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Glucose Production by Deconvolution in Intravenous and Oral Glucose Tolerance Tests: Role of Output Variable

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***Abstract*— Endogenous glucose production (EGP) after a glucose stimulus can be estimated by deconvolution of the endogenous component of glucose concentration, which is computed from noisy measurements. This study analyzes how measurement errors propagate to endogenous glucose and affect EGP reconstruction during intravenous (IVGTT) and oral (MEAL) glucose tolerance tests. Monte Carlo simulations show that the effect of errors on endogenous glucose and thus on EGP is more critical during IVGTT than during MEAL. A two-regularization-parameter deconvolution technique for IVGTT is proposed, which successfully handles this added difficulty.**

I. INTRODUCTION

Knowledge of endogenous glucose production (EGP) after a glucose stimulus, i.e. an intravenous (IVGTT) or oral (MEAL) glucose tolerance test, is of importance for understanding the role of the liver in glucose homeostasis. However, EGP is not directly measurable in vivo and an indirect estimation by deconvolution is needed, provided that system kernel and output are known [1]. If a glucose tracer is added to the glucose stimulus, the system kernel can be determined; in addition to that, it is also possible to reconstruct the endogenous component of plasma glucose concentration to be used as the output variable for deconvolution. Endogenous glucose is computed from noisy experimental measurements of both tracer and tracee concentrations with nonlinear operations, which can amplify the errors.

The purpose of this paper is to study how errors propagate to endogenous glucose and to assess how they affect EGP reconstruction by deconvolution in both IVGTT and MEAL. To this aim Monte Carlo error analysis simulations were designed, which show that the initial samples of endogenous glucose are far more sensitive to error in IVGTT than MEAL, thus often resulting in non physiological EGP profiles. To deal with this problem, an additional regularization parameter for endogenous glucose is introduced, which is estimated *a posteriori* by Maximum Likelihood (ML).

The paper is organized as follows. Section II is devoted to the mathematical formulation of the input estimation problem, as far as EGP reconstruction is concerned; a description of the stochastic deconvolution algorithm is also included. In Section III Monte Carlo simulation design is discussed and the results of EGP estimation are shown for both MEAL and IVGTT. Finally, Section IV covers the improved deconvolution method, which was used to handle the IVGTT difficulty.

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II. PROBLEM STATEMENT

A. Mathematical Formulation

The problem of EGP estimation during IVGTT and MEAL can be formulated as follows. $EGP(t)$ is the input of a linear, time-varying system, whose impulse response $h(t,\tau)$ is derived by means of a tracer experiment, performed concomitantly with the test. Thus, the system output is the component of total plasma glucose concentration due to $EGP(t)$ and is referred to as endogenous glucose concentration, $G_e(t)$. $G_e(t)$ is not directly measured, but can be computed from measurements of total glucose concentration $G_{tot}(t)$ and tracer-to-tracee ratio $z(t)$ (collected on a possibly nonuniform sampling grid), and of tracer-to-tracee in the IVGTT or MEAL dose, z_i, by subtracting from total cold glucose its exogenous component [2]:

$$G_e(t) = \frac{G_{tot}(t)}{z(t)+1} \cdot \left(1 - \frac{z(t)}{z_i}\right) \tag{1}$$

The relationship between $EGP(t)$ and $G_e(t)$ is described by a Fredholm integral equation of the first kind [1]:

$$G_e(t) = \int_{-\infty}^{t} h(t,\tau) EGP(\tau) d\tau \tag{2}$$

Assuming that IVGTT or MEAL glucose dose is administered at time 0 (and thus, system is in basal state before 0), it is possible to decompose $EGP(t)$ as follows:

$$EGP(\tau) = \begin{cases} EGP_b & \tau < 0 \\ EGP_b + \Delta EGP(\tau) & \tau > 0 \end{cases} \tag{3}$$

where $\Delta EGP(\tau)$ is the EGP deviation from its basal value. Exploiting (3) and substituting in (2), a new expression is derived:

$$\begin{aligned} G_e(t) &= \int_{-\infty}^{t} h(t,\tau) EGP_b d\tau + \int_{0}^{t} h(t,\tau) \Delta EGP(\tau) d\tau \\ &= G_b(t) + \int_{0}^{t} h(t,\tau) \Delta EGP(\tau) d\tau \end{aligned} \tag{4}$$

where $G_b(t)$ represents the glucose system response to EGP_b. Defining $\Delta G_e(t) = G_e(t) - G_b(t)$, it finally results:

$$\Delta G_e(t) = \int_{0}^{t} h(t,\tau) \Delta EGP(\tau) d\tau \tag{5}$$

The problem has been now reduced to estimating a causal signal $\Delta EGP(t)$ that is discretized, assuming it is a piecewise constant function. Considering that experimental measurements are affected by error, one finally ends up with the following matrix-vector model:

$$\mathbf{y} = H\mathbf{u} + \mathbf{v} \tag{6}$$

where $\mathbf{y} = [y_1\, y_2\, \ldots\, y_n]^T$ is the output vector, containing ΔG_e on the sampling grid; $\mathbf{v} = [v_1\, v_2\, \ldots\, v_n]^T$ the measurement error vector; $\mathbf{u} = [u_1\, u_2\, \ldots\, u_N]^T$ the unknown vector of the input signal (ΔEGP) on a uniform virtual grid of arbitrarily chosen size $N \gg n$; H is the $n \times N$ system transfer matrix.

In order to obtain H, first the $N \times N$ lower-triangular matrix H_v is computed, whose *i*th entry is given by:

$$\int_{t_{i-1}}^{t_i} h(t_i, \tau) d\tau \tag{7}$$

System transfer matrix H is then obtained from H_v by deleting the $N - n$ rows corresponding to temporal instants that do not belong to the sampling grid [3].

The problem expressed by (6) is ill-posed and is faced below in a Bayesian framework.

B. Stochastic Deconvolution

The unknown input vector $\mathbf{u}$ is characterized by some *a priori* information, expressed in terms of smoothness and regularity. A widely used prior [3] consists in describing $\mathbf{u}$ with a random-walk model:

$$u_k = u_{k-1} + w_k \quad k = 1, 2, \ldots N \quad u_0 = 0 \tag{8}$$

where $\{w_k\}$ is a zero-mean white noise process with a constant variance λ^2, which is unknown and needs to be estimated *a posteriori* with the input profile.

From (8) the covariance matrix of $\mathbf{u}$ is given by:

$$cov[\mathbf{u}] = \lambda^2 \left(F^T F\right)^{-1} = \lambda^2 \Sigma_u \tag{9}$$

where F is a $N \times N$ lower-triangular Toeplitz matrix whose first column is $[1\ -1\ 0\ \ldots\ 0]^T$.

Assuming that the measurement error is zero-mean with a covariance matrix denoted by Σ_v, then the input estimation problem can be stated as a linear minimum variance estimation problem:

$$\arg\min_u \left[(y - Hu)^T \Sigma_v^{-1} (y - Hu) + \gamma u^T F^T F u\right] \tag{10}$$

where $\gamma = 1/\lambda^2$. Equation (10) admits the closed form solution:

$$u_s = \Sigma_u H^T \left(H \Sigma_u H^T + \gamma \Sigma_v\right)^{-1} y \tag{11}$$

The role of the unknown regularization parameter γ is critical; large values of γ lead to over-smoothed estimates, while small ones produce ill-conditioned estimates. Here the Maximum Likelihood (ML) criterion [3] was adopted. It tunes γ until

$$WSSU(\gamma) = \frac{q(\gamma)}{\gamma} \tag{12}$$

where $WSSU = u_s^T F^T F u_s$ $[u_s^T \Sigma_u^{-1} u_s]$ is the sum of squared weighted estimates and

$$q(\gamma) = trace\left[H \Sigma_u H^T \left(H \Sigma_u H^T + \gamma \Sigma_v\right)^{-1}\right] \tag{13}$$

represents the so-called equivalent degrees of freedom [4].

III. MONTE CARLO SIMULATION

A Monte Carlo approach was used to study how measurement errors affect (1) and to assess their effects on EGP reconstruction. Two known profiles (i.e., population mean) of endogenous glucose production, shown in Fig. 1 and 2, were assumed for IVGTT (dose = 330 mg/kg) and MEAL (dose = 1 g/kg), from which reference profiles of plasma glucose G_{tot} and tracer-to-tracee ratio z were generated, by using the two-compartment IVGTT [5] and the one-compartment oral [6] models respectively, shown in Fig. 3, assuming the insulin profiles shown in Fig. 4 (population mean). 300 realizations of noisy data were obtained by perturbing the reference profiles of total glucose and tracer-to-tracee ratio with gaussian, zero mean measurement noise with a coefficient of variation (CV) equal to 2% for cold glucose, and to 5% for tracer-to-tracee ratio.

For each realization, endogenous glucose G_e is computed from (1), and the impulse response $h(t, \tau)$ of the two models shown in Fig. 3 is identified. Then, the system transfer matrix H is derived and G_b is obtained from (4). Finally, having computed $\Delta G_e = G_e - G_b$, stochastic deconvolution is performed to obtain ΔEGP from ΔG_e and H.

A. MEAL

Fig. 1 shows the mean reconstructed ΔEGP with its variability bands expressed as $\pm$ standard deviation (SD), compared with the reference profile. Overall, the mean reconstructed ΔEGP is in good accordance with the reference profile. This result indicates the low sensitivity of ΔG_e and thus EGP reconstruction to data measurement error.

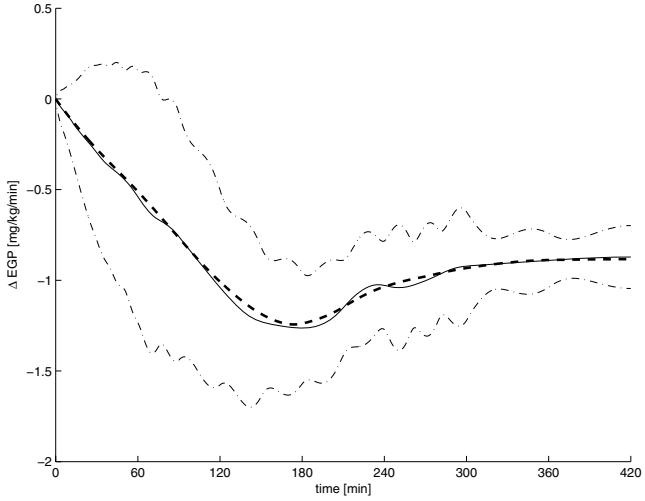

Fig. 1. MEAL simulation results. ΔEGP reference (dashed line), mean deconvoluted ΔEGP (continuous line) with variability bands (dash-dot line) expressed as mean $\pm$ standard deviation (SD).

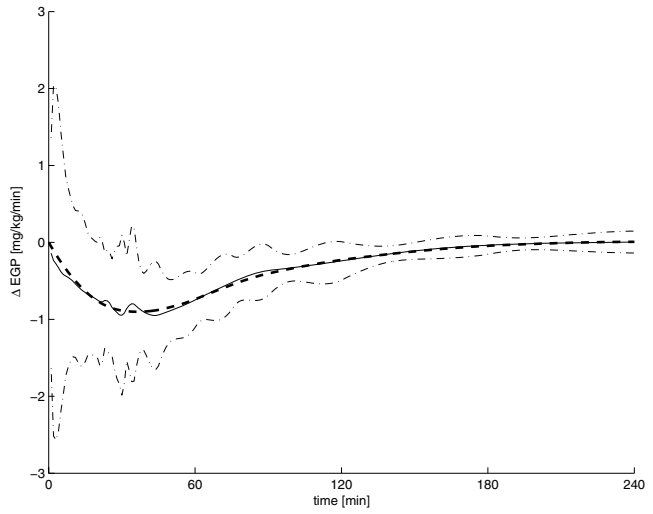

Fig. 2. IVGTT simulation results. ΔEGP reference (dashed line), mean deconvoluted ΔEGP (continuous line) with variability bands (dash-dot line) expressed as mean $\pm$ SD. The root-mean-square error (RMSE) of reconstructed signal is 0.37.

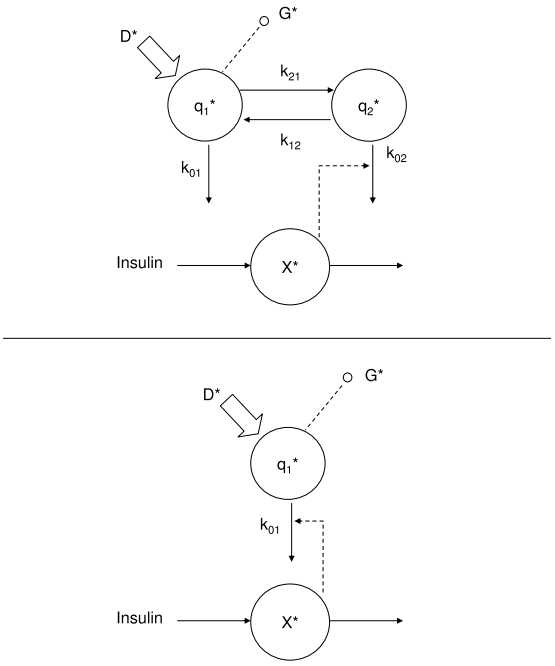

Fig. 3. IVGTT (top) and oral (bottom) glucose kinetics models.

B. IVGTT

The IVGTT situation is different. Mean reconstructed $\Delta EGP \pm SD$, compared with reference, is shown in Fig. 2. With respect to Fig. 1, one can note the wider variability bands in the initial period corresponding to 0–60 min, where mean EGP is affected by oscillations, reflecting the wide non-physiological oscillations observed in individual profiles (Fig. 6). This fact suggests that ΔG_e and reconstructed EGP are more sensitive to measurement error. Clearly, the initial samples of G_e and ΔG_e are important for a correct reconstruction of EGP, since the large uncertainty in these samples leads to poorly estimated EGP profiles.

IV. AN IMPROVED DECONVOLUTION METHOD

To handle this IVGTT difficulty, an improved deconvolution method is proposed. The results of Monte Carlo error analysis simulations show that the error of $\Delta G_e(t) = G_e(t) - G_b(t)$[1] is dominated by the error of $G_e(t)$, while the contribute of $G_b(t)$ can be considered negligible. Basically, the uncertainty on G_e and ΔG_e data is now expressed by means of a correction factor, say α, so that the expression of ΔG_e is now the following:

$$\Delta G_e(t) = \alpha G_e(t) - G_b(t) \tag{14}$$

The correction factor α, which is assumed unknown *a priori*, plays the role of an additional regularization parameter and is estimated *a posteriori* by Maximum Likelihood, together with γ.

Monte Carlo simulations were performed again and the new method was used to reconstruct EGP from simulated data. The resulting mean $\Delta EGP \pm SD$ is shown in Fig. 5. By comparing Fig. 5 with Fig. 2, one can see that the variability bands are now much narrower, especially in the early period. This is confirmed by a lower root-mean-square error (RMSE) of the estimate, decreasing from 0.37 with the original deconvolution method, to 0.23 with the new method. The mean estimated value of α is not different from one (1.00 ± 0.13), indicating that α is not related to a bias, but to a random error on G_e.

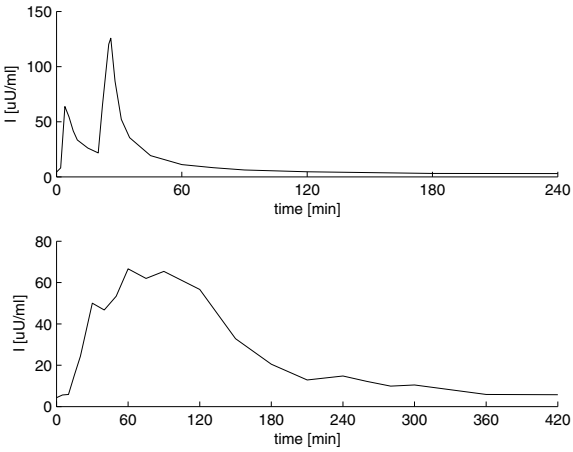

Fig. 4. Plasma insulin concentrations, expressed as $\mu U/ml$, for IVGTT (top) and MEAL (bottom) simulation studies

The improvement is even more evident if individual reconstructions are considered, as shown in Fig. 6, where two reconstructions of ΔEGP obtained from the same set of simulated ΔG_e data (set #5) are compared, without and with estimation of α.

The new deconvolution method was also tested on simu-

[1] $G_b(t)$ is the system response to EGP_b, as defined in Section II-A. See also (4)

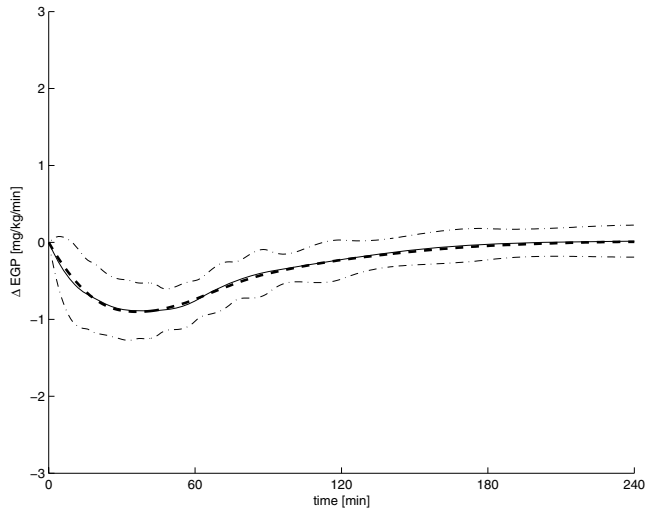

Fig. 5. IVGTT simulation results with estimation of α. ΔEGP reference (dashed line), mean deconvoluted ΔEGP (continuous line) with variability bands (dash-dot line) expressed as mean $\pm$ SD. The estimation of α reduces the uncertainty in the initial part of the experiment, 0–60 min. RMSE is 0.23.

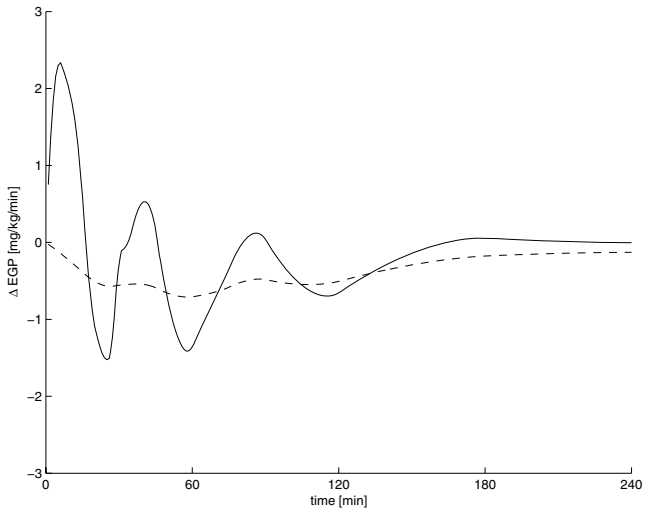

Fig. 6. IVGTT simulation results. Comparison of two ΔEGP reconstructions: without (continuous line) and with (dashed line) estimation of α. Estimated α is 0.88

lated MEAL data, but the resulting ΔEGP estimates showed no significant improvement, thus supporting the fact that MEAL data, minimally influenced by measurement error, do not require additional regularization.

V. CONCLUSION

Endogenous glucose production during IVGTT and MEAL can be reconstructed by deconvolution of the endogenous component of plasma glucose, which is analytically computed from experimental measurements.

The aim of this study was to analyze, by means of Monte Carlo simulations, how measurement errors propagate on endogenous glucose and to investigate how they affect the reconstruction of EGP by stochastic deconvolution. It was found that endogenous glucose and reconstructed EGP in MEAL are minimally influenced by measurement errors, while in IVGTT these errors propagate to endogenous glucose so that its initial samples show high uncertainty, thus making the reconstructed EGP in the early period uncertain too. The reason is that EGP is rapidly suppressed after IVGTT, so that endogenous glucose is calculated as the difference of two noisy terms, total and exogenous components of cold glucose, which are both elevated and similar to each other. On the contrary, after MEAL the total glucose is elevated, while the exogenous component slowly increases from zero.

A solution was proposed to minimize error influence on endogenous glucose during IVGTT, by means of an additional regularization parameter α for endogenous glucose, which is estimated *a posteriori* by Maximum Likelihood. Good results were obtained with this new method: the tuning of α made it possible to reduce the uncertainty on the initial samples of endogenous glucose and thus to improve the reconstruction of EGP. The choice of introducing a correction term that is proportional to endogenous glucose is simple and effective. Alternative and more comprehensive methods for error correction are under study and are subject of future work.

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