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Estimation of endogenous glucose production after a glucose perturbation by nonparametric stochastic deconvolution

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Abstract

The knowledge of the time course of endogenous glucose production (EGP) after a glucose perturbation is crucially important for understanding the glucose regulation system in both healthy and disease (e.g. diabetes) states. EGP is not directly accessible, and thus an indirect measurement approach is required. The estimation of EGP during an intravenous glucose tolerance test (IVGTT) can be posed as an input estimation problem solvable as a Fredholm integral equation of the first kind (A. Caumo and C. Cobelli, Am. J. Physiol., 264 (1993) E829–E841). The time-varying model of the kernel of the glucose system was identified from a concomitant tracer experiment, and EGP was reconstructed by employing the Phillips-Tikhonov regularization (deconvolution) algorithm. However, the proposed deconvolution approach left some issues open, e.g. how to choose the amount of regularization and how to deal with nonuniform/infrequent sampling. Here, a solution to these problems is provided by resorting to a new deconvolution algorithm. Thanks to the stochastic embedding into which the new deconvolution method is stated, the amount of regularization is determined in a statistically sound manner. In addition, in face of infrequent sampling, a time continuous profile of EGP is obtained. The method is shown to work reliably for reconstructing EGP in different IVGTT experimental protocols, both in normal and disease states.

Keywords: Input estimation; Intravenous glucose tolerance test; Mathematical model; Regularization

1. Introduction

The assessment of endogenous glucose production (EGP) in man after a glucose perturbation, e.g. during a clinical test like the intravenous glucose tolerance test (IVGTT), is of crucial importance to understand the glucose regulation system in both healthy and disease, e.g. diabetes, states. Unfortunately, EGP is not directly accessible and thus an indirect measurement approach is required. A method to measure EGP during an

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IVGTT has been recently proposed in [1]. By viewing EGP as the input of the glucose system and the plasma glucose concentration due to liver production (endogenous glucose) as the output, the measurement of EGP has been posed as an input estimation problem: a tracer was administered concomitantly with the IVGTT glucose dose to identify the model of the kernel of the glucose system, and EGP has been estimated by solving a Fredholm integral equation of the first kind (deconvolution, for sake of simplicity). In [1] the deconvolution problem was solved by resorting to the classic Phillips-Tikhonov regularization method [2,3], but some difficulties remained, namely the definition of a theoretically based criterion for the choice of the regularization parameter and the treatment of the infrequent sampling rate employed in the terminal portion of the IVGTT.

In this paper, we apply a recently developed, stochastic non-parametric deconvolution approach [4–7] to the estimation of EGP during the IVGTT. This will allow us to choose the regularization parameter by means of a new statistically based criterion and to provide a time-continuous estimate of EGP, in spite of infrequent sampling. The new method is shown to reliably reconstruct EGP in different IVGTT experimental protocols, both in normal and disease states.

2. Endogenous glucose production: an input estimation problem

2.1. The problem

An IVGTT consists in the intravenous administration of an impulse glucose dose. After the injection, glucose in plasma rises from its basal value to a peak and then returns to baseline. This perturbation affects EGP and the goal here is to reconstruct its time course. The relation (Fig. 1) between EGP and endogenous plasma glucose concentration during an IVGTT (assume the glucose impulse dose is given at time zero) can be described by the integral equation:

$$G_e(t) = \int_0^t h(t, \tau)\mathrm{EGP}(\tau)\,d\tau + G_b \quad (1)$$

where EGP (mg/kg/min) can be viewed as the system input, G_b (mg/dl) is baseline plasma glucose concentration, G_e is the endogenous glucose concentration, i.e. the component of plasma glucose concentration due to EGP only, and h (kg/dl) is the time-varying kernel of the glucose system.

If we split EGP(t) in two components, EGP_b, i.e. basal EGP, and $\Delta\mathrm{EGP}(t)$, i.e. the deviation of EGP from EGP_b, the integral in Eq. (1) can be split as:

$$G_e(t) = \int_0^t h(t, \tau)\mathrm{EGP}_b\,d\tau + \int_0^t h(t, \tau)\Delta\mathrm{EGP}(\tau)\,d\tau + G_b \quad (2)$$

Rearranging Eq. (2), we can write

$$G_e(t) - \left[\int_0^t h(t, \tau)\mathrm{EGP}_b\,d\tau + G_b\right] = \int_0^t h(t, \tau)\Delta\mathrm{EGP}(\tau)\,d\tau \quad (3)$$

The term between square brackets is the response of the glucose system in basal initial conditions to EGP_b.

Finally, having defined:

$$\Delta G_e(t) = G_e(t) - \left[\int_0^t h(t, \tau)\mathrm{EGP}_b\,d\tau + G_b\right] \quad (4)$$

one has:

$$\Delta G_e(t) = \int_0^t h(t, \tau)\Delta\mathrm{EGP}(\tau)\,d\tau \quad (5)$$

Considering ΔEGP unknown, and ΔG_e and h known, Eq. (5) is a Fredholm integral equation of the first kind. Therefore, the EGP estimation problem can be solved as follows [1]. Assuming h is available, ΔG_e can be calculated from the data.

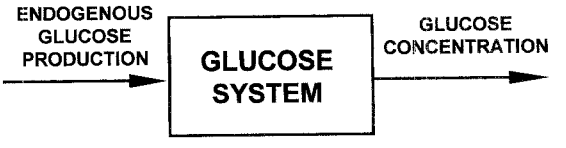

Fig. 1. The endogenous glucose production (EGP) input estimation problem.

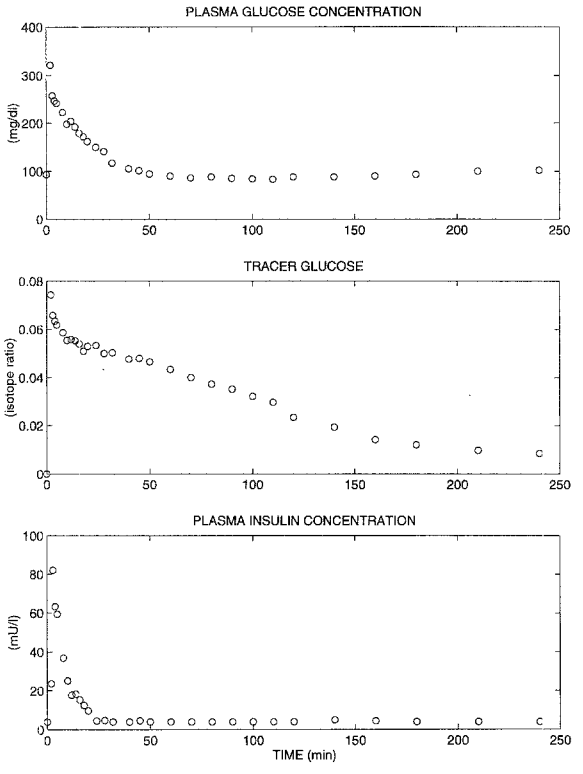

Fig. 2. Glucose (top panel), tracer glucose (middle panel) and insulin (bottom panel) concentrations in plasma during an IVGTT labeled with [6,6-$^2H_2$]glucose in a representative normal subject.

Then the Fredholm integral equation of the first kind Eq. (5) can be solved for ΔEGP. Finally, EGP can be calculated simply by adding EGP_b to ΔEGP. As anticipated in Section 1, for sake of simplicity we refer to the problem Eq. (5) as a 'deconvolution' problem, even if the kernel $h(t, \tau)$ is time-varying.

2.2. The data

A typical set of data (glucose concentration, tracer glucose and insulin concentration in plasma) obtained during an IVGTT labeled with a stable isotope tracer is shown in Fig. 2. From the tracer data, the kernel of the glucose system h is identified, using the time-varying two compartment model described in [1]. From glucose and tracer glucose concentrations, G_e can be calculated at each time point as shown in [8,9]. G_e measurement error can be found by error propagation from glucose and tracer glucose measurement errors. Finally, the term $[\int_0^t h(t, \tau)EGP_b\, d\tau + G_b]$ can be evaluated by using the calculated EGP_b (from h) and the measured G_b. In Fig. 3, we show the time courses of G_e and ΔG_e in the representative subject of Fig. 2. Note that ΔG_e can be positive or negative, depending whether G_e during the test is below or above the response of the glucose system in basal initial conditions to EGP_b.

3. Parametric versus nonparametric approaches

It is well known that an input estimation problem like Eq. (5) can be severely ill-conditioned, i.e. a small percentage error in the output can be amplified into a much larger percentage error in the estimated input, which can thus exhibit wide, spurious and unrealistic oscillations. The ill-conditioning of the deconvolution problem is a classic topic in the mathematics, physics and engineering literature. To face it, a widely used approach, parametric deconvolution, assumes the analytical expression of the input to be known except for a small number of parameters, so that the deconvolution problem becomes a parameter estimation problem. In [10], for example, the unknown input is assumed to be described by polynomials. Other

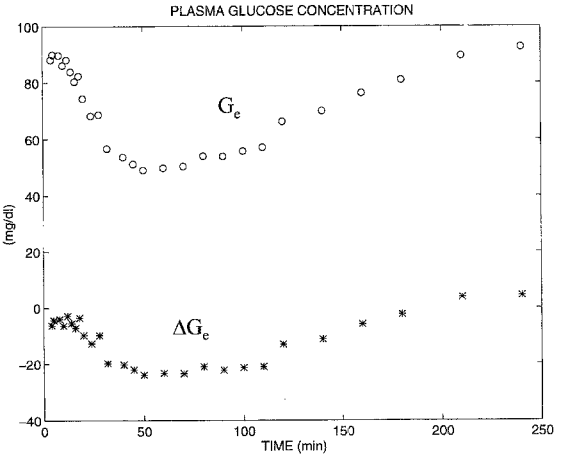

Fig. 3. Time courses of $G_e(t)$ and $\Delta G_e(t)$ (Eq. (4)) for the subject of Fig. 2.

cases are discussed in [11–13]. In parametric deconvolution, the ill-conditioning is circumvented by the a priori constraint on the input functional form, which guarantees the regularity of the profile. However, the adoption of a specific functional form for the input is a rather heavy assumption, and particularly so in EGP estimation. In addition, one has to deal with issues such as the choice of the model order, e.g. the order of the polynomials in [10], and the problem of local minima in parameter estimation. Finally, some parametric methods, e.g. [12], require a time-invariant kernel, e.g. an impulse response described by a sum of exponentials.

A nonparametric approach is therefore advisable to estimate EGP. Nonparametric deconvolution has been recently faced by resorting to regression splines, i.e. the unknown input is a spline whose parameters must be fitted against the output data [14,15]. Splines are very flexible and can be constrained to account for a priori knowledge of the input (e.g. nonnegativity, monotonicity). However, as illustrated in [15], splines require to cope with delicate issues, such as the choice of the number and location of the splines knots which determine the input smoothing degree and the behaviour of the estimate in presence of fast transients. The most widely used nonparametric deconvolution approach is based on the works of Phillips [2] and Tikhonov [3] and faces ill-conditioning by applying regularization techniques based on the known smoothness of the input. The only assumption required by this method is that the unknown input can be described by a staircase function, i.e. it is constant during each sampling interval. In place of regularization, some other nonparametric methods exploit truncated singular value decomposition techniques, e.g. [16], or the maximum entropy principle, e.g. [17,18].

In [1], the nonparametric approach of Phillips and Tikhonov was used, but two major questions were left open. First, the discrepancy regularization criterion [19] was considered for choosing the amount of regularization, but it was seen to lead to poor results in some subjects (this somewhat agrees with the fact, elsewhere reported [4,20], that the discrepancy criterion does not have a firm statistical basis and in fact is at risk of oversmoothing). On the other hand, other criteria available in the literature, not considered in [1], e.g. the generalized cross-validation [21] or the L-curve [16], do not exploit the available knowledge on the data measurement error. In conclusion, some new regularization criterion is desirable. Second, the staircase approximation of the EGP profile, in conjunction with the fact that the IVGTT sampling is nonuniform/infrequent, led to an EGP estimate which was constant for as long as 30 min. An improved picture of the EGP time course would be of help for physiological inferences.

In the following section, we will revisit the problem faced in [1] of estimating EGP during an IVGTT by resorting to a recently developed deconvolution algorithm which, for certain aspects, can be viewed as the reinterpretation of the Phillips-Tikhonov regularization method in a stochastic context.

4. Stochastic deconvolution

4.1. Coping with infrequent sampling: the virtual grid

Let us address first the problems arising from infrequent sampling. Consider Eq. (5); to simplify further the notation, we rewrite it as:

$$c(t) = \int_0^t h(t, \tau)u(\tau)\,\mathrm{d}\tau \tag{6}$$

where $u(t) = \Delta\mathrm{EGP}(t)$ and $c(t) = \Delta G_e(t)$.

The first step to take is to conveniently discretize Eq. (6). Let us decouple [5,7] the time grid used to discretize the unknown input $u(t)$, $\Omega_V = [T_1, T_2, \ldots, T_k, \ldots, T_{N_V}]$ from the sampling grid, $\Omega_S = [t_1, t_2, \ldots, t_k, \ldots, t_{N_S}]$, which is non-uniform and infrequently spaced. The grid Ω_V can be much finer ($N_V \geq N_S$) than Ω_S. It is convenient to assume Ω_V such that $\Omega_S \subseteq \Omega_V$, with Ω_V uniformly spaced. Apart from this, Ω_V is arbitrary and has no experimental significance. For this reason, it has been termed virtual grid [5,7]. Here we will adopt $\Omega_V = [1, 2, 3, \ldots, t_{N_S}]$, i.e. the time step is equal to one time unit.

Now, assume $u(t)$ constant during each time interval in the virtual grid. It follows:

$$c(T_k) = \sum_{i=1}^{k} u_i \int_{T_{i-1}}^{T_i} h(T_k, \tau)\, d\tau, \quad k: T_k \in \Omega_V \qquad (7)$$

where u_i is the value of $u(t)$ between T_{i-1} and T_i ($T_0 = 0$). In matrix notation, we can write:

$$c = H_V u \qquad (8)$$

H_V is a lower triangular square matrix (size N_V) whose nonzero entries are:

$$H_V(i, j) = \int_{T_{j-1}}^{T_j} h(T_i, \tau)\, d\tau, \quad i \le j \qquad (9)$$

Assuming an additive measurement error e, the measurements are described by:

$$y = Hu + e \qquad (10)$$

where u is a vector of dimension N_V, H is a $N_S \times N_V$ matrix (obtainable from the square matrix H_V by deleting the rows which do not correspond to any of the N_S samples), y is the sample vector (size N_S) and e is the vector of the measurement errors (size N_S), supposed to be uncorrelated and zero mean.

Note that the virtual grid formulation of the problem brings a number of unknowns (N_V) which exceeds by far the number of measurements (N_S): $N_V \gg N_S$. However, by virtue of the prior information available on u, we will see that the estimation problem still has a unique solution.

4.2. Coping with regularization: deconvolution as a linear minimum variance estimation problem

Let us consider the model (10) and state it in a stochastic embedding, i.e. all the vectors involved are random. If the a priori second order statistical description of u and e (assumed to be uncorrelated) is known, the input estimation problem can be stated as a linear minimum variance estimation (LMVE) problem.

While the statistical description of e ($E[e] = 0$, $Cov[e] = B$) is known, the statistical description of u needs to be assumed. However, physiological a priori knowledge tells us that EGP during an IVGTT should not be subject to large and abrupt swings, but it should be characterized by an overall smooth and regular profile. Therefore, one can model $u(t)$ on the virtual grid by the simple random-walk process [22]:

$$u_{k+1} = u_k + w_k, \quad k = 0, 1, \ldots, N_V - 1 \qquad (11)$$

where w_k is a white-noise process with zero mean, variance λ^2 and $u_0 = 0$. As λ^2, i.e. the variance of $\Delta u(k) = u(k+1) - u(k) = w(k)$, increases, the variability of $u(t)$ increases as well. However, λ^2 is unknown and must be estimated a posteriori together with the input profile.

The covariance matrix of u is given by

$$\mathrm{Cov}[u] = \lambda^2 (F^T F)^{-1} \qquad (12)$$

where F is the square Toeplitz matrix (size N_V) whose first column is $[1, -1, 0, \ldots, 0]^T$ [22]. Note that Cov[u] is positive definite.

Under the above assumptions, the linear mean square estimation of u given y is found as the solution $\hat{u}$ of the optimization problem:

$$\min_u [(y - Hu)^T B^{-1} (y - Hu) + \gamma u^T F^T F u] \qquad (13)$$

where $\gamma = 1/\lambda^2$. The closed form solution of Eq. (13) is:

$$\hat{u} = (H^T B^{-1} H + \gamma F^T F)^{-1} H^T B^{-1} y \qquad (14)$$

Of the two terms of Eq. (13):

- the term $(y - Hu)^T B^{-1} (y - Hu)$ takes into account the distance between model-reconstructed data and actual measurements,
- the term $u^T F^T F u$ accounts for the adherence of the estimated input to the stochastic model (11).

The unknown parameter γ plays a role analogous to that of the regularization parameter in the classical Phillips-Tikhonov approach. Large values of γ will determine very smooth solutions, small values of γ will lead to ill-conditioned estimates. For instance, in Fig. 4 (upper panel) we show the profile of EGP in a normal subject without any regularization ($\gamma = 0$). To measure how much the reconstructed profile of EGP is consistent with the original data, one can perform reconvolution, that is evaluate Eq. (5) using the reconstructed ΔEGP profile and compare the data so obtained to the original ΔG_e data. While the adherence to the data is fully pursued (bottom panel), the estimated input is characterized by

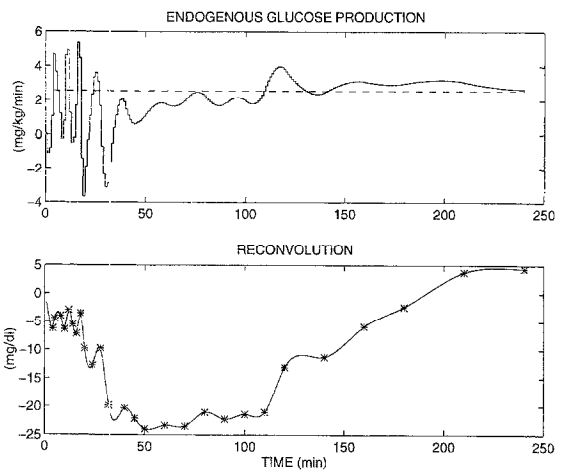

Fig. 4. Estimation of EGP from the data of Fig. 3. EGP profile (top panel) and reconvolution fit vs. $\Delta G_c(t)$ data (bottom panel) are shown. No regularization is used ($\gamma = 0$).

large swings, which do not allow us to give any physiological meaning to the estimated profile. Therefore, γ must be increased.

Thanks to the stochastic formulation of the problem, a new criterion can be used to choose the regularization parameter γ, i.e. tune γ until:

$$SSU(\gamma) = \frac{q(\gamma)}{\gamma} \tag{15}$$

where SSU is the sum of the squared (weighted) estimates, i.e. $SSU = \hat{u}F^TF\hat{u}$, and:

$$q(\gamma) = \text{trace}[B^{-1/2}H(H^TB^{-1}H + \gamma F^TF)^{-1}H^TB^{-1/2}] \tag{16}$$

where $B^{-1} = B^{-1/2}B^{-1/2}$.

This criterion has been shown to satisfy in general a consistency property of the linear minimum variance estimate [7]; moreover, if the involved random vectors are all gaussians, it also satisfies the condition of maximum likelihood of the observations vector y with respect to λ^2 [6]. The function $q(\gamma)$ varies with continuity from 0 (for $\gamma \to \infty$) to the number of measurements N_S (for $\gamma = 0$) and it can be interpreted as the 'degree of freedom' of the regularized estimator associated with γ [4,6,7].

4.3. Numerical aspects

Note that, by considering Ω_V to be finer and finer (the virtual grid is arbitrary), the prior one made on the discrete-time sequence $\{u_k\}$ will be closer and closer to that on the time-continuous input $u(t)$ and, accordingly, the vector u will determine a piecewise profile closer and closer to a time-continuous function. However, since in our case matrices H_V and H are large (an evenly spaced, 1 min virtual grid requires $N_V = T_{N_S}$, usually 240 for the IVGTT), the use of efficient numerical algorithms is mandatory. We used a recently proposed singular value decomposition (SVD) strategy [4], which dramatically speeds up the procedure for determining the solution for each different trial value of γ, until the regularization criterion is satisfied. Briefly, by the SVD strategy one first diagonalizes the set of linear equations behind Eq. (13) in $O(N_S^3)$ operations. Then, only $O(N_S)$ scalar operations are needed to compute the solution for each trial value of γ.

It is worth noting that, due to the time variance of the kernel $h(t, \tau)$, other efficient numerical tools proposed in the literature and based on Fourier transform methods, e.g. those of [22,23], can not be adopted (H_V has not a Toeplitz structure).

5. Endogenous glucose production case studies

We report here EGP profiles obtained in different IVGTT experimental protocols, both in normal and pathological conditions. In all the following examples, the glucose dose was labeled with the stable isotope [6,6-$^2H_2$]glucose.

5.1. An IVGTT in a normal subject

We reconstructed EGP in a normal subject (the same of Fig. 2). Glucose, tracer glucose and insulin concentrations were sampled in plasma at 30 times: 0, 2, 3, 4, 5, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210 and 240 min. Endogenous glucose concentration at each sampling time was directly computed from glucose and tracer glucose con-

centration in plasma [9,24]. The measurement error of endogenous glucose concentration was assumed to be independent, zero mean and with a variance at each time point calculated by error propagation from glucose and tracer glucose measurement errors [24]. In this subject (and this is also a typical range), the coefficient of variation was between 4.4–4% from 50 to 92 mg/dl. This completely defines the covariance matrix of the measurement error B in Eq. (13). The matrix H_V was calculated from Eq. (9) on a 1 min, evenly spaced virtual grid. ΔEGP was finally calculated from Eq. (13), tuning the parameter γ according to the criterion (15). EGP is shown in Fig. 5 (top panel). The value of γ was 31.4, the value of q in Eq. (16) was 8.1. The recovered EGP time course is virtually continuous and is characterized by a rather fast inhibition, a consistent rebound over

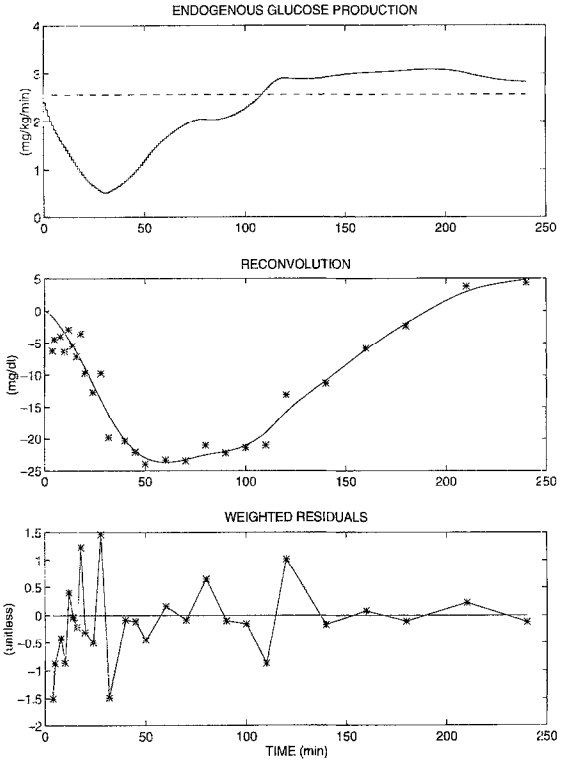

Fig. 5. Estimation of EGP from the data of Fig. 3 with the amount of regularization chosen according to the criterion (15). EGP profile (top panel), reconvolution fit vs. $\Delta G_e(t)$ data (middle panel) and weighted residuals (bottom panel) are shown. EGP_b (dashed line in the top panel) was 2.56 mg/kg per min.

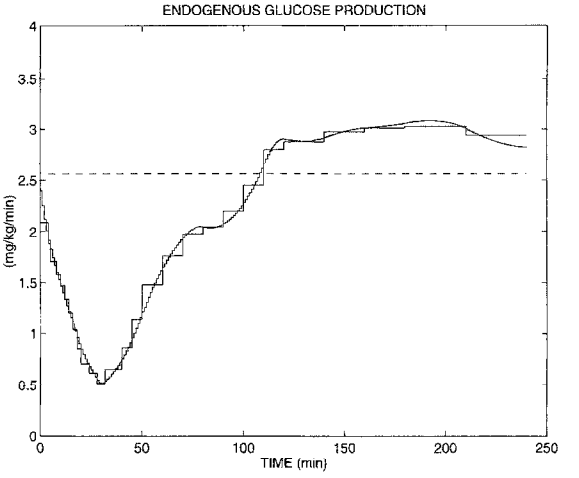

Fig. 6. EGP estimated in the same subject of Fig. 5, discretized on the sampling grid (stepwise profile) and on the virtual grid (continuous profile). In both cases, the regularization parameter is tuned according to Eq. (15). Dashed line is EGP_b.

basal and a slow return to baseline. The reconvolution fit is shown in the middle panel, and reconvolution weighted residuals, defined as $r_i = (y_i - \hat{y}_i)\sqrt{B_i}, i = 1,\ldots,N_S$ (where $\hat{y}_i$ is the model-predicted measurement y_i and B_i is the corresponding element of B), are shown in the bottom panel.

Choosing the unknown input to be piecewise constant on the virtual grid (that is, on a 1 min span) is much less critical than subjecting it to a piecewise constant approximation on the sampling grid (where it should be held constant for a maximum of 30 min), as it is done when $\Omega_V = \Omega_S$ (see [1]). The virtual grid allows us to reconstruct the time-continuous input profile even when changes of concavity occur: in fact, changes in concavity, which might be related to the time courses of glucose and insulin during the test, are hidden if the production is reconstructed using the sampling grid only. To clarify this aspect, in Fig. 6 we superimpose EGP profiles obtained in the same subject, using the sampling grid and the virtual grid respectively to discretize the input.

Finally, in Fig. 7, we compare the EGP estimates obtained according to the discrepancy criterion [19], largely used in [1], and to the new criterion Eq. (15). It can be seen that the profile obtained with the discrepancy criterion ($\gamma = 506.0$)

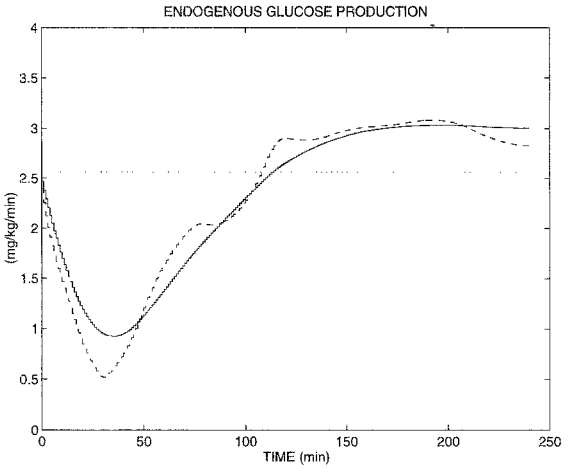

Fig. 7. EGP estimated in the same subject of Fig. 5, with the amount of regularization chosen according to the discrepancy criterion (continuous line) and to the criterion (15) (dashed line). Dotted line is EGP_b.

is smoother than that obtained with the new criterion. The reconvolution fit (Fig. 8) of the new criterion is however more satisfactory.

5.2. An insulin-modified IVGTT in a normal subject

The IVGTT protocol is often modified for use in diabetic subjects [25] with the injection at 20

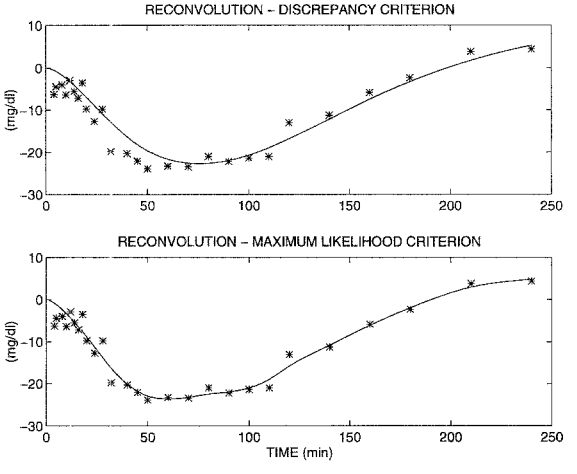

Fig. 8. Reconvolution fit for the two EGP estimates of Fig. 6, with regularization chosen according to the discrepancy criterion (upper panel) and to the new criterion Eq. (15) (lower panel).

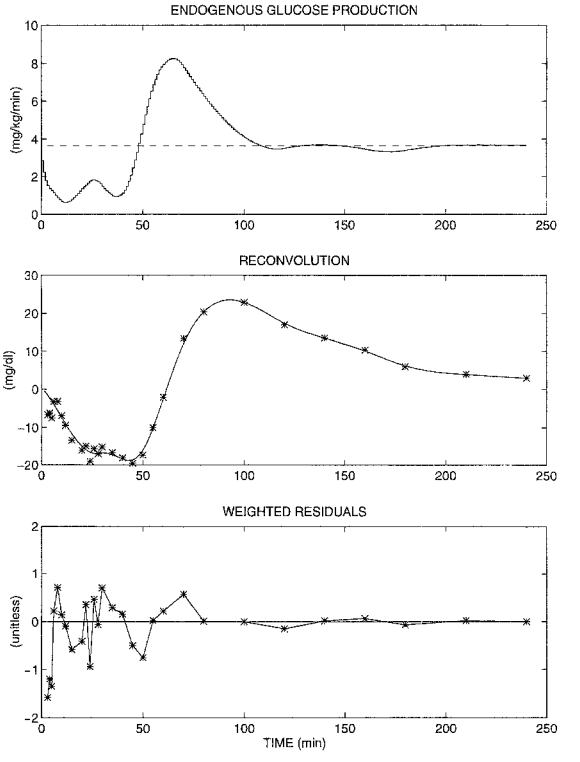

Fig. 9. EGP during an IVGTT modified with insulin injection in a normal subject. EGP profile (top panel), reconvolution fit vs. $\Delta G_e(t)$ data (middle panel) and weighted residuals (bottom panel) are shown. EGP_b (dashed line in the top panel) was 3.64 mg/kg per min.

min of a dose of exogenous insulin, administered as a bolus or a 5 min infusion. We reconstructed EGP in a normal subject during an insulin-modified IVGTT. The sampling grid consisted of 31 elements: 0, 2, 3, 4, 5, 6, 8, 10, 12, 15, 20, 22, 24, 26, 28, 30, 35, 40, 45, 50, 55, 60, 70, 80, 100, 120, 140, 160, 180, 210 and 240 min. A 1 min evenly spaced virtual grid was used. The profile of EGP is shown in Fig. 9 (top panel). The value of γ selected by Eq. (15) is 2.5, while q is equal to 12.1. The use of the virtual grid allows us to detect a bimodal pattern in the first hour of the test, with a secondary nadir, caused by the administration, at time 20 min, of an infusion of insulin lasting 5 min. Then, EGP consistently rebounds over baseline and slowly returns to basal, with some damped oscillations.

5.3. An insulin-modified IVGTT in a diabetic subject

EGP in a non-insulin dependent diabetic subject during an insulin-modified IVGTT has been estimated. The exogenous insulin infusion was administered between 20 and 25 min. The sampling grid consisted of 21 elements: 0, 2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30, 40, 60, 80, 100, 120, 140, 160, 180, 240 min. Results for a representative subject are shown in Fig. 10 (top panel). The regularization parameter γ selected by Eq. (15) is equal to 85.10, while q is 4.64. Since the insulin secretory response to the glucose challenge is negligible in diabetics, the only effect on EGP in the first 20 min is that caused by the glucose signal. There is virtually no inhibition of EGP during the first hour, then the effect of the exogenous insulin infusion comes into play, and EGP is almost completely suppressed.

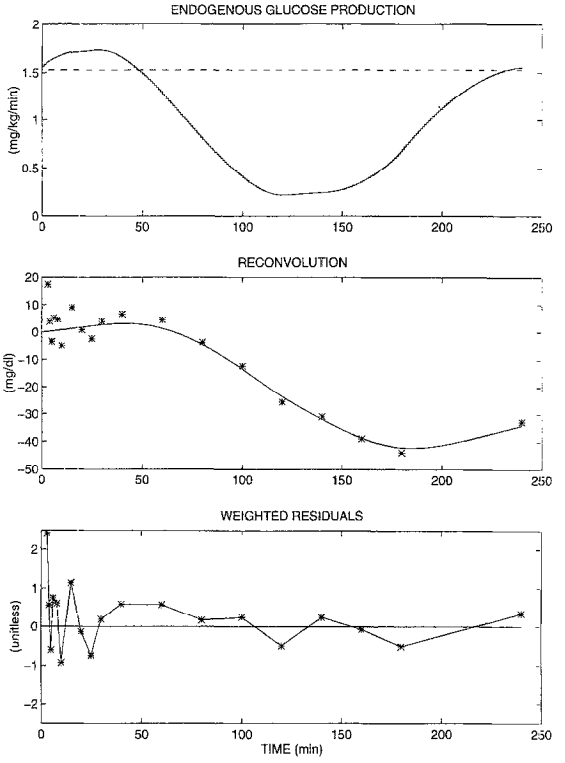

Fig. 10. EGP during an IVGTT modified with insulin injection in a non-insulin dependent diabetic subject. EGP profile (top panel), reconvolution fit vs. $\Delta G_e(t)$ data (middle panel) and weighted residuals (bottom panel) are shown. Dashed line in the top panel is $EGP_b = 1.53$ mg/kg per min.

6. Conclusions

The problem of a reliable estimation of EGP during an IVGTT has been addressed. This is crucial for understanding the glucose regulation system in normal and pathological states. We have proposed a new, nonparametric deconvolution method to estimate EGP which solves two problems left open in [1]: the choice of the amount of regularization and the infrequent sampling grid. An advantage of the method consists in the availability of a new statistically sound criterion, based on maximum likelihood, for the choice of the regularization parameter. In addition to its nice statistical basis, this criterion also allows, in contrast to other criteria available in the literature, to exploit the knowledge of the measurement error variance. The problem of infrequent sampling during the IVGTT has also been addressed by the introduction of the virtual grid. Thanks to this technique, a (quasi) time continuous profile of EGP can be derived, which allows a finer physiological insight with respect to the method used in [1]. We applied our method to three case studies: an IVGTT in a normal subject; an insulin-modified IVGTT in a normal subject; and in a non-insulin dependent diabetic subject. In all cases, reconstructed time courses of EGP are physiologically plausible, and agree with the expected pattern of liver production due to the administration of exogenous glucose and insulin. Also, the reconvolution fits are always satisfactory. The refinement via stochastic deconvolution of the method firstly introduced in [1] makes it a candidate for a reliable tool to investigate the glucose regulatory system in normal and disease states.

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