions under which two model parameters,

$F = \sum_{i=1}^n R_{0i} = \sum_{i=1}^n R_{i0}$ and $M_T = \sum_{i=1}^n M_i$, can be estimated from observed tracer concentrations.

RESULTS

OCCUPANCY PRINCIPLE

In an open, nonsingular, linear, stationary compartmental system, let the fraction of tracer entering any pool (p_i) from outside the system equal the fraction of tracee flux from outside the system (F) that enters that pool:

$$p_i = \frac{R_{i0}}{F} = \frac{R_{i0}}{\sum_{i=1}^n R_{i0}}.$$

That is, the tracer input labels all tracee fluxes into the system equally. Then $\int_0^\infty y_i dt$ is the same for all i and equals m/F , where m is the total amount of tracer entering the system ($\int_0^\infty z(t) dt$). The integral $\int_0^\infty (y_i/m) dt$ is defined as the occupancy [1]; the principle states that the occupancy is the same at all points in the system. The converse is also true: if the occupancy is the same at all points in the system, the tracer must label all fluxes into the system equally.

Proof—Since $A_{ii} = -R_{ii}/M_i$,

$$\begin{aligned} -M_i A_{ii} &= R_{ii} = \text{total flux into or out of pool } i \\ &= \text{flux into } i \text{ from other pools} + \text{flux into } i \text{ from outside} \\ &= M_i \sum_{j \neq i} A_{ij} + R_{i0}. \end{aligned}$$

So

$$M_i \sum_{j=1}^n A_{ij} = -R_{i0}. \quad (1)$$

The model $dy/dt = Ay + bz$ may be integrated from $t = 0$ to $t = \infty$:

$$y(\infty) - y(0) = A \int_0^\infty y(t) dt + b \int_0^\infty z(t) dt$$

We note that $y(\infty) = 0$ for a nonsingular system, $y(0) = 0$ by assumption and $\int_0^\infty z(t) dt = m$, the total amount of tracer entering the system. Thus,

$$A \int_0^\infty y(t) dt = -bm. \quad (2)$$

Solving, $\int_0^\infty y_i(t) dt = -m \sum_{k=1}^n A_{ik}^{-1} b_k = -m \sum_{k=1}^n A_{ik}^{-1} p_k / M_k$.

If the tracer input labels all tracee input fluxes equally, then $p_k = R_{k0}/F$, which equals $-M_k \sum_{j=1}^n A_{kj}/F$ from Equation (1). Therefore,

$$\begin{aligned} \int_0^\infty y_i(t) dt &= m \sum_{k=1}^n A_{ik}^{-1} \sum_{j=1}^n \frac{A_{kj}}{F} \\ &= \frac{m}{F} \sum_{j=1}^n \sum_{k=1}^n A_{ik}^{-1} A_{kj} \\ &= \frac{m}{F} \sum_{j=1}^n \delta_j^i = \frac{m}{F}, \end{aligned}$$

where δ_j^i is the Kronecker delta, equal to 1 if $i = j$ and 0 if $i \neq j$. Thus we prove that the occupancy is the same everywhere:

$$\int_0^\infty y_i dt = \frac{m}{F} \quad \text{for all } i. \quad (3)$$

To prove the converse (necessity), we begin with Equation (2) and solve for b :

$$b = -A \int_0^\infty y(t) dt / m.$$

If the occupancy is the same everywhere, the integrals $\int_0^\infty y_i(t) dt / m$ are all equal, say f . Then,

$$p_i = b_i M_i = -f M_i \sum_{j=1}^n A_{ij} = f R_{i0}$$

from Equation (1).

Thus the fraction of tracer entering the i th pool is proportional to the tracee flux into that pool from the outside. (This proof follows the development in Hearon [4].)

MEAN-TRANSIT-TIME THEOREM

If the occupancy principle holds (that is, tracer input labels all trace e fluxes into the system equally), and if all the flux out of the system, F , is through the observation point, then the total volume of distribution of the traced substance, M_T , can be obtained from the first moment of the observed concentration, x :

$$\frac{M_T}{F} = \frac{\int_0^\infty tx(t) dt - \frac{1}{F} \int_0^\infty tz(t) dt}{\int_0^\infty x(t) dt}.$$

Here, x may equal one of the y_i 's or a weighted mean of some or all the y_j 's. The converse is discussed at the end of the proof.

Proof—Let q_j be the fraction of F that leaves the system from pool j . Then $q_j F$ is the flux from pool j to outside the system:

$$\begin{aligned} q_j F &= (\text{total flux out of pool } j) - (\text{flux from pool } j \text{ to other pools}) \\ &= R_{jj} - \sum_{i \neq j} R_{ij} \\ &= -M_j A_{jj} - \sum_{i \neq j} M_i A_{ij}, \\ q_j F &= -\sum_{i=1}^n M_i A_{ij}. \end{aligned} \tag{4}$$

Also, since all flux out is through the observation point,

$$x = \sum_{j=1}^n q_j y_j.$$

The model $dy/dt = Ay + bz$ may be multiplied by t and integrated from $t = 0$ to $t = \infty$:

$$\int_0^\infty t \frac{dy}{dt} dt = A \int_0^\infty ty(t) dt + b \int_0^\infty tz(t) dt.$$

Integrating the left side by parts and noting that $ty(t)$ goes to zero as t goes to ∞ , that $\int_0^\infty y(t) dt$ equals mu/F by the occupancy principle (u is the unit column vector: $u^T = [1 \ 1 \ \dots 1]$), and that b can be substituted from Equation (2), we obtain

$$\int_0^\infty ty(t) dt = -A^{-1} \frac{mu}{F} + \frac{m_1 u}{F}$$

where m_1 stands for $\int_0^\infty tz(t) dt$. The j th element is given by

$$\int_0^\infty ty_j(t) dt = \frac{-m}{F} \sum_{k=1}^n A_{jk}^{-1} + \frac{m_1}{F}.$$

The first moment of the observed tracer concentration, x , is given by

$$\begin{aligned}\int_0^\infty tx(t) dt &= \sum_{j=1}^n q_j \int_0^\infty ty_j(t) dt \\ &= \frac{-m}{F} \sum_{j=1}^n q_j \sum_{k=1}^n A_{jk}^{-1} + \frac{m_1}{F} \sum_{j=1}^n q_j.\end{aligned}\quad (5)$$

Noting that $\sum_{j=1}^n q_j = 1$, and using Equation (4),

$$\begin{aligned}\int_0^\infty tx(t) dt &= \frac{m}{F^2} \sum_{j=1}^n \sum_{i=1}^n M_i A_{ij} \sum_{k=1}^n A_{jk}^{-1} + \frac{m_1}{F} \\ &= \frac{m}{F^2} \sum_{i=1}^n M_i \sum_{k=1}^n \sum_{j=1}^n A_{ij} A_{jk}^{-1} + \frac{m_1}{F} \\ &= \frac{m}{F^2} \sum_{i=1}^n M_i \sum_{k=1}^n \delta_k^i + \frac{m_1}{F}.\end{aligned}$$

Thus,

$$\int_0^\infty tx(t) dt = \frac{mM_T}{F^2} + \frac{1}{F} \int_0^\infty tz(t) dt.$$

Noting that $\int_0^\infty x(t) dt = m/F$ from the occupancy principle,

$$\frac{M_T}{F} = \frac{\int_0^\infty tx(t) dt - \frac{1}{F} \int_0^\infty tz(t) dt}{\int_0^\infty x(t) dt}.\quad (6)$$

This concludes the proof.

The quantity M_T/F is frequently termed the mean transit time. It equals the tracer mean transit time when the conditions specified are met.

Alternate proof—An alternate and simpler proof is from population balances, given by Danckwerts [5]. His proof begins by equating $x(t)$, the tracer impulse response at the observation point, to the exit-age distribution—the distribution of ages of the tracee at exit. Thus $x(t)$ is the tracer concentration at exit at time t after a unit impulse is introduced into the system and also the fraction of the tracee outflow that has spent time t in the system. Then, at any time, $Fx(t)$ is the flow rate of tracee that has spent time t in the system. The integral $\int_t^\infty Fx(t') dt'$ is the flux of tracee that has spent time t or more in the system. If we look at the fate of M_T , the total amount of tracee in the system initially, $dt[\int_t^\infty Fx(t') dt']$ is that part of M_T which leaves the system between t and $t + dt$. Then,

$$M_T = F \int_0^\infty dt \int_t^\infty x(t') dt'.$$

Integrating the right side by parts,

$$\begin{aligned}\frac{M_T}{F} &= t \int_t^\infty x(t') dt' \Big|_0^\infty - \int_0^\infty t dt \frac{d}{dt} \int_t^\infty x(t') dt' \\ &= 0 + \int_0^\infty t dt x(t).\end{aligned}$$

Thus the mean transit time of the tracee equals the first moment of the unit impulse response at the outlet. The proof is given for a unit-impulse input, but can be easily generalized to the more general $z(t)$ considered in the matrix proof.

CONVERSE

This proof is clearly simpler and more elegant than the matrix proof given here. However, the matrix proof enables us to look at the converse: if the first moment of the observed

concentration ($x = \sum_{j=1}^n q_j y_j$) yields M_T , then does q_j equal R_{0j}/F for all j ?

The converse can be proved for some specific model structures. If the model is a number of pools in series, the tracer mean transit time is longest at the observation point, where the tracee leaves the system. The tracer concentration in every other pool has a shorter mean transit time. If x involves any y_i other than y_n , it will have a shorter mean transit time than y_n does and thus cannot yield M_T .

However, the converse is in general not true. It is possible to find q_j such that the first moment of $x = \sum_{j=1}^n q_j y_j$ yields M_T and $\sum_{j=1}^n q_j = 1$, but q_j does not equal R_{0j}/F for all j . We can derive the conditions that such q_j would have to satisfy.

Let

$$q_j = \frac{R_{0j}}{F} + p_j,$$

where p_j are to be chosen, not all zero. There are three conditions:

1. $\sum_{j=1}^n q_j = 1 \Rightarrow \sum_{j=1}^n p_j = 0$.
2. From Equation (5), we also need $\sum_{j=1}^n p_j \sum_{k=1}^n A_{jk}^{-1} = 0$. That is,

$$p^T A^{-1} u = 0.$$

3. We also require that $R_{0j}/F + p_j \geq 0$.

Since there are n p_j to be chosen and two equality constraints, it is generally possible to choose the p_j , not all zero, so that the conditions are met.

Further conditions may be imposed on the q_j so that they are in some sense physically realizable. A physically realizable set of q_j would yield M_T for all values of R_{ij} , M_i , and p_i consistent with the assumed model structure and also assume one of three forms:

1. q_j independent of M_j and R_{ij} ;
2. $q_j = cM_j$ or $q_j = 0$ (mean concentration of a certain number of pools);

3. $q_j = cR_{ij}$ or $q_j = 0$ for some particular i , $0 \leq i \leq n$ (mean concentration of some of the flows into a specified pool or outside the system).

These further conditions may make it impossible to find q_j (other than R_{0j}/F) that yield the volume of distribution of the tracee. We have been unable to find a model in which the converse does not hold, when the q_j are constrained in this fashion.

DISCUSSION

The two theorems and the conditions under which the results hold are best understood by investigating some specific models. We present below a few examples where the two theorems apply, followed by examples where neither applies or only the first one does. This is followed by examples in which a theorem may apply in a part of a model even if inapplicable to the whole model. Finally, the converse of the mean-transit-time theorem is analyzed through some examples.

EXAMPLES

The occupancy principle requires that the tracer input label all influent tracee fluxes equally. The simplest case is a system with tracee input into only one pool, which is also the only pool where the tracer enters the system. An example is the four-pool model shown in Figure 1. The asterisk denotes tracer entry or observation.

Another case is a system with inflows into many pools but where all the inflows come through the point where the tracer enters the system. An example is a parallel-pathway model for capillary exchange or for blood flow through different organs (Jacquez [6], Bassingthwaite [7]), shown in Figure 2.

The mean-transit-time theorem requires in addition that all flux out of the system be through the observation point. This condition is satisfied by a model in which all flux out is from just one pool, and the tracer concentration in this pool is observed. An example is the three-pool mammillary model shown in Figure 3, in which all outflow is from pool 1 and the tracer concentration in pool 1 is observed.

The condition is also satisfied if there are fluxes out of the system from many pools, but all the fluxes combine into a single stream whose tracer concentration is observed. An example is the parallel-pathway model given in Figure 2.

COUNTEREXAMPLES

A simple model in which the occupancy principle holds but not the mean-transit-time theorem is the two-pool model given in Figure 4, with outflows from both pools; the tracer concentration in pool 1 (or pool 2) is observed. The tracer concentrations in the two pools have the same area, but neither has a first moment equal to $m(M_1 + M_2)/F^2$.

A simple model in which the occupancy principle does not hold is the two-pool model given in Figure 5, with tracee inflows into both pools but tracer inflow into just one pool. In this case, if tracer enters pool 1, the occupancy in pool 2 is smaller than in pool 1. It is worth noting that in this example, $\int_0^\infty y_1(t) dt$ does equal m/F , not because of the occupancy principle but simply because all outflow is from pool 1. Since $Fy_1(t)$ is the instantaneous rate of tracer leaving the system, $\int_0^\infty Fy_1(t) dt$ must equal m , the amount of tracer entering the system. This result, which holds for any model with all outflow through the observation point, is termed the outflow theorem by Perl et al. [2].

It is interesting that it is precisely this condition in addition to the occupancy principle that leads to the mean-transit-time theorem. Thus, the mean-transit-time theorem holds for a system if both the occupancy principle and the outflow theorem hold for that system.

STEWART - HAMILTON THEOREM

In biology, the Stewart-Hamilton theorem for calculating cardiac output is equivalent to partitioning the model into a part with multiple inputs but only one output (where the outflow theorem is applicable) and a part with a single input but multiple outputs (where the occupancy principle is applicable), as shown in Figure 6. So, when tracer is introduced at any input into the first part (the venous system), the area under the tracer concentration curve at the single output gives the tracee outflow at that point (the cardiac output). But this area equals the area at any point in the second part, since the tracer labels all tracee input into that part equally. Thus the area under the tracer concentration curve in any artery or vein yields the cardiac output, ignoring recirculation.

ANALYZING A PART OF A MODEL

The occupancy principle may be applied to a part of a model even if it is not applicable to the whole model. A trivial example is a number of pools in series, with tracer entering the first pool and tracee entering the first two pools from the outside. The model is given in Figure 7. The occupancy is the same in pools 2, 3, 4, and 5, since that part of the model has a single tracee inflow, into pool 2, and the tracer enters at the same point.

Another example in which the occupancy principle may be applied to a part of a model, even if it is not applicable to the whole model, is a mammillary model with all tracee inflow into the central pool but tracer entry in pool 2, shown in Figure 8. The occupancy principle does not hold for this model. But the part of the model consisting of pools 3, 4, ..., n receives all tracer and tracee from pool 1, thus having equal labeling of all tracer fluxes in. Therefore, the occupancy is the same in all these pools. In fact, pool 1 can also be included, since R_{10} can be assumed to mix with R_{12} just before entering pool 1. Then the model consisting of pools 1, 3, 4, ..., n (all but 2) have a single inflow $R_{10} + R_{12}$ with tracer entering only by this path. Therefore the occupancy is the same in all pools except in pool 2. Thus, in a mammillary model with all tracee inflow into the central pool and tracer entry into a side pool, the occupancy is the same everywhere except where the tracer is introduced.

The mean-transit-time theorem can be applied to a part of a model in a similar fashion. In the pools-in-series model shown in Figure 7 and discussed above, the theorem is applicable to the part of the model comprising pools 2, 3, 4, 5 if $x = y_5$, and z is the tracer concentration entering pool 2 [equal to $y_1 R_{21} / (R_{21} + R_{20})$].

CONVERSE OF MEAN-TRANSIT-TIME THEOREM

A trivial example where the converse of the mean transit time theorem does not hold is a model with n pools in parallel such that the mean transit time through one of the pools happens to equal the mean transit time through the whole system. Here q_j does not equal R_{0j}/F . However, any change in model parameters changes the relationship between the mean transit times.

A less trivial example is the three-pool model in Figure 9. If $k_1 = R_{31}/M_1$, $k_2 = R_{32}/M_2$, $k_3 = R_{31}/M_3$ and $k_4 = R_{32}/M_3$ are such that $1/k_2 - 1/k_1 > 1/k_3$, then

$$x = q_1 y_1 + (1 - q_1) y_2, \quad \text{where} \quad q_1 = \frac{k_3 - k_1 k_2 / (k_1 - k_2)}{k_3 + k_4},$$

has a first moment equal to $M_T m / F^2$. Here x yields M_T for a range of values of the model parameters, but q_1 is not physically realizable, since q_1 depends on the model parameters but x is not the tracer concentration at any point in the system.

When physical realizability is demanded, we have not been able to find a model in which q_j can be chosen other than R_{0j}/F so as to yield the tracee distribution volume.

We believe the following statement of the converse of the mean-transit-time theorem is worthy of attempts to prove or disprove:

CONJECTURE

In an open, nonsingular, stationary, linear system, if the observed concentration, given by

$x = \sum_{j=1}^n q_j y_j$, satisfies Equation (6) for all possible values of M_j and R_{ij} , and x is physically realizable, then $q_j = R_{0j}/F$, and the tracer labels all tracee inputs equally.

CONCLUSION

The occupancy principle and the mean-transit-time theorem are widely used to calculate the tracee flux out of a system and the total amount of tracee in the system. We have stated and proved the conditions under which such calculations yield the correct results. We have also examined the necessity of the conditions (the converses of the theorems). We are able to prove the necessity of the conditions for the occupancy principle. For the mean-transit-time theorem, the converse is not true if the observation does not have to be “physically realizable.” With physical realizability added, we are unable to find models in which the converse is not true, but we have not proved the converse. We believe attempts to prove or disprove the converse will be worth the effort.

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Fig. 1.
Model illustrating occupancy principle.

Fig. 2.
Parallel-pathway model.

Fig. 3.
Model in which mean-transit-time theorem is applicable.

Fig. 4.
Model in which mean-transit-time theorem is not applicable.

Fig. 5.
Model in which occupancy principle does not hold.

Fig. 6.
Model for use with Stewart-Hamilton theorem to calculate cardiac output.

Fig. 7.
Pools-in-series model in which occupancy principle and mean-transit-time theorem hold in part of the model.

Fig. 8.
Mammillary model in which occupancy principle holds in part of the model.

Fig. 9. Three-pool model in which the converse of the mean-transit-time theorem is not true when x can be physically unrealizable.