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Reconstructing by Deconvolution Plasma Glucose from Continuous Glucose Monitoring Sensor Data

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Abstract — In the recent past, several sensors have been developed which allow continuous glucose monitoring (CGM) for several days. CGM can improve diabetes management and in particular decrease the risk of hypoglycemic events. However, CGM sensors measure glucose concentration in the interstitial fluid (ISF) rather than in plasma and ISF lags plasma glucose. The purpose of this work is to investigate if plasma glucose can be reconstructed from ISF CGM data by using a deconvolution approach, based on the knowledge of the model of plasma-interstitium kinetics. Results obtained in 6 volunteers monitored for 2 days with simultaneous plasma and ISF glucose by the Freestyle Navigator CGM sensor measurements show that calibration is a critical component for a reliable reconstruction of plasma glucose from ISF data.

I. INTRODUCTION

GLUCOSE is the most important fuel for human beings and its level in the blood is controlled by insulin, using a negative feedback regulatory system. In diabetic patients, either pancreas does not secrete insulin (Type 1 diabetes) or insulin is not properly used (Type 2 diabetes). Last statistics say that diabetes affects over 177 millions of persons in the world and 1 over 20 adults [1]. Diabetes therapy is mainly based on insulin and drug administration, diet, and physical exercise, tuned according to the self-monitoring of blood glucose levels 3-4 times a day. However, in diabetic patients the concentration of glucose in the blood often goes outside the normal range (70 – 180 mg/dl). Hyperglycaemia mostly affects long-term complications, such as cardiovascular and heart diseases, while hypoglycaemia can be more dangerous in short-term, leading in the worst case to hypoglycaemic coma.

In the recent past, several sensors have been developed which allow continuous glucose monitoring (CGM) for several days [2-5]. CGM systems are noninvasive or minimally-invasive, and, in many cases, the fact that they are portable can allow their use in patient daily life. CGM devices can help the improvement of glucose management and the reduction of the risk of hypoglycaemic events. For instance, alerts can be generated automatically when glucose exceeds a certain threshold [6]. Research is also active for generating alerts from a glucose profile forecasted ahead in time by using time-series prediction methods [7].

CGM sensors measure glucose concentration in the interstitial fluid (ISF) rather than in plasma. This measure is an approximation of Blood Glucose (BG) concentration. Several studies have shown that there is a lag time in the

equilibration of glucose across the capillary endothelial barrier [8-9]. As a consequence, ISF glucose is a distorted version of plasma glucose [10], with the plasma-interstitium kinetics described by a linear time-invariant two compartment model [8].

The purpose of this work is to investigate if plasma glucose can be reconstructed from ISF CGM data by using a deconvolution approach based on the knowledge of the model of plasma-interstitium kinetics. In other words, letting $C_2(t)$ be the measured ISF glucose, the problem is to reconstruct the unknown plasma glucose $C_1(t)$ assuming that the impulse response of the system given by the cascade plasma-interstitium kinetics and sensor is known (Fig. 1). We exploit a data base consisting of 6 diabetic volunteers where 15 min evenly-spaced plasma samples and 1 min evenly-spaced ISF samples were measured in parallel for 2 days [11]. For each subject, we first identify the model of [8] on the first half of the time-series. Then, the model is used to recover the plasma profile by deconvolution in the second half. The deconvoluted plasma glucose profile is finally compared with the measured plasma, i.e. the reference profile, and the quality of the reconstruction is assessed. Results show that plasma glucose can be reconstructed only if ISF sensor data are accurately calibrated.

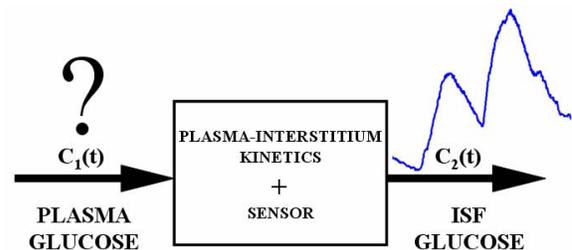


Fig. 1. Reconstruction of plasma glucose from CGM sensor data as solution of an input estimation problem.

II. DATA BASE

Data were taken from a larger data set used in [11]. In particular, we consider 6 type-1 diabetic volunteers where plasma and ISF glucose were simultaneously measured for 2 days in normal conditions. Plasma glucose concentration was measured every 15 min by YSI 2300 (Yellow Springs Instruments, Yellow Spring, OH). ISF glucose was measured every 1 min by the TheraSense FreeStyle Navigator CGM device. The Navigator is a subcutaneous, electrochemical sensor, which operates implanted at a site in the body. It produces an electrical voltage value (mV)

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which is transformed into ISF glucose level by means of a non-linear function which is tuned in each subject using a calibration procedure based on self monitoring blood glucose samples [11-12]. Figure 2 shows a portion of a representative data set (subject 1). The solid line represents the 1 min ISF profile, while the dotted line denotes the 15 min plasma data (in both cases a first order interpolation was used).

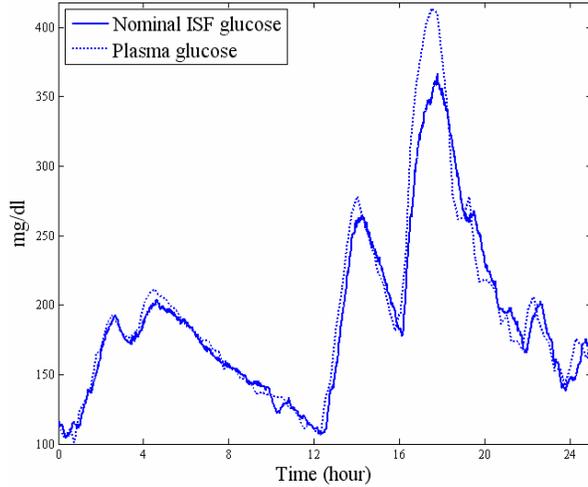


Fig. 2. Portion of data measured in parallel in subject 1. Plasma (dotted line) vs ISF glucose concentration (solid line).

III. RECONSTRUCTING PLASMA GLUCOSE BY DECONVOLUTION

A. Plasma-Interstitial Kinetics Model

The model consists of two compartments, with an irreversible loss in each. Exchanges between the two compartments describe the diffusion processes across the capillary barrier. Details can be found in [8]. Assuming that all the model parameters are constant in time [13], plasma and ISF concentration, C_1 and C_2 , are related through the differential equation:

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

In the parameterization of (1), g and τ are related to the transfer rate coefficients by $g = (k_{21}V_1/V_2)/\tau$ and $\tau = 1/(k_{02} + k_{12})$, with V_1 and V_2 being the plasma and ISF volumes and k_{ij} denoting the transfer rate from compartment j to compartment i (0 denotes the external environment). Note that g represents the steady state gain of the system. At steady state g is equal to the ratio of ISF and plasma concentration. For physiological reasons, we expect g to be equal to 1.

Model parameters in a given subject can be numerically determined from a data set of simultaneously measured plasma and ISF glucose samples.

B. Identification of Plasma-Interstitial Kinetics Model

Since plasma and ISF glucose are simultaneously measured for 2 days, the most natural approach is to identify g and τ in each subject from his/her first half of the time-series. Here, nonlinear least squares parameter estimation was performed assuming measurement error CV of 10%. The left side of Table 1 presents the results obtained for the 6 subjects.

TABLE 1
PARAMETERS ESTIMATED VALUES

Subject	ISF data		Recalibrated ISF data		
	g	τ (min)	α (mg/dl/mV)	g	τ (min)
N°1	0.944	7.6	0.548	1.014	6.7
N°2	0.786	17.9	0.394	0.984	18.0
N°3	0.727	11.1	0.433	0.866	10.8
N°4	0.972	27.8	0.320	0.976	24.4
N°5	1.081	33.8	0.386	1.060	28.7
N°6	0.979	18.9	0.406	1.034	18.9
SD	0.133	9.9	0.052	0.079	8.2

Even if parameters uncertainty is small (not shown), residuals appear to be biased (not shown), suggesting that this step can be improved (discussed below in Section IV). Also, of note is that g and τ significantly differ between individuals, with a standard deviation SD (calculated from the 6 subjects) of 14% and 50%, respectively.

C. Deconvolution

From (1), it follows that ISF and plasma glucose are related by:

$$C_2(t) = h * C_1(t), \quad h(t) = \frac{g}{\tau} \cdot \exp^{-t/\tau} \quad (2)$$

and C_1 can be recovered from C_2 by deconvolution (Fig. 1). Assuming $h(t)$ to be known, to perform deconvolution we have used a non-parametric regularization approach [14-15] which allows to simultaneously provide smoothed versions of both C_1 and C_2 . Figure 3 illustrates the results obtained for subject 1. Deconvoluted plasma glucose looks far apart from the measured one (upper panel). Of note is that the reconvoluted ISF glucose well fits the ISF data (middle panel), as witnessed by the fact that weighted (percent) residuals are small in amplitude and uncorrelated (lower panel). This suggests that the error on the deconvoluted plasma glucose profile is not due to the deconvolution algorithm per se, but it is likely due to a wrong description of the system impulse response (cascade of plasma-interstitium kinetics plus sensor).

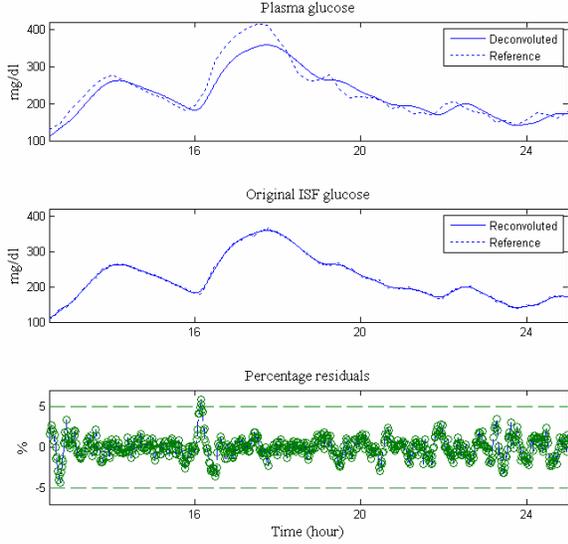


Fig. 3. Subject 1. Upper panel: deconvoluted plasma glucose (solid line) vs reference (dotted line). Middle panel: reconvoluted ISF glucose (solid line) vs reference (dotted line). Lower panel: Percentage residuals.

IV. ROLE OF CALIBRATION AND RESULTS

The reliability and quasi time-invariance of plasma-interstitium kinetics is on good physiological grounds. On the other hand, the steady state gain g results far from 1 in many subjects. Thus, a possible error source is the values provided by the sensor for ISF glucose, i.e. the calibration process.

A. The Recalibration Method

In order to evaluate if deconvolution results can be improved by correcting ISF glucose provided by the sensor, we have adopted the recalibration procedure proposed and validated for hypoglycaemic falls and recovery in [16]. In particular, here we considered the voltage data provided by the sensor and fitted them against the available plasma data. In order to place ourselves in the most favourable situation, all the available data participated to the determination of the calibration factor α . In practice, calibrated and voltage data in a given subject are described through the equation:

$$\alpha X + \varepsilon = Y \quad (3)$$

where Y is the vector containing all plasma glucose samples, X is the vector of voltage data (mV), α is the scalar recalibration parameter (common to the entire voltage time-series) and ε is the error vector. The parameter α is estimated by linear least squares as:

$$\alpha = (X^T X)^{-1} X^T Y \quad (4)$$

The values of α are shown in the central column of Table 1. Notably, they vary significantly among subjects. Having α in each subject, the recalibrated ISF glucose time-series is obtained multiplying the vector X by α .

B. Identification and Deconvolution from Recalibrated Data

Starting from ISF recalibrated data, we have re-identified the parameters of plasma-interstitium model. Results are reported on the right side of Table 1. The improvement is evident. For each time-series residuals are now less biased than in the previous case (not shown) and the steady state gain g is much closer to 1. Standard deviations of g and τ have been reduced by one third and one fifth respectively, evidencing that the inter-variability of parameters is much smaller.

Using the values of g and τ we applied deconvolution approach on recalibrated ISF data. Fig. 4 presents the results obtained for subject 1. Compared to Fig. 3, with the similar goodness of fit, the plasma deconvoluted profile is now much closer to the measured one.

In order to quantify the improvement due to calibration, mean absolute error (MAE) and mean absolute percent error (MAPE) between reconstructed and plasma data have been calculated and reported in Table 2.

TABLE 2
MAE AND MAPE ON 6 SUBJECTS

Profile	MAE (mg/dl)	MAPE (%)
Deconvoluted from ISF	16.1	9.6
Deconvoluted from recalibrated ISF	10.7	6.6

Results show that both indices are reduced by one third thanks to calibration.

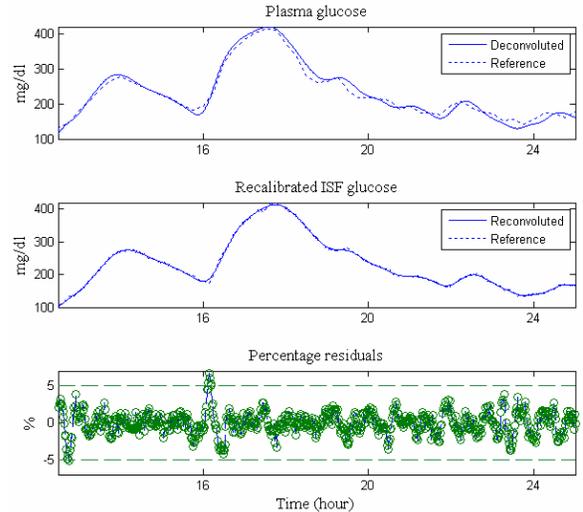


Fig. 4. Subject 1. Upper panel: deconvoluted plasma glucose (solid line) vs reference (dotted line). Middle panel: reconvoluted ISF glucose (solid line) vs reference (dotted line). Lower panel: Percentage residuals.

V. CONCLUSIONS

It is an accepted notion that, for preventing hypoglycaemic events in diabetic subjects, alerts generated using plasma glucose would be more effective than those generated from ISF CGM data. In theory, one could try to recover plasma glucose concentration from ISF CGM data, by using deconvolution and exploiting the linear time-invariant two compartment model of plasma-interstitium kinetics proposed in [8,13].

At first glance, reconstruction seemed not possible (Fig. 3) since the deconvoluted plasma glucose was far from the measured plasma. One source of error can lie in the ISF glucose values supplied by the sensor. The use of a recalibration procedure starting directly from the raw voltage sensor data provided a significant improvement in the quality of the reconstructed plasma profile, which resulted quite close to the measured one.

This demonstrates that the role of calibration is critical. The recalibration method based on the procedure proposed in [16] is straightforward and simple, since it employs a unique scale factor for the whole time-series (2 days). These positive results stimulate further research on this topic.

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