Journal of Diabetes Science and Technology
Volume 1, Issue 5, September 2007

SYMPOSIUM

Reconstruction of Glucose in Plasma from Interstitial Fluid Continuous Glucose Monitoring Data: Role of Sensor Calibration

Andrea Facchinetti, M.S., Giovanni Sparacino, Ph.D., and Claudio Cobelli, Ph.D.

Abstract

Background:
Continuous glucose monitoring (CGM) sensors measure glucose concentration in the interstitial fluid (ISF). Equilibration between plasma and ISF glucose is not instantaneous. Therefore, ISF and plasma glucose concentrations exhibit different dynamic patterns, particularly during rapid changes. The purpose of this work was to investigate how well plasma glucose can be reconstructed from ISF CGM data.

Methods:
Six diabetic volunteers were monitored for 2 days using the TheraSense FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA), a minimally invasive device that, on the basis of an initial calibration procedure (hereafter referred to as standard calibration), returns ISF glucose concentration. Simultaneously, plasma glucose concentration was also measured every 15 minutes. First we identified, in each subject, the linear time-invariant (LTI) two-compartment model of plasma-interstitium kinetics. Then, a nonparametric regularization deconvolution method was used to reconstruct plasma from ISF glucose.

Results:
Deconvoluted profiles were always closer to plasma glucose than ISF ones. However, the quality of the reconstruction is unsatisfactory. Some visible discrepancies between average plasma and ISF time series suggest problems either in the applicability of the LTI model of plasma-interstitium kinetics to normal life conditions or in the standard calibration with which ISF glucose is determined from the sensor internal readings. Assuming that the LTI model of plasma-interstitium kinetics is correct, we focused on the influence of calibration and we employed a recently proposed method to recalibrate ISF data.

Conclusions:
After the recalibration step, the relative error in reconstructing plasma glucose was reduced significantly. Results also demonstrate that further margins of improvement of plasma glucose reconstruction are possible by developing more sophisticated recalibration procedures.

J Diabetes Sci Technol 2007;1(5):617-623

Author Affiliation: Department of Information Engineering, University of Padova, Padova, Italy

Abbreviations: (CGM) continuous glucose monitoring, (CV) coefficient of variation, (ISF) interstitial fluid, (LTI) linear time invariant, (MAPE) mean absolute percentage error, (NLS) nonlinear least squares

Keywords: calibration, continuous glucose monitoring, deconvolution, delay, reconstruction of plasma glucose

Corresponding Author: Professor Claudio Cobelli, Ph.D., Department of Information Engineering (DEI), University of Padova, Via Gradenigo 6/B, 35131 Padova, Italy; email address *cobelli@dei.unipd.it*

Introduction

In the recent past, several noninvasive or minimally invasive sensors have been developed that allow continuous glucose monitoring (CGM) for several days.[1–4] CGM devices can improve glucose management and reduce the risk of hypoglycemic shocks, e.g., by generating alerts when glucose exceeds the hypo-threshold[5] or when a time-series prediction method forecasts its crossing.[6]

Continuous glucose monitoring sensors measure glucose concentration in the interstitial fluid (ISF). Several studies have shown that the equilibration of glucose across the capillary endothelial barrier is not instantaneous.[7,8] As a consequence, ISF and plasma glucose concentrations exhibit different dynamic patterns, particularly during rapid changes.[9] Obtaining a portrait of plasma glucose concentration more accurate than that given by ISF glucose readings could be important for several reasons. For instance, the physiological time lag of CGM sensor measurements could be compensated and hypo/hyperglycemic alerts could be generated more timely.

Using data of six diabetic volunteers, where plasma and ISF glucose were monitored simultaneously for 2 days by plasma sampling and the TheraSense FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA), we investigated if plasma glucose can be reconstructed from ISF CGM data. This is equivalent to solving the input estimation problem depicted in **Figure 1**, where the input arrow represents plasma glucose concentration and the output arrow represents ISF glucose concentration measured by the sensor. The block represents the plasma–interstitium system, for the description of which a linear time-invariant (LTI) two-compartment model has been proposed in literature on the basis of hypoglycemic clamp studies.[7] Assuming that the impulse response of the plasma–interstitium system is available, the input estimation problem can be attacked through deconvolution.

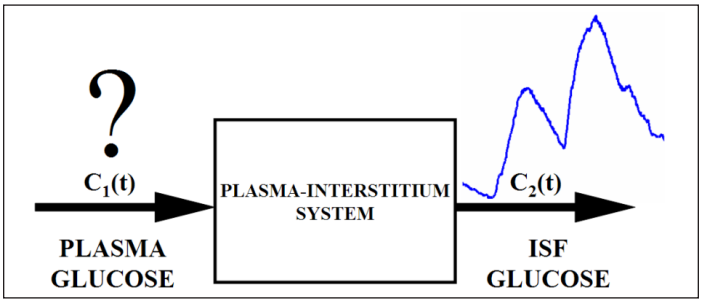

Figure 1. Reconstruction of plasma glucose from CGM sensor data as a solution of an input estimation problem.

Deconvoluted profiles will result always closer to the reference plasma glucose profiles than ISF ones. However, the quality of reconstruction will be unsatisfactory. Some visible discrepancies between average plasma and ISF time series will suggest problems either in the applicability of the LTI model of plasma–interstitium kinetics[7] to normal life conditions or in the calibration with which ISF glucose is determined from the sensor internal readings. Assuming that LTI modeling of plasma–interstitium kinetics is correct, we investigated the role of calibration, demonstrating that the accuracy of the profiles obtained by deconvolution can be improved significantly if ISF data are recalibrated.

Database

Six data sets were taken randomly from a larger database[10,11] consisting of 30 type 1 diabetic subjects (8 males and 22 females, a mean age of 40 years). In each subject, plasma and ISF glucose were measured simultaneously for 2 days in normal conditions. The plasma glucose concentration was measured every 15 minutes by the YSI 2300 (Yellow Springs Instruments, Yellow Spring, OH). During the night, blood sampling was, however, suspended. ISF glucose was determined every 1 minute by the TheraSense FreeStyle Navigator, a minimally invasive CGM device that, starting from a raw electrical signal (ADC counts), returns a glucose concentration level exploiting an initial internal calibration procedure (hereafter referred to as standard calibration).

A representative data set (subject #4) is shown in **Figure 2**. The solid line represents the 1-minute ISF profile (obtained with standard calibration), and the dotted line denotes 15-minute plasma data (blood collection was suspended between hours 14 and 26). In both cases, data were interpolated by straight lines.

Reconstruction of Plasma Glucose

Figure 2 shows how, because of plasma–interstitium kinetics, the ISF glucose profile is a distorted version of the plasma profile. The most apparent difference is the temporal delay of the ISF, which is obviously dependent on the pattern of the signal. For instance, for the representative time series of **Figure 2**, the MAPE distance, measured in window 2, between the plasma glucose time series and the ISF readings provided by the sensor with its standard calibration is 9.6. (The mean absolute

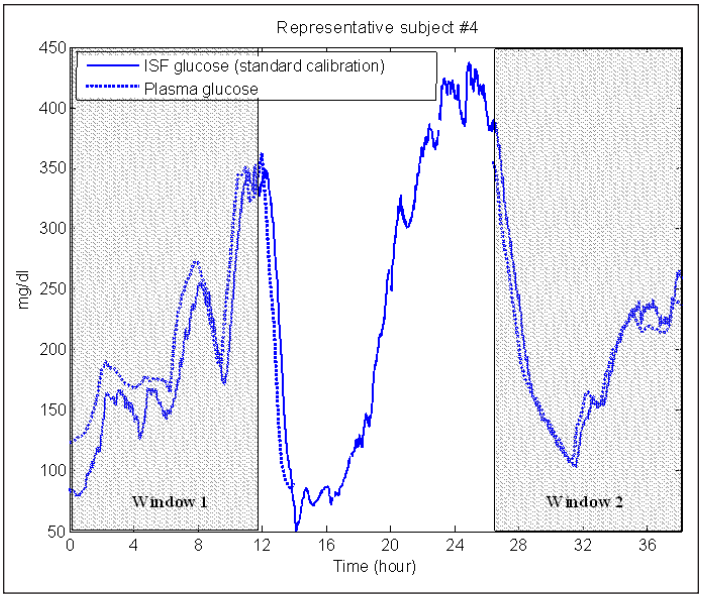

Figure 2. Representative subject (#4) data set with plasma and ISF glucose concentration.

percentage error (MAPE) between two time series in a given time window is defined as

$$\text{MAPE} = \frac{100}{P}\sum_{i=1}^{P}\frac{|ts_1(i) - ts_2(i)|}{ts_1(i)}$$

where $ts_1(i)$ and $ts_2(i)$ represent the ith sample of the two time series (taking ts_1 as reference) and P is the number of samples in the considered window.) Column 2 of **Table 1** reports the MAPE distance, measured in window 2, for all subjects. The average MAPE result equaled 10.6 (±3.6). In the following subsection, we investigate if such a distance can be reduced by using deconvolution and, more specifically, if the profile of glucose concentration in plasma can be reconstructed accurately.

Description of the Strategy

In order to assess the feasibility of plasma glucose reconstruction by deconvolution, the following cross-validation strategy is used. For each subject, we first exploit the first 12-hour data (window 1, see **Figure 2**) to identify the model of Rebrin and Steil.[7] Then, the model is used to reconstruct by deconvolution the plasma glucose profile in the second 12-hour period (window 2, see **Figure 2**). In this window, a qualitative and quantitative comparison of the reference and deconvoluted plasma glucose profiles is thus possible.

The Plasma–Interstitium Kinetic Model

Assessing if reconstruction of the plasma glucose concentration by deconvolution is feasible from the ISF concentration requires an input–output model to describe its relationship. In order to obtain it, we start from the classic two-compartment model,[7,12] which, to the best of our knowledge, is the state-of-the-art model of plasma–interstitium kinetics.

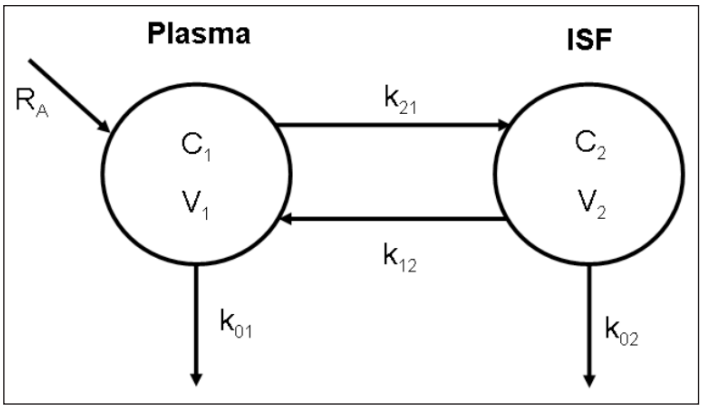

Figure 3. Two-compartmental model describing relationship and exchanges between plasma (compartment 1) and ISF (compartment 2) glucose.

Table 1.
MAPE in Window 2 with Standard Calibration and Two Recalibrated ISF Data

Subject	Reference plasma vs ISF (standard calibration)	Reference plasma vs deconvoluted plasma (standard calibration ISF)	Reference plasma vs deconvoluted plasma (after ISF recalibration of)	
			Window 1	Window 2
No. 1	7.6	6.6	5.8	3.8
No. 2	6.6	6.4	2.6	2.3
No. 3	15.1	18.3	11.2	5.8
No. 4	9.6	9.1	7.8	5.3
No. 5	9.7	4.7	3.7	2.6
No. 6	14.7	11.2	10.3	8.9
Mean (SD)	10.6 (3.6)	9.4 (4.9)	6.9 (3.5)	4.8 (2.4)

The model, displayed in **Figure 3**, is linear and time invariant with exchanges between plasma and interstitium compartments (labeled with 1 and 2) and two irreversible losses. In order to obtain a convolution relationship between plasma and ISF glucose, we consider the differential equation characterizing the ISF compartment:

$$\frac{dC_2(t)}{dt} = -(k_{02} + k_{12})C_2(t) + k_{21}\frac{V_1}{V_2}C_1(t) \quad (1)$$

where $C_1(t)$ and $C_2(t)$ are plasma and ISF glucose concentrations, respectively, V_1 and V_2 are plasma and ISF volumes, and k_{ij} denotes the transfer rate from compartment j to compartment i. Because we are interested in an input–output relationship, Equation (1) is transformed in

$$\frac{dC_2(t)}{dt} = -\frac{1}{\tau}C_2(t) + \frac{g}{\tau}C_1(t) \quad (2)$$

where $g = (k_{21}V_1/V_2)\tau$ and $\tau = 1/(k_{02} + k_{12})$. By integrating Equation (2), it follows that plasma glucose $C_1(t)$ and ISF glucose $C_2(t)$ are related through

$$C_2(t) = \int_{-\infty}^{t} h(t-u)C_1(u)du \text{ with } h(t) = \frac{g}{\tau}e^{-t/\tau} \quad (3)$$

In a given subject, g and τ can be estimated from a simultaneous measurement of plasma and ISF glucose samples.

Note: parameter g in Equation (2) has the meaning of "steady state gain" of the plasma–interstitium dynamic system. In fact, at steady state, Equation (2) becomes

$$0 = -\frac{1}{\tau}C_2 + \frac{g}{\tau}C_1 \quad (4)$$

so that g equals the ratio C_2/C_1 of the steady-state concentration. This interpretation of g gives us some expectations on its value. In fact, physiologically, we should expect g to be equal to 1.[9] In the present article, however, g is treated as an unknown parameter and is estimated from the data.

Identification of Plasma–Interstitium Model

In each subject, we identified g and τ in a 12-hour window (window 1) by nonlinear least squares (NLS), assuming CGM data to be affected by a measurement error with a constant coefficient of variation (CV) of 10%. Numerical implementation of NLS has been performed in MATLAB using the function lsqnonlin of the Optimization Toolbox (Mathworks Inc., Natick, MA). Initial guesses of g and τ were 1 and 12, respectively. Results of parameter estimation are shown in **Table 2**.

Table 2.
Plasma–Interstitium Parameters Estimated from Standard Calibration ISF Data

Subject	g	τ (min)
No.1	0.968	20.9
No.2	0.925	20.9
No.3	0.938	17.9
No.4	0.988	26.7
No.5	1.026	33.8
No.6	0.990	20.5
Mean (CV%)	0.972 (3.8)	23.4 (24.9)

Parameter precision is acceptable (on average <12% for both g and τ), but residuals are biased (not shown). Notably, in some subjects (e.g., #2), the estimated g is "relatively" far from 1. Once we have identified g and τ, we have also completely described, for each subject, the impulse response $h(t)$ of Equation (3).

Deconvolution

Assuming $h(t)$ in Equation (3) to be known, $C_1(t)$ can be recovered from $C_2(t)$ by deconvolution using a nonparametric regularization approach,[13,14] which allows providing smoothed versions of both C_1 and C_2. Notably, regularization allows dealing with the ill-conditioning of inverse problems, whereas other more straightforward operations, such as direct inversion of Equation (2) through numerical differentiation schemes, would not.

Column 3 of **Table 1** reports the MAPE in window 2 calculated for profiles obtained from deconvolution using g and τ of **Table 2** (identified numerically in window 1 of **Figure 2**). The average MAPE was reduced, albeit very modestly, from 10.6 to 9.4 ($p < 0.05$).

Figure 4 graphically shows results obtained for the representative subject of **Figure 2**. Notably, deconvoluted plasma glucose appears to be far from the reference one (**Figure 2**, top). Of note is that reconvoluted ISF glucose fits standard calibration ISF data well (**Figure 2**, middle), i.e., weighted (percentage) residuals are small in amplitude and uncorrelated (**Figure 2**, bottom). This suggests that the error on the deconvoluted plasma glucose profile is not attributable to the deconvolution algorithm, but should be caused from a wrong description of the system given by the cascade of plasma–interstitium kinetics and sensor.

In particular, the apparent discrepancies visible in **Figure 2** between the average levels of plasma and ISF

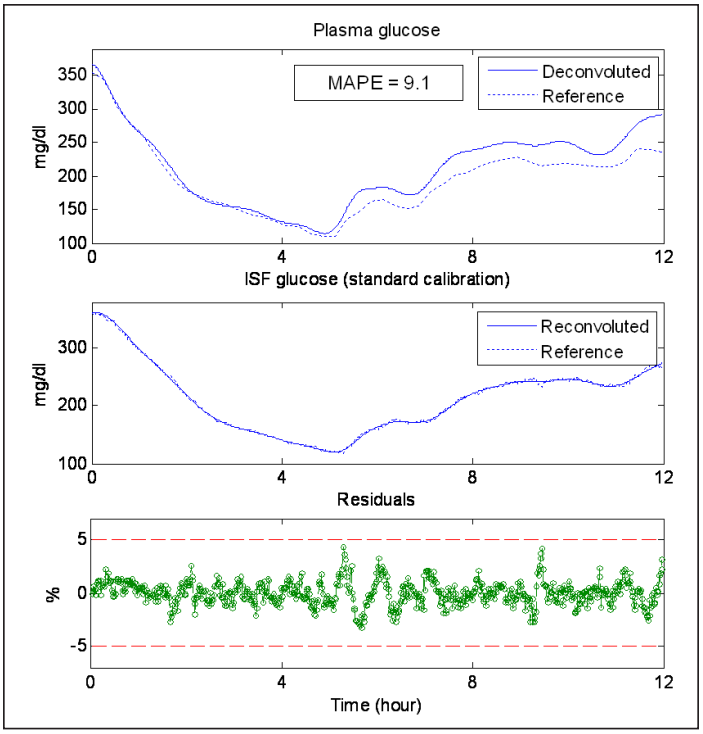

Figure 4. Representative subject (#4) results. (**Top**) Deconvoluted vs reference plasma glucose. (**Middle**) Reconvoluted vs reference ISF glucose. (**Bottom**) Residuals.

time series, e.g., in the interval (4–8) of window 2, suggest the existence of problems either in the applicability in normal life conditions of the LTI description of plasma–interstitium kinetics or in the standard calibration procedure with which ISF glucose is determined from the sensor internal readings. Both aspects deserve detailed investigations. While waiting for an assessment of the validity of the LTI model of plasma–interstitium kinetics under these more realistic conditions, the next section investigates the role of calibration, assuming that the LTI model is correct.

Role of Calibration

This section attributes discrepancies between the average levels of plasma and ISF time series to a systematic scale factor error that affects ISF data. This hypothesis is supported by the fact that, in many subjects, the steady state gain g (**Table 2**) resulted relatively far from 1, in contrast to physiological expectations.

A Recalibration Method

In order to evaluate if deconvolution results can be improved by correcting the values of ISF glucose provided by the sensor with standard calibration, we adopted a recently proposed recalibration procedure.[15] In this procedure, in a given subject, the recalibrated ISF time series is found as a_1X, where a_1 is a scalar recalibration parameter and X is the vector containing ADC counts. The recalibration parameter a_1 is defined as that giving the best fit of plasma samples vector Y through the equation

$$a_1X + \varepsilon = Y \quad (5)$$

where ε is a random error vector. The parameter a_1 is estimated in each subject by linear least squares in window 1. Results are shown in **Table 3**.

Notably, a_1 varies considerably among subjects, suggesting that sensor readings should be calibrated individually.

Identification and Deconvolution from Recalibrated Data

Starting from recalibrated ISF data of window 1, we reidentified the parameters of the plasma–interstitium model in each subject. Results are shown in **Table 4**.

In each subject, g is much closer to the physiologically expected value of 1. Therefore, the plausibility of its estimates is greater. Also, the intersubject variability of g and τ has been reduced. Residuals obtained from

Table 3.
Recalibration Factor a_1

Subject	a_1 (mg/dl/ADC counts)
No. 1	0.53
No. 2	0.39
No. 3	0.44
No. 4	0.33
No. 5	0.38
No. 6	0.41
Mean (CV%)	0.41 (16.4)

Table 4.
Plasma–Interstitium Parameters Estimated from Recalibrated ISF Data

Subject	g	τ (min)
No. 1	1.005	20.3
No. 2	0.996	18.0
No. 3	0.995	13.3
No. 4	1.000	24.0
No. 5	0.998	27.4
No. 6	0.983	18.8
Mean (CV%)	0.996 (0.7)	20.3 (24.1)

identification of the parameters of plasma–interstitium model are now less biased (not shown), confirming the fact that at least a part of the bias evidenced previously arose from a lack of calibration.

Using the values of g and τ, we applied deconvolution on recalibrated ISF data. In all six subjects, the deconvoluted profiles are much closer to the reference ones than the original ISF readings. The average MAPE, which from the original 10.4 (±3.6) was reduced by deconvolution to 9.4 (±4.9), is reduced further, thanks to calibration, to 6.9 (±3.5)($p < 0.05$) for all value comparisons. The improvement can be seen in **Figure 5**, albeit with some difficulty, also graphically for the representative subject (for whom the MAPE passed from 9.6 in **Figure 2**, to 9.1 in **Figure 4**, to 7.8 in **Figure 5**).

In the following subsection, we demonstrate that a much more significant improvement can be obtained by using a different calibration strategy.

Domain of Validity of the Recalibration Factor

Hitherto the value of a_1 was obtained from window 1, while deconvolution was done in window 2. One may wonder whether recalibrating data of window 2 through a scale factor fitted in the same window, say a_2, can improve the results. So, for each subject, a_2 has been computed in window 2, g and τ have been estimated (values not reported), and then the deconvolution procedure was performed. **Figure 6** displays, for the representative subject, results obtained applying deconvolution to an a_2-recalibrated ISF profile in window 2. The profile obtained through deconvolution is now quite accurate, as witnessed by the fact that the MAPE value was reduced to 5.3. Individual MAPE values in all six subjects are reported in **Table 1**. Notably, this "ideal" calibration allowed reducing the MAPE distance between plasma and deconvoluted glucose to 4.8 (±2.4), with $p < 0.001$.

This suggests that any window of data should have its own recalibration factor. In other words, use of a single recalibration factor for the entire time series is suboptimal in the presence of time-variance behavior of the sensor gain. As a consequence, further and larger improvements of plasma glucose reconstruction should be feasible by developing more sophisticated calibration procedures accounting for the possible time variance of sensor behavior.

Conclusions

Interstitial fluid and plasma glucose concentrations exhibit different dynamic patterns. Obtaining a portrait of plasma glucose concentration more accurate than that

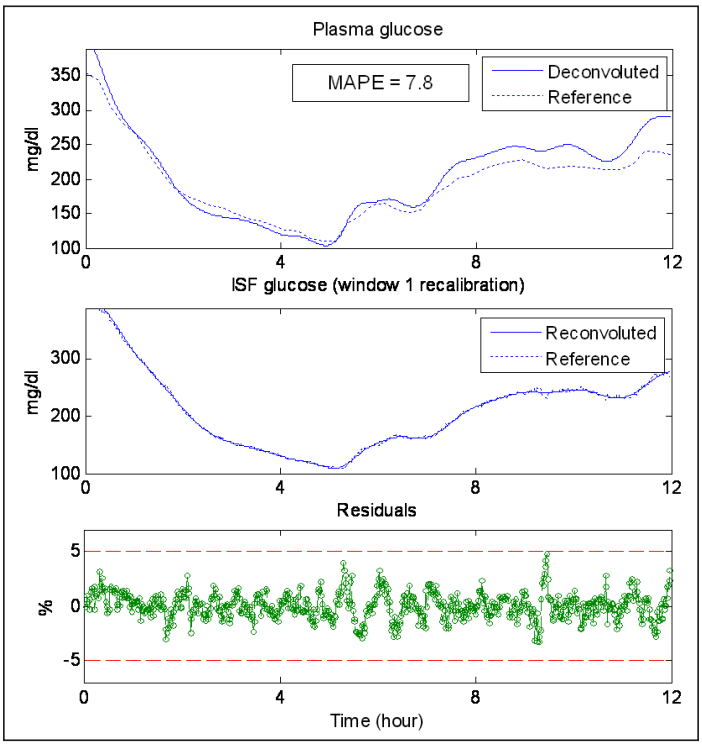

Figure 5. Representative subject (#4) results. (**Top**) Deconvoluted vs reference plasma glucose. (**Middle**) Reconvoluted vs reference ISF glucose. (**Bottom**) Residuals.

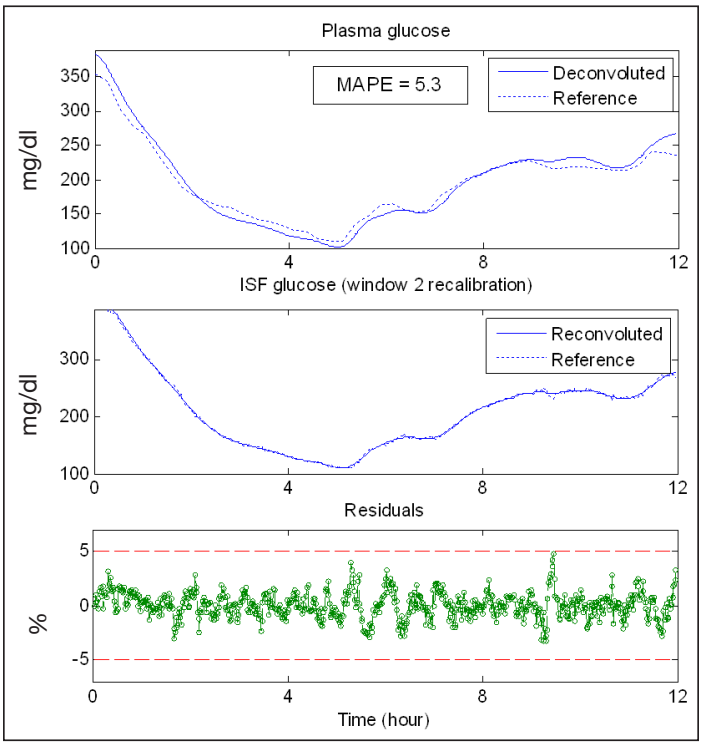

Figure 6. Representative subject (#4) results. (**Top**) Deconvoluted vs reference plasma glucose. (**Middle**) Reconvoluted vs reference ISF glucose. (**Bottom**) Residuals.

given by ISF glucose readings could thus be important for several reasons. In theory, one could try to recover the plasma glucose concentration from ISF CGM data using deconvolution and the LTI two-compartment model of plasma–interstitium kinetics proposed elsewhere.[7,12]

In the six subjects studied in this article, deconvoluted plasma profiles are closer to plasma time series (average MAPE 9.4 ± 4.9) than the ISF curves given by the sensor (average MAPE 10.6 ± 3.6). However, the accuracy of the reconstruction of plasma glucose is unsatisfactory (**Figure 4**). This can be due either to problems in the applicability to normal life situations of the LTI two-compartment model of plasma–interstitium kinetics, developed and validated elsewhere[7,12] under controlled physiological circumstances, or to the standard calibration by which ISF glucose was determined from sensor internal readings. In this article, we assumed that the description of the plasma–interstitium kinetics by a LTI model is correct and focused on the role of calibration. In particular, we demonstrated that the use of the straightforward recalibration procedure proposed by King and colleagues,[15] based on determination of a single time-invariant scaling factor, can provide a significant improvement in the quality of the reconstructed plasma profile (average MAPE 6.9 ± 3.5). Further enhancement can then be obtained (average MAPE 4.8 ± 2.4) if "local" calibration is adopted. This last result suggests that margins of improvement of plasma glucose reconstruction are possible by developing more sophisticated recalibration procedures providing a time-varying modulation of the sensor gain. Obviously, for allowing their use in practical situations, these new recalibration procedures should require no more than three to four plasma samples per day.

In any case, it is worthwhile stressing that the "optimal" calibration of ISF data represents a necessary, but not sufficient, condition for accurate reconstruction of plasma glucose through deconvolution. In fact, deconvolution requires perfect linearity and time invariance of the system of **Figure 1**. Whether plasma–interstitium kinetics in normal life conditions can be described by a LTI model, as that developed and validated elsewhere[7,12] under controlled physiological circumstances, remains a matter of investigation.

Acknowledgements:

The authors are grateful to Professor Boris Kovatchev (University of Virginia) for having supplied data[10,11] and for useful discussions on the topic of the manuscript and to Dr. C. King for having provided us with details on the recalibration procedure.[15]

References:

1. Robert JJ. Continuous monitoring of blood glucose. Horm Res. 2002;57 Suppl 1:81-4.
2. Tierney MJ, Tamada JA, Potts RO, Eastman RC, Pitzer K, Ackerman NR, Fermi SJ. The GlucoWatch biographer: a frequent automatic and noninvasive glucose monitor. Ann Med. 2000 Dec;32(9):632-41.
3. Mastrototaro JJ. The MiniMed continuous glucose monitoring system. Diabetes Technol Ther. 2000;2 Suppl 1:S13-8.
4. Poscia A, Mascini M, Moscone D, Luzzana M, Caramenti G, Cremonesi P, Valgimigli F, Dongiovanni C, Varalli M. A microdialysis technique for continuous subcutaneous glucose monitoring in diabetic patients (part 1). Biosens Bioelectron. 2003 Jul;18(7):891-8.
5. Bode B, Gross K, Rikalo N, Schwartz S, Wahl T, Page C, Gross T, Mastrototaro JJ. Alarms based on real-time sensor glucose values alert patients to hypo- and hyperglycemia: the Guardian continuous monitoring system. Diabetes Technol Ther. 2004;6(2):105-13.
6. Sparacino G, Zanderigo F, Corazza S, Maran A, Facchinetti A, Cobelli C. Glucose concentration can be predicted ahead in time from continuous glucose monitoring sensor time series. IEEE Trans Biomed Eng. 2007 May;54(5):931-7.
7. Rebrin K, Steil GM. Can interstitial glucose assessment replace blood glucose measurements? Diabetes Technol Ther. 2000;2(3):461-72.
8. Steil GM, Rebrin K, Hariri F, Jinagonda S, Tadros S, Darwin C, Saad MF. Interstitial fluid glucose dynamics during insulin-induced hypoglycaemia. Diabetologia. 2005;48(9):1833-40.
9. Steil GM, Rebrin K, Mastrototaro J, Bernaba B, Saad MF. Determination of plasma glucose during rapid glucose excursions with a subcutaneous glucose sensor. Diabetes Technol Ther. 2003;5(1):27-31.
10. Kovatchev BP, Gonder-Frederick LA, Cox DJ, Clarke WL. Evaluating the accuracy of continuous glucose-monitoring sensors: continuous glucose-error grid analysis illustrated by TheraSense Freestyle Navigator data. Diabetes Care. 2004 Aug;27(8):1922-8.
11. Feldman B, Brazg R, Schwartz S, Weinstein R. A continuous glucose sensor based on wired enzyme technology--results from a 3-day trial in patients with type 1 diabetes. Diabetes Technol Ther. 2003;5(5):769-79.
12. Rebrin K, Steil GM, van Antwerp WP, Mastrototaro JJ. Subcutaneous glucose predicts plasma glucose independent of insulin: implications for continuous monitoring. Am J Physiol. 1999 Sep;277(3 Pt 1):E561-71.
13. De Nicolao G, Sparacino G, Cobelli C. Nonparametric input estimation in physiological systems: problems, methods, case studies. Automatica. 1997;33:851-70.
14. Sparacino G, Pillonetto G, Capello M, De Nicolao G, Cobelli C. WINSTODEC: a stochastic deconvolution interactive program for physiological and pharmacokinetic systems. Comput Methods Programs Biomed. 2002 Jan;67(1):67-77.
15. King C, Anderson S, Breton M, Clarke WL, Kovatchev BP. Modeling of calibration effectiveness and blood-to-interstitial glucose dynamics as potential confounders of the accuracy of continuous glucose sensors. J Diabetes Sci Technol. 2007 May;1(3):317-22.