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An Application of Berman's Work on Pool-Model Invariants in Analyzing Indistinguishable Models for Whole-Body Cholesterol Metabolism

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Abstract

Berman and Schoenfeld used matrix transformations to study unidentifiable pool models. It is possible to use the method to examine if two models are output-indistinguishable, that is, if given the nature of tracer injections and observations, the two models have the same responses. The method is applied to two three-pool models for whole-body cholesterol metabolism. The indistinguishability of a mammillary model from a catenary model is proved using matrix transformations. The method is used in two ways, directly as well as after simplifying the problem. The two ways, as well as an analysis of the converse, help to show how the method is to be applied as well as the strengths and weaknesses of the method.

INTRODUCTION

Moses Berman's early work on invariants in kinetic data [1], published in 1956, is a major contribution to the theory of linear models of physiological phenomena fitted to experimental data. Berman and Schoenfeld studied unidentifiable models—models that have more parameters than can be uniquely determined from the data—and developed a method for relating the parameters of such a model to those of an identifiable model, through matrix transformations.

This method of matrix transformation is quite powerful. But outside of research that Berman himself was involved in [2, 3], it was not used very much for nearly twenty years after the publication of the original paper [4, 5].

In recent years, there has been a considerable amount of work in formalizing the method and generalizing it, particularly by Walter and associates [6–8] and Vajda [9, 10], who have applied it to the study of output-indistinguishability and to exhaustive modeling, the generation of all models that are output-indistinguishable from a given model with particular values for its parameters. A review of other work may be found in [11].

This paper describes the application of the matrix transformation method to a study of two possible models for whole-body cholesterol kinetics. It is shown how one model can be shown to be output-indistinguishable from the other. The converse appears to be difficult to show with this method. Besides the result being of use in cholesterol kinetics, the example

brings out the strengths as well as the limitations of the method. First, certain preliminaries concerning pool models are defined.

BACKGROUND

An arbitrary linear, stationary model with n pools is considered. The i th pool has a distribution volume M_i (also denoted by V_i when considering two models simultaneously). Tracer enters the system at the known rate of $U(t)$ at time t ; the fraction entering the i th pool is P_i . Initially, before time zero, there is no tracer in any of the pools. The volumes and flow rates or fluxes are for the traced substance or tracee.

Stationarity implies that volumes and fluxes are constant with time. Linearity implies that linear differential equations can be written for x_i , the tracer concentration, in each pool:

$$\frac{dx_i(t)}{dt} = \sum_{j=1}^n A_{ij}x_j(t) + \frac{Up_i}{M_i}, \quad x_i(0)=0, \quad i=1, \dots, n,$$

where $-A_{ii}$ equals the flow out of pool i divided by M_i , and A_{ij} equals the flow from pool j to pool i divided by M_i .

The r observed variables y_i are linear combinations of the tracer concentrations:

$$y_i = \sum_{j=1}^n C_{ij}x_j, \quad i=1, \dots, r.$$

The quantities A_{ij} , C_{ij} , p_i , and M_i cannot be negative. Also, since the p_i are fractions of the tracer impulse input, $\sum_{i=1}^n p_i = 1$; since the total flow out of a pool cannot be smaller than the total flow into that pool, $\sum_{i=1}^n A_{ij} \leq 0$ for each j ; since the total flow out of a pool cannot be smaller than the total flow from that pool into other pools, $\sum_{i=1}^n A_{ij}M_i \leq 0$ for each j .

Often each y_i equals the tracer concentration in some pool; then, each row of C has just one nonzero element (equal to 1). If the total amount of tracer in a pool is being observed, the corresponding C_{ij} equals M_j .

The function $U(t)$ assumes one of two forms in most tracer experiments. In constant-infusion experiments, $U(t) = u$, the rate of tracer infusion. If the tracer enters the system as a bolus or impulse, $U(t)$ is $m\delta(t)$, where m is the amount injected and $\delta(t)$ is the Dirac delta function. Alternately, as is usually done and will be here, $U(t)$ is set equal to zero and $x_i(0)$ set equal to mp_i/M_i . The solutions are identical. The development here will be for impulse inputs; the responses to other inputs can be constructed from the impulse response [12]. For instance, the response to a constant infusion at rate u is the integral of the response to an impulse of magnitude u .

Thus we can state the differential equations and constraints that any linear, stationary pool model must satisfy, for an impulse tracer input:

$$\begin{aligned}\frac{dx_i(t)}{dt} &= \sum_{j=1}^n A_{ij}x_j(t), & x_i(0) &= \frac{mp_i}{M_i}, & i=1, \dots, n, \\ y_i &= \sum_{j=1}^n C_{ij}x_j, & i &= 1, \dots, r,\end{aligned}$$

where A_{ij} , C_{ij} , M_i , and p_i satisfy the following inequality constraints:

$$\begin{aligned}A_{i,j} \geq 0 \quad \text{for } i \neq j, \quad A_{ii} < 0, \quad p_i \geq 0, \quad M_i \geq 0, \quad C_{ij} \geq 0, \\ \sum_{i=1}^n p_i = 1, \quad \sum_{j=1}^n A_{ij} \leq 0, \quad \sum_{i=1}^n M_i A_{ij} \leq 0.\end{aligned} \quad (1)$$

In matrix notation,

$$\frac{dx}{dt} = Ax, \quad y = Cx,$$

where x is a vector with n elements $x_1, \dots, x_n$; A is an $n \times n$ matrix; y is a vector with r elements; C is an $r \times n$ matrix; and $x_i(0) = mp_i/M_i$.

The description here is for a general pool model structure. A particular model for a particular experiment specifies the following:

1. n , r , e , and N ;
2. e equality constraints

$$E_i(A, C, M, p) = 0 \quad \text{for } i=1, \dots, e, \quad (2)$$

3. all elements of A , C , M , and p in terms of N parameters $b_1, \dots, b_N$.

For instance, if there is no flow from pool 3 to pool 5, then $A_{53} = 0$ is an equality constraint;

if no tracee enters pool 6 directly from outside the system, $\sum_{j=1}^n A_{6j} = 0$ is an equality constraint; if no tracee leaves the system directly from pool 8, $\sum_{i=1}^n M_i A_{i8} = 0$; if no part of the impulse directly enters pool 4, $p_4 = 0$.

The numerical values of $b_1, \dots, b_N$ are usually not known. The purpose of the tracer study is to estimate these parameters. Constraints on A specify the structural connectivity of the model; constraints on p specify the nature of the tracer input; constraints on the observation matrix C specify what is observed.

If the response of one model can be reproduced identically by the response of a second model by appropriately choosing the parameters of the second model, then the first model is said to be indistinguishable from the second. The converse need not be true. If the converse

is true, the two models are said to be indistinguishable from each other; they can be used perfectly interchangeably. If one is rejected for being statistically inadequate, the other must be rejected too. If one is accepted as statistically adequate, the other must be too. It is possible to distinguish the two from each other only on physical grounds or by changing the nature of the experiment—e.g., injecting the tracer into other pools, using multiple tracers, observing other pools.

MATRIX TRANSFORMATION

We now describe the method of matrix transformation applied to output-indistinguishability.

Given a model $dx/dt = Ax$ and $y = Cx$, if $x = P^{-1}z$, where P is any nonsingular matrix, the model is transformed as follows:

$$P^{-1} \frac{dz}{dt} = AP^{-1}z, \quad x(0) = P^{-1}z(0).$$

So

$$\begin{aligned} \frac{dz}{dt} &= PAP^{-1}z, & z(0) &= Px(0), \\ y &= CP^{-1}z. \end{aligned}$$

Thus a second model $dz/dt = Bz$ and $y = Dz$, where $B = PAP^{-1}$, $D = CP^{-1}$, and $z(0) = Px(0)$, has the same observed responses as the first model. If P can be chosen so that PAP^{-1} , CP^{-1} , and $Px(0)$ satisfy the e characteristic equality constraints [Equation (2)] of the second model as well as the inequality constraints that any pool model must satisfy [Equation (1)], the first model is indistinguishable from the second. If the n^2 elements of P cannot be chosen to satisfy the e equations (2) and the general pool-model conditions (1), the first model is distinguishable from the second.

To illustrate, let the tracer be introduced into pool 1 of a four-pool model, and let $x_2(t)$ alone be measured ($x_i(0)$ is zero except for $x_1(0)$, $C = [0 \ 1 \ 0 \ 0]^T$). Suppose that, in a second model, tracer input is into pool 3 and sampling from pool 4. Some of the model constraints are $z_1(0) = 0$, $z_2(0) = 0$, $z_4(0) = 0$, $D = [0 \ 0 \ 0 \ 1]^T$. Now, $Px(0) = x_1(0)$ [column 1 of P]. Then the constraints on $z(0)$ are satisfied by making column 1 of P zero except for element 3. Then $D = CP^{-1}$, or $C = DP = [\text{row 4 of } P]$. Since $C = [0 \ 1 \ 0 \ 0]^T$, row 4 of P must be $[0 \ 1 \ 0 \ 0]^T$. Other constraints arising from model structure lead to further constraints on P .

The e constraints lead to e equations among the n^2 elements of P . Of these, e' equations are independent. [Even though the e constraints on A , C , M , p are independent, the e equations for P_{ij} may not be. In the example above, there are three constraints on $x(0)$ and four on C , but only six elements of P — P_{11} , P_{21} , P_{41} , P_{42} , P_{43} , P_{44} — are determined by the seven constraints.] Four cases may arise:

1. If $e' > n^2$ or the e' equations and the general pool model constraints are inconsistent among themselves, the second model cannot match the responses of the first model; the first model is distinguishable from the second.
2. If $e' = n^2$, and there is a single solution for P , which also satisfies the general pool model constraints, the first model is indistinguishable from the second.
3. If $e' = n^2$, and there is more than one solution that also satisfy the general pool model constraints, the first model is indistinguishable from the second but there is more than one set of values for the second model's parameters that match the given responses of the first model.
4. If $e' < n^2$, and the general pool model constraints can be satisfied, the first model is indistinguishable from the second but the second is not identifiable.

APPLICATION TO CHOLESTEROL KINETICS

Goodman et al. [13] considered two models for cholesterol kinetics, shown in Figure 1. The asterisks denote tracer injection and observation. The double arrow in the middle stands for indistinguishability. Goodman et al. considered both models to provide equally good fits to their kinetic data, which consisted of specific-activity measurements of plasma cholesterol (pool 1) following a bolus injection of radiolabeled cholesterol into the same pool. The mammillary model, shown on the left, was chosen as being more physiological. Here we consider the question, are the two models output-indistinguishable? That is, given any plasma decay curve following the injection of labeled cholesterol into plasma, do the two models provide identical fits to the data? We consider the indistinguishability of each from the other in turn.

INDISTINGUISHABILITY BY COMPONENTS AND MATRIX TRANSFORMATION

First we consider a modification to the method that simplifies the problem. We can write the models under consideration as shown in Figure 2. The two models on the left are clearly the same, and so are the two models on the right. The two models in the middle are indistinguishable if the two lower parts or submodels, with pools 2 and 3, are indistinguishable from each other if tracer input is at the point where tracer enters the submodels and observations are made at the point where tracer leaves the submodels.

Thus the problem is simplified from one with two 3-pool models to one with two 2-pool models. This is shown in Figure 3. [Pools 1 and 2 in Figure 3 correspond to pools 2 and 3, respectively, in Figure 2; F in Figure 3 is $R_1 + R_2$ in Figure 2; G in Figure 3 is R_3 in Figure 2; R in Figure 3 is R_4 in Figure 2.]

For the parallel-flow model, on the right,

$$\begin{aligned} \frac{dx_1}{dt} &= -\frac{kF}{V_1}x_1, & x_1(0) &= \frac{mk}{V_1}, \\ \frac{dx_2}{dt} &= -\frac{(1-k)F}{V_2}x_2, & x_2(0) &= \frac{m(1-k)}{V_2}. \end{aligned}$$

$y = kx_1 + (1 - k)x_2$ is observed. In matrix notation,

$$\frac{dx}{dt} = \begin{bmatrix} -kF/V_1 & 0 \\ 0 & -(1-k)F/V_2 \end{bmatrix} x, \quad x(0) = \begin{bmatrix} mk/V_1 \\ m(1-k)/V_2 \end{bmatrix}.$$

Thus,

$$A = \begin{bmatrix} -kF/V_1 & 0 \\ 0 & -(1-k)F/V_2 \end{bmatrix}, \quad C = [k \quad 1-k].$$

For the main-pool–side-pool model, on the left,

$$\begin{aligned} \frac{dz_1}{dt} &= -\frac{G+R}{M_1}z_1 + \frac{R}{M_1}z_2, & z_1(0) &= m/M_1, \\ \frac{dz_2}{dt} &= \frac{R}{M_2}z_1 - \frac{R}{M_2}z_2, & z_2(0) &= 0. \end{aligned}$$

$y = z_1$ is observed. In matrix notation,

$$\frac{dz}{dt} = \begin{bmatrix} -(G+R)/M_1 & R/M_1 \\ R/M_2 & -R/M_2 \end{bmatrix} z, \quad z(0) = \begin{bmatrix} m/M_1 \\ 0 \end{bmatrix}.$$

Thus,

$$B = \begin{bmatrix} -(G+R)/M_1 & R/M_1 \\ R/M_2 & -R/M_2 \end{bmatrix}, \quad D = [1 \quad 0].$$

If the parallel-flow model is compared with the main-pool–side-pool model, P must be such that the general pool-model constraints along with the following equality constraints of the main-pool–side-pool model are satisfied:

- i. $z_2(0) = 0$;
- ii. $z_1(t) = kx_1(t) + (1 - k)x_2(t)$;
- iii. $PAP_{21}^{-1} + PAP_{22}^{-1} = 0$.

From (ii), the first row of P must be $[k \ 1 - k]$. From (i),

$$z(0) = Px(0) = \begin{bmatrix} \frac{k^2m}{V_1} + \frac{(1-k)^2m}{V_2} \\ \frac{P_{21}km}{V_1} + \frac{P_{22}(1-k)m}{V_2} \end{bmatrix}$$

So $P_{21} = -a(1-k)/V_2$, $P_{22} = ak/V_1$, a being arbitrary;

$$P^{-1} = \frac{1}{d} \begin{bmatrix} \frac{k}{V_1} & \frac{k-1}{a} \\ \frac{1-k}{V_2} & \frac{k}{a} \end{bmatrix}$$

where $d = k^2/V_1 + (1-k)^2/V_2$; and

$$PAP^{-1} = \frac{F}{d} \begin{bmatrix} -\left[\frac{k^3}{V_1^2} + \frac{(1-k)^3}{V_2^2}\right] & \left[\frac{k}{V_1} - \frac{1-k}{V_2}\right] \frac{k(1-k)}{a} \\ \left[\frac{k}{V_1} - \frac{1-k}{V_2}\right] \frac{k(1-k)a}{V_1 V_2} & -\frac{k(1-k)}{V_1 V_2} \end{bmatrix}$$

From (iii), $a = V_1 V_2 / [kV_2 - (1-k)V_1]$.

Now all elements of P are determined. We need to check if PAP^{-1} and $Px(0)$ satisfy the general pool-model constraints applied to the main-pool-side-pool model:

$$z_1(0) > 0; \quad B_{12}, B_{21} > 0; \quad B_{11}, B_{22} < 0; \quad B_{11} + B_{12} < 0,$$

where

$$B = \begin{bmatrix} -(G+R)/M_1 & R/M_1 \\ R/M_2 & -R/M_2 \end{bmatrix}, \quad z(0) = \begin{bmatrix} m/M_1 \\ 0 \end{bmatrix}.$$

Now $PAP_{21}^{-1} = [k/V_1 - (1-k)/V_2]^2 Fk(1-k)/d > 0$, since $d > 0$. Also, $PAP_{11}^{-1} + PAP_{22}^{-1} < 0$, and $z_1(0) = md > 0$. Finally,

$$PAP_{11}^{-1} + PAP_{12}^{-1} = - \left[\frac{k^2}{V_1} + \frac{(1-k)^2}{V_2} \right]^2 = -Fd < 0.$$

Thus all the constraints of a general pool model are satisfied by the transformation. Hence the parallel-flow model is indistinguishable from the main-pool-side-pool model.

If G , M_1 , M_2 , and R are desired in terms of F , V_1 , V_2 , and k , they may be found by solving $B = PAP^{-1}$ and $z(0) = Px(0)$.

INDISTINGUISHABILITY BY MATRIX TRANSFORMATION ALONE

If we do not use the simplification described above, we work with three-pool models.

For the mammillary model,

$$A = \begin{bmatrix} -k_{11} & k_{21} & k_{31} \\ k_{12} & -k_{12} & 0 \\ k_{13} & 0 & -k_{13} \end{bmatrix}, \quad x(0) = \begin{bmatrix} m/V_1 \\ 0 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix},$$

where $k_{ij} = R_{ij}/V_j$ and $k_{11} = k_{01} + k_{21} + k_{31}$.

For the catenary model, the equality constraints are

$$z_2(0) = z_3(0) = 0, \quad D = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}, \quad B_{13} = B_{31} = 0, \\ B_{21} + B_{22} + B_{23} = B_{32} + B_{33} = 0.$$

These nine conditions lead to a solution for P .

From the constraints on D , $z_1 = x_1$ and so $P_{12} = P_{13} = 0$. Since $z_2(0) = z_3(0) = 0$, it follows that $P_{21} = P_{31} = 0$. The matrix P can then be written as follows.

$$P = \begin{bmatrix} 1 & 0 & 0 \\ 0 & a & b \\ 0 & c & d \end{bmatrix},$$

where a, b, c, d are arbitrary.

Then,

$$PAP^{-1} = \frac{1}{ad - bc} \begin{bmatrix} -k_{11} & dk_{21} - ck_{31} & -bk_{21} + ak_{31} \\ ak_{12} + bk_{13} & -adk_{12} + bck_{13} & ab(k_{12} - k_{13}) \\ ck_{12} + dk_{13} & cd(k_{13} - k_{12}) & bck_{12} - adk_{13} \end{bmatrix}.$$

Now the four equality constraints on B may be applied to PAP^{-1} to solve for a, b, c, d . We find

$$a = \frac{k_{21}}{k_{31} + k_{21}} = 1 - b, \\ c = \frac{k_{13}}{k_{13} - k_{12}} = 1 - d.$$

Thus,

$$P = \begin{bmatrix} 1 & 0 & 0 \\ 0 & \frac{k_{21}}{k_{31} + k_{21}} & \frac{k_{31}}{k_{31} + k_{21}} \\ 0 & \frac{k_{13}}{k_{13} - k_{12}} & \frac{k_{12}}{k_{12} - k_{13}} \end{bmatrix}.$$

The matrix PAP^{-1} is given below:

$$\begin{bmatrix} -k_{11} & k_{31}+k_{21} & 0 \\ \frac{k_{31}k_{13}+k_{21}k_{12}}{k_{31}+k_{21}} & \frac{-(k_{31}k_{13}^2+k_{21}k_{12}^2)}{k_{31}k_{13}+k_{21}k_{12}} & \frac{k_{21}k_{31}(k_{12}-k_{13})^2}{(k_{21}+k_{31})(k_{31}k_{13}+k_{21}k_{12})} \\ 0 & \frac{k_{12}k_{13}(k_{31}+k_{21})}{k_{31}k_{13}+k_{21}k_{12}} & \frac{k_{12}k_{13}(k_{31}+k_{21})}{k_{31}k_{13}+k_{21}k_{12}} \end{bmatrix};$$

we have

$$Px(0) = \begin{bmatrix} m/V_1 & 0 & 0 \end{bmatrix}^T, \quad CP^{-1} = \begin{bmatrix} 1 & 0 & 0 \end{bmatrix}.$$

It can easily be verified that PAP^{-1} and $Px(0)$ satisfy the constraints of a general pool model. Thus the mammillary model is indistinguishable from the catenary model.

CONVERSE

The converse turns out to be much more difficult to prove using matrix transformation. Here we will consider only a simplified problem, that of the indistinguishability of the main-pool-side-pool model from the parallel-flow model. For the former,

$$A = \begin{bmatrix} -(G+R)/M_1 & R/M_1 \\ R/M_2 & -R/M_2 \end{bmatrix}, \quad x(0) = \begin{bmatrix} m/M_1 \\ 0 \end{bmatrix}, \quad C = \begin{bmatrix} 1 & 0 \end{bmatrix}.$$

The equality constraints in the parallel-flow model are

$$B_{12}=0, \quad B_{21}=0, \quad D = \begin{bmatrix} k & 1-k \end{bmatrix}.$$

Since $D = CP^{-1}$, or $DP = C$,

$$P = \begin{bmatrix} a & -b \\ \frac{1-ka}{1-k} & \frac{bk}{1-k} \end{bmatrix},$$

where a , and b are arbitrary.

The elements of PAP^{-1} are given below:

$$\begin{aligned} PAP_{11}^{-1} &= -ak \frac{G+R}{M_1} - bk \frac{R}{M_2} + (ka-1)R \left(\frac{a}{bM_1} + \frac{1}{M_2} \right), \\ PAP_{21}^{-1} &= \frac{1}{1-k} \left[k(ka-1) \frac{G+R}{M_1} + bk^2 \frac{R}{M_2} - R(ka-1) \left(\frac{k}{M_2} + \frac{ka-1}{bM_1} \right) \right], \\ PAP_{12}^{-1} &= (1-k) \left[-a \frac{G+R}{M_1} - b \frac{R}{M_2} + aR \left(\frac{1}{M_2} + \frac{a}{bM_1} \right) \right], \\ PAP_{22}^{-1} &= (ka-1) \frac{G+R}{M_1} + bk \frac{R}{M_2} - aR \left(\frac{k}{M_2} + \frac{ka-1}{bM_1} \right). \end{aligned}$$

PAP_{12}^{-1} and PAP_{21}^{-1} must be set equal to zero and the resulting equations solved for a and b . However, there is no simple solution.

SUMMARY OF THE METHOD

Given two models:

Model 1: $dx/dt = Ax$, $x(0)$, and $y = Cx$;

Model 2: $dz/dt = Bz$, $z(0)$, and $w = Dz$,

to test whether model 1 is indistinguishable from model 2:

1. Let $z = Px$. Fix some of the elements of P so that the equality constraints arising from $z(0)$ and D are satisfied by $Px(0)$ and CP^{-1} , respectively. Let the remaining elements of P be arbitrary.
2. Compute PAP^{-1} .
3. Solve for the remaining unknown elements of P by applying the equality constraints arising from B to PAP^{-1} .
4. If there is a solution, check that it satisfies the general pool-model constraints. If it does, model 1 is indistinguishable from model 2. Otherwise, or if there is no solution, model 1 is distinguishable from model 2.
5. The parameters of model 2 may be computed in terms of those of model 1 by solving $B = PAP^{-1}$, $z(0) = Px(0)$, and $D = CP^{-1}$.

CONCLUSION

The method of matrix transformation, as summarized above, is straight-forward and appears to lend itself to computer implementation. The method systematizes the comparison of two models, which can be helpful in bringing out the salient points of similarity and difference among models. At the same time, since the matrices P , P^{-1} , and A have to be manipulated symbolically, the matrix inverse and products become increasingly complex as the number of pools increases in comparison with the number of injections and the number of pools observed. As seen above, even a two-pool model can be problematic.

One area where the method is likely to be of particular use is when specific numerical values have been obtained for the parameters of one model and that model's indistinguishability from others is under study. In this case, the problem becomes one of numerically solving a set of nonlinear equations for the elements of the transformation matrix P .

In sum, then, the method is of great help in formalizing the comparison of two models or when specific numerical values have been obtained for one model; its utility in studying indistinguishability in general would seem to depend on the availability of good symbol-manipulation programs.

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Fig. 1.
Two models for whole-body cholesterol kinetics.

Fig. 2.
Indistinguishability of three-pool models in terms of their two-pool components.

Fig. 3.
A main-pool-side-pool model and a parallel-flow model.