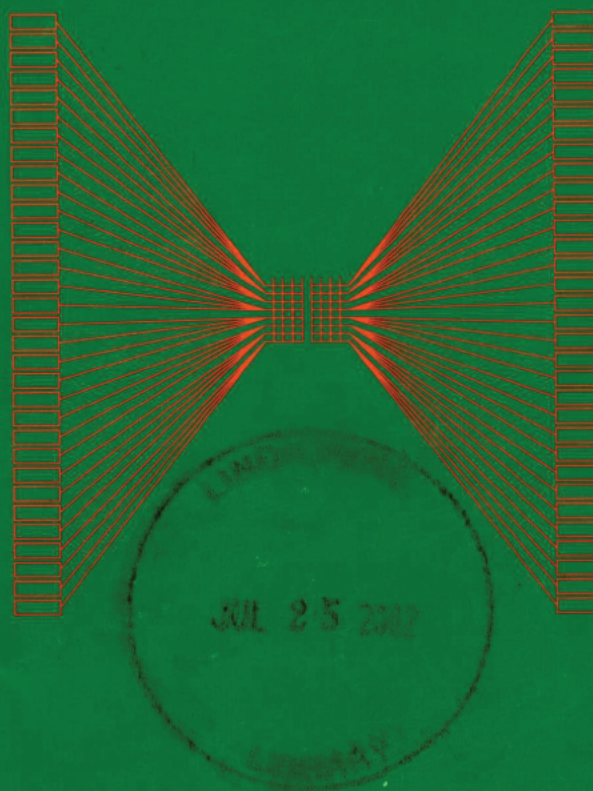


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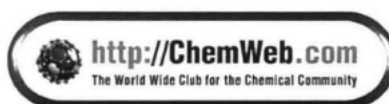
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Calibration of a subcutaneous amperometric glucose sensor

Part 1. Effect of measurement uncertainties on the determination of sensor sensitivity and background current

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Abstract

The calibration of a continuous glucose monitoring system, i.e. the transformation of the signal $I(t)$ generated by the glucose sensor at time (t) into an estimation of glucose concentration $G(t)$, represents a key issue. The two-point calibration procedure consists of the determination of a sensor sensitivity S and of a background current I_0 by plotting two values of the sensor signal versus the concomitant blood glucose concentrations. The estimation of $G(t)$ is subsequently given by $G(t) = (I(t) - I_0)/S$. A glucose sensor was implanted in the subcutaneous tissue of nine type 1 diabetic patients during 3 ($n = 2$) and 7 days ($n = 7$). For each individual trial, S and I_0 were determined by taking into account the values of two sets of sensor output and blood glucose concentration distant by at least 1 h, the procedure being repeated for each consecutive set of values. S and I_0 were found to be negatively correlated, the value of I_0 being sometimes negative. Theoretical analysis demonstrates that this phenomenon can be explained by the effect of measurement uncertainties on the determination of capillary glucose concentration and of sensor output.

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Keywords: Glucose sensor; Calibration; Subcutaneous tissue; Type 1 diabetes

1. Introduction

There are currently several technologies under consideration for developing a continuous glucose monitoring system to be used on line, especially as a hypoglycemic alarm, thus improving the safety of insulin therapy (Reach and Wilson, 1992). A crucial issue in glucose sensing is the calibration of the system, especially if it is supposed to be used in real time, for instance as a hypoglycemic alarm system: the signal generated by the sensor, originally described by Clark and Lyons (1962), is a current (in nA) and has to be transformed in real time into an estimation of glucose

concentration (in mM or mg/dl). Since it is well known that the sensor sensitivity is different when evaluated in vitro or in vivo (Thomé-Duret et al., 1996), an in vivo sensor calibration is mandatory.

Fig. 1 represents the principle of in vivo sensor calibration. During an increase in blood glucose concentration G from G_1 to G_2 (in mg/dl), the sensor current I (in nA) increases from I_1 to I_2 . Plotting I versus G yields a graphical representation of the sensor sensitivity S , expressed in nA/mg per dl, and of the intercept I_0 with the current axis, i.e. the theoretical sensor output which would be observed in the absence of glucose. The parameters S and I_0 are subsequently used to transform at any time the sensor output $I(t)$ into an estimation of glucose concentration $G(t)$.

If I_0 is not negligible, a two-point calibration procedure is required, using two determinations of blood glucose concentration and of the concomitant sensor

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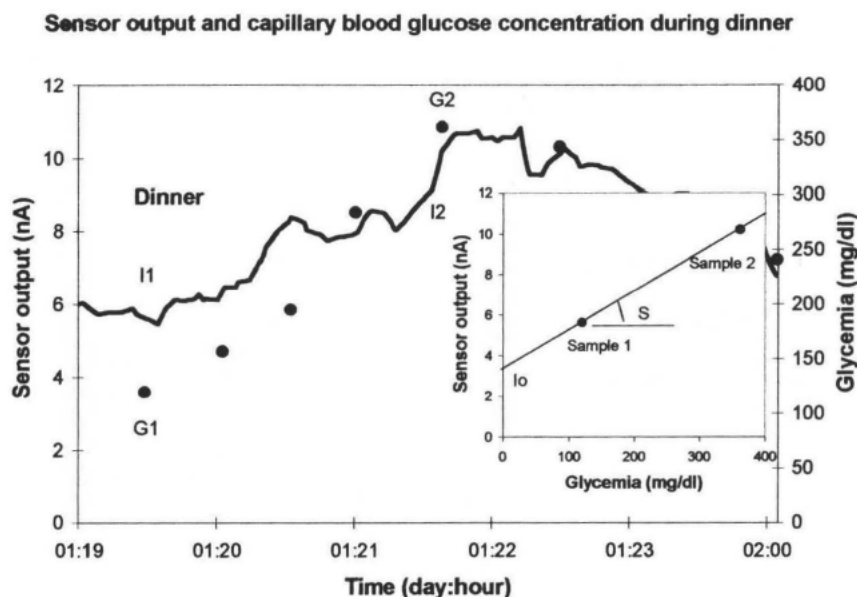


Fig. 1. Sensor output (continuous line) and capillary blood glucose (closed circles) recorded during the meal 24 h after sensor implantation in the subcutaneous tissue of a diabetic patient. The value of the blood glucose determination and of the concomitant sensor output, determined before (sample 1), and after the meal (sample 2), are used to determine, by linear extrapolation shown in the insert, the sensor sensitivity S (in nA/mg per dl) and the background current I_0 (in nA).

outputs (Velho et al., 1988; von Woedtke et al., 1989): first, the sensor sensitivity is determined as the ratio between the increments in I and G , i.e. as:

$$S = (I_2 - I_1)/(G_2 - G_1)$$

I_0 can be determined from experimental data as:

$$I_0 = I_1 - (S \times G_1)$$

Subsequently, the glucose concentration can be estimated at any time from the current I as:

$$G(t) = (I(t) - I_0)/S$$

Understanding the calibration issue is crucial for the design of a calibration procedure to be implemented in a continuous glucose monitoring system, in which the sensing element is not directly placed in the vascular bed. In this study, we demonstrate that the positive or negative values of I_0 calculated from the two-point calibration procedure can be at least in part be explained by measurement uncertainties.

2. Materials and methods

2.1. The glucose sensor

In the past 10 years, our laboratories have developed a miniaturized enzymatic sensor, which is the size of an insulin injection needle (outer diameter 0.35 mm), is flexible, and can be implanted through a 21-gauge needle in the subcutaneous tissue. The preparation of the glucose sensor has been described elsewhere (Ausse-

dat et al., 2000). The in vitro sensitivity of the sensors used in this study, determined in phosphate buffer, at 36 °C, was 46.4 ± 6.6 nA/100 mg per dl, $n = 9$. The time to reach in vitro 90% of sensor maximal response to a 5 mM increase in glucose concentration was less than 3 min.

2.2. The electronic control unit

We have developed a wearable ($3 \times 8 \times 15$ cm, 240 g weight), battery-driven (6 V) electronic control unit (ECU). The ECU controls the sensor applied potential, acquires and stores the sensor current, and performs data processing: filtering and transforming the sensor output into an estimation of glucose concentration through a calibration procedure described below. Finally, it displays on an LCD the sensor current in nanoamps or, once the system is calibrated, the estimation of glucose concentration in mg/dl (Ausse-dat et al., 1997); in these experiments the filter, using mathematical morphology techniques, averaged five consecutive values of the current sampled every 30 s, thus introducing a 2.5-min delay.

The sensor was indwelled inside a module equipped with a battery and an electronic board containing the integrated circuits for providing the sensor polarization (+0.65 V at the anode) and for converting the sensor current into a proportional voltage. The output voltage was sent to the ECU through a cable connecting the sensor module to the ECU. The advantage of this configuration is that sensor disconnection from the

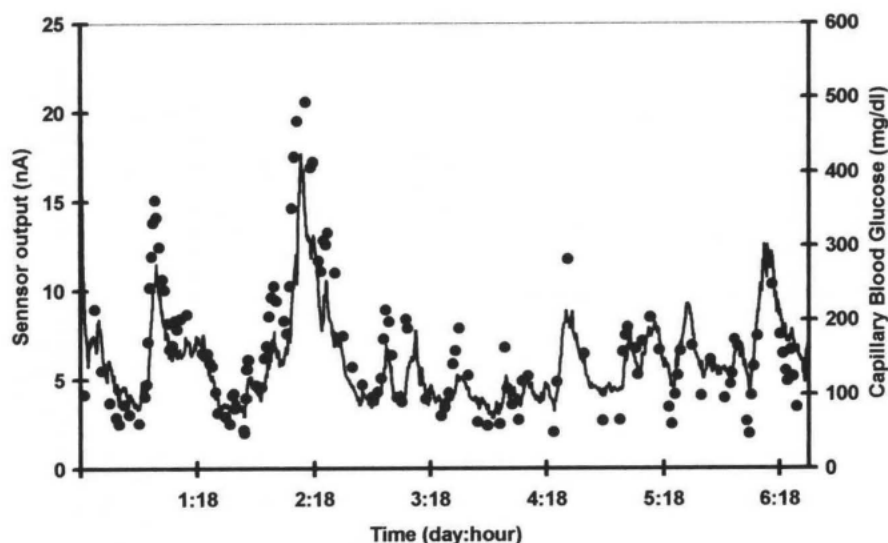


Fig. 2. Sensor output (continuous line) and capillary blood glucose concentration (closed circles) during 6 days in a diabetic patient.

ECU is feasible without losing sensor polarization, for instance during a shower.

2.3. Trial design

Nine type 1 diabetic patients participated in this study, which was approved by the Ethical Review Board of Hôtel-Dieu Hospital and was performed in accordance with the Huriet Law. At approx. 6 p.m., a 21-gauge needle was implanted over 1 cm into the subcutaneous tissue of the abdomen after careful skin disinfection with Betadine®. No anesthesia was used. The sensor was indwelled through the needle after which the needle was pulled out. The sensor was secured with sterile film (Tegaderm®), and linked, via the sensor module, to the ECU. The duration of the study was 7 days in seven patients and 3 days in two patients. During the first 3 days, the patients were hospitalized for teaching purposes in the diabetes department. The last 4 days of the study were run under ambulatory conditions. During the study, no change was made in the patient insulin regimen. Patients were asked to determine their capillary blood glucose concentration at least 20 times per day during the inpatient period (including night measurement performed every 2 h by a nurse) and 12 times during the outpatient period, by using a Glucotrend Meter® (Roche), the internal clock of which was synchronized with the clock of the ECU. At the end of the study, the glucose data stored in the Glucotrend memory were uploaded into a PC using the CAMIT® software for further analysis. During the study period, only the current was displayed on the LCD screen of the ECU.

2.4. Determination of S and I_o

For each individual trial, S and I_o were determined from the 12th hour after sensor implantation by taking into account the values of two sets of sensor output and blood glucose concentration distant by at least 1 h, with an initial glucose concentration between 50 and 200 mg/dl and a change of at least 20% in the sensor output and in the capillary blood glucose concentration. The procedure was repeated for each consecutive set of values meeting these criteria.

3. Results

Fig. 2 represents a trial in which the sensor output had been determined during 6 days together with capillary blood glucose concentrations, and Fig. 3 represents the evolution of S and I_o during the time course of this trial. The value of S mirrored that of I_o . Furthermore, as shown on Fig. 4, by plotting I_o versus S , a strong correlation was observed ($I_o = 5.07 - (122 \times S)$, $r^2 = 0.7642$). Similar observations were obtained from the analysis of the other trials (data not shown), with a mean value of r^2 of 0.58 ± 0.08 (mean $\pm$ S.E.M., $n = 9$, including a case where there was no correlation between I_o and S , $r^2 = 0.09$).

4. Discussion

The two-point calibration procedure (Velho et al., 1988; von Woedtke et al., 1989) had been designed to avoid any assumption of the value of I_o , since the use of a one-point calibration assumes that I_o is negligible.

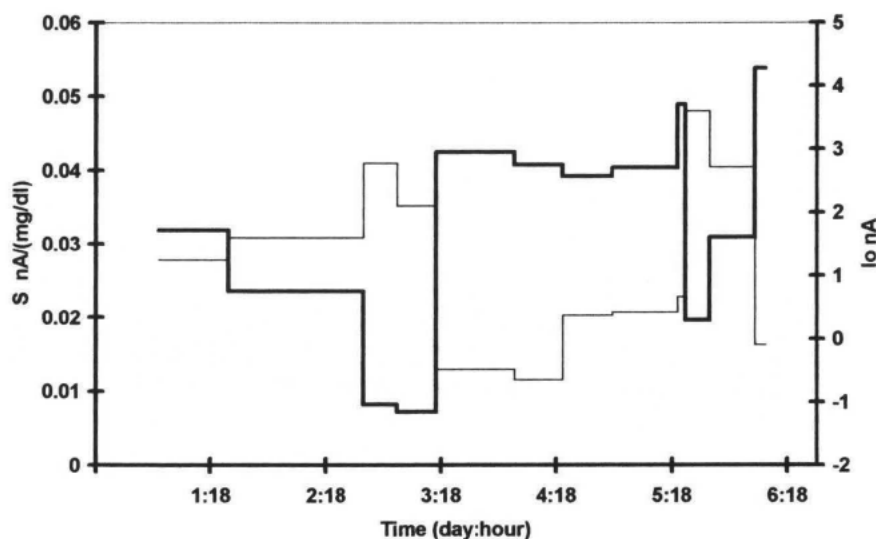


Fig. 3. Evolution of S (thin line) and I_o (bold line) determined from the trial shown in Fig. 2.

It is important to realize that the parameters S and I_o are not determined exclusively by the sensor sensitivity and the non specific current, i.e. the current related to interferences. Instead, they are mathematical operators describing the assumed linearity between the sensor output and the blood glucose concentration. For instance, Fig. 5 describes a situation in which a specific sensor response can apparently produce a non-zero value of I_o , linked to a measurement artifact during the two-point calibration procedure. The statistics of a straight line dictate that the precision (assuming a normal distribution) of both the measurements of the sensor response and the blood glucose translate directly into the precision of the slope of the line (the sensitivity) and the intercept (I_o). It is therefore expected that the precision of S and of I_o will be poorer in the case of a two-point calibration procedure because the variances of the two points are additive.

This can be shown by including the measurement errors (εg for G and εi for I) in equations describing the sensitivity and the background current

$$S = \frac{I_1 - I_2}{G_1 - G_2} \quad (1)$$

and

$$I_o = I_1 - \frac{I_1 - I_2}{G_1 - G_2} \times G_1 \quad (2)$$

The estimations S_{est} and $I_{o\text{est}}$ of S and I_o can be written as

$$S_{\text{est}} = \frac{(I_1 \pm \varepsilon i_1) - (I_2 \pm \varepsilon i_2)}{(G_1 \pm \varepsilon g_1) - (G_2 \pm \varepsilon g_2)} \quad (3)$$

and

$$I_{o\text{est}} = I_1 \pm \varepsilon i_1 - S_{\text{est}} \times G_1 \pm \varepsilon g_1 \quad (4)$$

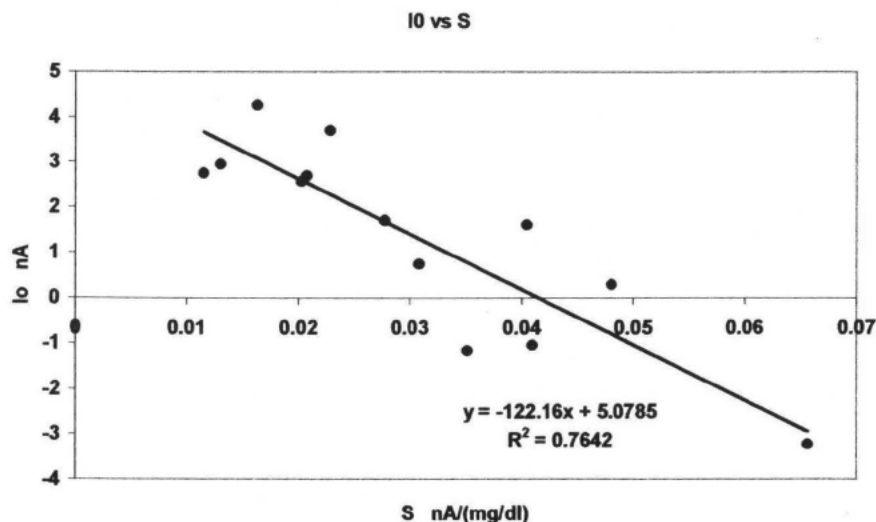


Fig. 4. Correlation between I_o and S .

Sensor output (nA)

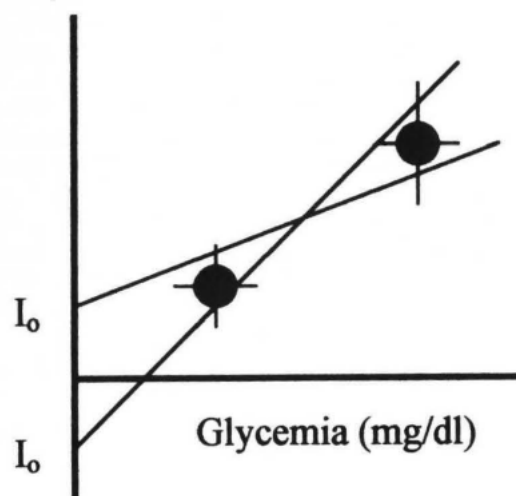


Fig. 5. Generation of a positive or of a negative value of I_o due to uncertainties on the determination of the sensor output and of glycemia, represented by horizontal and vertical uncertainty bars.

We demonstrated this relationship between I_{oest} and S_{est} by a simulation using a virtual sensor with a theoretical sensitivity of 0.03 nA/mg per dl and a theoretical background current of 2 nA. ε_g was assumed to be equal to $n \times G$ with n randomly distributed: $-0.05 < n \leq 0.05$ (5% error), and ε_i to $m \times I$ with m randomly distributed: $-0.1 < m \leq 0.1$ (10% error). One hundred values of $G1$ and $G2$ were randomly generated

between the following limits: $80 < G1 \leq 180$ mg/dl and $200 < G2 \leq 300$ mg/dl. S_{est} and I_{oest} were determined from Eqs. (3) and (4) described above. These estimations of I_o and S were found to be negatively correlated (Fig. 6); negative values of I_{oest} were also found like in the in vivo trials.

In conclusion, if I_o is not negligible, a two-point calibration procedure seems to be mandatory. Actually, as shown herein, errors in the measurement of capillary blood glucose concentration and in the determination of the sensor output can theoretically contribute to generate a significant value of I_o in addition to the obvious explanation, i.e. the presence of interferents or discrepancies between blood and subcutaneous glucose concentrations if the calibration measurements are performed under non-steady state conditions. In the companion paper, we show that I_o can actually be considered as negligible, and that the system can be calibrated using a one-point calibration procedure.

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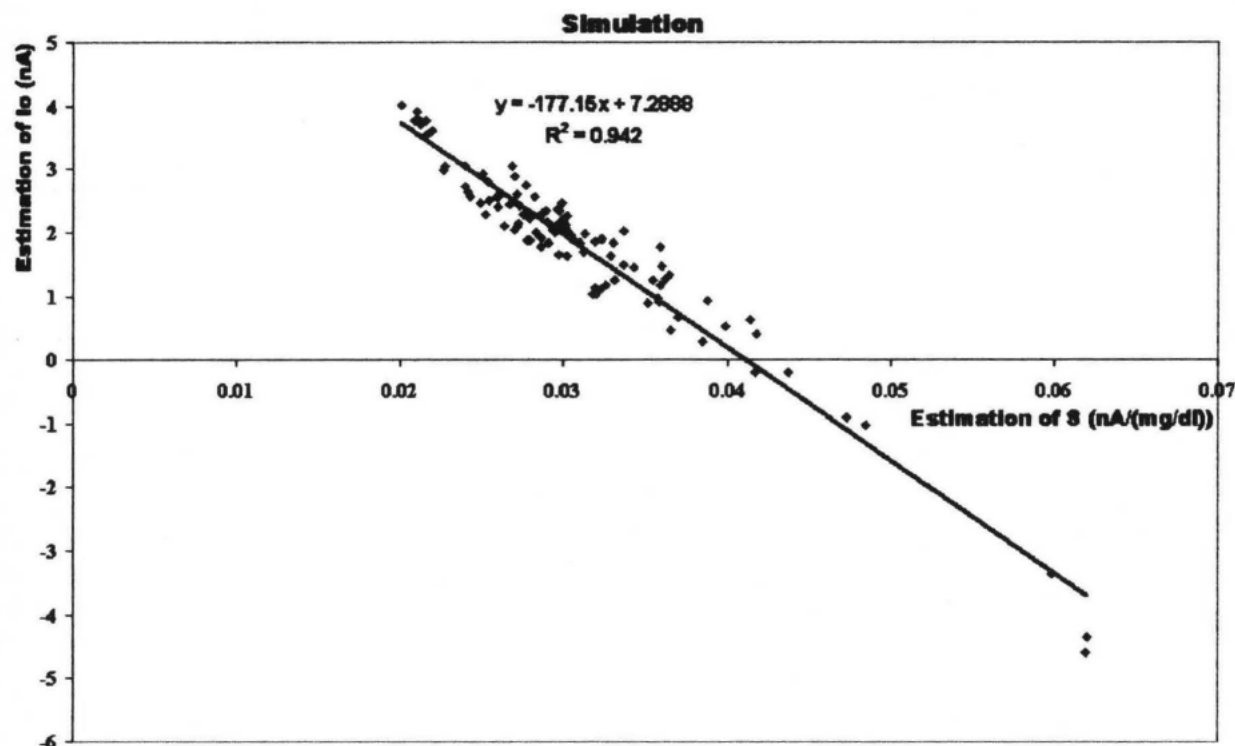


Fig. 6. Negative correlation between the estimations of I_o and S due to measurement uncertainties: simulation using a virtual sensor with a 0.03 nA/mg per dl sensitivity and a 2 nA I_o , and applying an error on glucose measurement of 5% and on sensor output of 10%. See text for details.

References

- Aussedat, B., Thomé-Duret, V., Reach, G., Lemmonier, F., Klein, J.C., Hu, Y., Wilson, G.S. 1997. A user-friendly method for calibrating a subcutaneous glucose sensor-based hypoglycaemic alarm. *Biosens. Bioelectron.* 12, 1061–1111.
- Aussedat, B., Dupire-Angel, M., Gifford, R., Klein, J.C., Wilson, G.S., Reach, G. 2000. Interstitial glucose concentration and glycemia: implications for continuous glucose monitoring. *Am. J. Physiol.* 278, E716–E728.
- Clark, L.C., Jr, Lyons, C. 1962. Electrode systems for continuous monitoring in cardiovascular surgery. *Ann. NY Acad. Sci.* 102, 29–46.
- Reach, G., Wilson, G.S. 1992. Continuous glucose monitoring for the treatment of diabetes mellitus: can an electrochemical approach fulfil the clinical requirements? *Anal. Chem.* 64, 381–386.
- Thomé-Duret, V., Moatti-Sirat, D., Reach, G., Zhang, Y., Hu, Y., Wilson, G.S. 1996. Modification of the sensitivity of glucose sensor implanted into subcutaneous tissue. *Diabetes Metab.* 22, 174–178.
- Velho, G., Froguel, P., Thévenot, D.R., Reach, G. 1988. In vivo calibration of a subcutaneous glucose sensor for determination of subcutaneous glucose kinetics. *Diabetes Nutr. Metab. Clin. Exp.* 1, 227–233.
- von Woedtke, T., Rebrin, K., Fischer, U., Abel, P., Wilke, W., Vogt, L., Albrecht, G. 1989. In situ calibration of implanted electrochemical glucose sensors. *Biomed. Biochim. Acta* 48, 943–952.