Removal of catheter distortion in multiple indicator dilution studies: a deconvolution-based method and case studies on glucose blood–tissue exchange

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Abstract—*The study of blood–tissue exchange by the multiple indicator dilution technique often needs frequent sampling in the blood of the indicator dilution curves (IDC). Usually, this requires the use of a catheter supported by a pump. This causes a distortion in the IDC, which must be removed for proper interpretation of the data. A deconvolution-based methodology to remove IDC distortion is presented. First, the catheter impulse response is modelled by means of data obtained from a suitable experiment. Then the reconstruction of the blood IDC is tackled by a new nonparametric deconvolution algorithm, which provides (quasi) time-continuous signals and exploits statistically based criteria for the choice of the regularisation parameter. The methodology is applied to the removal of cathether distortion in studies of glucose blood–tissue exchange in the human forearm and myocardium.*

Keywords—*Input estimation, Regularisation, Tracer kinetics*

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1 Introduction

THE STUDY of blood–tissue exchange in physiological systems by the multiple indicator dilution technique often requires the frequent sampling in the blood of the indicator dilution curves (IDCs). Usually this is accomplished by means of a catheter, e.g. frequently sampled IDC time series are obtained by continuously withdrawing small quantities of blood through a catheter supported by an electrical or mechanical pump (we will refer to the catheter and pump apparatus as the catheter system). Each IDC measurable at the end of the catheter system is a distorted version of the blood IDC. Distortions are more relevant the changes in the blood IDC are faster. In general, the IDC at the cuvette of the catheter is delayed, less sharp and also lower in amplitude than the blood IDC. On the other hand, slow trends in the IDC are usually preserved. Data analysis, e.g. for the calculation of the mean residence time, often cannot be made directly on the distorted IDC, and there is thus the need to remove the catheter distortion. The importance of the problem has been well known for a long time (MILNOR and JOSE, 1960; GORESKY and SILVERMAN, 1964; NORWICH, 1977).

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In this paper we describe a two-stage procedure to remove catheter distortion. First, we obtain the impulse response of the catheter system by a suitably designed experiment. Then we obtain the blood IDC by a new non-parametric deconvolution algorithm which estimates (quasi) time-continuous curves and exploits new statistically funded criteria to choose the amount of smoothing. We apply the proposed methodology in studies of glucose blood–tissue exchange in the human forearm and myocardium employing the multiple indicator dilution technique.

2 The problem

Consider, for the sake of simplicity, a single indicator, e.g. a radioactive tracer, a pulse of which is injected in the blood at the inlet of an organ to obtain information on the blood–tissue exchange. Assume that the resulting blood IDC, say $u(t)$ (mass × volume^{-1}), cannot be monitored by manual sampling and that it must be withdrawn by a catheter system. Let $z(t)$ denote the IDC measurable at the cuvette of the catheter. Because of the distortion due to the catheter system, $z(t)$ is shifted to the right along the time axis and it is broader and lower than $u(t)$. In practice, only a noisy IDC time series can be measured:

$$y(t_k) = z(t_k) + v(t_k), \quad k = 1, 2, \ldots, n \tag{1}$$

having assumed that the error which corrupts each IDC sample is additive.

By viewing the desired but unknown $u(t)$ as the input of the catheter system, we can pose its reconstruction as an input estimation problem from the noisy samples $\{y(t_k)\}$ of its causally related output $z(t)$. If the tracer transport through the catheter occurs with a steady flow rate and is mainly convective, the catheter can be represented by a linear and time-invariant system (NORWICH, 1977) and $z(t)$ is related to $u(t)$ by a convolution integral

$$z(t) = \int_0^t g(t-\tau)u(\tau)\,d\tau \tag{2}$$

where $g(t)$ (time^{-1}) represents the catheter impulse response. We can then pose recovering the input $u(t)$ from the available output samples $\{y(t_k)\}$ as a deconvolution problem. Its solution requires, however, the availability of the impulse response $g(t)$.

3 Methdology

3.1 *Catheter impulse response modelling*

A proper knowledge of the impulse response $g(t)$ is needed to solve the deconvolution problem accurately. In fact, errors in $g(t)$ would be reflected in errors on the estimate of $u(t)$ provided by deconvolution.

A model of $g(t)$ can be determined from a suitably designed experiment. In principle, we could determine the impulse response of the catheter system by measuring, at the cuvette, the response to a pulse input. However, it may be more convenient to determine the impulse response by measuring the response of the catheter system to a step. In fact, there are at least two advantages in this procedure. First, the experimental realisation of a step is usually simpler than that of a pulse (NORWICH, 1977). Second, because the unknown IDC is regular, it is important to provide a good description of the catheter behaviour, especially in the low-frequency range. The step input is thus convenient because its spectral content decreases as $1/f$, f being the frequency, and this makes it easier to observe the low-frequency spectrum of the catheter system.

A sum of M delayed exponentials usually describes well the impulse response of a catheter system. If all the indicator entering the catheter system eventually leaves, the area under $g(t)$ is unitary. With fixed model order, parameters can be determined by fitting the model against the, say, step response data by nonlinear least squares. Model order can be chosen by considering goodness of fit, precision of parameter estimates and parsimony criteria (CARSON *et al.*, 1983; LANDAW and DISTEFANO, 1984).

Note that, because IDC distortion depends on the geometric characteristics of the sampling device and on the speed of the electrical pump and not on the subject under study, we use the same model of $g(t)$ to remove distortion from the IDCs of different patients collected with the same catheter system.

3.2 *Deconvolution*

After having determined $g(t)$, we can attack the deconvolution problem (BERTERO, 1989; DE NICOLAO *et al.*, 1996). Many deconvolution methods have been presented in the literature. A first approach is non-parametric and it includes: regularisation (PHILLIPS, 1962; TIKHONOV, 1963); truncated singular value decomposition (HANSEN, 1992); and maximum entropy (CHARTER and GULL, 1991). An alternative class of methods, where the unknown input has a known functional form with parameters to be estimated from the data, is named parametric deconvolution (NORWICH, 1977; CUTLER, 1978; VENG-PEDERSEN, 1980). Recently, deconvolution has also been faced by using regression splines (VEROTTA, 1993).

3.2.1 *Stochastic deconvolution approach.* We now describe a new non-parametric deconvolution method which, for certain aspects, can also be viewed as an evolution of the Phillips–Tikhonov (PT) regularisation approach.

Consider the time-continuous model of eqn. (2). Define two grids: let $\Omega_s = \{t_1, t_2, \ldots, t_k, \ldots, t_n\}$ denote the (experimental) sampling grid and let $\Omega_v = \{T_1, T_2, \ldots, T_k, \ldots, T_N\}$ be an arbitrary uniform grid, possibly finer than Ω_s ($N \geqslant n$) but with $\Omega_s \subseteq \Omega_v$. The grid Ω_v does not need to have any experimental counterpart and can be arbitrary. For such a reason, we call Ω_v the virtual grid. We assume that $u(t)$ can be approximated as a piecewise constant within each time interval of the virtual grid. By properly discretising the convolution integral (DE NICOLAO *et al.*, 1995), we can thus model the n-dimensional vector of the measurements, say y, as:

$$y = z + v = Gu + v \tag{3}$$

where v is the n-dimensional vector of the measurement error, assumed to be additive (see eqn. 1), u is the N-dimensional vector of the input considered on the virtual grid, and G is a $n \times N$ near-to-Toeplitz matrix.

The above discretisation procedure is different from that originally considered in (PHILLIPS, 1962) and related papers, where the input is assumed to be piecewise constant on the sampling grid.

Consider u, v and y of the model of eqn. 3 to be stochastic vectors. It is thus possible to pose the deconvolution problem as a linear minimum variance estimation problem (BECK and ARNOLD, 1977), i.e. 'Find the estimate $\hat{u}$, linearly depending on the data vector $y = Gu + v$, such that $E[\|u - \hat{u}\|^2]$ is minimised'.

Assume that the second-order *a priori* statistical description of u and v is available. In particular, consider that u and v are uncorrelated zero mean random vectors with covariance matrices given by $\Sigma_u = \lambda^2 R = \lambda^2 (F^T F)^{-1}$ and $\Sigma_v = \sigma^2 B$, respectively, where λ^2 and σ^2 are scalars and R and B are N- and n-dimensional positive definite matrices. Under these hypotheses, the linear minimum variance estimator is found by solving

$$\min_{\hat{u}} (y - G\hat{u})^T B^{-1} (y - G\hat{u}) + \gamma \hat{u}^T F^T F \hat{u} \tag{4}$$

where $\gamma = \sigma^2/\lambda^2$. The solution of the problem of eqn. 4 is

$$\hat{u} = (G^T B^{-1} G + \gamma F^T F)^{-1} G^T B^{-1} y \tag{5}$$

When the vectors involved in the model of eqn. 3 are Gaussian, the linear estimator of eqn. 5 has the minimum error variance among all the estimators of u given y.

However, linear minimum variance estimation requires a second-order *a priori* statistical description, i.e. mean and covariance matrix, of both v and u.

3.2.2 *Second-order statistic description of v and u.* In most cases we have quantitative *a priori* information about the precision of the data. The measurement error vector v can be often assumed (Gaussian and) uncorrelated. In this case its covariance matrix Σ_v is diagonal. For instance, by assuming a constant measurement error CV, we have $\Sigma_v = \sigma^2 B$ with $B = \text{diag}\,(y_1^2, y_2^2, \ldots, y_n^2)$ and $\sigma = CV$ (σ possibly unknown).

Conversely, because an *a priori* statistical description of u based on firm grounds is obviously not available, we must postulate some structure for $\Sigma_u = \lambda^2 R = \lambda^2 (F^T F)^{-1}$ by simply

exploiting the 'rough' information that $u(t)$ is regular. An easy way to describe the regularity of $u(t)$ consists in modelling the stochastic process $\{u_k\}$ by a random walk (COMMENGES, 1984):

$$u_k = u_{k-1} + w_k \tag{6}$$

where, assuming that Ω_v is uniformly spaced, $\{w_k\}$ is a stationary white noise process with zero mean and variance λ^2 and $u_0 = 0$. The degree of regularity of $\{u_k\}$ depends on the scalar λ^2 which will need to be determined *a posteriori* together with the input profile. An alternative but still simple way to describe the smoothness of $u(t)$ is to assume that the process $\{u_k\}$ can be modelled by an integrated random walk:

$$u_k = u_{k-1} - 2u_{k-2} + w_k \tag{7}$$

where $\{w_k\}$ is a stationary white noise process with zero mean and variance λ^2 and $u_{-1} = u_0 = 0$. For the models of eqns. 6 and 7, the matrix F is an N-dimensional square Toeplitz matrix whose first column is $[1, -1, 0, \ldots, 0]^T$ and $[1, -2, 1, 0, \ldots, 0]^T$, respectively. Note that the models of eqns. 6 and 7 describe a stochastic process obtained by the simple or double integration of a white noise process, respectively. We cannot address the choice of the best model on theoretical firm grounds, and one usually determines by trials which is the most appropriate number of integrators in a particular case study.

3.2.3 *Choice of the regularisation parameter.* In eqns. 4 and 5 the parameter $\gamma = \sigma^2/\lambda^2$ is unknown. In fact, although σ^2 can be known (e.g. known data *CV*), λ^2 is always unknown. If we interpret eqn. 4 in a deterministic setting, the first term of the cost function weights the adherence to the experimental data and the second is proportional to the input roughness (expressed by the energy of the mth time-differences, $m = 1$ or $m = 2$). The parameter γ balances their relative importance. By raising γ the cost of roughness increases and matching the data becomes relatively less important. For such a reason γ is called the regularisation parameter. Its choice is commonly recognised as a critical problem. Too large values of γ will lead to very smooth realisations of $\hat{u}$ which well explain the data at the cost of wide and spurious oscillations (the estimate a which may be not able to explain the data (oversmoothing). Conversely, too small values of γ will lead to ill-conditioned solutions $\hat{u}$ which well explain the data at the cost of wide and spurious oscillations (the estimate a explains both data and noise). To avoid subjectivity on the choice of γ, several criteria have been proposed (GOLUB *et al.*, 1979; HALL and TITTERINGTON, 1987; HANSEN, 1992). When σ^2 is known, a very popular and easy-to-use criterion to tune γ is as follows (TWOMEY, 1965).

Criterion 1. Adjust γ until $\mathrm{WRSS}(\gamma) = n\sigma^2$, where $\mathrm{WRSS} = (y - G\hat{u})^T B^{-1}(y - G\hat{u})$ denotes the weighted residuals sum of squares.

However, neither Criterion 1 nor any of the above-mentioned criteria are based on firm statistical grounds, and their use in the linear minimum variance estimation context would make the estimator of eqn. 5 suboptimal. Indeed, the stochastic approach enables the derivation of statistically based criteria for the choice of γ, either when σ^2 and λ^2 are both unknown or when only λ^2 needs to be adjusted.

Criterion 2 (λ^2 unknown, σ^2 known). Tune γ until $\mathrm{WESS}(\gamma) = q(\gamma)/\gamma$, where $\mathrm{WESS} = \hat{u}^T R^{-1} \hat{u}$ denotes the weighted estimates sum of squares and

$$q(\gamma) = \mathrm{trace}(B^{-1/2} G[G^T B^{-1} G + \gamma F^T F]^{-1} G^T B^{-1/2})$$

with $B^{-1/2}$ such that $B^{-1} = B^{-1/2} B^{-1/2}$.

Criterion 3 (λ^2 and σ^2 unknown). Tune γ until

$$\mathrm{WRSS}/(n - q(\gamma)) = \gamma \mathrm{WESS}(\gamma)/q(\gamma)$$

and estimate σ^2 *a posteriori* as $\sigma^2 = \mathrm{WRSS}/(n - q(\gamma))$.

The quantity $q(\gamma)$ is a real number varying from 0 to n, and it is named the degree of freedom associated with γ. It has been shown (DE NICOLAO *et al.*, 1997) that under Gaussian assumptions the above criteria have a nice interpretation in terms of maximum likelihood of the data. In the non-Gaussian case, they are still meaningful, because they are consistent with average properties of linear minimum variance estimation (SPARACINO and COBELLI, 1996). It is also possible to see that the widely used Criterion 1 is not consistent with linear minimum variance estimation properties and it is at risk of oversmoothing.

To conclude, an additional advantage of the stochastic embedding consists in providing closed-form expressions to compute confidence intervals of the input IDC which also account for bias error (DE NICOLAO *et al.*, 1997).

The guidelines for the numerical implementation of the above deconvolution algorithm are given by De Nicolao *et al.* (DE NICOLAO *et al.*, 1997).

4 Case studies

4.1 *Study of glucose blood–tissue exchange in the human forearm*

The experiments are designed to study glucose blood–tissue exchange in the human forearm in normal subjects. The study protocol has been approved by the Institutional Ethical Committee of the Helsinki University School of Medicine, where the experiments are performed. We explain the purpose, nature and potential risks of the study to the volunteers, and obtain written consent before their participation.

Three tracers (indocyanine green, an intravascular reference, [^{3}H]-D-mannitol, an extracellular marker of glucose, and [^{14}C]-3-O-methyl-glucose, a permeant tracer which enters cells but is not metabolised) are simultaneously injected into the brachial artery, and we collect plasma samples from the forearm deep vein for 15 min. To monitor early tracer dynamics, we use a catheter supported by an electrical pump in the first 90 s. The catheter is a standard 20G two-inch, suitable for cannulation of forearm deep vein. We collect samples with a constant period of $T = 0.858$ s. Subsequently, when the blood IDC is known to vary very slowly, we take samples manually. A reliable measure of the uncertainty of the deconvolution data is not available. However, measurement errors can be assumed to have an approximately constant, even if unknown, *CV*.

We determine the model of $g(t)$ by measuring the response of the catheter system to the unitary step $1(t)$. In this paper only [^{3}H]-D-mannitol, i.e. the less expensive tracer, is used at this stage. We prepare a blood solution, containing [^{3}H]-D-mannitol at a known concentration, and then withdraw it through the catheter. We collect samples at the cuvette using the same sampling grid as in the multiple tracer experiments. To improve the precision of the impulse response model and to evaluate the reproducibility of the experiment, the entire procedure is repeated four times. We fit the functions

$$g(t) = \alpha e^{-\alpha(t - t_d)} 1(t - t_d) \tag{8}$$

$$g(t) = \left\{ \frac{\alpha\beta}{\alpha - \beta} e^{-\alpha(t - t_d)} - \frac{\alpha\beta}{\alpha - \beta} e^{-\beta(t - t_d)} \right\} 1(t - t_d) \tag{9}$$

to the data, where t_d is the catheter time-delay and α and β are non-negative parameters. The impulse response models of

eqns. 8 and 9 result from the unitary constraint on the area under $g(t)$ and, for the model of eqn. 9, from the additional assumption of the continuity of $g(\cdot)$ for $t = t_d$. We estimate the model parameters by nonlinear least squares. Figure 1 displays the fits of the monoexponential model (top panel, $\alpha = 0.300$ and $t_d = 13.216$) and of the two-exponential model (bottom panel, $\alpha = 0.305$, $\beta = 4.119$ and $t_d = 13.020$) against the [^{3}H]-D- mannitol step response 2. In all the experiments, fitting the model of eqn. 9 against the data returns residuals only slightly smaller than those obtained by the model of eqn. 8, at the price of an estimate of parameter β overly sensitive to data noise. In addition, both the Akaike and Schwartz criteria indicate the monoexponential model in three out of four cases. In the deconvolution procedure below we thus adopt a monoexponential model whose parameters, i.e. $\alpha = 0.255$ and $t_d = 12.655$, are obtained by averaging those obtained by each of the four step responses ($\alpha = 0.230$ and $t_d = 12.624$ in experiment 1, $\alpha = 0.254$ and $t_d = 12.620$ in 3, $\alpha = 0.231$ and $t_d = 12.165$ in 4).

Catheter distortion is removed from each IDC time series separately. Figure 2*a* shows a representative data set [^{3}H]-D-mannitol, subject 1). Owing to severe ill-conditioning, the least squares (LS) estimate (obtained from eqn. 3 as $\hat{u} = G^{-1}y$, with $\Omega_v = \Omega_s$) shows unrealistic oscillations and negative values (Fig. 2*b*, thin line). Regularised deconvolution is then performed, assuming the unknown vector u to be modelled on $\Omega_v = \{kTv\}$, $Tv = T/8$, by the doubly integrated white noise of eqn. 7. We use Criterion 3 for the choice of the regularisation parameter and estimate the measurement error *CV a posteriori* accordingly. Figure 2*b* (thick line) shows the estimate for the representative data set ($\gamma = 1 \times 10^{-10}$, $q(\gamma) = 46.56$, *a posteriori* estimated $CV = 4.5\%$). Figure 2*c* also shows the percentage residuals, being the residuals calculated by subtracting the model predictions, calculated by using the regularised IDCs in place of $u(t)$ in eqn. 2, to the experimental data. The same time series is also deconvoluted by modelling the unknown IDC by a random-walk process. Results (not shown) indicate that, here, the doubly integrated white noise is more appropriate than the random-walk process, because it leads to smoother and more realistic IDC profiles.

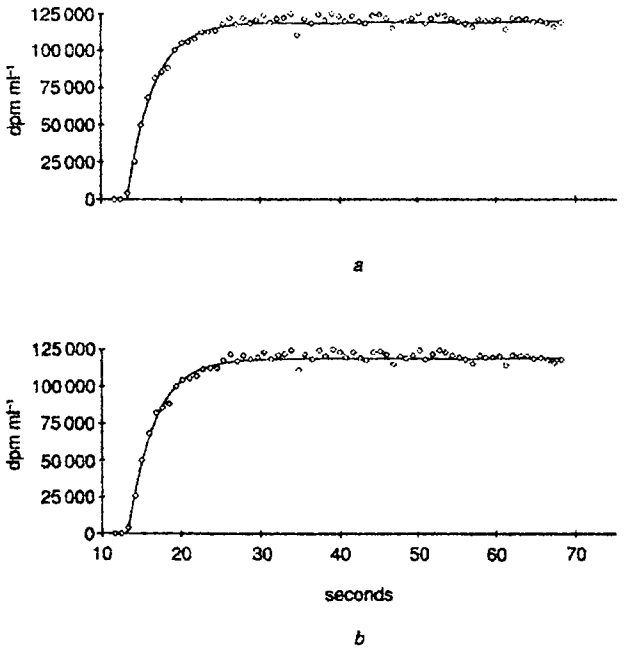

Fig. 1 *(a) Fit of the monoexponential model against the samples of the step response ([^{3}H]-D-mannitol, experiment 2); (b) fit of the two-exponential model against the same data*

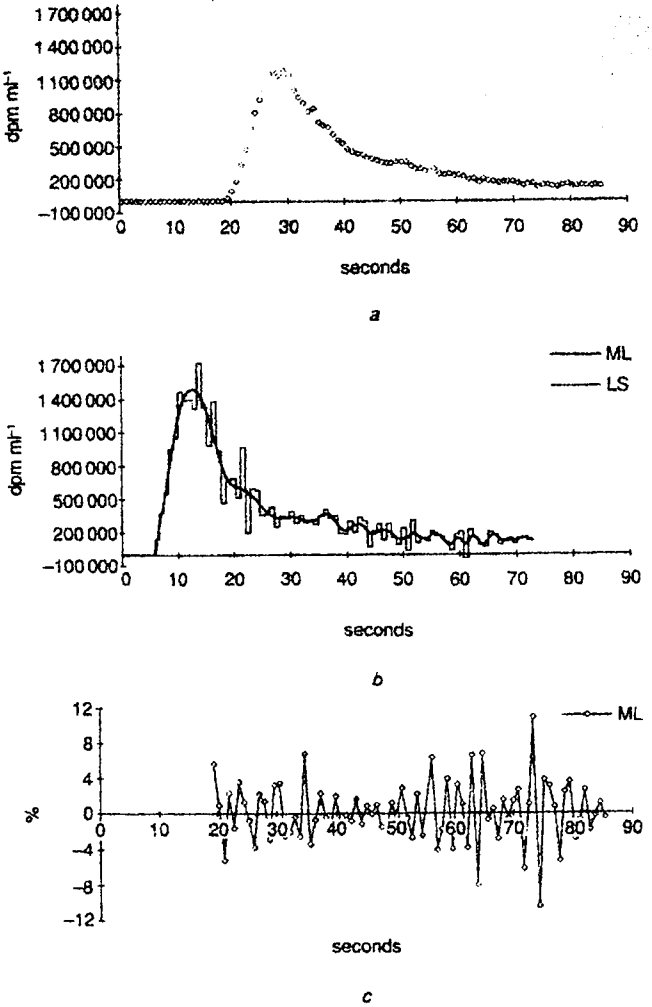

Fig. 2 *Study of glucose blood–tissue exchange in the human forearm; (a) a representative data set ([^{3}H]-D-mannitol, subject 1); (b) IDC reconstructed by least squares (thin line) and by regularised deconvolution by using the virtual grid and the new maximum likelihood (ML) criterion (thick line); (c) percentage residuals of the regularised estimate*

The deconvoluted blood IDCs are anticipated, and they show in general a sharper and higher peak and are, rather expectedly, less smooth than the IDCs measured at the cuvette of the catheter. The deconvoluted blood IDC, complemented by the rest of the data provided by the manual sampling, are being analysed by mathematical models of blood–tissue exchange (BONADONNA *et al.*, 1995).

4.2 *Study of glucose blood–tissue exchange in the human myocardium*

We design the experiments to study glucose blood–tissue exchange in the myocardium of normal humans. The study protocol has been approved by the Institutional Ethical Committee of the CNR Institute of Clinical Physiology, Pisa, Italy, where the experiments are performed. We explain the purpose, nature and potential risks of the study to the volunteers, and obtain written consent before their participation.

Three tracers ([^{3}H]-D-mannitol, [^{14}C]-3-O-methyl-glucose, and [^{3}H]-3-D-glucose, which enters the cell and is metabolised) are simultaneously injected into the left coronary artery. Then, we collect plasma samples from the main cardiac vein for 5 min. In the first 42 s, we withdraw the IDC by means of a catheter system and sample it with a constant period $T = 0.8814$ s. Thereafter, we collect samples manually each

15 s. The catheter is a standard 7-F catheter suitable for coronary sinus catheterisations. Measurement error variance of the data is known and it corresponds to an approximately constant *CV* of around 3%.

We determine catheter impulse response by repeating four times a step response experiment with [^{3}H]-D-mannitol, as in Section 4.1. We fit the impulse response models of eqns. 8 and 9 to the four step response data sets by nonlinear least squares. In two out of four cases, the model of eqn. 9 is not solvable from the data. In the other two, we obtain overall comparable residuals but with an estimate of the parameter β overly sensitive to data noise; in addition, both the Akaike and Schwartz criteria indicate the monoexponential model to be more parsimonious. We then obtain the parameters of the monoexponential model adopted below in the deconvolution procedure, i.e. $\alpha = 0.370$, $t_d = 9.956$, by averaging those determined by the single step responses ($\alpha = 0.334$, $t_d = 9.21$ for experiment 1, $\alpha = 0.368$, $t_d = 10.62$ for 2, $\alpha = 0.436$, $t_d = 9.90$ for 3, $\alpha = 0.365$, $t_d = 10.07$ for 4).

The unknown vector u was described on a uniformly spaced virtual grid (period $T_v = T/8$) by the doubly integrated white noise, which is again seen to have a better behaviour than the random walk (not shown). Fig. 3*a* displays a representative set of experimental data ([^{3}H]-D-mannitol, subject 2). Fig. 3*b* (thin line) shows the regularised estimate obtained by adopting Criterion 1 for the choice of the regularisation parameter ($\gamma = 4 \times 10^{-7}$, $q(\gamma) = 14.06$) and by having assumed a constant 3% *CV*. Fig. 3*c* (squares) shows the percentage residuals. Criterion 1 is known, in theory, to be at risk of oversmoothing. In fact, in Fig. 3*b* (thick line), we show the profile obtained by adopting Criterion 2 ($\gamma = 3 \times 10^{-8}$, $q(\gamma) = 21.63$). In Fig. 3*c* (diamonds) we display the related percentage residuals. Note how Criterion 2 leads to lower values of the regularisation parameter, leaving more freedom to the estimate than Criterion 1, as was theoretically expected from Section 3.2.

Lastly, we report a simulation study whose aim is to show how the virtual grid can allow the reconstruction of accurate input IDCs from output samples collected even much more rarely than above. We extract from the representative data set $n = 8$ samples, shown in Fig. 4*a*. The classic PT regularised estimate ($\Omega_v = \Omega_s$) is shown in Fig. 4*b* (thin line). The staircase approximation of the input is evidently rough and unrealistic. Then we define $\Omega_v = \{kT_v\}$, T_v as above and apply the new algorithm. Results are shown in Fig. 4*b* (thick line). Note that the deconvoluted profile shown in Fig. 4*b* and calculated from $n = 8$ data points does not show a big difference from the one displayed in Fig. 3*b* and based on the complete data set. This underlines the importance of optimal experiment design strategies (CARSON *et al.*, 1983); if the reduced sampling scheme contains enough information, the virtual grid can allow an accurate reconstruction of the continuous-time blood IDCs.

Similarly to the previous case study, the deconvoluted IDCs are quite different from the measured IDCs, taking into account the importance of correcting for catheter distortion. The deconvoluted IDC, complemented with the manually collected data, are being used to develop distributed models of glucose kinetics in the human myocardium (VICINI *et al.*, 1994).

Remark: In this paper we determine the model of the impulse response of the catheter system using [^{3}H]-D-mannitol. This impulse response model can be safely applied only to deconvolve the dilution curves of the extracellular tracers, i.e. indocyanine green and [^{3}H]-D-mannitol. Should we want to remove the catheter distortion from the dilution curves of [^{14}C]-3-O-methyl-glucose (which is transported in and out of the cell) or [^{3}H]-3-D-glucose (a permeant tracer which is also metabolised), we should take care due to the fact that these

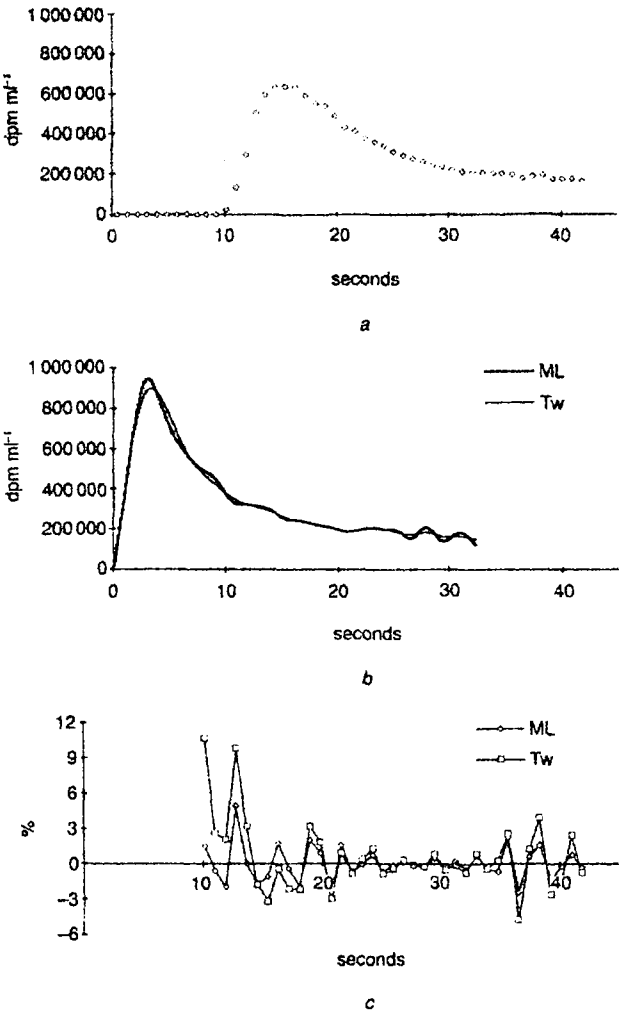

Fig. 3 *Study of glucose blood–tissue exchange in the human myocardium; (a) a representative data set ([^{3}H]-D-mannitol, subject 2); (b) IDC reconstructed by adopting Twomey's (Tw) criterion ($\gamma = 4 \times 10^{-7}$, thin line) and the new maximum likelihood (ML) criterion ($\gamma = 3 \times 10^{-8}$, thick line); (c) percentage residuals (diamonds for ML, squares for Tw)*

tracers also permeate red blood cells. Thus additional experiments need to be performed to determine the catheter impulse response model with these tracers, and to assess if eventual variations in hematocrit at the catheter tip site occur (in this case they could not be properly handled by the present approach) and the effect of interindividual hematocrit variations. However, we would expect the related variations to be small.

5 Conclusions

The study of blood–tissue exchange in physiological systems by the multiple indicator dilution technique requires frequent sampling in the blood of the IDC. The use of a catheter system causes a distortion which must be removed before data analysis. In this paper we approach the reconstruction of the actual IDC profile in the blood as a deconvolution problem. Its solution requires a model of the catheter impulse response, which we obtain by measuring the response of the catheter to a step. Having obtained the impulse response, we tackle the reconstruction of the blood IDC by a new deconvolution algorithm. Thanks to the introduction of the so-called virtual grid, the algorithm provides quasi time-continuous IDC profiles, in the face of a finite sampling rate, without having imposed any functional constraint. A simulated example

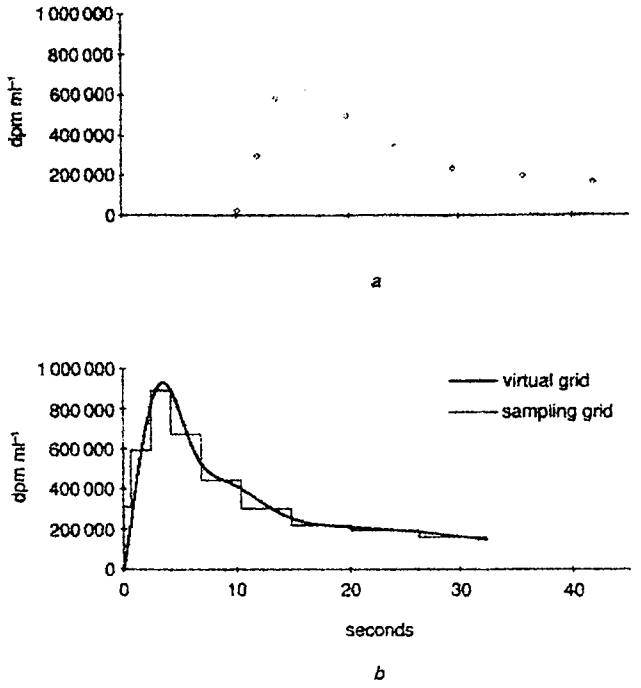

Fig. 4 *Study of glucose blood–tissue exchange in the human myocardium (same data as in Fig. 3): role and usefulness of the virtual grid; (a) reduced data set; (b) blood IDC reconstructed by the classic Phillips–Tikhonov regularisation method (thin line) and blood IDC reconstructed by means of the virtual grid (thick line)*

shows how the virtual grid can also be useful when optimal experiment design strategies are designed. Thanks to the statistic framework into which the input estimation problem is stated, the deconvolution method adopts new statistically based criteria for choosing the amount of regularisation. This gives to the estimate some favourable statistical properties, e.g. closed-form expressions are available to compute confidence intervals.

The deconvoluted IDC has been shown to be anticipated, with a sharper and higher peak and less smooth than the measured IDC. This confirms that removal of catheter distortion is necessary to properly model the data. In fact, the identification of a physiologic model from the measured and the deconvoluted IDC would give different results, not only regarding the macro parameters of the system, such as the mean transit time, but also for the micro parameters describing the blood–tissue exchange, e.g. transport parameters into the cell.

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