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Amperometric Glucose Sensors: Sources of Error and Potential Benefit of Redundancy

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Abstract

Amperometric glucose sensors have advanced the care of patients with diabetes and are being studied to control insulin delivery in the research setting. However, at times, currently available sensors demonstrate suboptimal accuracy, which can result from calibration error, sensor drift, or lag. Inaccuracy can be particularly problematic in a closed-loop glycemic control system. In such a system, the use of two sensors allows selection of the more accurate sensor as the input to the controller. In our studies in subjects with type 1 diabetes, the accuracy of the better of two sensors significantly exceeded the accuracy of a single, randomly selected sensor. If an array with three or more sensors were available, it would likely allow even better accuracy with the use of voting.

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Introduction

The commercialization of amperometric glucose sensors has significantly impacted the treatment of type 1 diabetes. Glucose sensors are now widely available as small, minimally invasive devices that measure interstitial glucose levels in subcutaneous fat. The ability to measure glucose levels every several minutes has not only improved the treatment of type 1 diabetes,[1,2] it has also launched research efforts into methods of automated glycemic management. The accuracy of present-day sensors, while generally good, remains imperfect. For this reason, the U.S. Food and Drug Administration does not allow the use of sensor data to make critical decisions regarding diabetes management without confirmation from standard capillary blood glucose readings. The success of closed-loop systems, which utilize sensor values in the determination of insulin delivery rates, will be improved by further enhancements of sensor accuracy. This commentary discusses the known causes of sensor inaccuracy and how the use of sensor redundancy might improve accuracy.

Sources of Sensor Inaccuracy

There are three major brands of glucose sensors on the U.S. market today: DexCom™ SEVEN® Plus, Medtronic Guardian®, and FreeStyle Navigator®. Although one study found substantial differences in accuracy among these devices,[3] later studies using updated versions of these devices found similar accuracy with each having mean absolute relative differences (ARD) of approximately 15%.[4,5] The fact that median ARD values are usually lower than mean ARD values underscores the finding

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Abbreviations: (ARD) absolute relative difference, (NASA) National Aeronautics and Space Administration, (NIH) National Institutes of Health, (ZMAD) Z score with median absolute deviation

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that a small number of sensors have very high ARD values, indicating substantial inaccuracy. Two situations of particular clinical importance include the ability of a sensor to (a) function well during hypoglycemia and (b) avoid overestimating glucose, which could lead to excessive insulin delivery and the development of hypoglycemia. Factors that may affect sensor accuracy adversely are numerous and include calibration error, sensor delay, and sensor drift. Each is addressed here.

Calibration Error

Amperometric glucose sensors estimate interstitial glucose values by measuring an electrical current generated by the reaction of glucose either with oxygen or with an immobilized redox mediator. Reference capillary blood glucose is input into the system for the purpose of calibration, which includes quantification of the sensitivity of the sensor to glucose. After calibration, the sensor current is used in conjunction with the sensitivity to estimate glucose values arithmetically. Not all of the current generated by the glucose sensor is specific to glucose. Typically, there is a small background current that is unrelated to the glucose level. This background current must be subtracted from the total current during calibration and during the process of estimating each unknown glucose level.

Glucose sensors require calibration at regular intervals, and accurate calibration is critical to sensor accuracy. The DexCom and Medtronic devices require calibration at least every 12 hours. The FreeStyle Navigator has a more complex calibration scheme. More frequent calibration of these devices likely improves accuracy, although there is a paucity of published data on this topic. The accuracy of the reference glucose measurement method,[6] the rate of glucose change during calibration, and the accuracy of the background current estimation all impact sensor accuracy and are potential sources of calibration error. The presumption of linearity in the setting of a nonlinear sensor response to glucose also adds to calibration error. In such a case, if calibration occurs at a low glucose level, but measurement of glucose takes place at a high level, the glucose value will be underestimated. Overestimation will result when calibration is carried out at high glucose values in the non-linear range and measurement takes place at lower values. The magnitude of error is greatest when the glucose level changes markedly between the time of calibration and the time of glucose measurement. This error magnification during marked glucose level change is also seen when the background current is estimated incorrectly.

Sensor Delay

Sensor delay is another important source of sensor inaccuracy and refers to the lag of the sensed interstitial glucose values behind blood glucose values. A small part of sensor delay is physiologic and accounts for the time it takes for glucose in the intravascular compartment to equilibrate with the interstitial compartment. Physiologic delay is now thought to be short and probably less than 5 minutes.[7] The delay inherent to the sensor itself and to data filtering and smoothing techniques, depending on the particular system, can be of greater magnitude. The time required for glucose to diffuse across outer sensor membranes into the enzyme layer and for hydrogen peroxide to reach the indicating electrode, when an inner membrane is present, contribute to sensor delay. If a sensor is calibrated during a rapid change in glycemia, the effect of sensor delay, if not accounted for, is magnified.

Sensor Drift

Although sensor drift is, to some extent, universal, it is poorly understood. In an attempt to better understand the phenomenon of drift and oscillation, we studied fully implantable subcutaneous sensor arrays, with each array having multiple indicating electrodes. During these studies in rabbits, half of the indicating electrodes were coated with glucose oxidase and the other half were uncoated. Over time, there was substantial drift of the coated electrodes, which also demonstrated electrical current oscillations with several dominant frequencies. Interestingly, in the uncoated electrodes, the output of which was only a background current, there was very little drift and very little oscillation.[8] Our interpretation of the findings was guided by the fact that the enzyme-coated electrodes, by design, respond to glucose and oxygen. The uncoated electrodes do not respond to either compound, but do respond to extraneous, nonphysiologic interference. Because oscillation and drift were seen almost exclusively in the enzyme-coated electrodes, we believe that changes in blood flow and oxygen provision, not extraneous interference, were likely to be a major source of the oscillations. It is known that there are regular cycles of vasoconstriction and vasodilation in the skin and subcutaneous tissue that participate in thermoregulation.[9] The role of changes in vascular tone on sensor current was studied by Gilligan and colleagues.[10] They found that administration of a vasoconstrictor drug reduced sensor output, despite the absence of a glucose change. Similarly, in unpublished data, we have observed that direct pressure over the site of an implanted sensor leads to a transient loss of current, likely due to a temporary reduction in blood flow.

It is likely that the presence of a foreign body creates a state of heightened inflammation. After sensor insertion, the measurement medium is not normal interstitial fluid, but rather interstitial fluid enriched with inflammatory cells, cytokines, and mediators. During the entire dwell time of a foreign body, macrophages are present and secrete many cytokines and signaling compounds. For the first few days, up to one week, there are also acute inflammatory cells such as neutrophils and eosinophils. Although not well studied, it is likely that some of these cells consume oxygen and glucose and produce compounds such as hydrogen peroxide. For these reasons, a foreign implant can perturb the apparent local glucose concentration in interstitial fluid. In the first several hours after sensor insertion, the signal is often unstable and more likely to be inaccurate. At later time points, collagen and other proteins are secreted into the extracellular matrix, due in part to the effect of transforming growth factor β1 and connective tissue growth factor,[11] which lead to a reduced diffusion of glucose into the sensor.[12–14]

Nitric oxide may also play a key role. For example, Gifford and associates[15] observed that changes in nitric oxide appear to affect sensor output and affect the magnitude of current drift. Although not yet peer reviewed, the Kreutzer group at the University of Connecticut reported a very interesting finding regarding mast cells at the 2009 American Diabetes Association scientific session. They presented data showing that mast cells, and released histamine, appeared to have a direct effect of reducing sensor current over time. When mast cells were stabilized with cromolyn, the loss of current was decreased. This finding may contribute to the phenomenon of biofouling, the deposition of material on the sensor surface, which tends to reduce sensor output over time.

Use of Multiple Sensing Units to Improve Accuracy

The causes and mitigations of suboptimal accuracy are complex and require further study. We address here the question of whether the use of two or more sensors yields better accuracy than one.

The concept of redundancy is not new. It has long been used in settings in which failure could be catastrophic. For example, many computer systems on National Aeronautics and Space Administration (NASA) spacecrafts are redundant and employ the concept of voting. Voting algorithms process multiple data streams and reject discrepant or outlying data. In this manner, the impact of a malfunctioning unit can be minimized. The occurrence of severe hypoglycemia in a person with diabetes is analogous to failure of the flight control system of a NASA spacecraft; both are life-threatening.

The use of two or more sensors in a closed-loop system is attractive for several reasons. From a practical standpoint, it provides a reserve device for cases of sensor or telemetry failure. In addition, depending on the specific sensor, when a new sensor is inserted, it must be in place for at least 2 to 10 hours before calibration can proceed and sensed glucose readings are provided. If the only sensor in place fails, one must wait 2 to 10 hours for the new sensor to stabilize.

The concurrent use of two sensors in an individual also increases the chance of at least one being highly accurate. We routinely use two sensors concurrently in our closed-loop studies and choose the more accurate one to provide input to the controller. From recent closed-loop data, we prepared two figures. These figures illustrate sensor data in different individuals with type 1 diabetes, each of whom wore two sensors. In both figures, the sensor is calibrated only once, at the beginning of the study. **Figure 1** represents a situation in which the two sensors track each other very closely over the 9-hour period. The situation in **Figure 2** is quite different. In this case, sensor 2 (the higher tracing) tracked blood glucose quite well and had a mean ARD of 11.7%, whereas sensor 1 functioned poorly with a mean ARD of 24.8%. In a closed-loop system, this degree of inaccuracy would affect the rate of insulin delivery substantially. If the less accurate sensor were used in this case, it would have led to inadequate delivery of insulin with subsequent hyperglycemia. Fortunately, sensor 2 was used for the vast majority of this study to control the insulin delivery rate, and good glycemic control was achieved.

There are several potential ways of using data from more than one sensor, and this topic has not been well studied. Using the average of two signals is not always the optimal method because if one sensor is performing very poorly, the average is also inaccurate to some extent. Another option is to compare the two sensor signals and avoid using sensor data when the two signals are discrepant beyond a specified criterion. This method was examined by Schmidtke and colleagues[16] several years ago. This technique significantly improved the number of glucose readings in regions A and B of the Clarke error grid from 92.4 to 98.8%. Of course, in a closed-loop setting, the choice to avoid using either sensor deprives the controller of afferent input.

In order to address possible advantages of sensor redundancy, we examined the last year of data from our human closed-loop study. Given this study has not yet been completed and data have not yet been submitted for peer review, our findings are presented in general form. During each study, subjects with type 1 diabetes wore two sensors for 28 hours. Early in the course of the study, the more accurate of the two sensors was selected for the control of insulin and glucagon delivery. The accuracy of both sensors was followed for the duration of the study and was compared to venous glucose performed every 10 minutes on the highly accurate HemoCue® analyzer. Each sensor was calibrated at the start of the study and again 4 hours later. The "selected" sensor had a mean ARD of 14%, which was significantly lower when compared to the unselected sensor, with a mean ARD of 19%. In approximately 65% of subjects, the mean ARD of the two sensors were within four mean ARD percentage points of each other and close to 75% were within seven points of each other. Thus, in approximately 25% of cases, there was a large discrepancy in accuracy that exceeded seven mean ARD percentage points. The accuracy difference in this group of individuals would have led to substantial differences in the amounts of insulin and glucagon given by the algorithm, depending on which sensor was used. These findings support the use of two sensors in settings where accuracy is critical. We also found that in over 80% of cases, the sensor that was selected early continued to be the more accurate of the two throughout the remainder of the 28-hour study. In the small number of cases in which this was not the case, the overall difference in accuracy between selected and unselected sensors was less than 1.5 mean ARD percentage points.

Although wearing three or more sensors is impractical with current sensor technology, sensor arrays with multiple sensing units may be available in the future. The advantage of three or more sensors lies in the ability to "vote out" data from one or more sensors when the reading is discrepant from the others. This technique is based on the fact that sensor signals that are quite similar to others in the array are usually almost always more accurate than outliers. In animals, we tested such a technique using a statistical technique termed the Z score with median absolute deviation (ZMAD), which is based on median statistics. The subcutaneous sensor arrays contained four sensing units, each with its own platinum indicating electrode and its own telemetric channel. The Ag/AgCl reference electrode was shared among the four sensing units. A Z score for each sensing unit was calculated every several minutes. This score

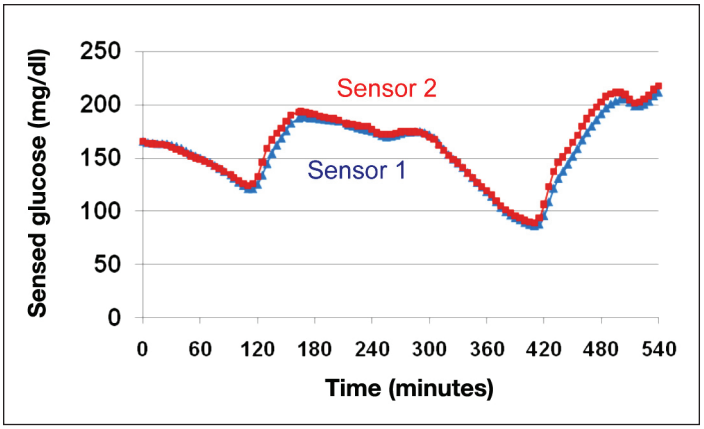

Figure 1. Two subcutaneous sensors in a person with type 1 diabetes undergoing closed-loop control. Blue symbols indicate data from sensor 1, and red symbols indicate data from sensor 2. Note that the two sensors track each other very well; the tracings are nearly superimposable. Sensors were calibrated once at the onset of the study.

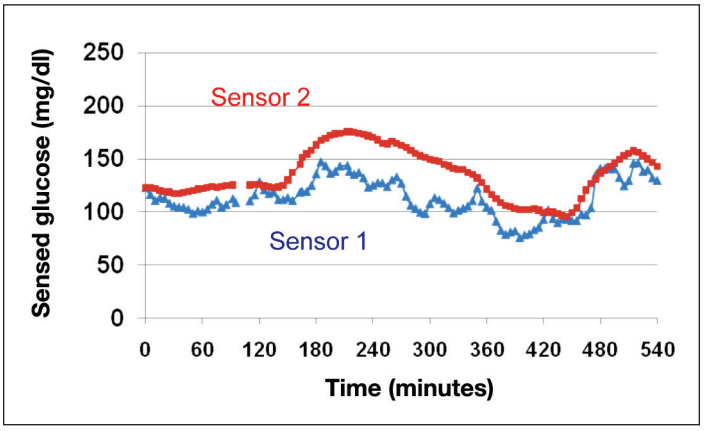

Figure 2. Two subcutaneous sensors in a person with type 1 diabetes undergoing closed-loop control. Blue symbols indicate data from sensor 1, and red symbols indicate data from sensor 2. Note that the two sensors track each other poorly. Sensor 1 registered low glucose values at times that sensor 2 and reference glucose were normal. Sensors were calibrated once at the onset of the study.

compared how much the sensed glucose from one unit deviated from the median sensed glucose of all units. If the Z score rose above a predetermined threshold, then data from that unit were considered an outlier and were therefore automatically excluded. This technique can be employed in real time. During long-term implantations, sensor array accuracy using the ZMAD technique was significantly and substantially better than using an average of the sensed glucose values.[17]

The use of redundant sensors addresses sensor drift, but does not address sensor delay. Delay, which is influenced by physiologic elements, inherent sensor properties, and data filtering, is expected to affect all sensors similarly. In a similar fashion, if all sensors in an array are similarly

affected by calibration error, such as nonlinearity or miscalculation of background current, redundancy would be unlikely to improve accuracy.

Conclusion

Most sensors are reasonably accurate. Causes of sensor error include drift, calibration error, and delay of the interstitial sensor value behind the blood value.

Use of at least two sensors in situations where the accuracy of sensor data is critical has several potential advantages over use of a single sensor. In contrast, when the first and second sensors have similar accuracy, there is no need for the second device. In a substantial minority of cases, the degree of accuracy in the two devices is discrepant and can be markedly so in rare cases. In these cases, great benefits are realized by the use of more than one device, accompanied by a short early period of observation, after which the better device is chosen. Generally, when there is a discrepancy, the more accurate sensor remains so for a prolonged period. To the extent that an array with many sensing units becomes available, a voting scheme using three or more units would be expected to lead to a further improvement in accuracy.

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