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Numerical Deconvolution Using System Identification Methods

Sandor Vajda,[1,3] Keith R. Godfrey,[1,4] and Peter Valko[2]

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A deconvolution method is presented for use in pharmacokinetic applications involving continuous models and small samples of discrete observations. The method is based on the continuous-time counterpart of discrete-time least squares system identification, well established in control engineering. The same technique, requiring only the solution of a linear regression problem, is used both in system identification and input identification steps. The deconvolution requires no a priori *information, since the proposed procedure performs system identification (including optimal selection of model order), selects the form of the input function and calculates its parametric representation and its values at specified time points.*

KEY WORDS: numerical deconvolution; algorithm for deconvolution; linear systems analysis; system identification; least squares fitting; calculation of drug input rates; input response in pharmacokinetic systems.

1. INTRODUCTION

Let u, y, and g denote, respectively, the input, output, and weighting function of a single-input, single-output, linear, time-variant system. If we assume that $y(t) = 0$ for $t < 0$, the three functions are related by the convolution integral

$$y(t) = \int_0^t g(t-\tau)u(\tau)\, d\tau \tag{1}$$

Deconvolution means solving Eq. (1) either for g in terms of y and u (system identification) or for u in terms of y and g (input identification).

[1]Department of Engineering, University of Warwick, Coventry, CV4 7AL, England.
[2]Eötvös Lorand University, Budapest, Hungary.
[3]On leave from Eötvös Lorand University, Budapest, Hungary.
[4]To whom all correspondence should be addressed.

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In pharmacokinetics, system identification often involves parametric models, e.g., compartmental models, whereas deconvolution for input identification is a basic tool for modeling drug release and absorption, in which case g is the plasma concentration following an intravenous bolus dose and y is the plasma concentration following a dose administered via an extravascular route (most commonly, an orally administered dose) (1–3).

Because it generally involves noisy, discrete observations, deconvolution in pharmacokinetics is a numerical problem. Standard techniques of numerical deconvolution based on discrete Fourier transformation (4) or Kalman filtering (5) require large samples of equally spaced (in time) data. Such samples are not usually available in pharmacokinetics and so several methods of specific application to pharmacokinetics have been proposed in the literature. The simplest of these is the point-area deconvolution approach (1–3,6,7) but its success is heavily dependent on proper data smoothing and choice of computation parameters (3). The more advanced methods of Cutler (8,9) and Veng-Pedersen (10–12) involve assumptions about the form of output and/or input functions.

In this paper, a new deconvolution technique is described, based on modern system identification and model selection methods of control engineering. Its numerical properties are demonstrated by solving a test example studied in previous papers on deconvolution (8–12). The technique is compared numerically with all the methods described in (9–12), but the general properties are compared in particular with one of the methods of Veng-Pedersen (12), which is based on fitting polyexponentials both to the impulse response and output data; the input, computed in terms of these parameter estimates, is also in the form of a polyexponential. As shown by Veng-Pedersen (12), the polyexponential procedure can be implemented as a simple computer program and it works well in the test problems considered.

The technique described here is similar to the method of polyexponentials (12) in terms of basic assumptions, but it has two advantages. First, the class of input functions that may be considered is extended without introducing additional parameters to be estimated. Second, instead of fitting polyexponentials through the use of nonlinear search algorithms, parameters in linear differential equations are estimated by the direct integral (DILS) method which involves only linear regression. This simple technique is used both in the system identification and input identification steps.

It should be emphasized that solution of a deconvolution problem requires several computational steps. For example, to use the method of polyexponentials (12), one first has to select the number of exponential terms in the polyexponential and fit it to the impulse response data in order to identify the weighting function g of the system. Second, a similar model

order selection and fitting is required for the observed values of the output y. Knowledge of the parameters in g and y then enables the unknown input u to be determined and usually only this third step is strictly regarded as deconvolution (12).

In the present paper, the whole problem is considered. The procedure described selects the model order, estimates its parameters, selects the form of the input function as a parametric expression, and computes its values at specified time points. Such a unified procedure is superior to approaches separating model identification from deconvolution, since a weighting function that describes the impulse response data very well is not necessarily the best model of the system if the goal of the study is to determine an unknown input function. A simpler weighting function, fitting the impulse response data less well, may result in a better estimate of the input.

The paper is organized as follows: In Section 2, the inherent difficulties of numerical deconvolution are shown in order to justify our assumptions. The DILS method of parameter estimation is described in Section 3 and the use of the method for system identification is discussed in Section 4. In Section 5, the input identification stage of our deconvolution technique, again based on the simple DILS approach, is described. The method is illustrated in Section 6 by solving a Test Example studied in previous papers (8–12).

2. PROBLEMS OF NUMERICAL DECONVOLUTION

Assume that the system weighting function g is known exactly. The weighting function is the response of a linear system, initially at rest, to a unit impulse input. In addition to its weighting function, the linear system can also be approximated by the transfer function

$$G(s) \equiv \frac{Y(s)}{U(s)} = \frac{b_1 s^{m-1} + b_2 s^{m-2} + \cdots + b_m}{s^n + a_1 s^{n-1} + a_2 s^{n-2} + \cdots + a_n} \tag{2}$$

or by the linear differential equation

$$\frac{d^n y}{dt^n} + a_1 \frac{d^{n-1} y}{dt^{n-1}} + a_2 \frac{d^{n-2} y}{dt^{n-2}} + \cdots + a_n y = b_1 \frac{d^{m-1} u}{dt^{m-1}} + b_2 \frac{d^{m-2} u}{dt^{m-2}} + \cdots + b_m u \tag{3}$$

where $Y(s)$ and $U(s)$ are the Laplace transforms of $y(t)$ and $u(t)$, respectively, and $a_1, \ldots, a_n, b_1, \ldots, b_m$ are constants.

The three representations are equivalent in the sense that any one of them enables the others to be determined uniquely [see, for example,

(13), chap. 2]. Since a physiological system does not act as a pure differentiator and does not transfer material directly, $(m-1)<n$ and so G is a proper rational function.

The conceptually simple solution $U(s)=[G(s)]^{-1}Y(s)$ of Eq. (2) gives rise to two problems in pharmacokinetics applications.

Problem 1. The inverse problem is ill-conditioned so that any noise in y may result in a solution u that oscillates wildly and is unstable (4); examples are given in (14) and (15). Any meaningful solution requires constraints or penalties on u, which in turn requires some prior assumptions.

Problem 2. Even in the noise-free case, input identification requires assumptions if only sampled data, $\tilde{y}_i$, $i=0, 1, \ldots l$ are available. For example, if $n=1$, we have from Eq. (3)

$$u(t)=\frac{a_1}{b_1}y(t)+\frac{1}{b_1}\frac{dy}{dt}(t) \tag{4}$$

and any function $y(t)$ interpolating the values $\tilde{y}_i$ gives an equivalent solution.

In view of these problems, any continuous-time deconvolution algorithm dealing with noisy sampled observations is based on assumptions. There are two main approaches. In the first, the "true" continuous output y is approximated by some function, for example an adaptive least squares spline (10) or by a polyexponential (12) and the model inversion method is then applied. In the second approach, a known form of input function $u(p)$ depending on unknown parameters p is assumed and the parameters are then estimated by minimizing the least squares objective function

$$\sum_{i=0}^{l}[\tilde{y}_i-y(t_i,u(p))]^2$$

where y is the response of the model to the input $u(p)$ (8,9,11). In these approaches, the basic assumptions are clearly formulated, so ensuring reproducibility of results.

There is a third type of approach, and this is based on the assumption of a piecewise-constant input u such that $u(t)=u_i$ on the interval $[t_{i-1}, t_i]$. Then Eq. (1) is reduced to the sum

$$y(t_j)=\sum_{i=1}^{j}\bar{u}_i\bar{g}_{j-i+1}(t_i-t_{i-1}) \tag{5}$$

where

$$\bar{g}_{j-i+1}(t_i-t_{i-1})=\int_{t_j-t_i}^{t_j-t_{i-1}}g(\tau)\,d\tau \tag{6}$$

Replacing $y(t_j)$ by the observed value $\tilde{y}_j$ for $j = 0, 1, \ldots, l$ the solution of the resulting set of linear equations for $\bar{u}_1, \ldots, \bar{u}_l$ is the point-area deconvolution algorithm (1-3,7). [The integral mean in Eq. (6) is often approximated by the midpoint value or by the trapezium rule (3)]. Discrete approximation overcomes Problem 2 but not Problem 1, although according to Langenbucher (3), a suitable selection of computation parameters, supplemented by conventional smoothing methods, is sufficient in most situations for avoiding the tendency to instability.

Equations of the form of Eq. (5) with constant $\Delta t = t_i - t_{i-1}$ have traditionally been used for estimating the points of discrete-time weighting functions and, as shown by Hunt (4), this is equivalent to the (similarly traditional) method of discrete-time identification using Fourier transforms, in which windowing procedures are used to overcome Problem 1. Akaike (16) shows that variance of the results can be significantly reduced by applying parametric models, thus estimating the order and parameters of the autogressive-moving average (ARMA) model

$$y_t + a_1 y_{t-1} + \cdots + a_n y_{t-n} = b_1 u_t + \cdots + b_m u_{t-m} \tag{7}$$

In this paper, we adopt a similar parametric approach to system identification, as illustrated in Sections 3 and 4.

3. DIRECT INTEGRAL LEAST SQUARES (DILS) PARAMETER ESTIMATION

To illustrate the approach, consider the estimation of parameters in the second-order linear system described by

$$\frac{d^2y}{dt^2} + a_1 \frac{dy}{dt} + a_2 y = b_1 \frac{du}{dt} + b_2 u \tag{8}$$

Assume

$$y(t) = \frac{dy(t)}{dt} = 0 \quad \text{for } t < 0 \tag{9}$$

The traditional approach of fitting the model of Eq. (8) to observations $\tilde{y}_0, \ldots, \tilde{y}_l$ and $\tilde{u}_0, \ldots, \tilde{u}_l$ is to estimate the parameters in its solution (often of polyexponential form) which is inherently a nonlinear parameter estimation problem requiring iterative search techniques.

It is desirable to exploit the linearity of Eq. (8) in its parameters. In discrete-time process identification, mainly involving ARMA models of the form of Eq. (7), only such "direct" methods are used. In the continuous-time case, however, the derivatives in Eq. (8) are unmeasurable and their estimation from noisy discrete data is unreliable and heavily dependent on additional assumptions.

To eliminate the need for numerical differentiation of the data, Eq. (8) is integrated twice to give

$$y(t)+a_1\int_{0_-}^{t} y(\tau)\,d\tau+a_2\int_{0_-}^{t}\int_{0_-}^{\tau} y(\tau_1)\,d\tau_1\,d\tau$$

$$=b_1\int_{0_-}^{t} u(\tau)\,d\tau+b_2\int_{0_-}^{t}\int_{0_-}^{\tau} u(\tau_1)\,d\tau_1\,d\tau \tag{10}$$

where $t=0_-$ denotes time just before $t=0$. We consider input functions of the form

$$u(t)=D\delta(t)+u_0H(t)+u_c(t) \tag{11}$$

where $\delta(t)$ and $H(t)$ are, respectively, unit impulse and unit step functions and $u_c(t)$ is a continuous function such that $u_c(0)=0$. In Eq. (11), D denotes the dose given as an intravenous bolus at $t=0$, so that

$$y(0_+)=b_1D \tag{12}$$

since $\lim_{t\to 0_+}\int_{0_-}^{t} u(\tau)\,d\tau=D$ and the other terms in Eq. (10) vanish. (Here $t=0_+$ denotes time just after $t=0$.)

The basic idea of the DILS method is to approximate the integrands in Eq. (10) by functions interpolating the observed values $\tilde{y}_0, \tilde{y}_1, \ldots, \tilde{y}_l$ and $\tilde{u}_0, \tilde{u}_1, \ldots, \tilde{u}_l$. Then the integrals can be evaluated and for $t=t_i$, $i=1,\ldots,l$ we obtain the linear regression model

$$Y=Xp+\varepsilon \tag{13}$$

where

$$X=\begin{bmatrix} -\int_{0_-}^{t_1} y\,d\tau & -\int_{0_-}^{t_1}\int_{0_-}^{\tau} y\,d\tau_1\,d\tau & \int_{0_-}^{t_1} u\,d\tau & \int_{0_-}^{t_1}\int_{0_-}^{\tau} u\,d\tau_1\,d\tau \\ \vdots & \vdots & \vdots & \vdots \\ -\int_{0_-}^{t_l} y\,d\tau & -\int_{0_-}^{t_l}\int_{0_-}^{\tau} y\,d\tau_1\,d\tau & \int_{0_-}^{t_l} u\,d\tau & \int_{0_-}^{t_l}\int_{0_-}^{\tau} u\,d\tau_1\,d\tau \end{bmatrix} \tag{14}$$

$Y=[\tilde{y}_1,\ldots,\tilde{y}_l]^T$ and $p=[a_1,a_2,b_1,b_2]^T$; $\varepsilon=[\varepsilon_1,\ldots,\varepsilon_l]^T$ represents the vector of equation errors. The least squares estimates of the parameters are then given by

$$\hat{p}=[X^TWX]^{-1}X^TWY \tag{15}$$

where W is an $l\times l$ weighting matrix [(17), Section 4.1.4].

We use natural cubic splines [see, for example, (18)] for interpolation and hence evaluate the integrals in Eq. (14) analytically. The spline function

is fitted only to the points of the continuous component $u_c(t)$ of Eq. (11) and further terms $\int_{0_-}^{t_i} D\delta(\tau)\, d\tau = D$ and $\int_{0_-}^{t_i} u_0 H(\tau)\, d\tau = t_i u_0$ are added when evaluating the integrals in Eq. (14).

The DILS approach is not new. For example, Foss (19) considered derivatives of polyexponential expressions in order to estimate their parameters by the DILS method. Himmelblau *et al.* (20) estimated parameters in first-order linear differential equations modeling chemical reaction kinetics. Sinha and Qijie (21) have demonstrated the superiority of using spline functions for interpolation and the statistical properties of DILS estimates have been studied by Vajda *et al.* (22). Whitfield and Messali (23) applied the method without assuming that the system is initially at rest for $t < 0$, but for most pharmacokinetic applications, it is reasonable to assume that the system is initially at rest, so that the integral Eq. (10) does not contain the initial conditions.

Fitting a differential equation of the form Eq. (3) to input-output data by the DILS method is simpler than fitting a polyexponential function, i.e., the solution of the differential equation. No initial estimates for the parameters are needed and the solution is obtained in the single computational step [Eq. (15)] instead of an iterative search, so eliminating the convergence problems sometimes encountered in applications of the nonlinear least squares method. A further advantage of the DILS method is that, in its original form, it applies to any input function. For example, it is not uncommon that the reference response y is from a discontinued constant rate infusion, with data from both the infusion and postinfusion phases. To use the polyexponential fitting method, it is necessary to obtain an algebraic expression for the response to this specific form of input, whereas the form of the differential Eq. (3) does not depend on the form of the input u and the integrals of the input in Eq. (14) can easily be evaluated for any u.

Application of the DILS method is slightly more difficult for data with significant absorption lag time in the response. In such cases, it is necessary to introduce an additional parameter t_{lag} to represent this time and to use t_{lag} as the lower integration limit of the integrals involving y in Eq. (14), since now $y(t) = dy(t)/dt = 0$ for $t < t_{lag}$. Estimation of t_{lag} requires a one-dimensional search, (i.e., minimization of the least squares objective function with respect to t_{lag}) where the other parameters are computed by Eq. (15) for each value of t_{lag}. Although this is an iterative procedure, it is one-dimensional and it is considerably simpler than the multidimensional search required in the nonlinear least squares problems.

The DILS method, in conjunction with spline interpolation, gives reasonable estimates even from data with widely spaced observations (22,24,25), so that large gaps or missing data do not lead to difficulties.

The method is more sensitive to large measurement errors. The prediction matrix X in Eq. (13) is based on spline functions interpolating the observed values $\tilde{y}_i = y(t_i) + \varepsilon_i$ instead of the "true" values $y(t_i)$. Therefore one of the basic assumptions of linear regression is violated and the procedure results in biased estimates. On the other hand, at least for moderate measurement errors (up to about 10%), the DILS method usually gives smaller squared deviations from the true parameters than the polyexponential fit [see (24) for discussion] and this may compensate for the biasedness. Methods for reducing bias are available (24,26).

The type of data from pharmacokinetic experiments, where the input functions are often restricted to impulsive (bolus) and step (constant infusion) forms, can give rise to additional problems. The columns of X containing higher integrals may then tend to become collinear, resulting in near-singularity of $X^T WX$. The well-known consequences are parameter estimates that are inflated and sensitive to small perturbations in the data [see, for example, (24)]. This problem becomes really serious if one wishes to estimate also nonzero initial conditions (23). This is eliminated in the approach described here by the assumption that the system is in zero state for $t < 0$.

Summarizing these properties, the DILS method is a fast and approximate technique of parameter estimation, similar to the method of residuals (peeling), which requires only linear regression rather than nonlinear least squares. The DILS method is superior to peeling, because (i) it does not require logarithmic transformation of the data; (ii) it applies to any input function and not just an impulse; and (iii) it is free of the intuitive steps (i.e., the selection of straight sections of the logarithmic curve) inherent in the method of residuals.

Before proceeding further, it is necessary to emphasize two points. First, in this section, the properties of the DILS method have been discussed, regarding it as a parameter estimation technique for computing the parameters of a function of a given functional form [Eq. (8)]. In the present application, DILS is used for system identification, i.e., the order of the differential Eq. (8) is not fixed *a priori* and it is selected simultaneously with parameter estimation. The simplest (i.e., the lowest order) model fitting the data within the range of experimental errors is fitted on the basis of the parsimony principle (16,27,28). As is shown by considering simulated data, this is not necessarily the true model, but keeping the model order as low as possible for an acceptable goodness of fit effectively eliminates the problem of near-singularity of $X^T WX$.

The second point is that, although the model is described by the parametric expression Eq. (8) instead of the points of the weighting function for the purposes of identification, the deconvolution stage of the procedure

uses only the values of the weighting function computed from the parametric representation and not the parameter values themselves. Therefore, as is shown in the numerical results, bias in the parameter estimates does not propagate into the estimates of the input function.

4. SYSTEM IDENTIFICATION

The two main problems faced when identifying a linear system by the DILS method are that the order of the system is not known *a priori* and that, for input identification, an estimate of the weighting function is needed instead of the parameters in the differential Eq. (3). These two problems are discussed in turn.

Model order selection is analogous to the problem of determining the number of exponentials in a polyexponential response or the number of compartments in compartmental analysis. We also solve it analogously, by fitting differential equations of increasing order and terminating the procedure when no significant improvement is obtained, the decision being based on the Akaike Information Criterion (AIC), given by

$$AIC = 2 \log RSS + \alpha k \tag{16}$$

where RSS is the residual sum of squares, k is the number of parameters in the model and $\alpha = 2$ (16,28). The minimum value of AIC is sought. This test is now widely used in discrete time process identification, and has tended to displace the more traditional F test.

The AIC is based on maximum likelihood considerations and is a mathematical formulation of the principle of parsimony in model building (16,27). By increasing the model order, one can improve the goodness of fit, thereby reducing RSS in Eq. (16). However, the term αk is then increased and the minimum AIC is a compromise between goodness of fit and model complexity. As discussed earlier in this paper, the system is being identified for use in deconvolution. Deconvolution itself can be regarded as a problem of optimal control, seeking an input function u to minimize the squared deviations between the observed and computed responses of the system. Similar control problems have been studied by Edmunds (29), who found that the value $\alpha = 2$, originally used by Akaike (16,28), tends to overestimate the model order for the purposes of control applications. Edmunds suggested using the more conservative value $\alpha = 16$, which implies the selection of a lower order model, whose parameters can then be estimated to within a 25% error margin (29). System identification is performed by repeated parameter estimation, terminating the procedure when an increase in model order leads to an increase in AIC. While the model is identified in the form

Table I. Calculation of Weighting Function Parameters From First and Second-Order Differential Equations

Model order	Condition	Weighting function	Parameters	Parameter transformation
1	—	$Ae^{\alpha t}$	$A=b_1$, $\alpha=-a_1$	$\hat{A}=Ae^{-\alpha t_0}$ α unchanged
2 with $E\equiv a_1^2-4a_2$	$E>0$ different real roots	$Ae^{\alpha t}+Be^{\beta t}$	$\alpha=-a_1/2+\sqrt{E}/2$ $B=-a_1/2-\sqrt{E}/2$ $A=(b_1\alpha+b_2)/\sqrt{E}$ $B=-(b_1\beta+b_2)/\sqrt{E}$	$\hat{A}=Ae^{-\alpha t_0}$ $\hat{B}=Be^{-\alpha t_0}$ α, β unchanged
	$E=0$ identical real roots	$(A+Bt)\,e^{\alpha t}$	$\alpha=-a_1/2$ $A=b_1$ $B=b_1\alpha+b_2$	$\hat{A}=(A-Bt_0)e^{-\alpha t_0}$ $\hat{B}=Be^{-\alpha t_0}$ α, β unchanged
	$E<0$ complex roots	$(A\cos\beta t+B\sin\beta t)\,e^{\alpha t}$	$\alpha=-a_1/2$ $\beta=\sqrt{-E}/2$ $A=b_1$ $B=(b_1\alpha+b_2)/\beta$	$\hat{A}=(AC-BS)e^{-\alpha t_0}$ $\hat{B}=(BC+AS)e^{-\alpha t_0}$ where $S=\sin(\beta t_0)$ $C=\cos(\beta t_0)$ α, β unchanged

of a differential Eq. (3), only its weighting function is used in the deconvolution stage.

The lower integration limit in Eq. (14) is $t=0$, but observations of y are very often missing at this point. If the input u does not contain an impulse function, i.e., $D=0$ in Eq. (11), then $y(0)=0$ and we can integrate from $t=0$ in Eq. (14). If there is an intravenous bolus at $t=0$, but the response is first sampled at time $t_0>0$, then the DILS is applied with a lower limit of t_0 in all integrals of Eq. (14), with $y(t_0)$ as the first observation. Extrapolation to $t=0$ is thus avoided, but the system identified is one whose behavior at time t is that of the original system at time $t+t_0$, so that a weighting function $\tilde{g}(t)=g(t+t_0)$ is obtained. The true weighting function is $g(t)=\tilde{g}(t-t_0)$ and this translation of the time scale results in parameter transformations shown in the right hand column of Table I. For example, in the case of a first-order model and $y(t_0)$ as the first point, we obtain $\tilde{g}(t)=A\exp(\alpha t)$, so that $g(t)=\tilde{g}(t-t_0)=A\exp(-\alpha t_0)\exp(\alpha t)$, with the parameter $\hat{A}=A\exp(-\alpha t_0)$ as shown in Table I.

The procedure can readily be programmed using generally available scientific subroutines, e.g., from the NAG (Numerical Algorithms Group) Library. Many subroutines for spline interpolation also compute the integrals required in Eq. (14). The most involved part of the program consists of the algebraic expression given in Table I.

5. INPUT IDENTIFICATION

We recall that the problem is: Given a linear system S with its weighting function g and output function y, determine the input u that satisfies Eq.

(1). Consider a second linear system S* with input $u^* = g$ and output $y^* = y$. Then

$$y^*(t) = \int_0^t g^*(t-\tau)u^*(\tau)\,d\tau = \int_0^t u^*(t-\tau)g^*(\tau)\,d\tau$$

$$= \int_0^t g(t-\tau)g^*(\tau)\,d\tau \qquad (17)$$

Since $y^* = y$, comparison of Eqs. (17) and (1) shows that the weighting function g^* of S* equals the input function u which is being sought. Now, g^* can be estimated by identifying a linear system of the form of Eq. (3), as described in Sections 3 and 4 and this is the basic idea of the present paper. The approach preserves the symmetry of system identification and input identification, similarly to the point–area deconvolution method.

It is clear from Eq. (17) that u $(= g^*)$ is in the class of weighting functions generated by single-input, single-output, linear, time-invariant systems and as shown in Table I, for the particular case of a second-order model, this class includes polyexponentials and other functions. Thus, the present approach involves weaker restrictions on the form of output than the approach of Veng-Pedersen (12).

A further advantage of the present approach is the minimal parameterisation of the input function. To demonstrate this, consider the second-order system of Eq. (8), with weighting function

$$g(t) = Ae^{\alpha t} + Be^{\beta t} \qquad (18)$$

and let the input be a single exponential $u(t) = Ce^{\gamma t}$. If $\alpha \neq \gamma$ and $\beta \neq \gamma$, the output $y(t)$ is the sum of three exponentials including terms with exponents α and β. The method of Veng-Pedersen is based on estimating the six parameters in $y(t)$ and then computing the input from these parameters and those in Eq. (18) for $g(t)$, a total of eight parameters in all, because both $y(t)$ and $g(t)$ include α and β. Using the method described in this paper, only the two parameters of the first-order system with $g(t) = Ce^{\gamma t}$ are estimated in addition to the four parameters in Eq. (18), a total of six parameters in all. This difference of two between the two methods is maintained for higher-order systems and while not seeming dramatic, is nevertheless important in practical terms because of the sensitivity of parameters of a three-exponential curve to noise. By reducing the number of parameters to be estimated, the stability of the resulting input function is increased.

In addition to the sampled output $y_0, y_1, \ldots, y_l$, input identification requires the values $g(t_0), g(t_1), \ldots, g(t_l)$ at the same time points. These

can be computed from the algebraic expressions for g provided by the system identification stage. If system identification is based on impulse response data and we use the same time points in input identification, then the only goal of system identification is to smooth the observed impulse response.

Though the same operations are performed in system and input identification, there is a definitive difference in the principle of model order determination. As discussed in Section 4, it is advisable to select a low-order model in the system identification stage. On the other hand, in input identification, the derived weighting function is our final result and some overestimation of the model order is feasible provided the residual sum of squares is still decreasing.

Finally, it is of interest to note that the linear system S*, defined as a purely hypothetical one for solving the deconvolution problem, may in fact have a physical meaning in pharmacokinetic applications. For example, for the type of problem formulated in Section 1, S* is a linear system whose response is the bioavailability of the drug following an impulse administration via an extravascular route.

6. TEST EXAMPLE

To compare the method with previously published approaches, we use the four sets of simulated data presented by Cutler (8), also considered in (9–12). Each set consists of 11 points of a simulated unit impulse response and 11 points of the response to a particular (known) input function, both with added normally distributed random noise. The input functions are shown in Table II, along with the standard error of the noise expressed as a percentage. Veng-Pedersen (11) has noted that the models used to generate the test data are commonly employed in drug release and drug absorption analyses. All data sets can be associated with a two-compartment model;

Table II. Input Functions and Noise Levels in Data Sets 1-4 (8)

Data set	Input function	% standard error
1	$1.2e^{-2t}$	1
2		10
3	$\frac{1.8}{1.15}\left(1-\frac{t}{1.15}\right)^2$ if $t \leq 1.15$	1
4	0 if $t > 1.15$	10

Data Sets 1 and 2 then correspond to a first-order input rate and Data Sets 3 and 4 to a cube-root input rate, often observed in drug-release studies.

We first illustrate the properties of the DILS approach as a parameter estimation method and then discuss the system identification and input identification stages of the deconvolution procedure.

Parameter Estimation

Since the weighting function is of the form of Eq. (18), we fit the second-order differential Eq. (10) to the unit impulse response data. Parameter values computed from DILS estimates of the parameters in Eq. (10) through the algebraic expressions of Table I are shown in Table III. Following Cutler (8,9) and Veng-Pedersen (10–12), unweighted least squares is used so $W = I$ in Eq. (15). Table III also presents the indirect least squares (ILS) estimates, obtained by fitting Eq. (18) to the data by the Gauss-Marquardt algorithm. Since the unit impulse response data are identical in Data Sets 2 and 4, these results are listed only once.

Both methods yield reasonable estimates from Data sets 1 and 3 (with 1% standard error noise), and rather biased estimates from Data sets 2 and 4 (with 10% standard error noise). Though the DILS estimates are within the 95% confidence intervals of the ILS estimates, the latter are closer to the true values particularly for Data Sets 2 and 4. In the system identification stage, however, as we will see, the best solution is to adopt a first-order model for these latter data, so avoiding large variances in the estimates.

Table III. Estimates of Weighting Function Parameters

Data set	Parameter[a]	DILS Estimate	ILS Estimate	ILS SD
1	A	0.9575	0.9758	0.0523
	B	1.0593	1.0428	0.0407
	α	−0.9612	−0.9754	0.0431
	β	−4.9574	−5.0500	0.3844
2, 4	A	0.3355	0.5214	0.5862
	B	1.5012	1.3396	0.5022
	α	−0.3745	−0.6079	0.6841
	β	−2.7577	−3.1783	1.5841
3	A	1.0554	1.0486	0.0342
	B	1.0233	1.0309	0.0271
	α	−1.0315	−1.0261	0.0285
	β	−5.9103	−5.9129	0.3557

[a]Original values used by Cutler (8): $A = B = 1$; $\alpha = -1$; $\beta = -5$.

Table IV. System Identification

Data set	Model order	*RSS*	s_r^2	*AIC*	*F*
1	1	5.54E−2	6.16E−3	0.17	78.20
	2	5.51E−4	7.87E−5	−18.54	<1.0
	3	6.51E−4	1.30E−4	5.29	
2, 4	1	9.12E−2	1.01E−2	5.66	1.73
	2	4.08E−2	5.83E−3	28.81	5.01
	3	5.81E−3	1.16E−3	29.37	
3	1	5.75E−2	6.39E−3	0.58	122.19
	2	3.66E−4	5.23E−5	−23.04	<1.0
	3	4.90E−3	9.80E−4	2.16	

In the original data (8), the first time point considered is $t_0 = 0.1$. This was used as the lower integration limit in Eq. (14), the time scale transformation formulas in the right-hand column of Table I were used subsequently to compute the parameter values listed in Table III.

System Identification

The residual sum of squares *RSS*, the residual variance s^2, the modified *AIC*, and the *F* values obtained by fitting models of order 1, 2, and 3 to the three sets of unit impulse response data are listed in Table IV. There are 9 and 7 degrees of freedom in fitting the first-order and second-order models, respectively, and at $p = 0.01$, the corresponding point of the *F* distribution is 6.72. Thus for Data Sets 1 and 3, the second-order model is significantly better than the first-order model, but this is not so for Data Sets 2 and 4. This is also shown by *AIC*, which clearly indicates use of model order 2 for Data sets 1 and 3 and model order 1 for Data Sets 2 and 4. For Data Sets 1 and 3, use of a third-order model increases the residual variance, as a result of the near-singularity of the matrix to be inverted.

Input Identification

The quantity, $Q(t)$, of drug absorbed into the plasma up to time t is given by

$$Q(t) = \int_0^t u(\tau)\, d\tau.$$

For either of the forms of $u(t)$ given in Table II, $Q(0) = 0$. Cutler (8) gives the response function only for $t \geq 0.1$ and in this application, we have considered $y(0) = 0$ as an additional point in the input identification. Previous deconvolution methods also can only generate input functions not

Table V. Input Identification

Data set	Model	*RSS*	s_r^2	*AIC*	*F*
1	M_{21}	1.63E−4	1.63E−5	−72.66	1.34
	M_{22}	9.76E−5	1.22E−5	−46.81	
2	M_{21}	8.52E−3	8.52E−4	−25.18	2.01
	M_{22}	3.39E−3	4.23E−4	−4.24	
	M_{11}	3.51E−3	3.51E−4	−35.82	<1.0
	M_{12}	3.43E−3	4.28E−4	−4.10	
3	M_{21}	1.03E−2	1.03E−3	−22.90	12.93
	M_{22}	6.37E−4	7.96E−5	−24.30	
	M_{23}	2.54E−3	4.25E−4	14.29	<1.0
4	M_{21}	2.39E−2	2.39E−3	−12.81	3.79
	M_{22}	5.04E−3	6.31E−4	0.52	
	M_{11}	7.49E−3	7.49E−4	−26.73	1.01
	M_{12}	5.94E−3	7.43E−4	2.48	

containing impulses, so the same assumption has been used, although not explicitly stated.

The values on which model order determination is based in the input identification stage are shown in Table V. The notation M_{ij} is used to denote a system identification–input identification sequence, with i denoting the model order in the system identification stage and j denoting the model order in the input identification stage. To study the consequences of overestimating model order in system identification, weighting functions computed from both first-order and second-order models were used for Data Sets 2 and 4.

From Table V, we see that for input identification, a second-order model is preferable for Data Set 3, but that for the other Data Sets, a first-order model is suggested both by the *F* test and the *AIC*. We show, however, that in the input identification stage, it is better to choose the model with the least residual sum of squares, in spite of a possible overestimation of model order according to *AIC*.

To compare the derived input function with the estimates of Cutler (9) and Veng-Pedersen (10–12), its accuracy is expressed in terms of percentage differences, defined by $100 \times$ (calculated rate − exact rate)/initial rate (10). Tables VI to IX show the mean and standard deviation of the absolute values of these percentage differences for the time points $t_i \geq 0.1$.

Data Set 1 (Table VI)

The errors are small and the input is an exponential, so we expect very good performance; as seen in Table III, even the DILS estimates of the

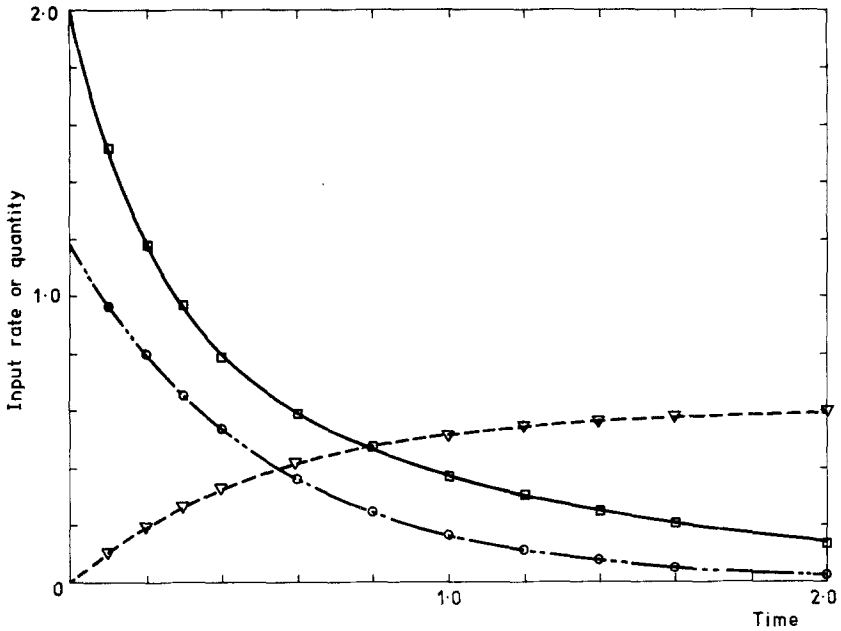

Fig. 1. Original and estimated weighting functions and input functions for Data Set 1 (second-order system; first-order input rate): □ = Original impulse response data of Cutler (8); ——— = fitted impulse response; ○ = calculated input rate; — - - — = original input rate given by Cutler (8); ▽ = calculated input quantity; - - - = original input quantity from the input rate given by Cutler (8).

weighting function parameters are close to the true values. The selected system identification–input identification sequence M_{21} gives the input $u(t) = 1.1757 \exp(-1.9488t)$, close to the true input (Table II). Figure 1 shows that the calculated and exact input rates and cumulative quantities are almost identical.

Other deconvolution procedures are compared in Table VI. As expected, the method of Veng-Pedersen (12), involving polyexponential functions, performs very well. Our method with M_{21} involves estimating fewer parameters and it further improves the result. From the M_{22} column of Table VI, it may be seen that overestimation of model order slightly increases the percentage differences.

Data Set 2 (Table VII)

With the larger observation errors, the weighting function estimates are rather biased using the true second-order model and the system identification procedure suggests a first-order model. Even so, the sequence M_{21} results in $u(t) = 1.1444 \exp(-1.6452t)$ which is more accurate than previously published input functions. M_{22} means overestimating the model

Table VI. Input Rate Estimates From Data Set 1

Time	Exact rate	Estimated input rate: Cutler (9)	Veng-Pedersen (10)	Veng-Pedersen (11)	Veng-Pedersen (12)	This paper M_{21}	This paper M_{22}
0.0	1.2000	1.145	—	—	—	1.1757	1.1178
0.1	0.9825	0.967	0.9666	0.9712	0.9625	0.9675	0.9607
0.2	0.8044	0.810	0.8366	0.8146	0.8107	0.7962	0.8066
0.3	0.6586	0.674	0.6884	0.6780	0.6732	0.6552	0.6687
0.4	0.5392	0.556	0.5500	0.5598	0.5535	0.5392	0.5505
0.6	0.3614	0.370	0.3658	0.3732	0.3676	0.3651	0.3693
0.8	0.2423	0.240	0.2339	0.2434	0.2420	0.2473	0.2463
1.0	0.1624	0.156	0.1555	0.1590	0.1601	0.1675	0.1638
1.2	0.1089	0.105	0.1160	0.1084	0.1077	0.1134	0.1091
1.4	0.0730	0.076	0.0790	0.0803	0.0742	0.0768	0.0726
1.6	0.0489	0.057	0.0404	0.0631	0.0527	0.0520	0.0483
2.0	0.0220	0.003	0.0230	0.0160	0.0292	0.0238	0.0214
Mean of % diff.		0.79	0.99	0.80	0.59	0.41	0.46
SD of % diff.		0.50	0.84	0.56	0.54	0.33	0.56

order in both stages and gives larger percentage differences, while M_{11} gives results comparable in accuracy to those obtained from M_{21}. The best results of all are given by M_{12}, which is based on correct model order in system identification but less conservative order determination in the input identification stage. This in fact implies a first-order model and a second-order input, the reverse of the true situation.

Table VII. Input Rate Estimates From Data Set 2

Time	Exact rate	Estimated input rate: Cutler (9)	Veng-Pedersen (10)	Veng-Pedersen (11)	Veng-Pedersen (12)	This paper M_{21}	This paper M_{22}	This paper M_{11}	This paper M_{12}
0.0	1.2000	0.996	—	—	—	1.1444	1.0291	1.1825	1.1641
0.1	0.9825	0.904	0.8784	0.8303	0.9159	0.9708	0.9180	0.9971	0.9826
0.2	0.8044	0.813	0.8087	0.7426	0.8199	0.8235	0.8147	0.8407	0.8290
0.3	0.6586	0.724	0.7242	0.6595	0.7242	0.6986	0.7190	0.7089	0.6989
0.4	0.5392	0.639	0.6358	0.5810	0.6319	0.5926	0.6307	0.5977	0.5886
0.6	0.3614	0.479	0.4771	0.4378	0.4651	0.4265	0.4747	0.4249	0.4154
0.8	0.2423	0.338	0.3308	0.3129	0.3269	0.3069	0.3442	0.3021	0.2896
1.0	0.1624	0.219	0.2199	0.2065	0.2180	0.2208	0.2365	0.2148	0.1970
1.2	0.1089	0.125	0.1409	0.1184	0.1355	0.1589	0.1489	0.1527	0.1271
1.4	0.0730	0.058	0.0708	0.0486	0.0750	0.1144	0.0790	0.1086	0.0720
1.6	0.0489	0.020	0.0129	−0.0027	0.0324	0.0823	0.0243	0.0772	0.0254
2.0	0.0220	0.027	0.0091	−0.0503	−0.0152	0.0426	−0.0484	0.0390	−0.0625
Mean of % diff.		4.41	4.65	4.59	4.29	3.47	4.98	3.48	2.86
SD of % diff.		3.45	3.46	3.41	2.86	1.56	2.99	1.41	2.05

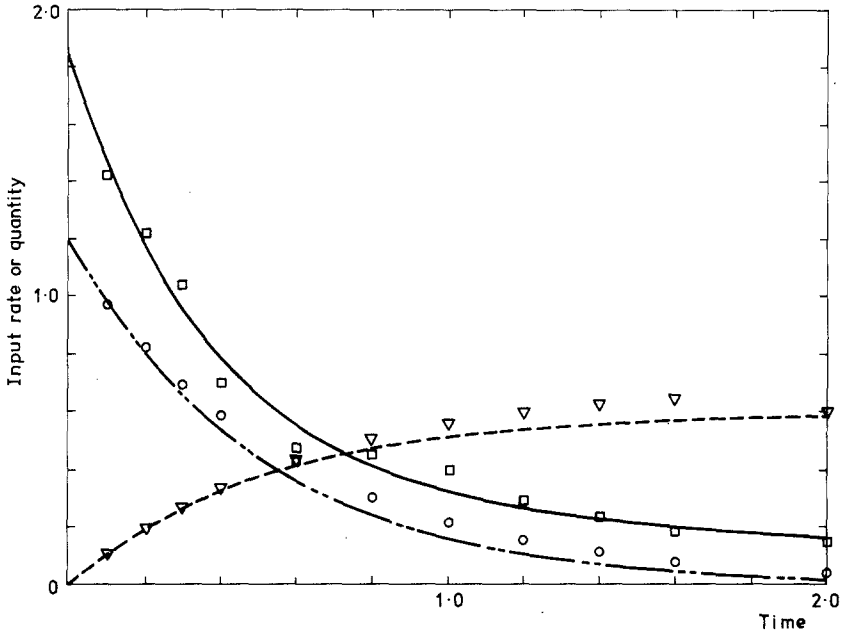

Fig. 2. Original and estimated weighting functions and input functions for Data Set 2 (second-order system; first-order input rate). Symbols and lines as for Fig. 1.

Estimation of the impulse response and input functions using M_{21} and M_{12} are shown in Figs. 2 and 3, respectively. System identification is far from perfect in the second case (for example, in the last five samples, all impulse response observations are above the fitted curve) but the derived input rate $u(t) = -0.0041 \exp(1.6143t) + 1.1682 \exp(-1.6808t)$ gives better estimates of the true rate and amount of input than the single exponential calculated from the sequence M_{21}, shown in Fig. 2.

Data Set 3 (Table VIII)

Although the noise level is low, the true input is not a polyexponential. With no assumption on the form of the input, the first method of Veng-Pedersen (10) works well. Correct model order selection in our procedure gives M_{22}, which also works well. Results for M_{22} are shown in Fig. 4. The form of the calculated input function $u(t) = [1.3446 \cos(2.0571t) + 2.6431 \sin(2.0571t)] \exp(-3.6095t)$ differs substantially from the form of the true cube-root input at the initial stage of the process, but differences at the sample times are small and the calculated and exact cumulative quantities are almost indistinguishable.

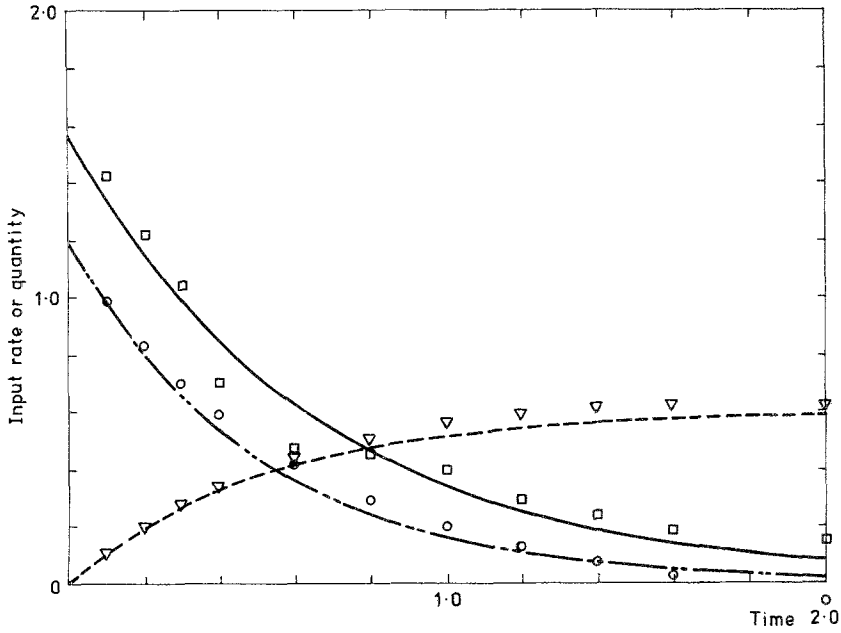

Fig. 3. Original and estimated weighting functions and input functions for Data Set 2 (first-order system; second-order input rate). Symbols and lines as for Fig. 1.

As we have seen in Table V, M_{21} represents an underestimation of model order in the input identification stage and this shows up in the considerably larger percentage difference in Table VIII.

Data Set 4 (Table IX)

Although the true input function is not an exponential, the results for M_{21}, M_{22}, M_{11}, and M_{12} are similar to those for Data Set 2 (Table VII). The correctly selected sequence M_{11} performs very well, but the true input is even better recovered by M_{12}, results for which are shown in Fig. 5. Comparison of Tables VII and IX shows that the attained accuracy is almost independent of the form of the true input function.

7. CONCLUSIONS

The main advantage of the deconvolution algorithm presented in this paper is its computational simplicity. Starting from the raw data, the procedure identifies both the model and the input, solving only linear regression equations at each stage. Therefore it is not necessary to fit polyexponential expressions to the impulse response and output observations, as required

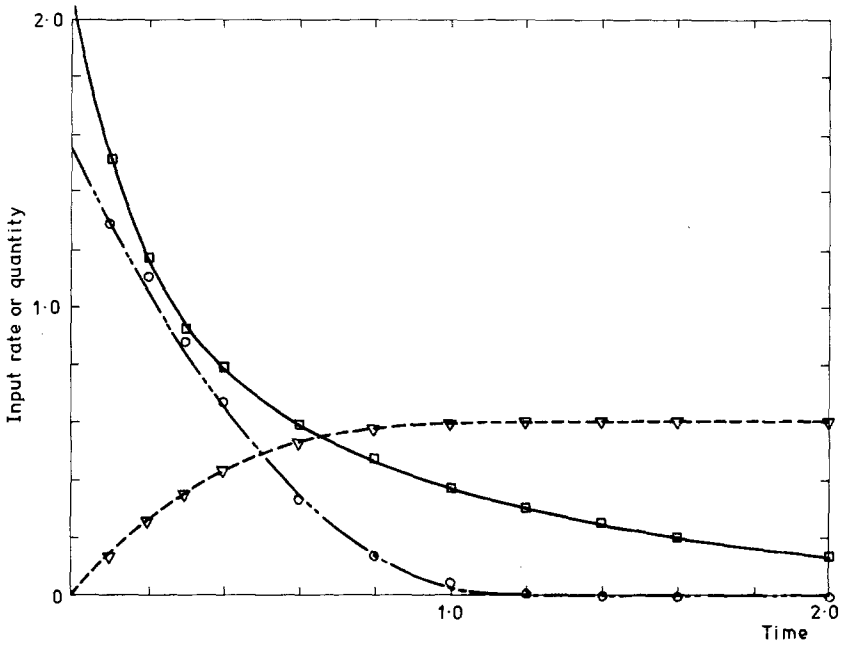

Fig. 4. Original and estimated weighting functions and input functions for Data Set 3 (second-order system; second-order input rate). Symbols and lines as for Fig. 1.

Table VIII. Input Rate Estimates From Data Set 3.

		Estimated input rate					
			Veng-Pedersen			This paper	
Time	Exact Rate	Cutler (9)	(10)	(11)	(12)	M_{21}	M_{22}
0.0	1.5652	1.608	—	—	—	1.7993	1.3446
0.1	1.3048	1.256	1.2780	1.3133	1.3002	1.3439	1.2938
0.2	1.0681	1.060	1.1080	1.0924	1.0639	1.0039	1.1123
0.3	0.8551	0.893	0.8959	0.8844	0.8418	0.7498	0.8893
0.4	0.6657	0.715	0.6839	0.6936	0.6473	0.5601	0.6732
0.6	0.3580	0.356	0.3609	0.3758	0.3529	0.3125	0.3370
0.8	0.1450	0.115	0.1312	0.1543	0.1690	0.1743	0.1412
1.0	0.0266	0.026	0.0202	0.0305	0.0639	0.0973	0.0462
1.2	0.	0.004	0.0011	−0.0082	0.0086	0.0543	0.0078
1.4	0.	−0.010	0.0010	0.0112	−0.0172	0.0303	−0.0039
1.6	0.	0.048	0.0008	0.0478	−0.0269	0.0169	−0.0053
2.0	0.	−0.526	0.0007	−0.0625	−0.0259	0.0053	−0.0021
Mean of % diff.		4.44	0.88	1.45	1.08	3.29	0.93
SD of % diff.		9.76	1.00	1.18	0.69	2.10	0.88

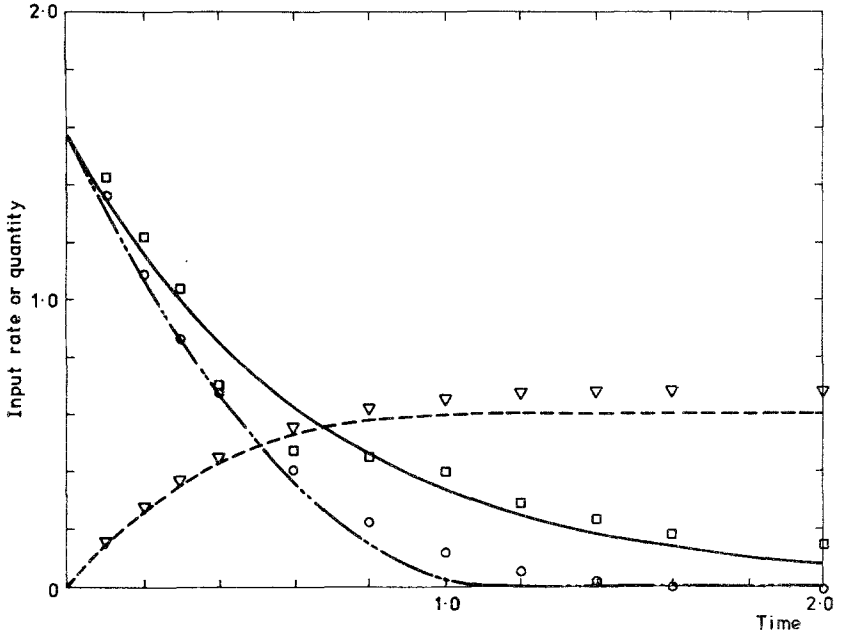

Fig. 5. Original and estimated weighting functions and input functions for Data Set 4 (first-order system; second-order input rate). Symbols and lines as for Fig. 1.

Table IX. Input Rate Estimates From Data Set 4

		Estimated input rate							
			Veng-Pedersen			This paper			
Time	Exact rate	Cutler (9)	(10)	(11)	(12)	M_{21}	M_{22}	M_{11}	M_{12}
0.0	1.5652	1.423	—	—	—	1.6959	1.3929	1.7979	1.6863
0.1	1.3048	1.235	1.1761	1.1487	1.2589	1.3305	1.2431	1.3878	1.3622
0.2	1.0681	1.058	1.0614	0.9863	1.0562	1.0438	1.0813	1.0712	1.0906
0.3	0.8551	0.895	0.9224	0.8353	0.8738	0.8189	0.9180	0.8268	0.8650
0.4	0.6657	0.744	0.7740	0.6956	0.7123	0.6424	0.7604	0.6382	0.6794
0.6	0.3580	0.481	0.4934	0.4504	0.4503	0.3954	0.4827	0.3802	0.4056
0.8	0.1450	0.270	0.2480	0.2507	0.2605	0.2433	0.2677	0.2266	0.2298
1.0	0.0266	0.109	0.0859	0.0964	0.1290	0.1498	0.1169	0.1350	0.1211
1.2	0.	0.000	0.0057	−0.0125	0.0422	0.0922	0.0217	0.0804	0.0569
1.4	0.	−0.059	0.0008	−0.0759	−0.0121	0.0567	−0.0309	0.0479	0.0209
1.6	0.	−0.066	0.0000	−0.0938	−0.0434	0.0349	−0.0535	0.0285	0.0023
2.0	0.	0.074	0.0000	0.0067	−0.0647	0.0132	−0.0509	0.0101	−0.0089
Mean of % diff.		4.34	3.57	4.32	3.46	3.28	4.23	3.03	2.44
SD of % diff.		2.51	3.55	2.95	2.29	2.33	2.43	2.25	2.05

in one of the methods of Veng-Pedersen (12), based on similar assumptions as the new algorithm.

A well-studied test example shows that by choosing the model order as low as possible in system identification and selecting the best fitting model in input identification, the simple procedure results in very good estimates of the input function.

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