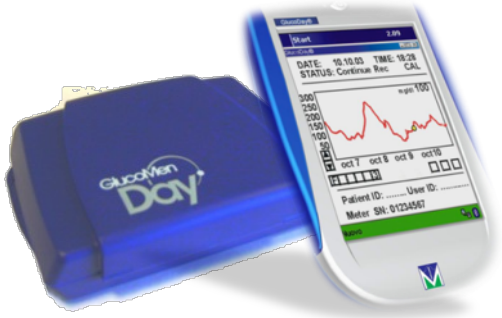

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Overview of Commercially Successful Implantable Glucose Sensors

Key Features and Requirements for Performance, Safety and Reliability

F. Valgimigli PhD

Head of Technology and Scientific Affairs
A. Menarini Diagnostics srl
Florence, Italy

SPIMD 2011 - Lausanne- April 1st, 2011

Background

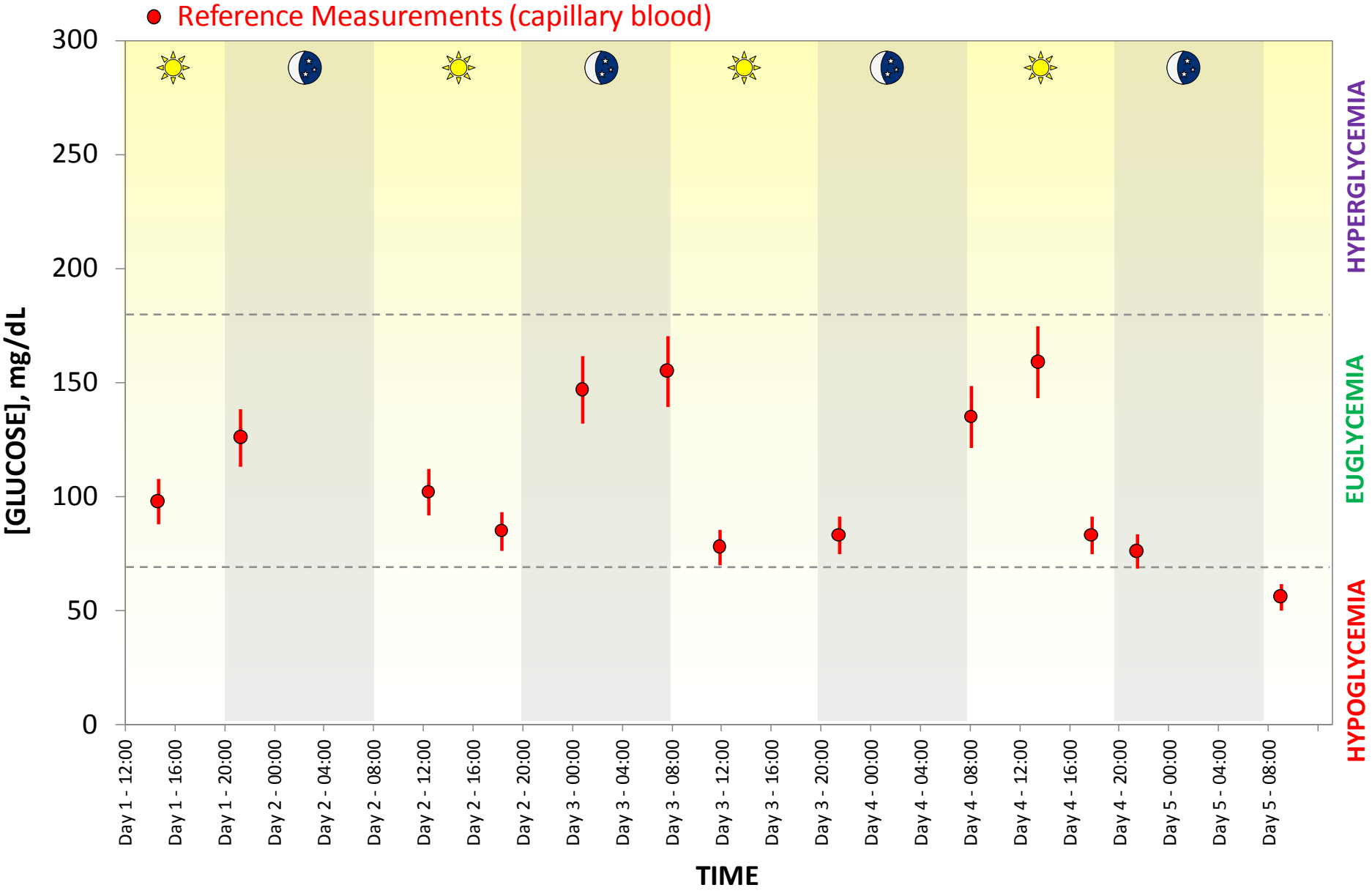
Diabetes mellitus (DM) is a metabolic disorder in which the blood glucose levels fluctuate outside the normal range as a result of underproduction or underutilization of the hormone insulin.

Diabetes is classified into two types, namely, type 1 diabetes mellitus (T1DM), which results from underproduction of insulin as result of loss of insulin-producing beta cells in the pancreas, and type 2 diabetes (T2DM), which is due to underutilization of insulin produced in the pancreas.

Background

There are currently about **230 million** diabetes patients around the world, out of which approximately 90% have T2DM. Complications arising from diabetes can be both acute and long term and include hypoglycemia, ketoacidosis, coma, renal failure, amputations, neuropathy, and retinal damage. By 2025 IDF estimates there will be more than 300 million people with DM.

In the last decade Glucose Sensing Technology became the major research focus in diabetes management area, and a major arena of industrial competition.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250
200
150
100
50
0
[GLUCOSE], mg/dL
HYPERGLYCEMIA
EUGLYCEMIA
HYPOGLYCEMIA
Day 1 - 12:00
Day 1 - 16:00
Day 1 - 20:00
Day 2 - 00:00
Day 2 - 04:00
Day 2 - 08:00
Day 2 - 12:00
Day 2 - 16:00
Day 2 - 20:00
Day 3 - 00:00
Day 3 - 04:00
Day 3 - 08:00
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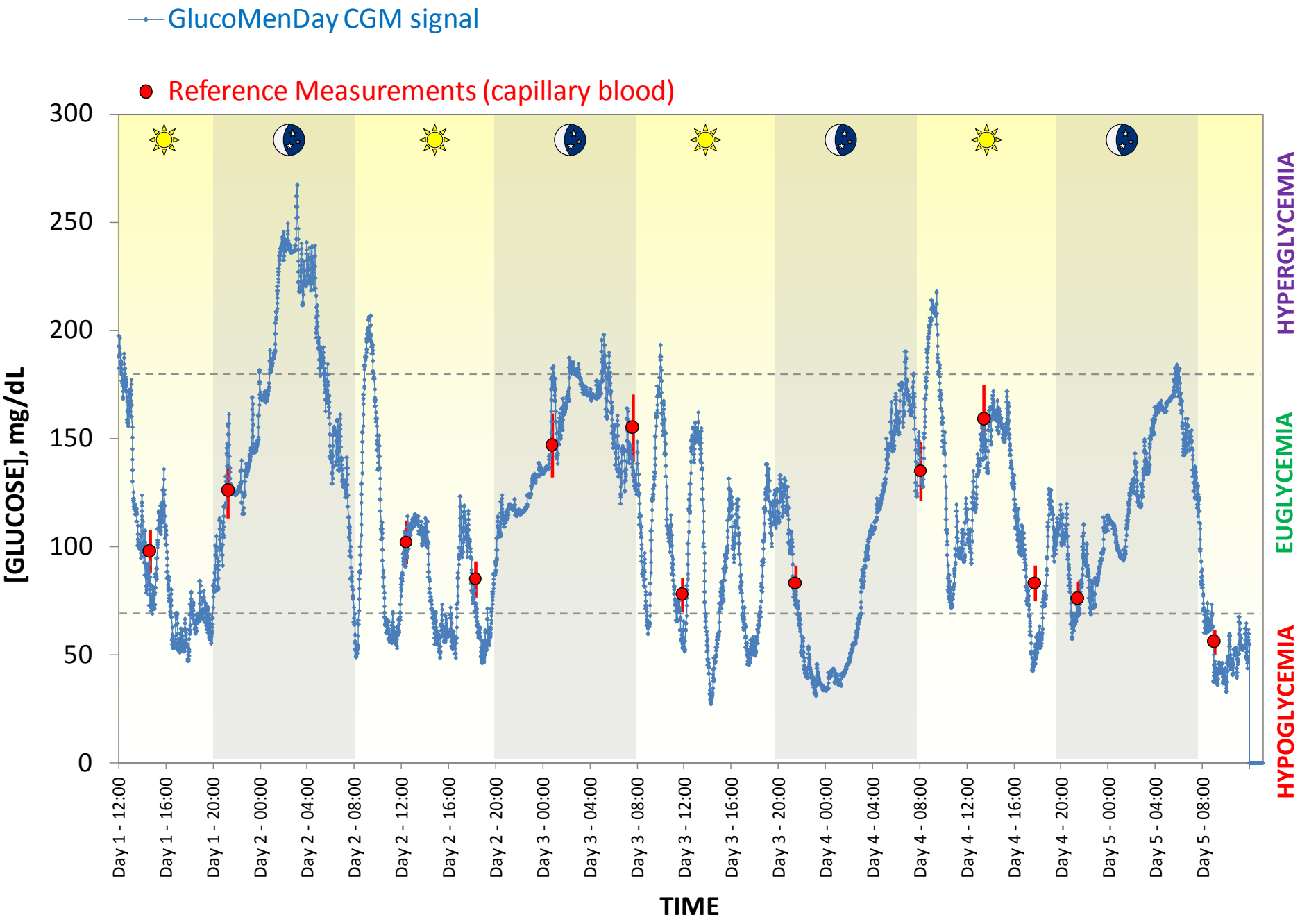
TIME


GlucoMenDay CGM signal
Reference Measurements (capillary blood)
[GLUCOSE], mg/dL
300
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HYPERGLYCEMIA
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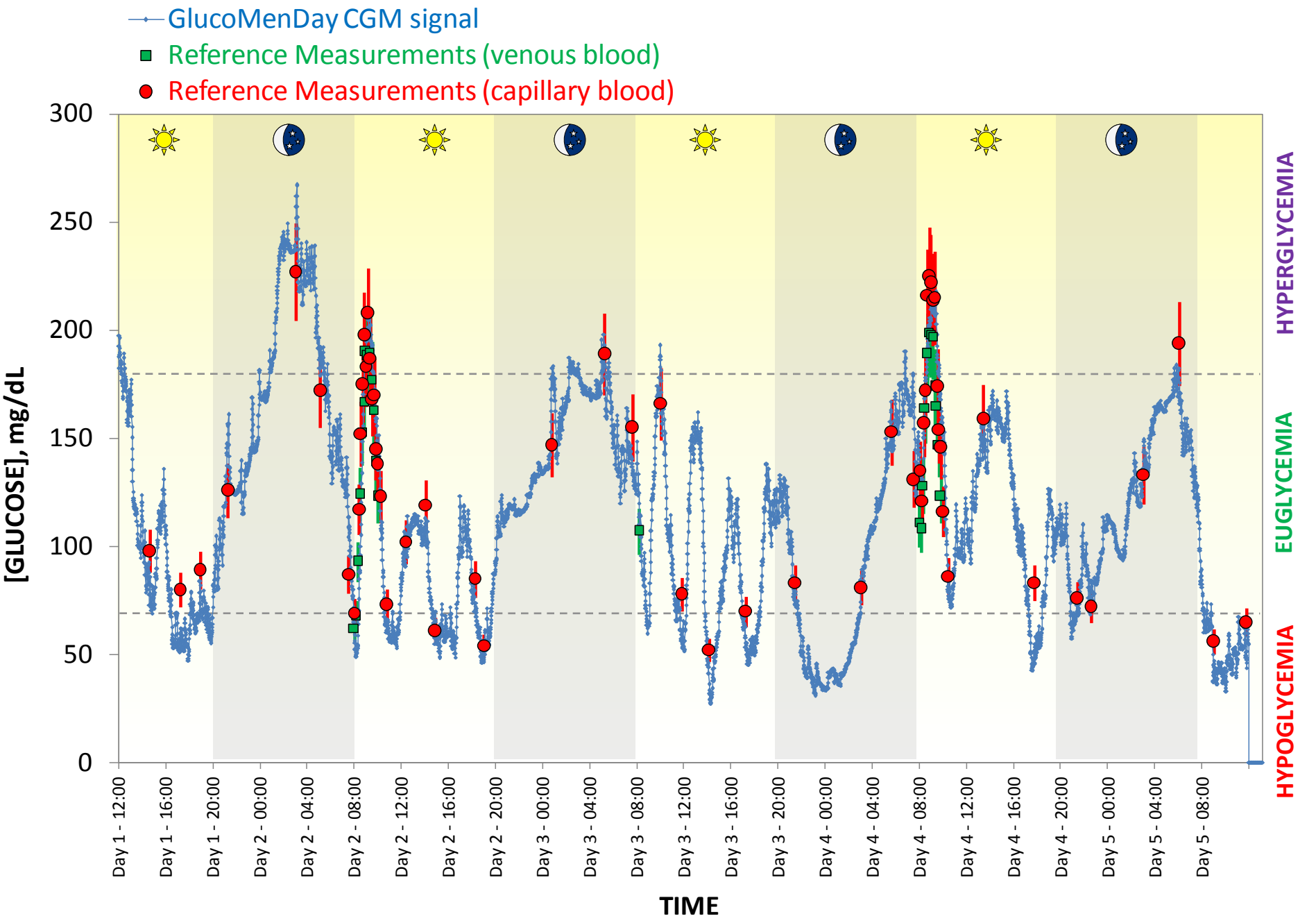
GlucoMenDay CGM signal
Reference Measurements (venous blood)
Reference Measurements (capillary blood)
[GLUCOSE], mg/dL
300
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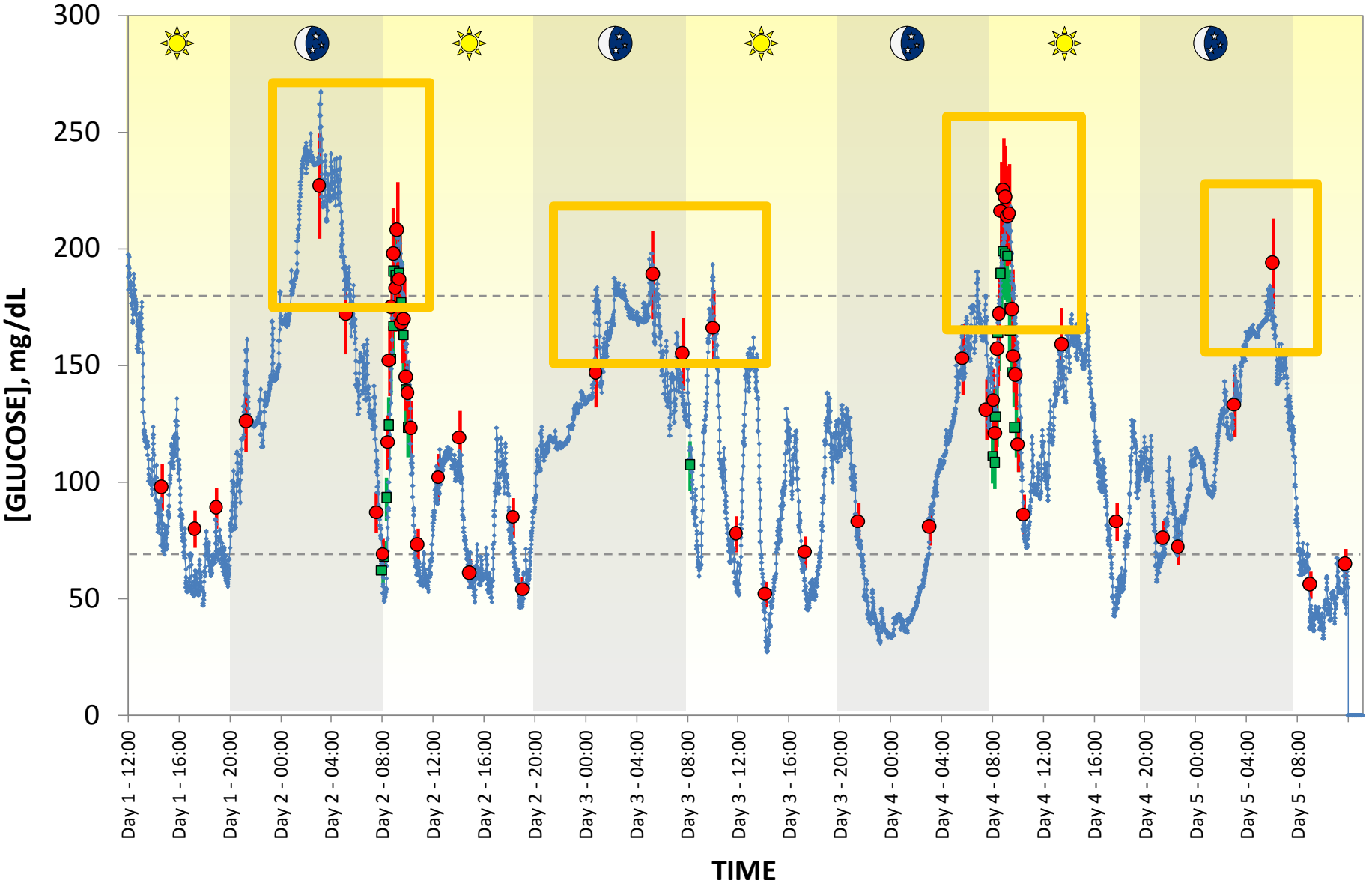
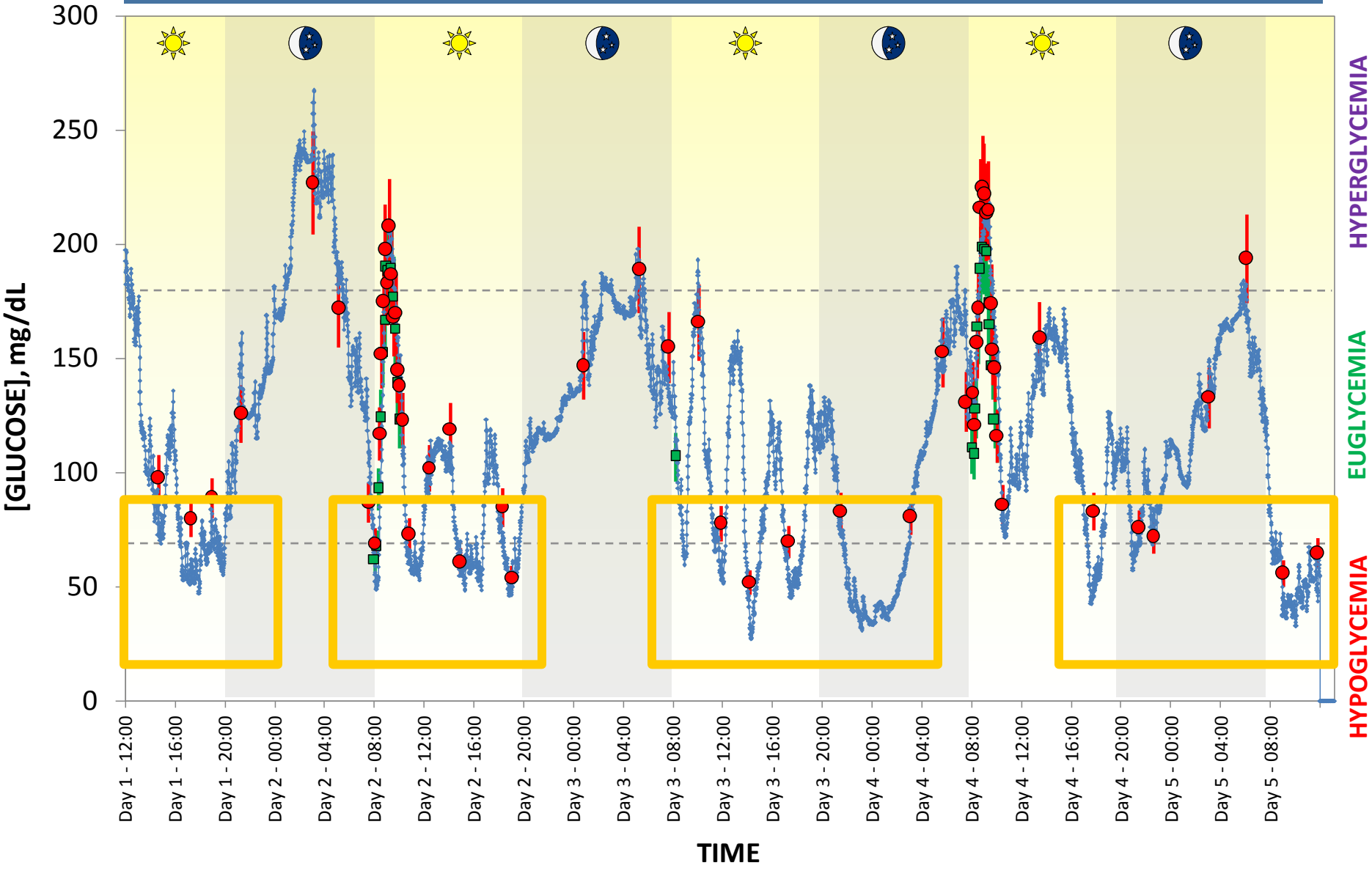
Day 5 - 08:00
TIME

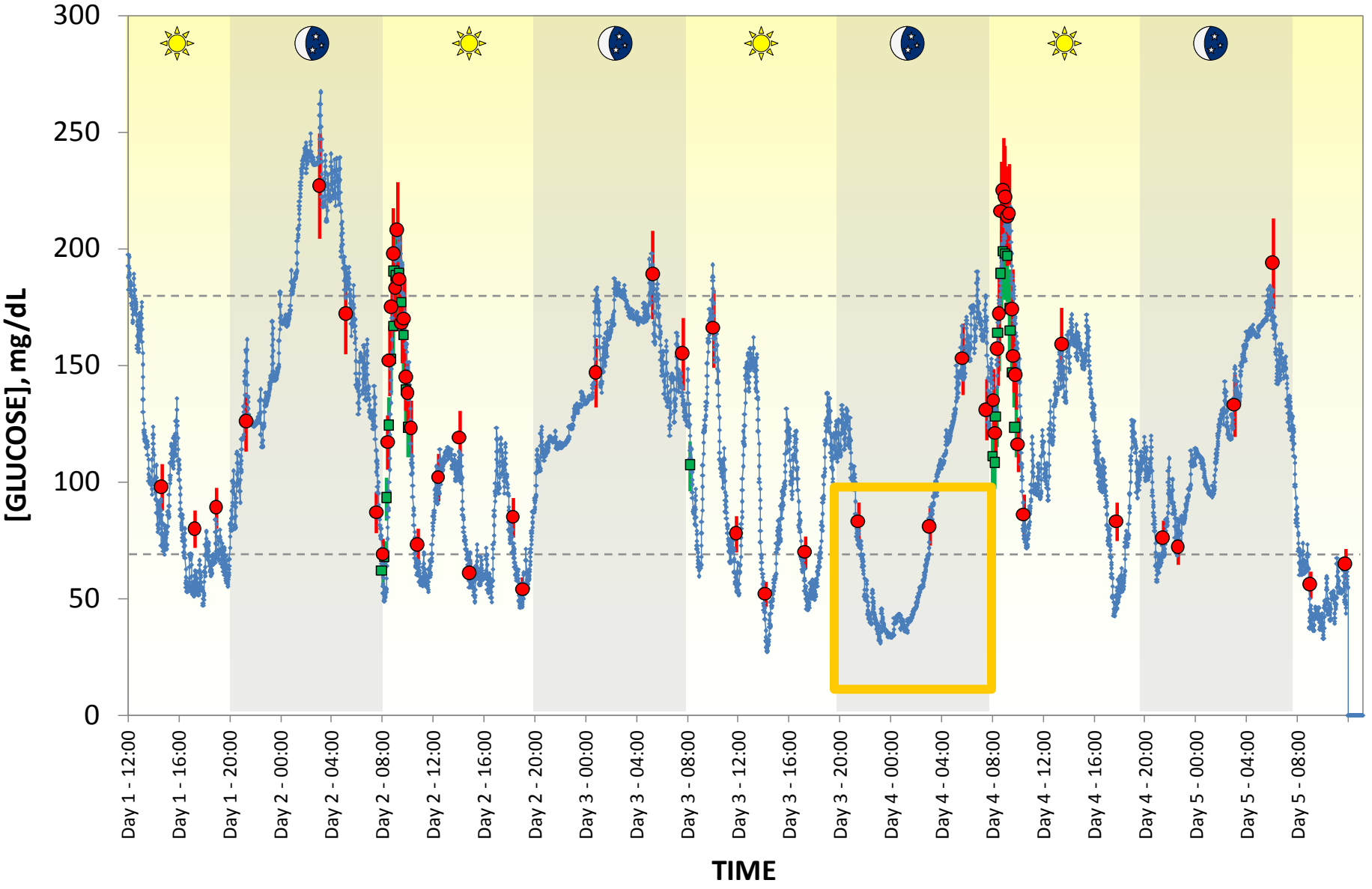
Hyperglycemia Events



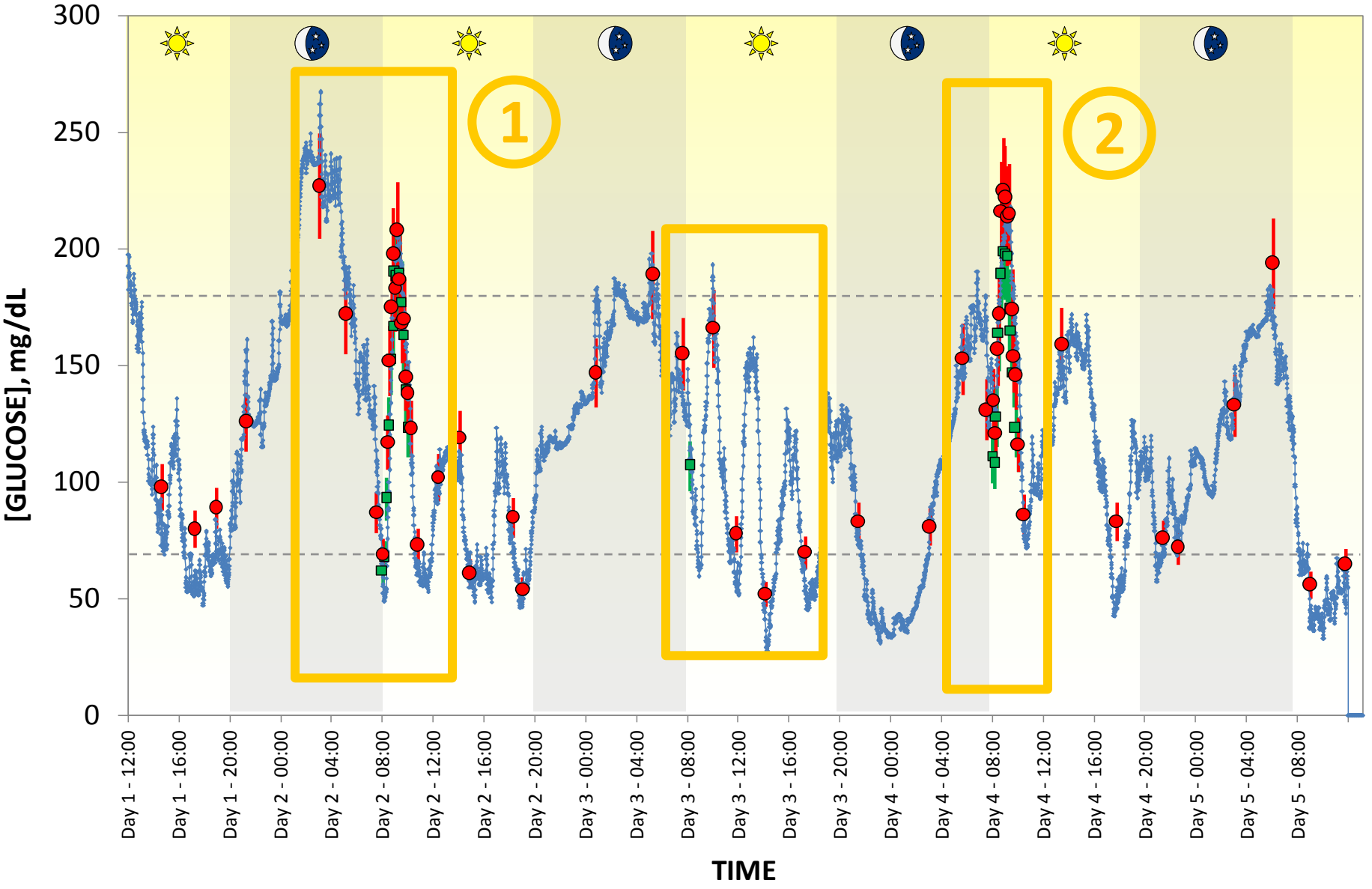
Hypoglycemia Events



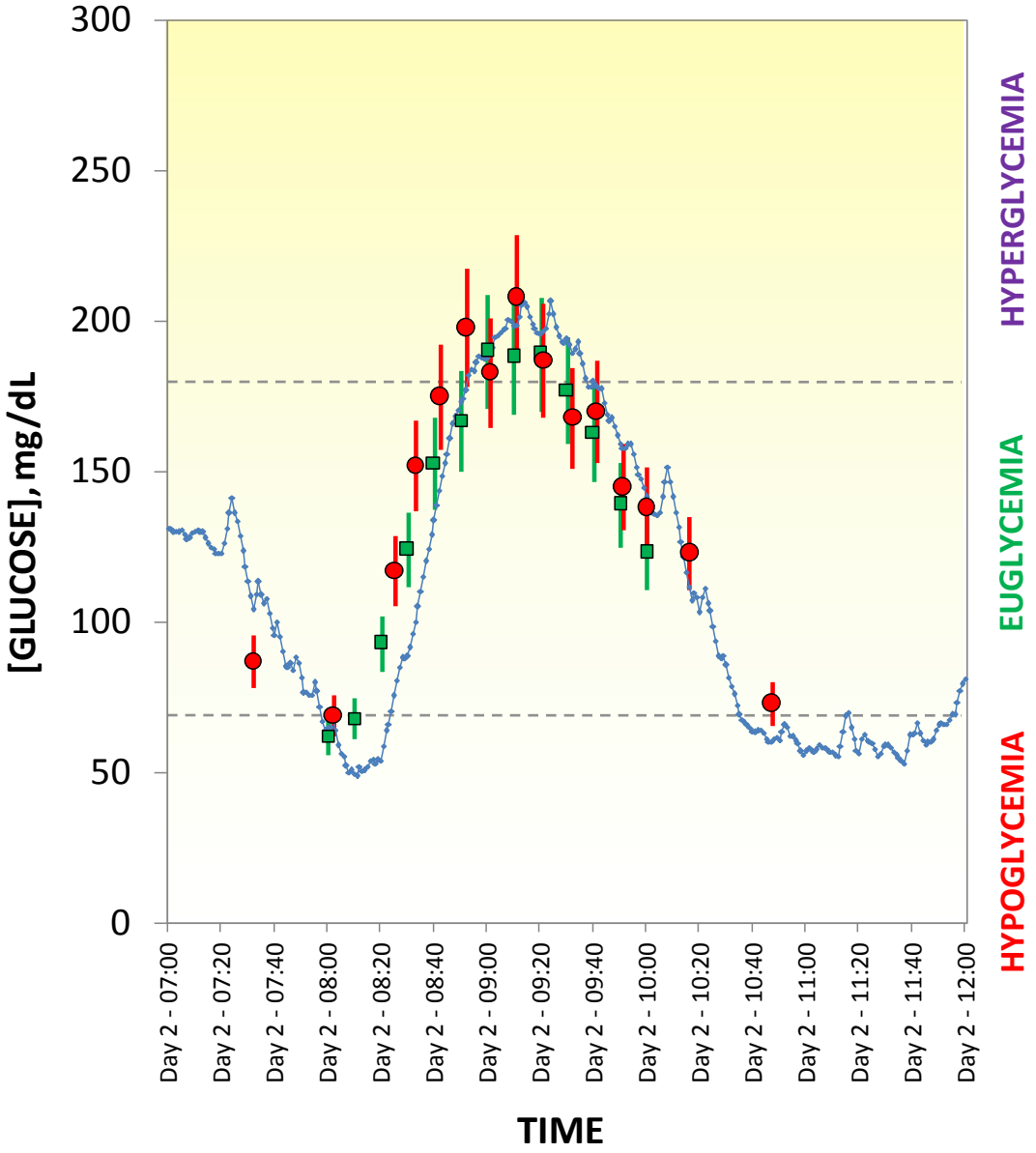
Nocturnal Hypoglycemia



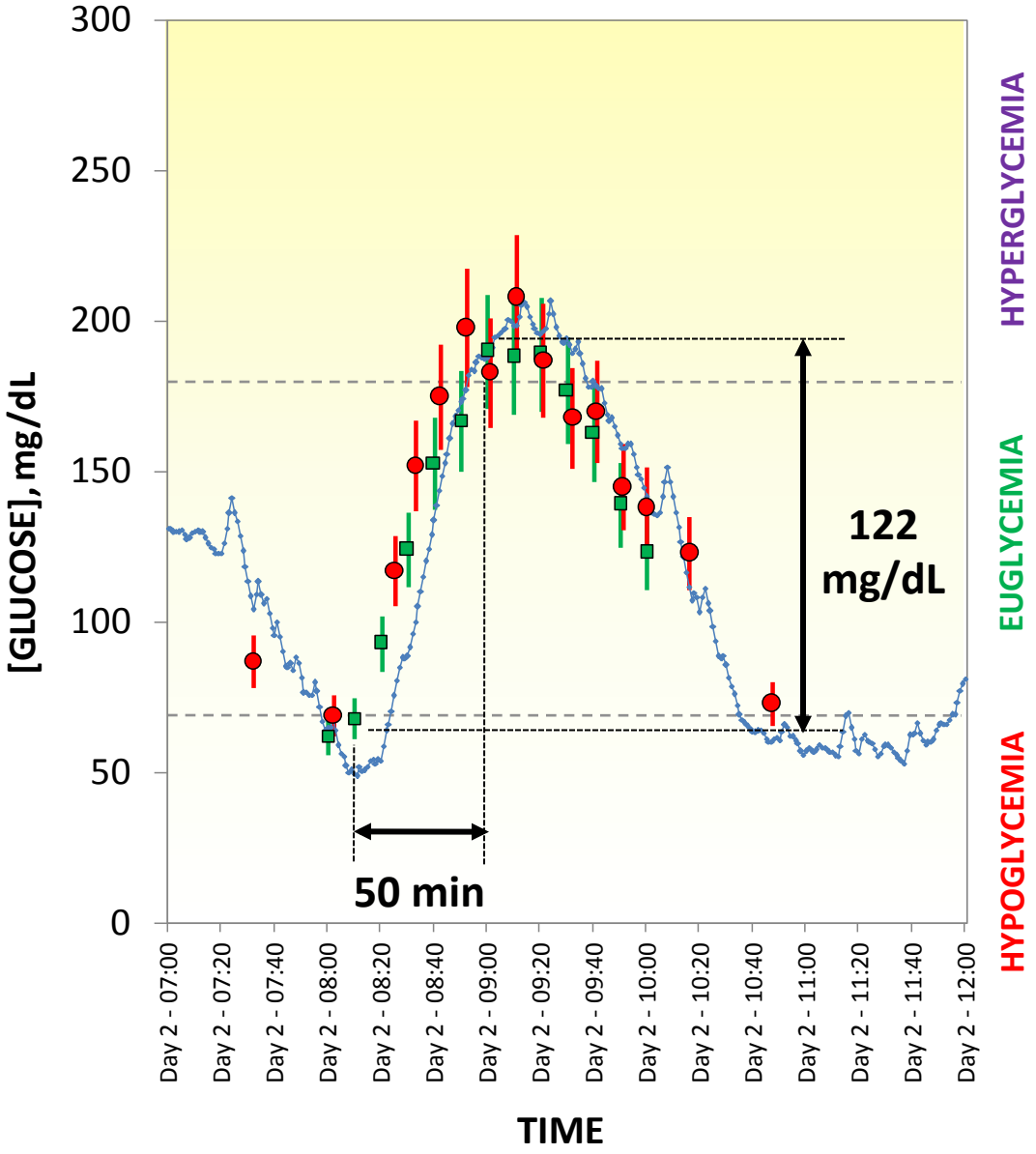
Rapid Glycemic Excursions

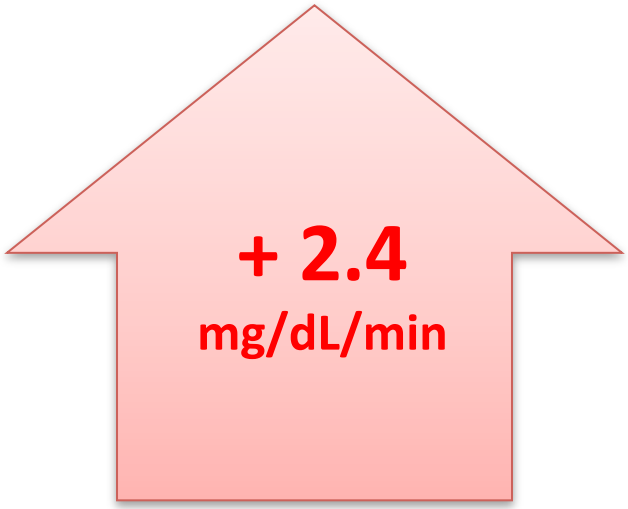


Rapid Glycemic Excursions

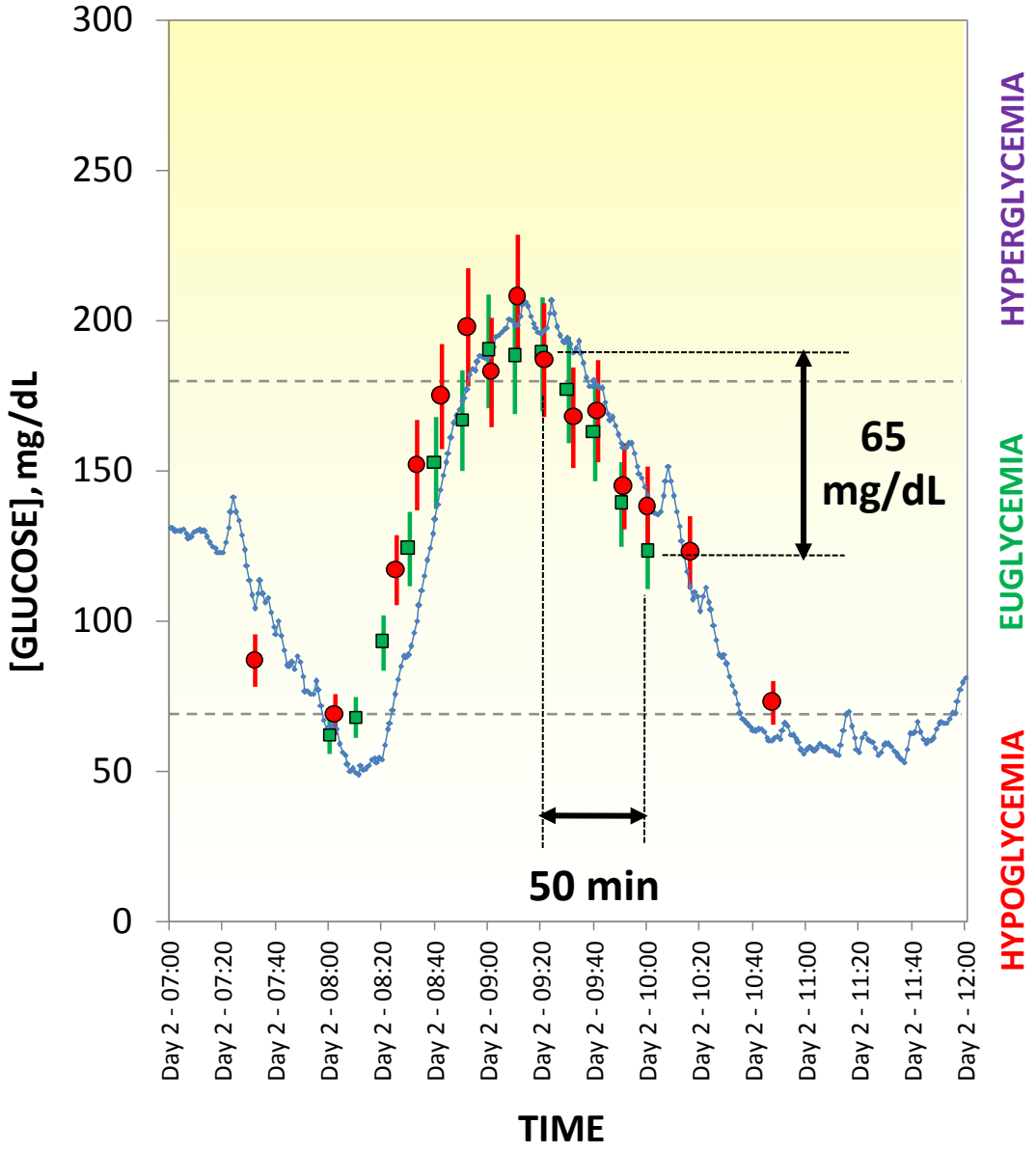


Rapid Glycemic Excursions





Rapid Glycemic Excursions



+ 2.4
mg/dL/min

- 1.3
mg/dL/min

List of Topics

- The Amperometric Biosensor for Self Monitoring of Blood Glucose (SMBG) in diabetic patients: the winning technology to achieve Reliable Glucose Readings

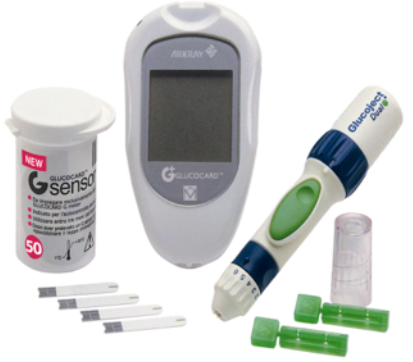
- Evolution toward Implantable Continuous Glucose Sensors: Key factors of a successful CGMs and engineering challenges

- Continuous Glucose Sensors as Heart of future strongly demanded Clinical Applications: Tight Glycemic Control (TGC) in ICU and Artificial Pancreas (AP)

- Next decade market expectations for Implantable Glucose Sensors

Self Monitoring of Blood Glucose (SMBG)

- SMBG permits to control excursion targets especially in T1DM



- Test frequency may vary from 2 times/week to 7 times/day

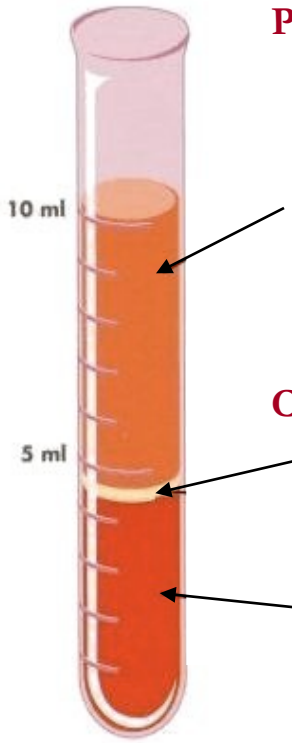
- Glucose meters measure the concentration of D-glucose (dextrose monohydrate) by a variety of methods (mainly electrochemistry), but all require the delivery of a drop of capillary blood on to a reagent strip (Glucose Biosensor) that is inserted into the meter for measurement.

- Achieving clinically acceptable accuracy and precision with SMBG is of key importance for optimal glucose control and management of the therapeutic protocol.

Blood: target substance + interferents

Blood is the specialised bodily fluid that delivers all necessary substances (i.e., nutrients and oxygen) to the body's cells and transports away the waste products.

Whole blood is composed of *blood cells* suspended in a liquid called *blood plasma*.



Plasma - 55% of total blood volume

91% water
7% blood proteins (fibrinogen, albumin, globulin)
2% nutrients(aminoacids, sugars, lipids)
hormones (erythropoietin, insulin, etc.)
electrolytes (sodium, potassium, calcium, etc.)

Cellular components - 45% of total blood volume

Buffy Coat
White Blood Cells (or leukocytes, about 8.000/mm^3)
Thrombocytes (or platelets, about 300.000/mm^3)

Red Blood Cells (or erythrocytes, about 5.000.000/mm^3)

Essential Rquirements for SMBG Detection Technology:

- Specificity
- Reading time
- Immunity to interferents
- Linearity in the range 20-600 mg/dl
- Accuracy vs. Plasma reference
- Shelf-life of the biosensor

Interferences at the Electrode level: Hematocrit
(blood volume occupied by erythrocytes)

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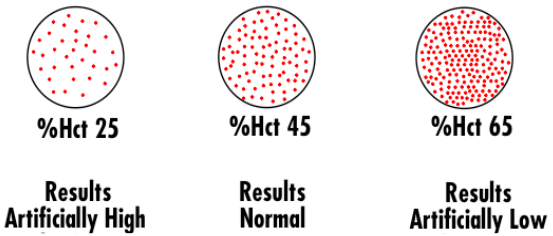
Both unusually low and unusually high **hematocrit (Hct) levels** can compromise the accuracy of blood glucose quantitation.



Hct { 38 - 52% males
37 - 47% females

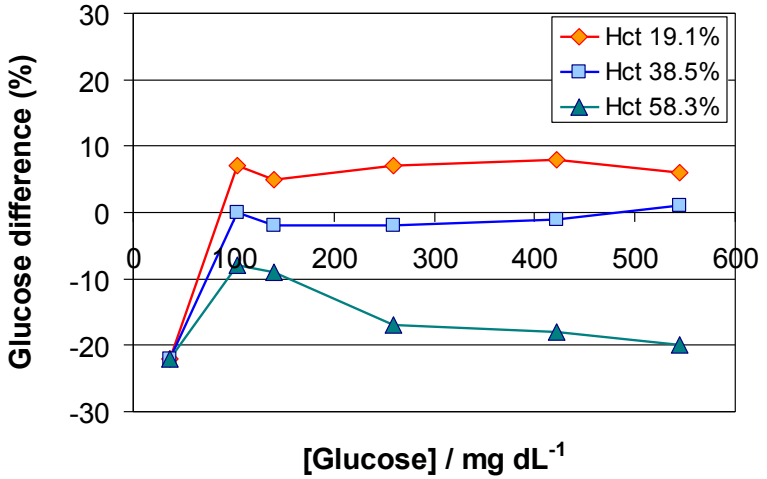


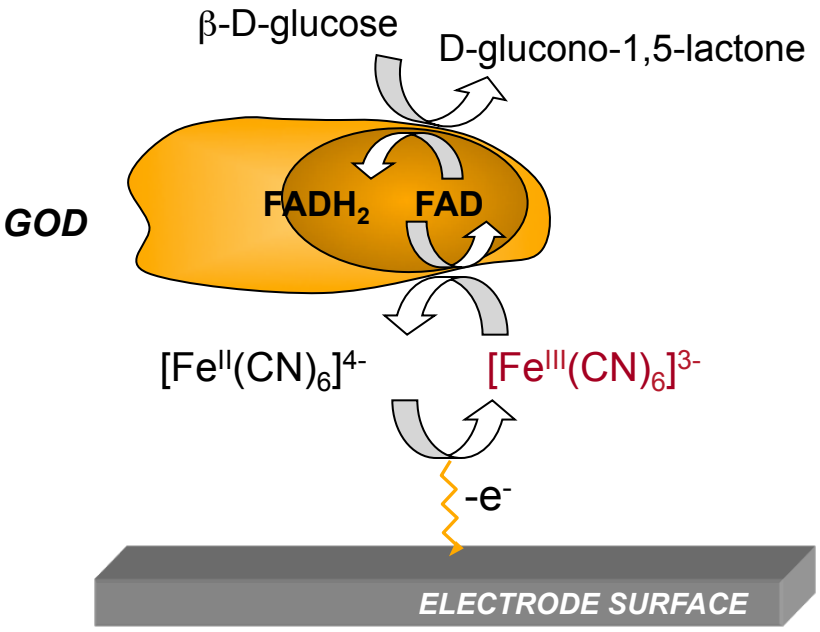
Figure. *Influence of hematocrit on the response of blood-glucose strips: constant Hct levels vs. variable glucose concentration.**

* From: *Tang A, Du X, Louie RF, Kost GJ : Effects of drugs on glucose measurements with handheld glucose metes and a portable glucose analyser. Am J Clin Pathol 113: 75-86, 2000.*

Typical list of Interferents

Glucose Level	3.9 mmol/L (70 mg/dL)	13.3 mmol/L (240mg/dL)
Acetaminophen	7 mg/dL	35 mg/dL
Ascorbic acid	3 mg/dL	6 mg/dL
Bilirubine	13 mg/dL	36 mg/dL
Cholesterol	2500 mg/dL	2000 mg/dL
Dopamine	23 mg/dL	30 mg/dL
Ephedrine	4 mg/dL	4 mg/dL
Galactose	1700 mg/dL	700 mg/dL
Gentisic Acid	6 mg/dL	25 mg/dL
Ibuprofen	100 mg/dL	120 mg/dL
L-Dopa	750 µg/dL	300 µg/dL
Methyl-Dopa	2 mg/dL	7 mg/dL
Salicylate	150 mg/dL	200 mg/dL
Tetracycline	200 mg/dL	200 mg/dL
Tolazamide	100 mg/dL	240 mg/dL
Tolbutamide	100 mg/dL	300 mg/dL
Triglycerides	3000 mg/dL	2000 mg/dL
Uric Acid	9 mg/dL	12 mg/dL
Creatinine	1000 mg/dL	3000 mg/dL
Urea	500 mg/dL	1200 mg/dL
Sodium Citrate	400 mg/dL	400 mg/dL
Sodium Heparin	3000 IU/dL	3000 IU/dL
Fetal Bilirubin	10 mg/dL	10 mg/dL
Lactose	2000 mg/dL	3500 mg/dL
Maltose	3600 mg/dL	2400 mg/dL
Xylitol	350 mg/dL	800 mg/dL
Xylose	3000 mg/dL	3000 mg/dL
Galactose	1700 mg/dL	700 mg/dL
Fructose	1000 mg/dL	1500 mg/dL
Mannose	800 mg/dL	1500 mg/dL
Sorbitol	3000 mg/dL	3000 mg/dL

Electrochemical glucose detection based on enzymatic "redox mediated" reaction



Mediator-assisted bio-electrochemical oxidation of glucose (GOD-based glucosensor).

I) A "redox" reagent is used as the final electron acceptor instead of oxygen;

II) This reagent shuttles the electrons from the active site of the enzyme to the electrode surface where an electrical current is generated.

Glucose/gluconolactone: E'° = - 0.320 V

$FAD/FADH_2$: E'° = + 0.030 V

$[Fe^{III}(CN)_6]^{3-}/[Fe^{II}(CN)_6]^{4-}$: E'° = + 0.360 V

Electrode surface: E ≥ + 0.360 V

e^-

(second-generation glucose biosensors)

First generation ("Oxigen-mediated") glucose biosensors

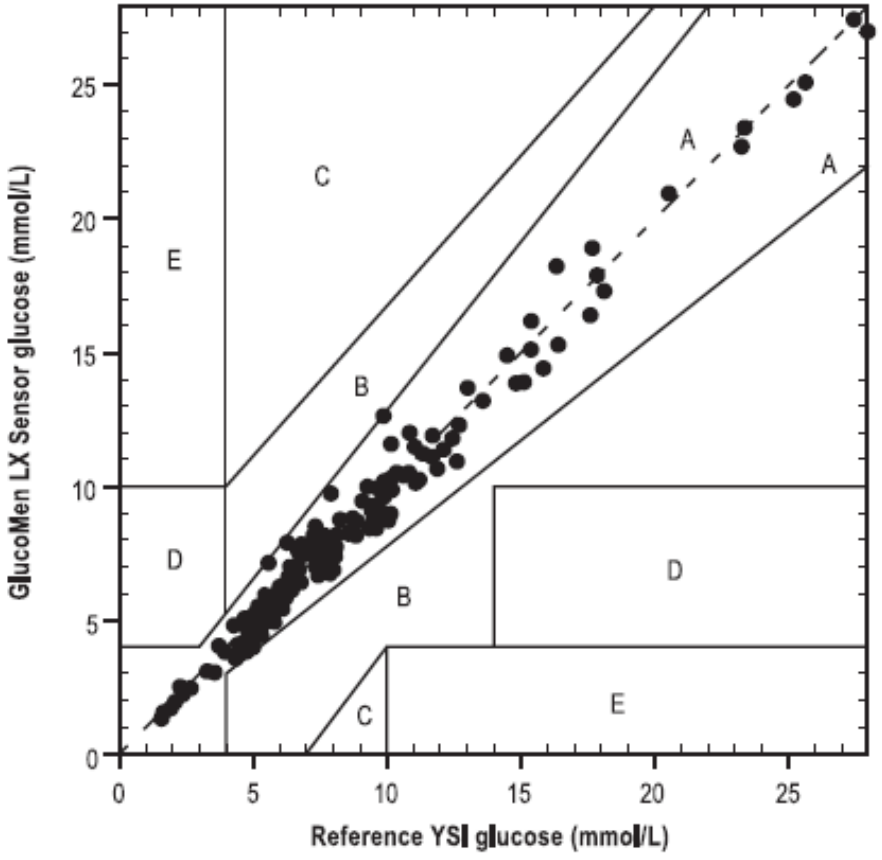
- as in nature, O_2 is used as the electron acceptor for regenerating the active form of the enzyme;
- the electrical response arises from the oxidation of H_2O_2 (product of the enzymatic reaction)

Second generation ("Redox-mediated") glucose biosensors

- a "redox" reagent acts as the electron acceptor;
- the reagent shuttles the electrons from the active site of the enzyme to the electrode surface

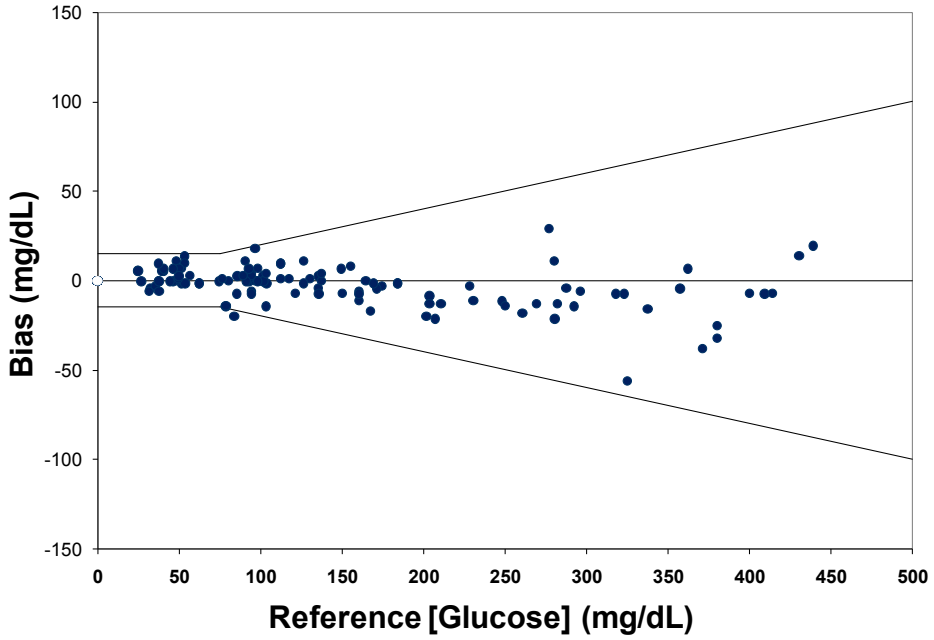
The second generation amperometric biosensor is succesfully applied in current state-of-the-art SMBG devices

Clinical Accuracy (Clarke - Error Grid Analysis)



Study on SMBG system (Bias plot)

(Lab. Fanfani, Florence-April 2010)



n. of patients = 120

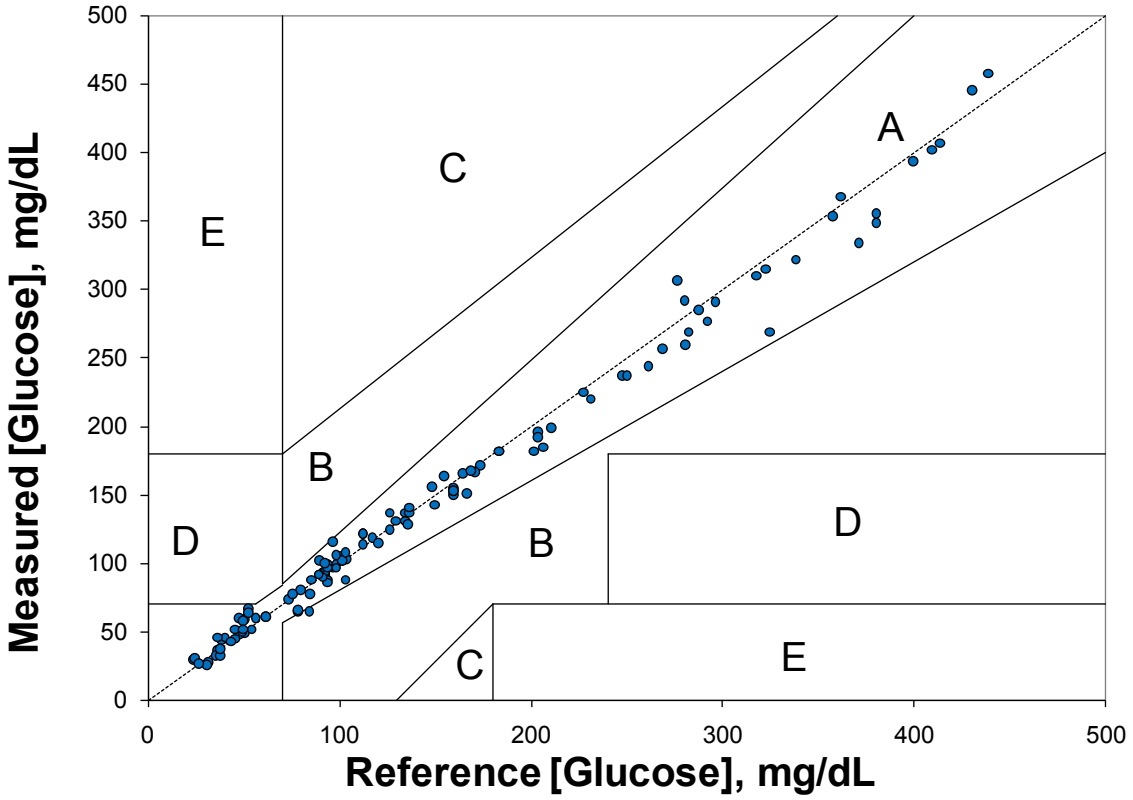
Accuracy results for [Glucose] < 75 mg/dL , N=30			ISO 15197 acceptance
Within ± 5 mg/dL	Within ± 10 mg/dL	**Within ± 15 mg/dL**	**COMPLIANT**
20 (30) 67%	28 (30) 93%	30 (30) 100%	

Accuracy results for [Glucose] ≥ 75 mg/dL , N=90				ISO 15197 acceptance
Within ± 5 %	Within ± 10 %	Within ± 15 %	**Within ± 20 %**	**COMPLIANT**
58 (90) 64%	79 (90) 88%	85 (90) 94%	89 (90) 99%	

Combined system accuracy results (absolute and relative deviations)

Within ± 15 mg/dL & ± 20%	ISO 15197 acceptance
119 (120) 99%	**COMPLIANT**

Clarke-Error Grid Analysis



EGA acceptance				Number of cases	120
COMPLIANT					
ZONE	**A**	**B**	**C**	**D**	**E**
Cases	119	1	0	0	0
Percentage	99%	1%	0%	0%	0%

Figure. *Examples of glucometers for diabetes self-testing + GlucoDay S continuous glucose monitoring system*

Strip: glucose biosensor

Meter: amperometric detector

Pocket-size, light and battery operated.

Relies on a potential-step (amperometric) operation in connection with a short incubation (reaction) step.

Continuous Glucose Monitoring- Rational

- The traditional method of monitoring glucose involves sticking finger to gain access to glucose. The inconvenience associated with this method makes it difficult for the patient to maintain tight glycemic level because of the inconvenience involved.

- Episodic monitoring of glucose does not provide information about changes in level of glucose between two consecutive measurements. Unawareness regarding a patient falling or rising glycemic level could lead to serious medical condition.

- Continuous Glucose Monitoring is of help for patients who have vast fluctuations in their glycemic level. Using this method the treatment plan of a diabetic can be well adjusted all through the day.Therapy assessment of the patient also based on periodic CGM sessions (holter), is also of great help for health care professionals.

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Present CGM Devices concept

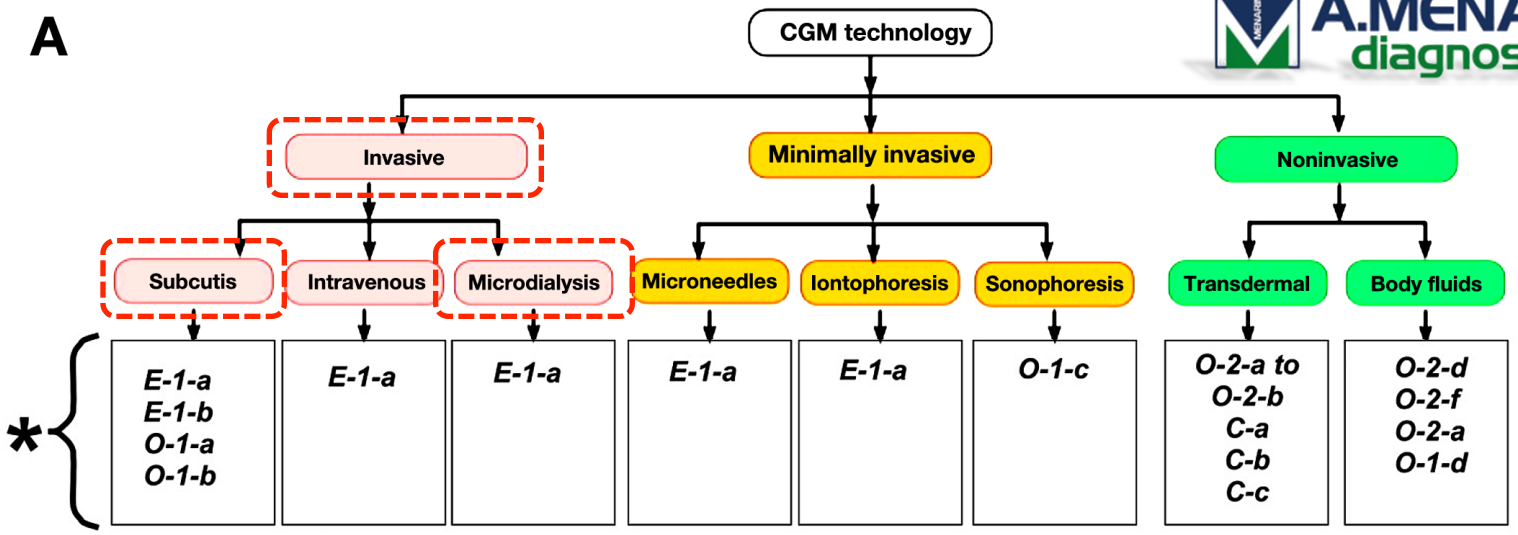
•A continuous glucose monitor uses a sensor or a probe with a transmitter attached to the body that communicate with a hand held receiver or an insulin pump.

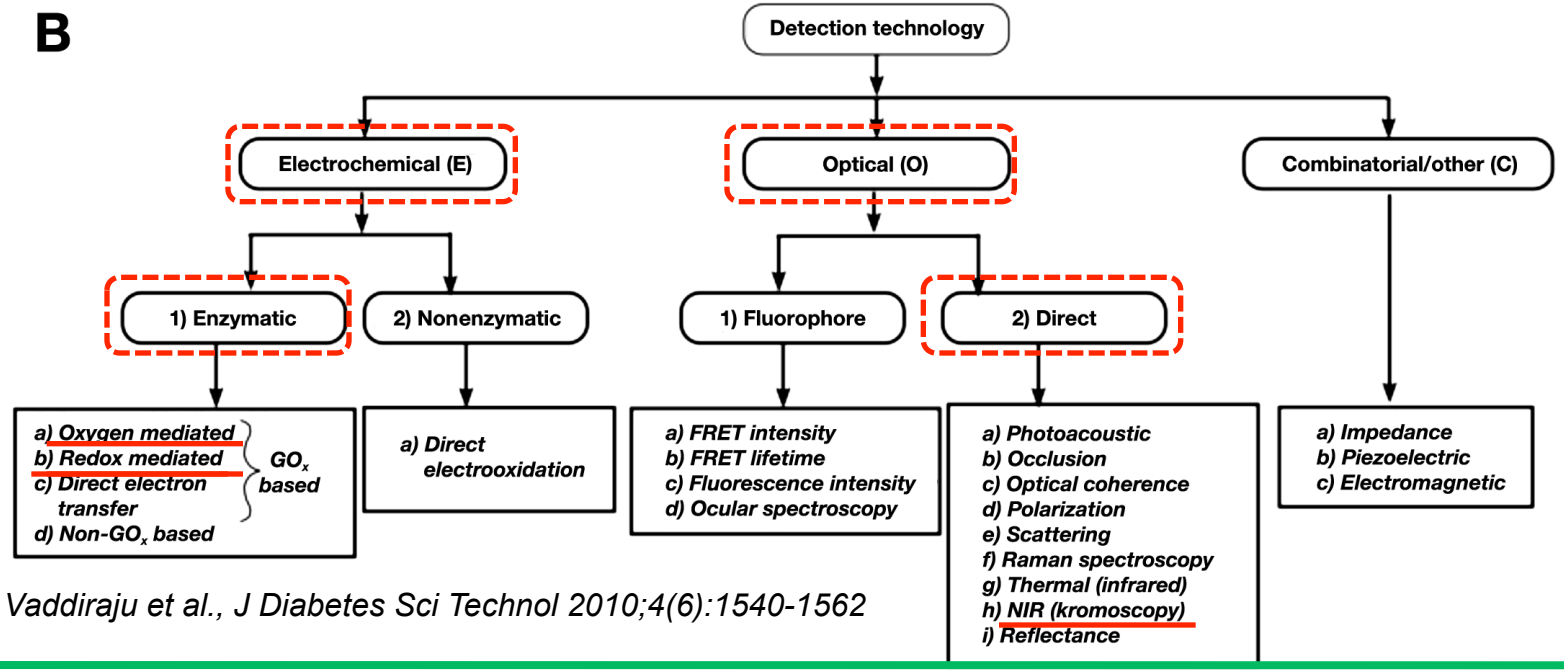
•The calibration of CGM is based on the standard meter.The average number of calibrations would be two finger tip blood glucose test per 24 hours. Calibrating the CGM on a regular basis or more frequently is essential for accurate readings.

•CGM measure glucose in the interstitial fluid so the lag effect seems to be evident when compared to traditional blood glucose level.

Essential Rquirements for CGM Detection Technology:

- Specificity
- Response time
- Immunity to interferents
- Linearity
- Accuracy vs. Plasma reference
- Biocompatibility/Biofunctionality
- Operational lifetime





Vaddiraju et al., J Diabetes Sci Technol 2010;4(6):1540-1562

Comparison of the Implantable CGMs according to Invasiveness

	Modality	Merits	Drawbacks
Invasive	SC	1. No open wound 2. No subject-to-subject variability 3. Comfort and ease of adaptability 4. Ease of implantation	1. Calibration inaccuracy due to lack of correlation between ISF and blood glucose 2. Foreign body response and biofouling-induced sensor degradation 3. Sensor migration and difficulty in extraction
	Intravenous	1. No open wound 2. No subject-to-subject variability 3. Comfort and ease of adaptability	1. Foreign body response and biofouling-induced sensor degradation in addition to sensor damage due to shearing forces of blood flow 2. Sensor migration and difficulty in extraction as well as tedious implantation procedures
	Microdialysis	1. Sensor is outside the body and so no foreign body response and biofouling-induced degradation 2. No subject-to-subject variability	1. Open wound with significant tissue inflammation 2. Calibration inaccuracy due to lack of correlation between ISF and blood glucose 3. Large response times needed for the ISF fluid to reach the sensor 4. Discomfort because of presence of protruding microdialysis probes
	Transcutaneous	1. No subject-to-subject variability 2. No sensor migration and ease of extraction	1. Open wound with significant tissue inflammation 2. Foreign body response and biofouling-induced sensor degradation 3. Calibration inaccuracy due to lack of correlation between ISF and blood glucose

Vaddiraju et al., J Diabetes Sci Technol 2010;4(6):1540-1562

Comparison of the Electrochemical Glucose Sensors according to Transduction Principle

Detection Technology			Merits	Drawbacks
Electrochemical	Enzymatic	First generation	1. Highly specific to glucose 2. High sensor sensitivity	1. Interferences from co-substrate (i.e., oxygen) and endogenous species 2. High operating potential required 3. Must use outer membranes, which increase sensor response times
		Second generation	1. Highly specific to glucose and free of changes in levels of co-substrate 2. Low overpotential renders the sensor free of interferences	1. Mediators used may be toxic 2. Competition between mediators and oxygen still exists
		Third generation	1. Highly specific to glucose and free of changes in the level of co-substrate 2. Low overpotential renders the sensor free from interferences	1. Toxicity and biocompatibility of required nanomaterials is untested 2. The issue of repeatability is still untested
		Non-GO_x based	1. Does not use oxygen as co-substrate and so no interferences from oxygen	1. Shown to oxidize other sugars as well as common alcohols
	Nonenzymatic		1. No enzymes used and so no question of degradation	1. Not specific to glucose 2. Substantial electrode fouling by the products of glucose oxidation

Vaddiraju et al., J Diabetes Sci Technol 2010;4(6):1540-1562

Commercial CGMs

Despite the big world wide efforts to introduce commercial CGMs, only 4 companies are currently present into the market:

Company	Products
Medtronic Inc.MiniMed	Paradigm® Veo™ System Guardian REAL-Time Enlite Sensor
Abbott Laboratories	Abbott FreeStyle Navigator®
DexCom Inc	SEVEN® PLUS
A. Menarini Diagnostics	**GlucoDay®S** **GlucoMen®Day**

Two successful technologies:

Subcutaneously Inserted User-Replaced Miniature Amperometric Sensors

Needle-type CGMs

Systems with Subcutaneous Ultrafiltration and Microdialysis Fibers and Externally-Worn Sensors

Microdialysis CGMs

Principle of “needle-type” amperometric sensors

A thin, sub-1 mm diameter, flexible sensor, having a working electrode with an immobilized enzyme (usually GOx) and an AgCl/Ag counter or counter-reference electrode is inserted under the skin. The electrooxidation of glucose is mediated by either O_2 (6.5.1), or by an immobilized redox mediator (6.5.2). A glucose flux-limiting membrane (6.5.3) overlays at least the working electrode of the sensor.

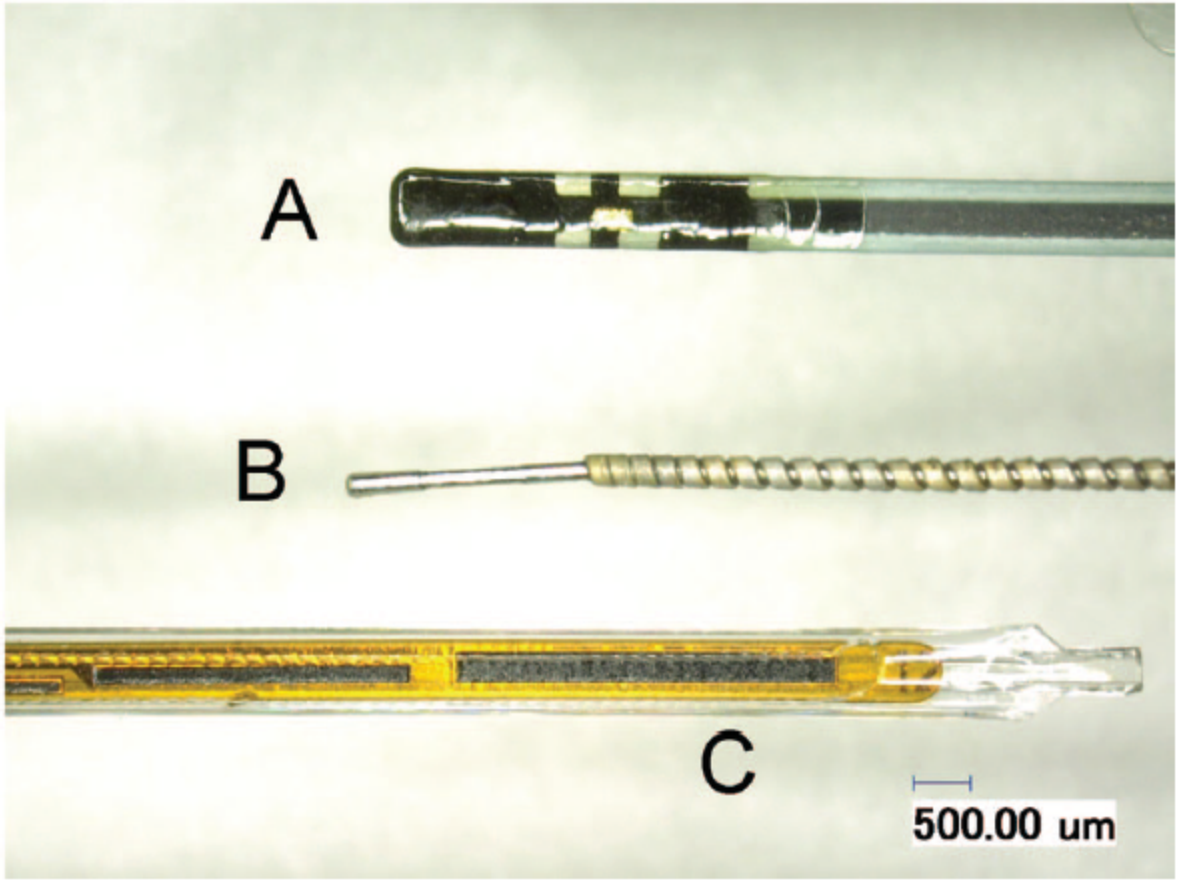
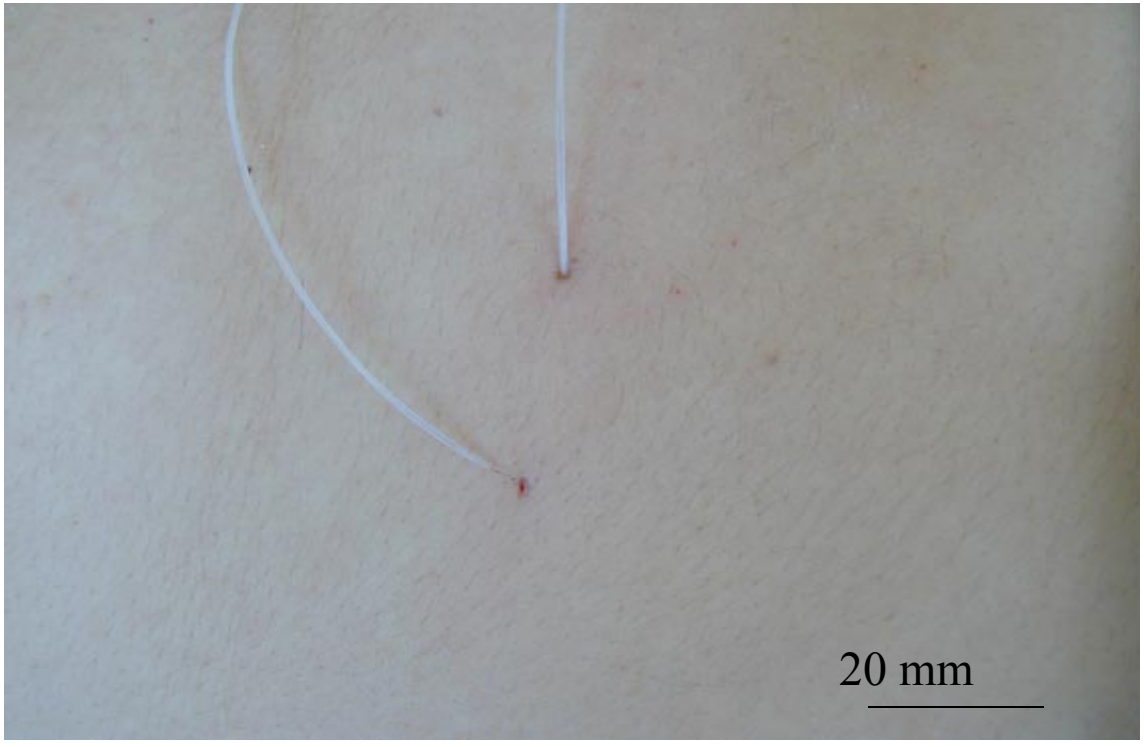


Figure 6. Commercially available transcutaneous sensors. (A) FreeStyle Navigator; (B) Dexcom STS; (C) Guardian RT.

Principle of "Microdialysis based" sensors

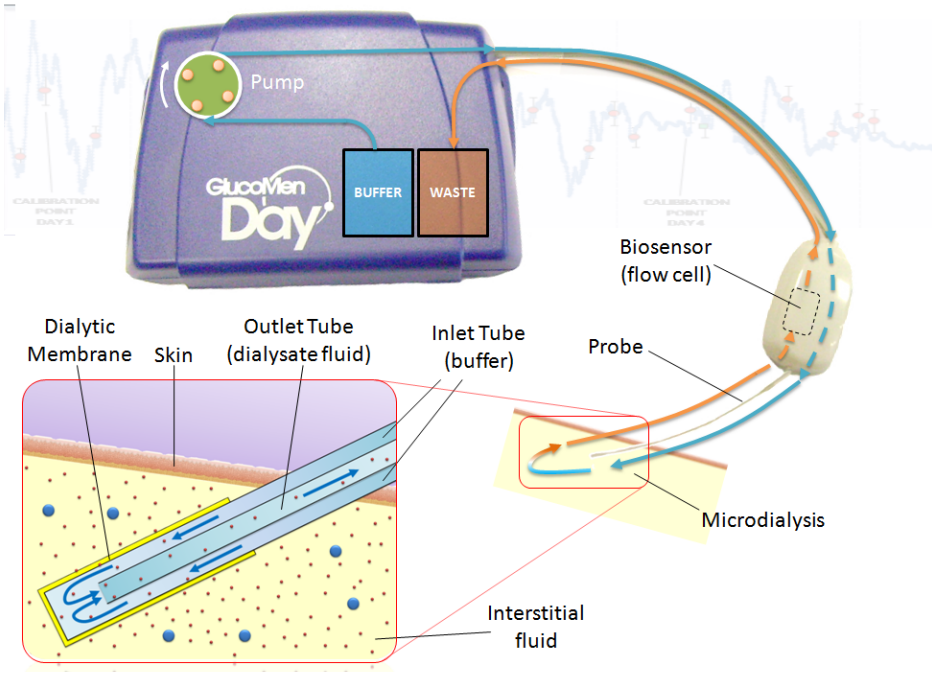
In microdialysis, an isotonic buffer solution is forced to flow through a hollow and microporous fiber. The flowing solution acquires a glucose concentration, which increases with the concentration of glucose in the surrounding adipose tissue.]



Commercially available Microdialysis Glucose sensor GlucoDay S


Navigator
144


160
02:03 P
3hr
OK
dexcom
seven PLUS


Pump
GlucoMen Day
BUFFER
WASTE
Biosensor (flow cell)
Probe
Dialytic Membrane
Skin
Outlet Tube (dialysate fluid)
Inlet Tube (buffer)
Microdialysis
Interstitial fluid

Guardian REAL-Time (Medtronic MiniMed, Sylmar, CA)

The Guardian sensor

three-electrode device that uses immobilized GOx with O2/H2O2 as the mediator

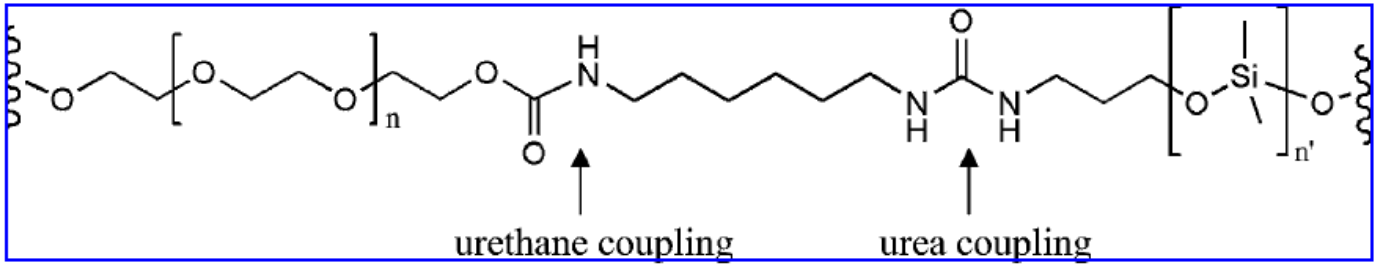
A key proprietary technology of this sensor is a polymer membrane that limits the glucose flux to the enzyme while maximizing the oxygen availability.

Membrane polymer is composed of a diisocyanate, a diamino silane, and a diol, which form a polyurethane polyurea polymer.

The hydrophobic siloxane
is highly permeable to oxygen with negligible permeability to water and thus glucose, and the hydrophilic diol imparts water/glucose permeability.

By altering the ratio of siloxane to diol, the membrane can be tuned to give optimum oxygen and glucose transport.

This sophisticated polymer provides
an elegant solution to the oxygen deficiency encountered in the subcutaneous environment



Polyurethane polyurea block copolymer

DexComTM STSTM-7 (DexCom, Inc., San Diego, CA) continuous glucose monitoring system

Project of long-term implanted glucose electrode changed to a short-term subcutaneous sensor.

two-electrode device with a coiled Ag/AgCl wire serving as a counter/eference electrode

The working electrode uses immobilized GOx with O2/H2O2 as the mediator

A glucose barrier membrane, composed of a hydrophobic polyurethane and a hydrophilic polyurethane mixture, addresses the subcutaneous oxygen deficit.

The hydrophobic polymer allows oxygen flux and blocks glucose, and the hydrophilic polymer enables glucose flux.

The membrane is tuned to a glucose permeability that generates the minimum accurately measurable current. In this manner, the required oxygen concentration and the hydrogen peroxide generated are minimized.

Hydrogen peroxide is a strong oxidizing agent that can damage both the enzyme and the membrane.

Keeping oxygen dependence and hydrogen peroxide formation to a minimum is particularly necessary for a long-term implantable device, but it also adds robustness to a shortlived sensor with less rigorous design parameters

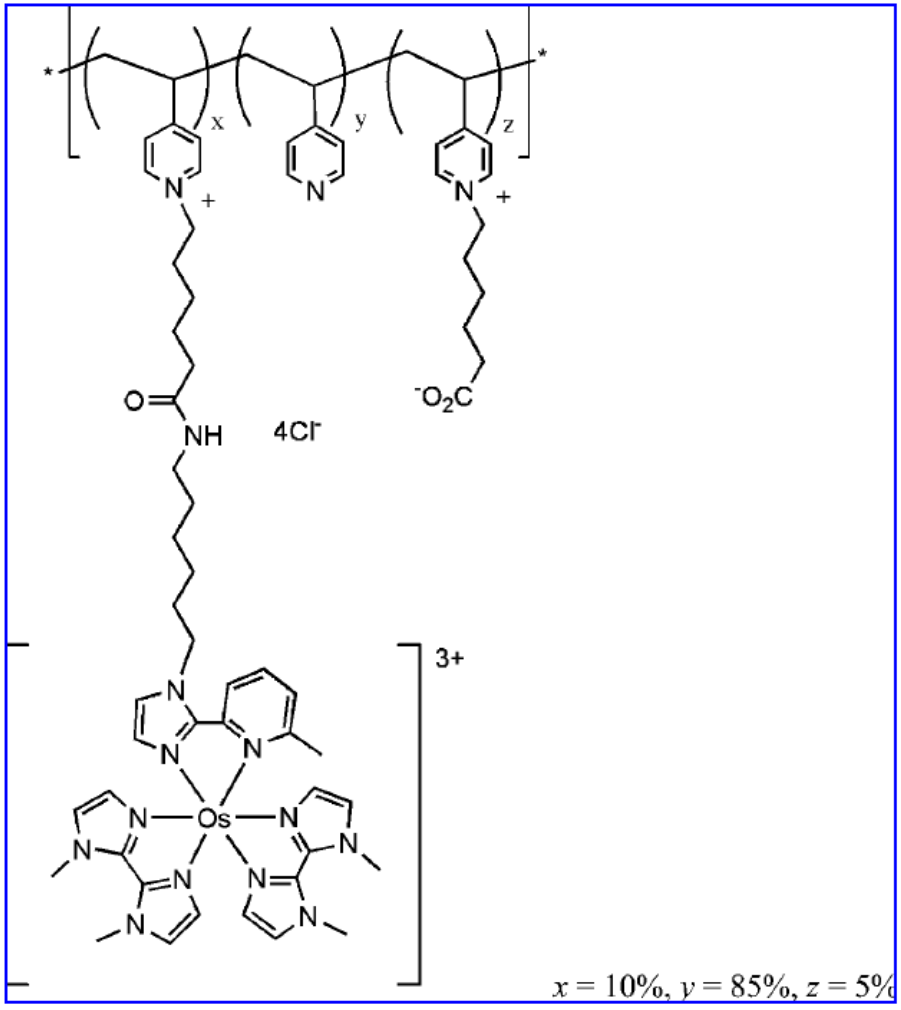
FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA) continuous glucose monitoring system

Three-electrode sensor where GOx is immobilized on the working electrode, but an alternative mediator substituting for oxygen is also immobilized in a scheme referred to as a Wired Enzyme.

A vinyl pyridine polymer with pendant osmium complexes (Fig) serves as the wire.

An advantage of the wired enzyme is the osmium complex was designed to react at a relatively low potential, 0.2 V. At the 0.4–0.7V required to reduce hydrogen peroxide, interference from the oxidation of endogenous substances such as uric acid or exogenous substances such as acetaminophen can be expected; these species do not react at 0.2 V.

Although the Wired Enzyme is not subject to the subcutaneous oxygen deficit, the enzyme concentration that can be immobilized on the surface of an electrode is too low to accommodate the high physiological glucose concentrations; the enzyme is saturated at a very low glucose level.

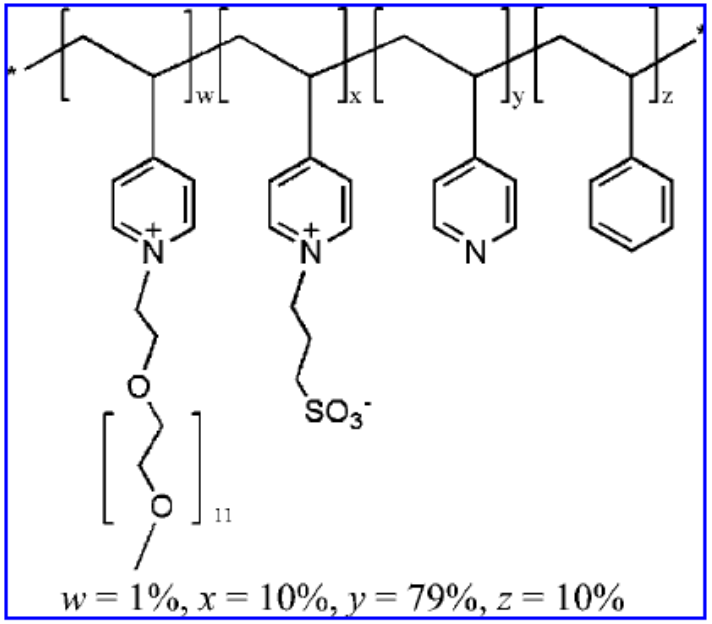


FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA) continuous glucose monitoring system

Vinyl pyridine-styrene copolymer (Fig. 14) with an epoxy cross-linker (Fig. 15) as a glucose limiting hydrogel membrane.

The backbone copolymer provides the necessary barrier to glucose diffusion, but this polymer can be easily functionalized to impart additional desirable properties such as enhanced hydration and biocompatibility.

The membrane-coated sensor is highly biocompatible, exhibiting no encapsulation for at least 1 year when implanted in rabbit muscle.



GlucoDay-GlucoMenDay(A. Menarini I.F.R. S.r.l., Florence, Italy)

Microdialysis employs a semipermeable membrane filter in the form of a hollow fiber inserted subcutaneously.

The membrane is permeable to glucose and other small molecules and impermeable to larger molecular species.

An isotonic fluid containing no glucose is pumped through the membrane fiber, and the glucose in the interstitial fluid diffuses through the membrane into the fluid stream by osmotic forces.

The glucose concentration in the pumped fluid will approach an equilibrium concentration equal to a fraction of the glucose concentration in the interstitial fluid, depending on the flow rate.

The fluid flowing through the microdialysis membrane is pumped to a glucose detector.

The detector can be exposed to atmospheric oxygen, eliminating the subcutaneous oxygen deficit in a GOx electrochemical sensor using O2/H2O2 as the mediator

Another principal advantage of this method is the sensing element is outside the body where biofouling mechanisms cannot interfere with the measurements.

Unfortunately, the foreign body response can block the flow of interstitial glucose through the membrane, and a biocompatible microdialysis membrane is a necessity.

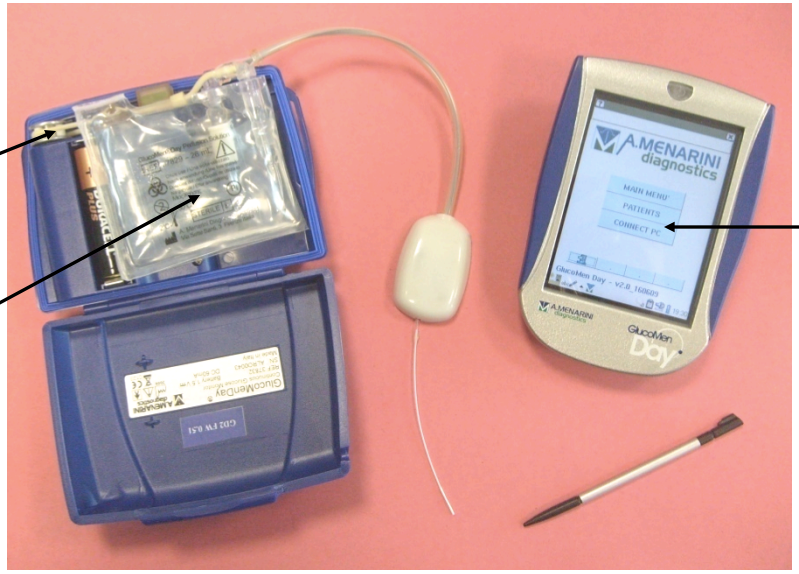
The plumbing between the microdialysis membrane and the glucose sensor introduces a time lag into the measurements.

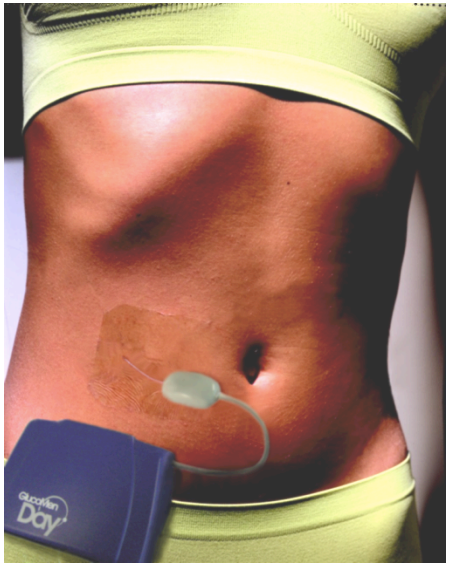
Principle & Technology

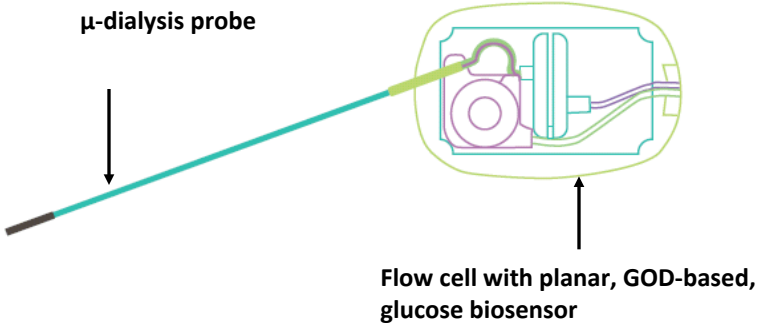
- GlucoMen®Day is a medical device intended for **Continuous 100-hours Real-Time Glucose Monitoring** in diabetic patients.

- Glucose is measured in the interstitial fluid by a disposable **GOD-based Amperometric Biosensor** placed downstream of a subcutaneously implanted **Microdialysis Probe**

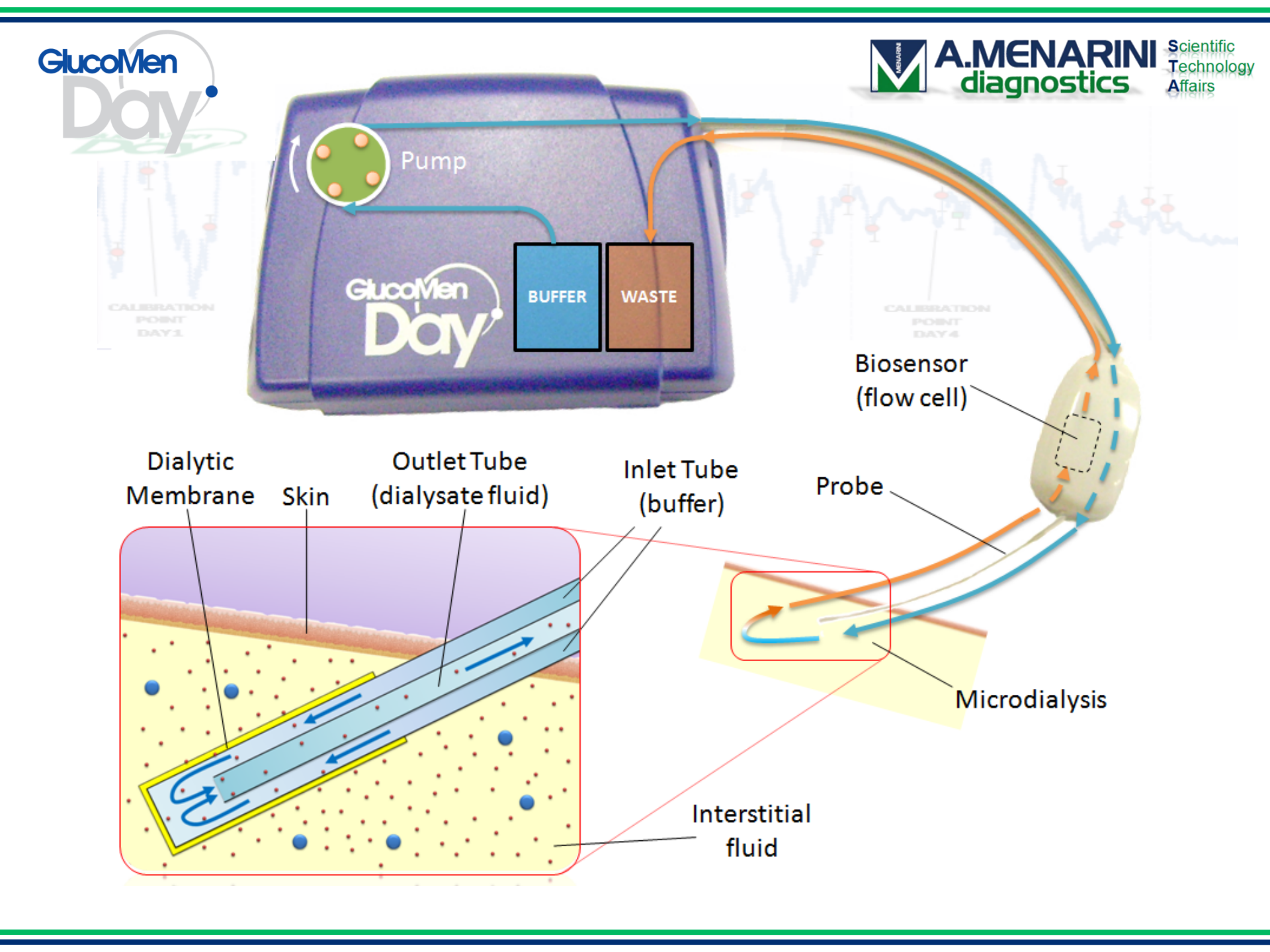
Components & Application



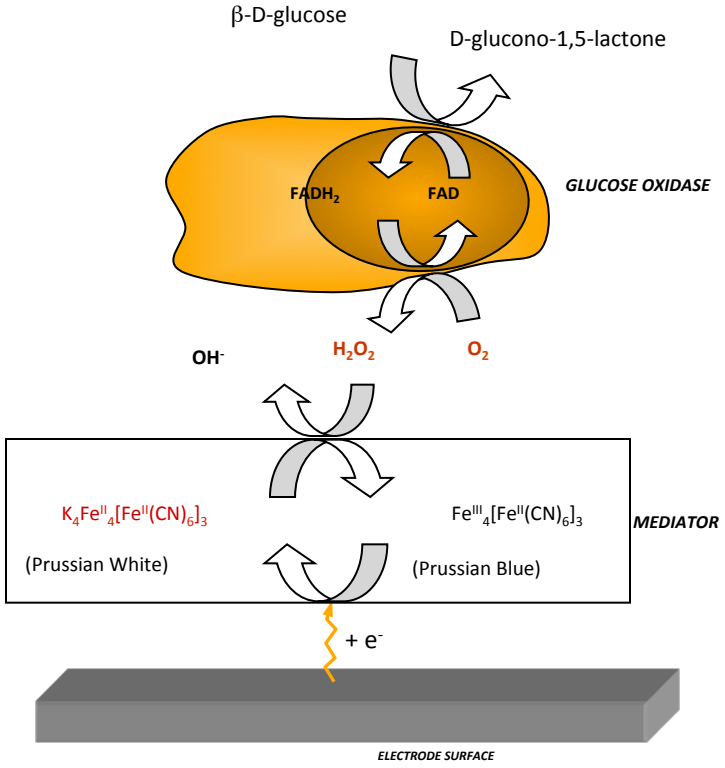




- Microdialysis probe **(Cut off 6 kDa):** implanted in the abdominal region.
- Glucose concentration: measured at **1 minute intervals** and stored in the GlucoMen®Day Recorder.

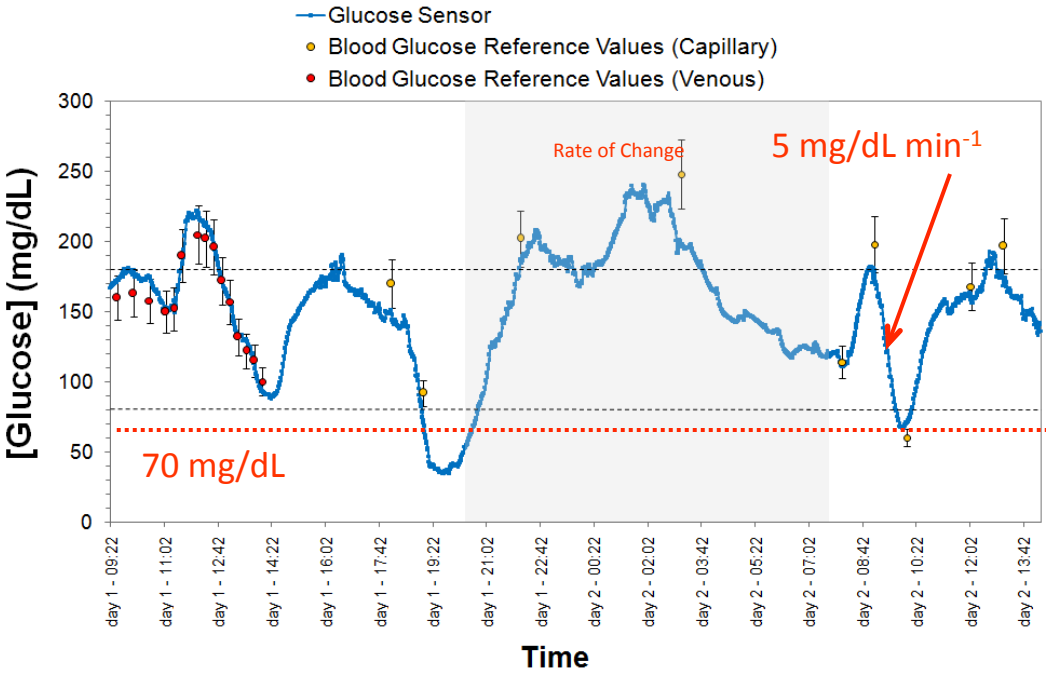

GlucoMen Day
A.MENARINI diagnostics
Scientific Technology Affairs
Pump
BUFFER
WASTE
GlucoMen Day
Biosensor (flow cell)
Probe
Microdialysis
Dialytic Membrane
Skin
Outlet Tube (dialysate fluid)
Inlet Tube (buffer)
Interstitial fluid

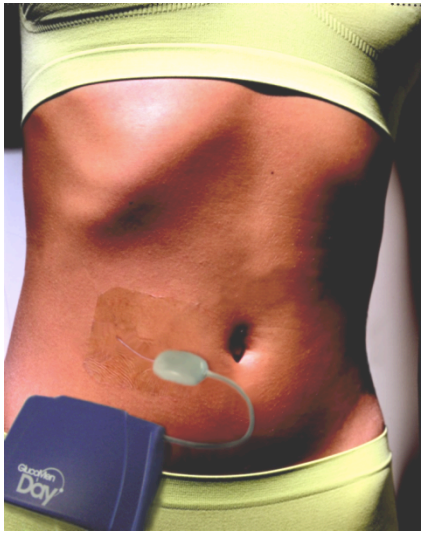
Sensor Technology



GOD catalyses the oxidation of glucose into gluconolactone and hydrogen peroxide. The **Prussian Blue** mediator allows electrocatalytic reduction of hydrogen peroxide at very low potentials (about 0.0 V vs. Ag/AgCl), where **most of the common endogenous/ exogenous species do not interfere**.

Typical Sensor Signal





Example of rapid glucose change tracking
(DT1)

Assessment of Clinical Performances

Journal of Diabetes Science and Technology
Volume 4, Issue 5, September 2010

ORIGINAL ARTICLES

Evaluating the Clinical Accuracy of GlucoMen®Day: A Novel Microdialysis-based Continuous Glucose Monitor

Francesco Valgimigli, Ph.D., Fausto Lucarelli, Ph.D., Cosimo Scuffi, Sara Morandi, Ph.D., and Iolanda Sposato, M.D.

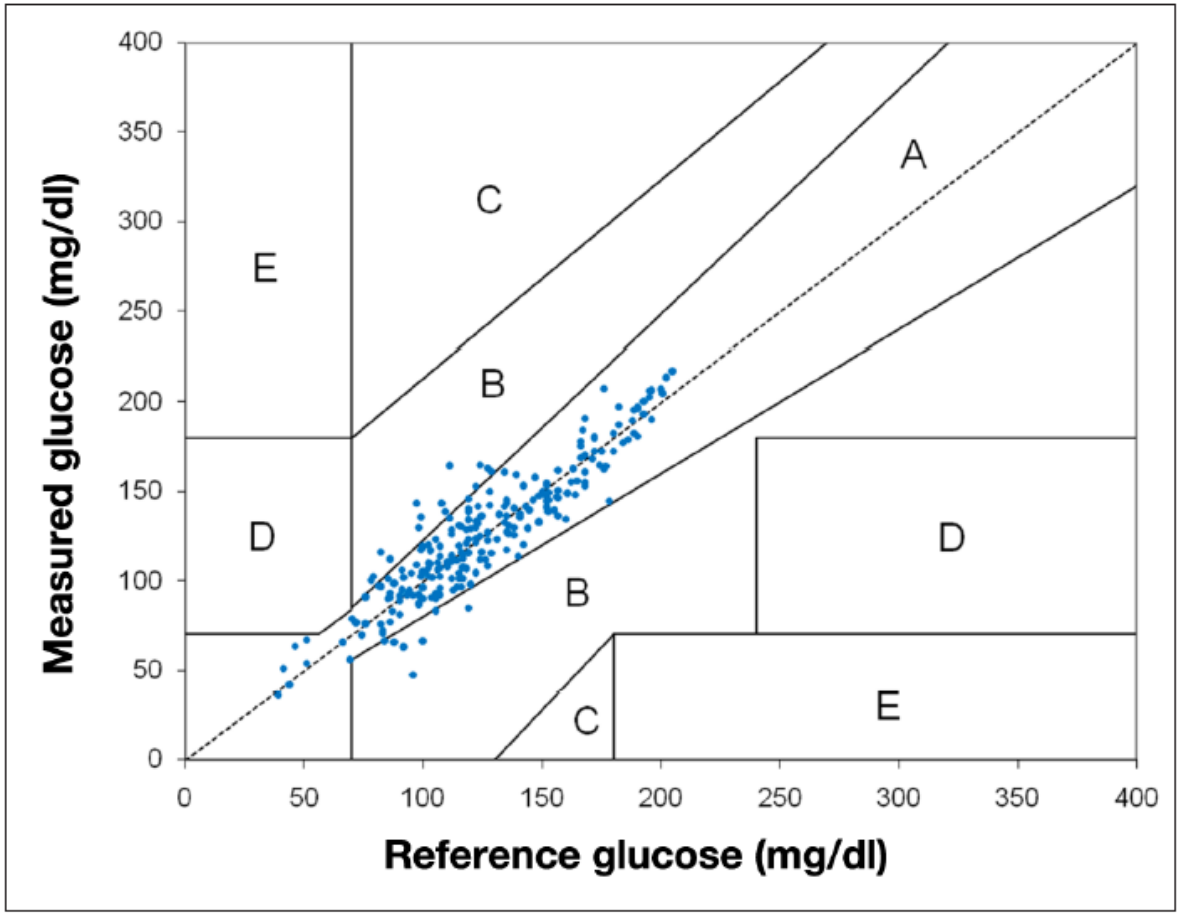


Figure 8. Clarke EGA of the combined GMD_02/GMDCP06 data (n = 236).

GlucoMen Day

A.MENARINI diagnostics Scientific Technology Affairs

CG-EGA Summary Output

EUGLYCEMIA (70<BG<=180 mg/dL)

RATE ERROR-GRID ZONES \ POINT ERROR-GRID ZONES	A	B	C
A	76,7%	5%	0%
B	13,3%	1,7%	0%
C	1,7%	0%	0%
uD	1,7%	0%	0%
ID	0%	0%	0%
uE	0%	0%	0%
IE	0%	0%	0%

This range contains 68,2% of the data

Accurate = 96,7%

Benign Errors = 3,3%

Significant Errors = 0%

HYPOGLYCEMIA (BG<=70 mg/dL)

RATE ERROR-GRID ZONES \ POINT ERROR-GRID ZONES	A	D	E
A	100%	0%	0%
B	0%	0%	0%
C	0%	0%	0%
uD	0%	0%	0%
ID	0%	0%	0%
uE	0%	0%	0%
IE	0%	0%	0%

This range contains 8% of the data

Accurate = 100%

Benign Errors = 0%

Significant Errors = 0%

HYPERGLYCEMIA (BG>180 mg/dL)

RATE ERROR-GRID ZONES \ POINT ERROR-GRID ZONES	A	B	C	D	E
A	85,7%	0%	0%	0%	0%
B	9,5%	0%	0%	0%	0%
C	0%	0%	0%	0%	0%
uD	0%	0%	0%	0%	0%
ID	4,8%	0%	0%	0%	0%
uE	0%	0%	0%	0%	0%
IE	0%	0%	0%	0%	0%

This range contains 23,9% of the data

Accurate = 95,2%

Benign Errors = 4,8%

Significant Errors = 0%

Evaluation of the GlucoMen® Day Time Lag*

(Poincaré Plot)

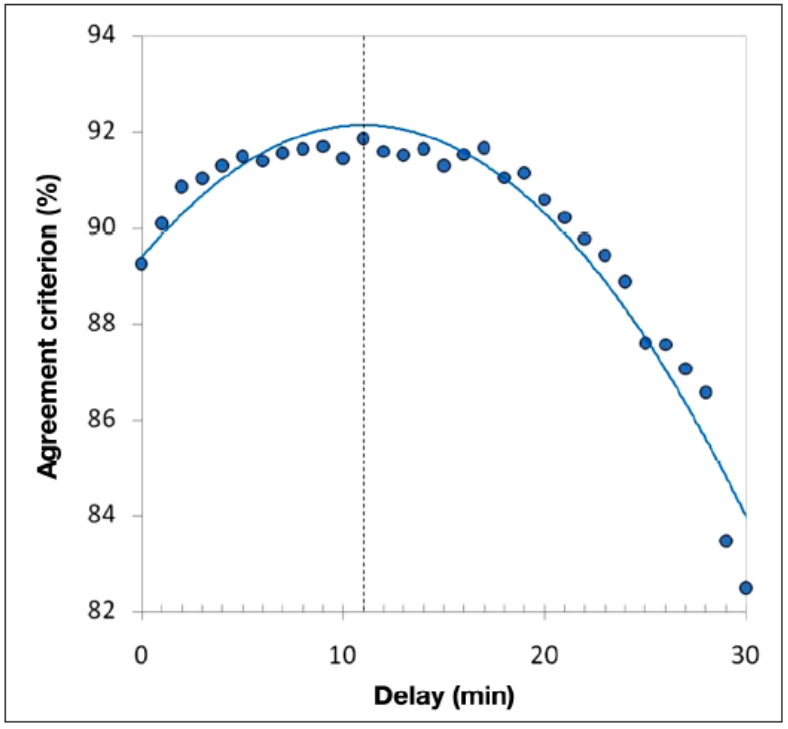
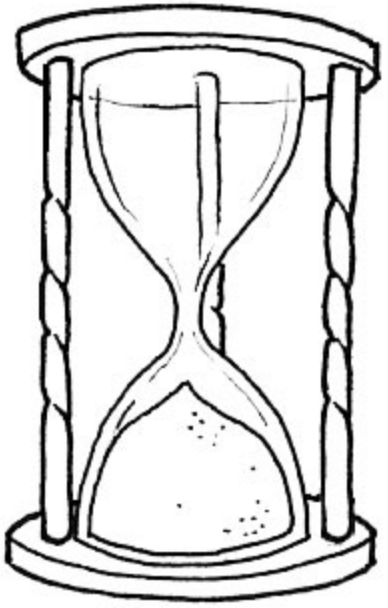


Figure 5. Agreement criterion (%) versus applied time delay. The maximum of the second-order polynomial function that fitted the obtained agreement criterion (%) values (blue curve) corresponds to the system time-lag.

Estimated

Lag-Time

11 min



(*) Boris P. Kovatchev - "*Graphical and Numerical Evaluation of Continuous Glucose Sensing Time Lag*"- DIABETES TECHNOLOGY & THERAPEUTICS, Volume 11, Number 3, 2009

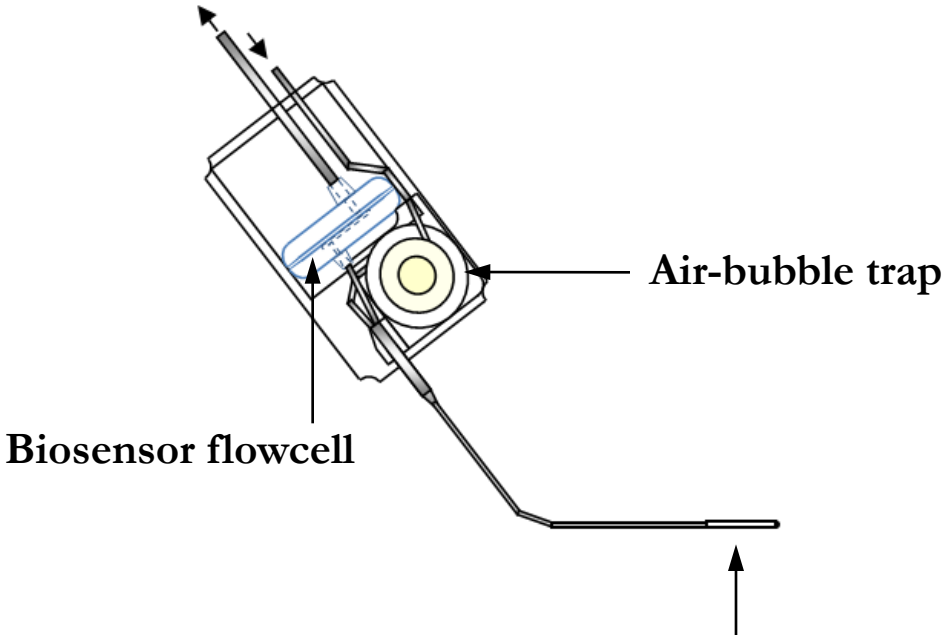
Table 2.
Comparison of Point and Trend Accuracy Parameters for Different Commercially Available CGM Devices

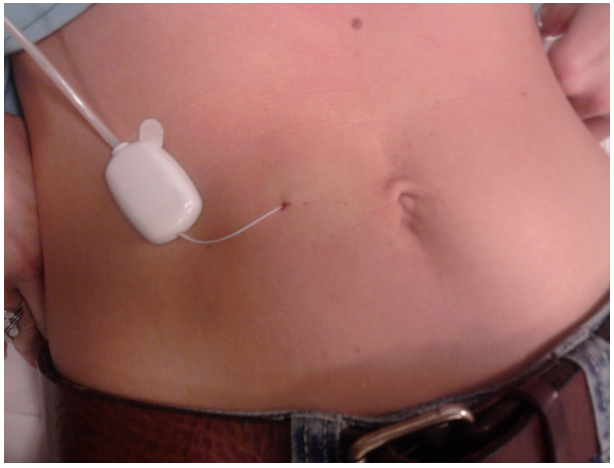
		Guardian®[b]	DexCom STS®[b]	DexCom SEVEN PLUS®[c]	Navigator®[b]	GlucoDay®S[b]	GlucoMen® Day
Point accuracy – Euglycemia, 70 < BG < 180 mg/dl (3.9–10.0 mmol/liter)[a]							
Mean absolute error	mg/dl	16.4	22.3	n.a.[d]	16.0	15.7	11.9
	mmol/liter	0.91	1.24	n.a.	0.89	0.87	0.66
Mean absolute relative error (%)		15.2	21.2	15.0	15.3	15.6	10.4
Median absolute error	mg/dl	14.8	19.1	n.a.	15.3	10.8	10.1
	mmol/liter	0.82	1.06	n.a.	0.85	0.60	0.56
Median absolute relative error (%)		13.3	18.4	13.0	11.8	10.7	7.7
% readings within ISO 15197 requirements[e]		73.2	52.2	74.0	72.2	76.9	89.3
Point Accuracy – Hypoglycemia, BG ≤ 70 mg/dl [3.9 mmol/liter][f]							
Mean absolute error	mg/dl	9.9	13.1	n.a.	6.5	8.5	7.4
	mmol/liter	0.55	0.73	n.a.	0.36	0.47	0.41
Mean absolute relative error (%)		16.1	21.5	25.0	10.3	17.5	14.2
Median absolute rrror	mg/dl	7.6	11.52	n.a.	4.3	7.2	5.9
	mmol/liter	0.42	0.64	n.a.	0.24	0.40	0.33
Median absolute relative error (%)		13.8	22.5	20.0	7.4	15.6	9.6
% readings within ISO 15197 requirements[e]		76.5	52.9	n.a.	79.4	83.0	80.0
Rate accuracy – Descent into hypoglycemia							
Absolute rate deviation	mg/dl/min	0.87	0.72	n.a.	0.66	1.74	0.75
	mmol/liter/h	2.9	2.4	n.a.	2.2	5.8	2.5
Rate accuracy – Ascent from hypoglycemia							
Absolute rate deviation	mg/dl/min	0.90	0.99	n.a.	0.99	2.79	0.45
	mmol/liter/h	3.0	3.3	n.a.	3.3	9.3	1.5

[a] DexCom SEVEN PLUS system assumes the euglycemic range to be 80–180 mg/dl (4.4–10.0 mmol/liter).[30]
[b] Data from Kovatchev BP, Anderson S, Heinemann L, Clarke WL. Comparison of the numerical and clinical accuracy of four continuous glucose monitors. Diabetes Care. 2008;31:1160-4.[20]
[c] Data from: SEVEN PLUS User Guide. Dexcom, Inc: San Diego, CA.[30]
[d] n.a., data not available
[e] Overall percentage of readings falling within ±15 mg/dl (if <75 mg/dl) and ±20% (if ≥75 mg/dl) of the reference values, according to the ISO 15197 accuracy requirements (bias plot).[23] ISO, International Organization for Standardization.
[f] DexCom SEVEN plus system defines as hypoglycemia BG levels ≤80 mg/dl (≤4.4 mmo/liter).[30]

Disposable Sensor Kit

The GlucoMen® Day disposable sensor kit is a fluidic circuit comprising an air-bubble trap, the microdialysis probe, and the biosensor flowcell.

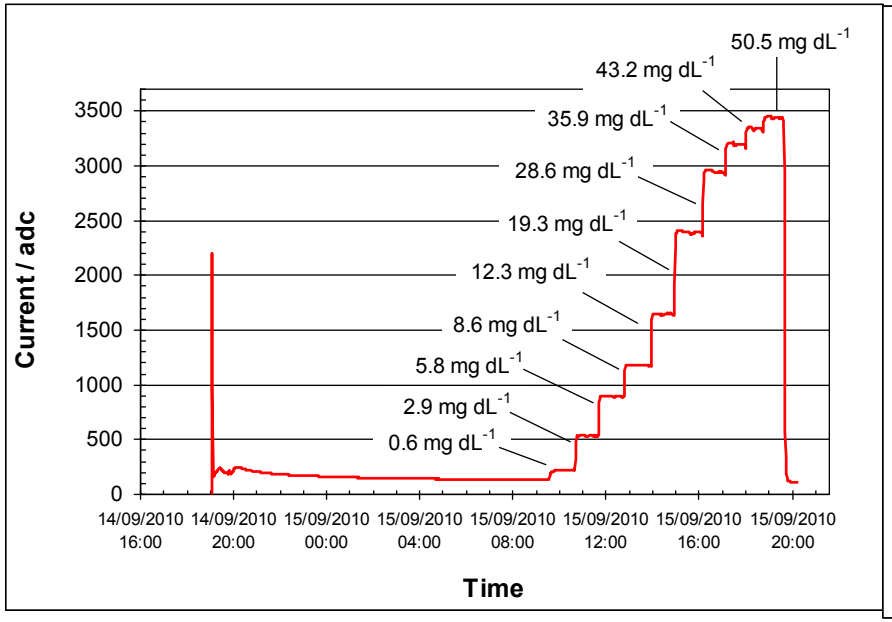


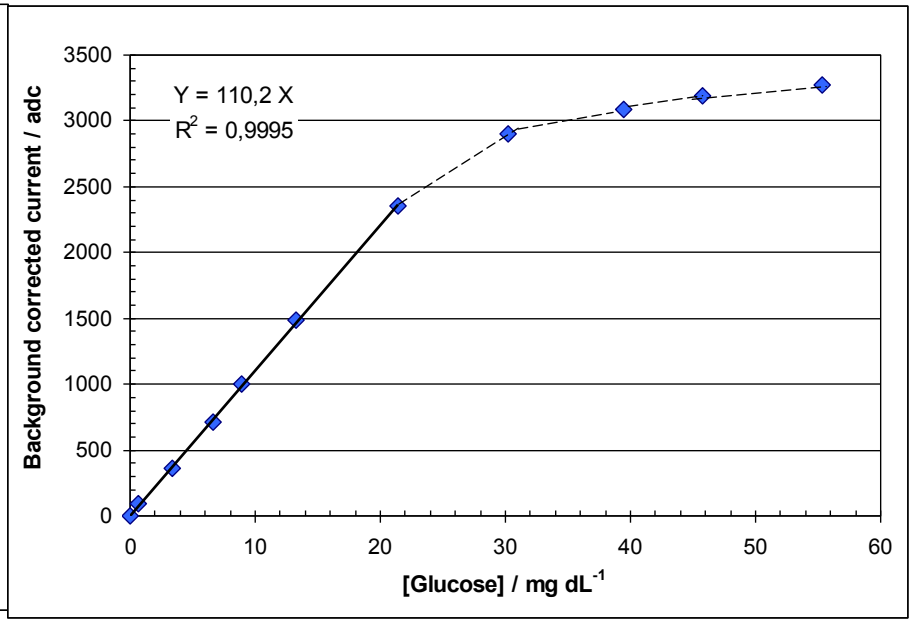


Coaxial microdialysis probe (polyethersulfone/polyvinylpyrrolidone)
external diameter = 814 µm
effective microdialysis length = 8 mm
cut-off = 6 kDa

Glucose Biosensor: analytical performance

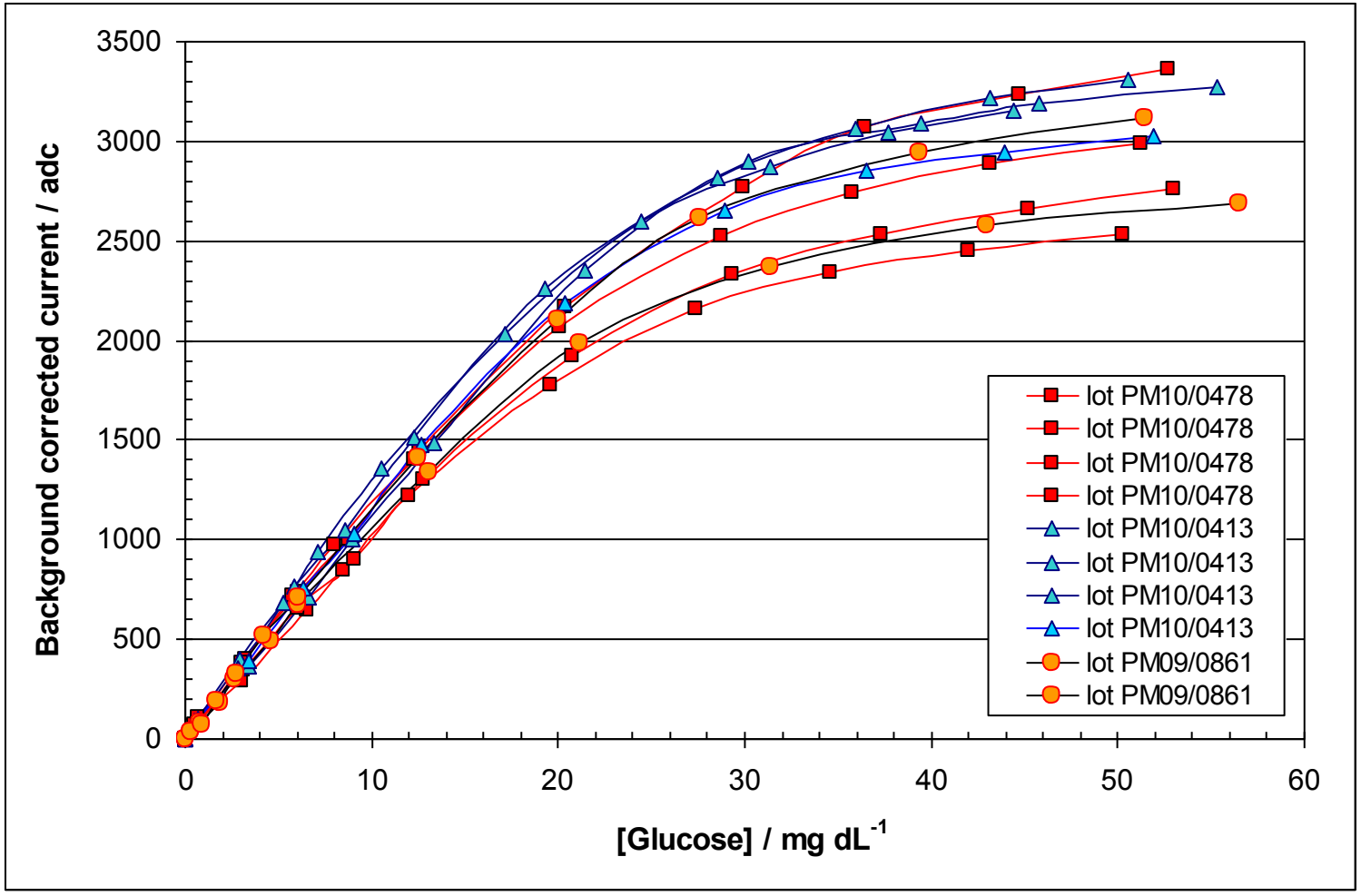
When perfused at 2.5 µL/min, the biosensor responds to an instantaneous change in glucose concentration in about 2 min (instrumental lag-time), with a typical *in vivo* recovery for glucose of (10 ± 4)%. Taking this into account, the biochemical mix dispensed onto the sensor surface was defined in order to ensure accurate tracking of *in vivo* glyceamic excursions in the range 5 - 400 mg/dL (0.3 – 22.2 mmol/L).





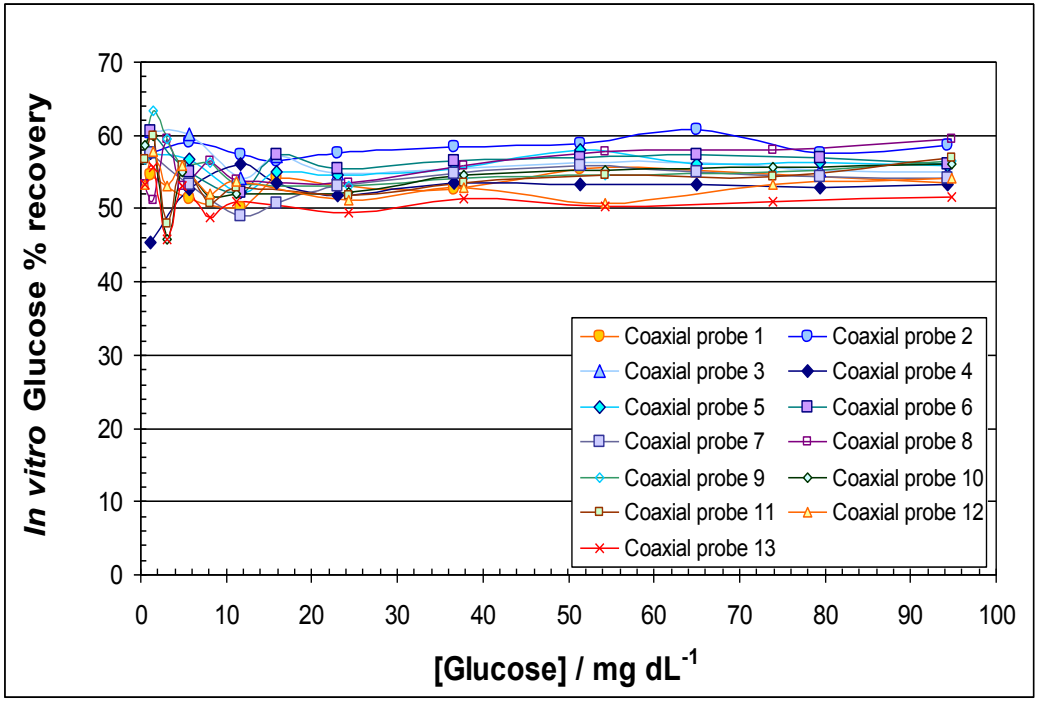
Glucose Biosensor: analytical performance (1)

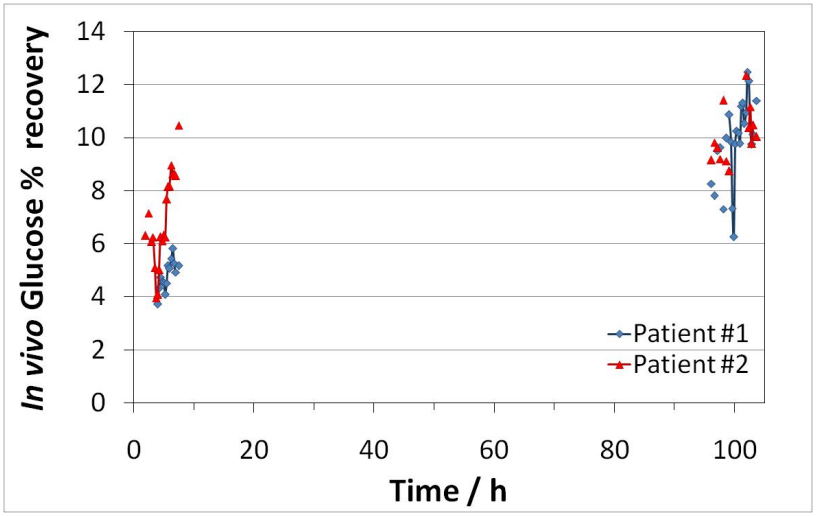
Highly consistent sensitivity between different production lots [(108 ± 9) adc / mg dL^{-1} over 3 lots]

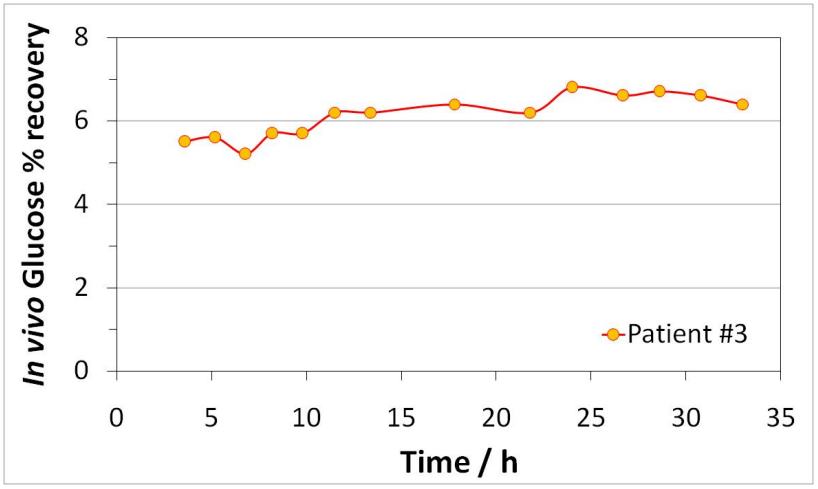


Coaxial microdialysis probe: performance

Highly consistent *in vitro* and *in vivo* Glucose % recovery:







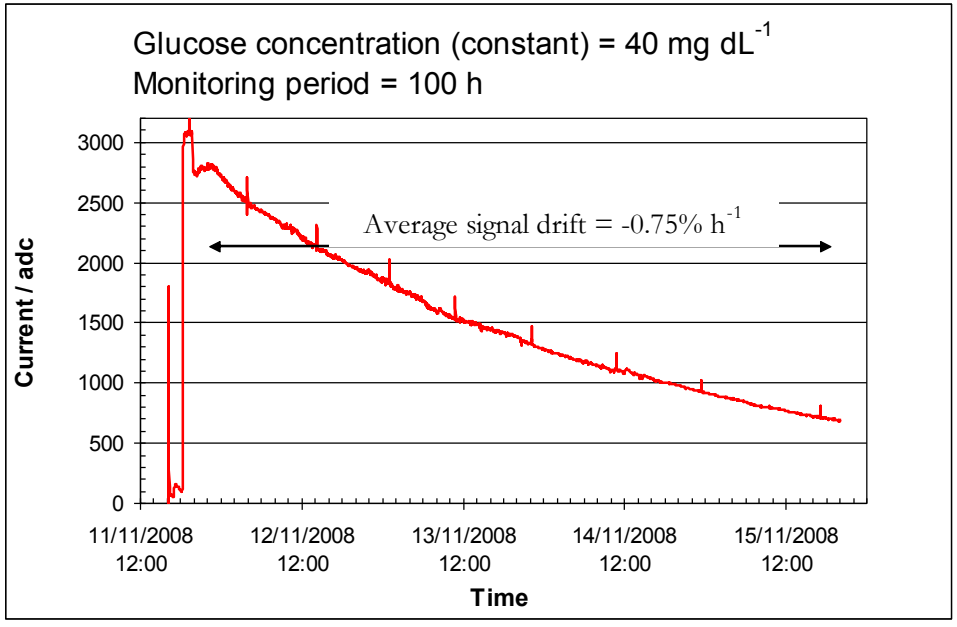
Challenges

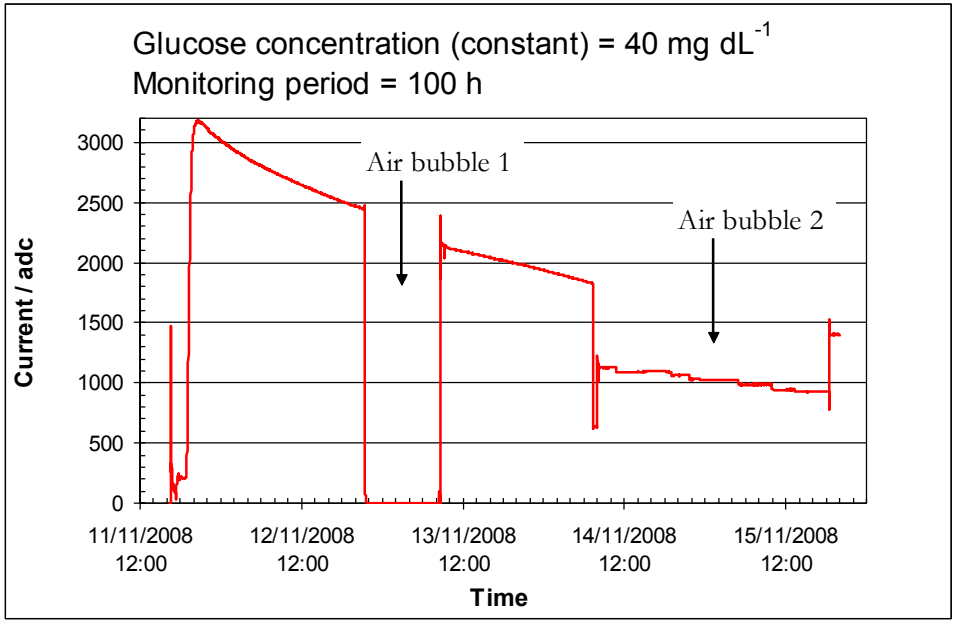
Main challenges to be addressed for a Microdialysis-based GOD biosensor:

I) progressive inactivation of the enzyme ("*drift*");

II) possible nucleation/movement of *air bubbles* into the system's fluidics;

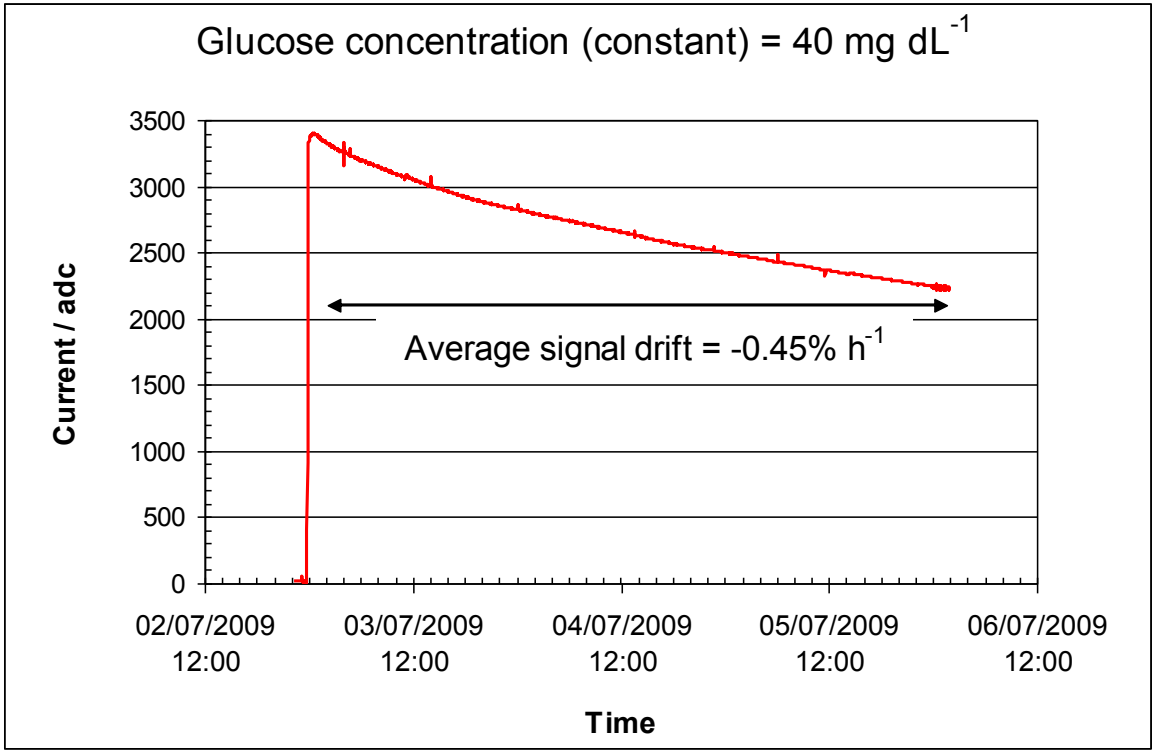
III) Temperature dependence of the enzyme kinetics





Implemented solutions (1)

The "drift" problem was mitigated by changing the surface chemistry of the biosensor (via inclusion of a protein which stabilised GOD and improving cross-linking of the reagents)



The "drift" was substantially reduced from -0.75% h^{-1} to -0.45% h^{-1}.

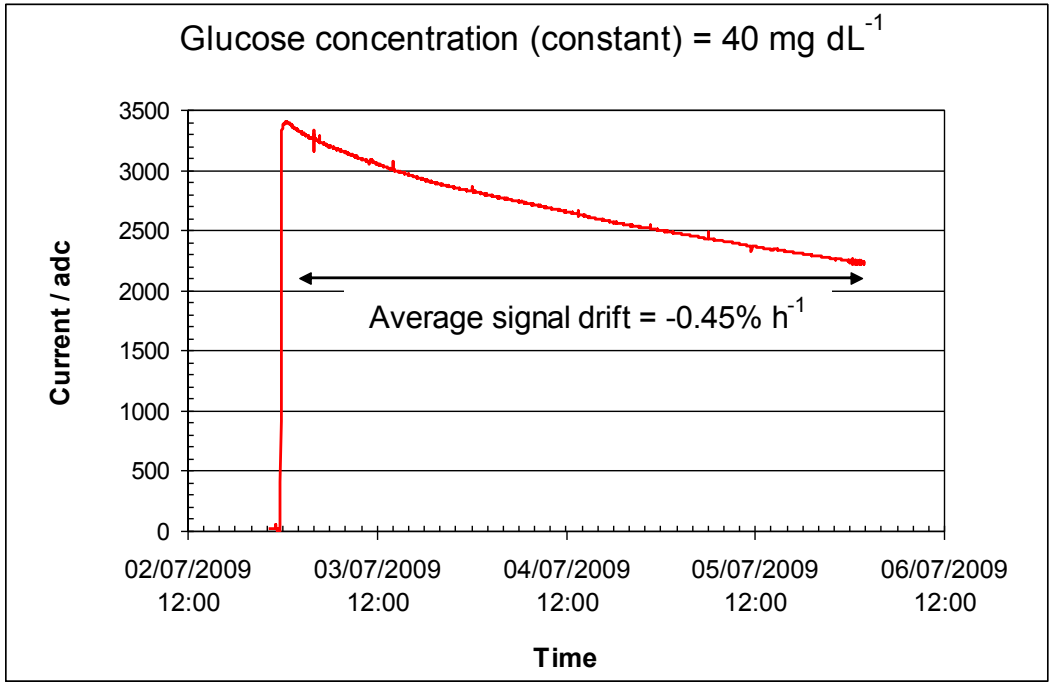
The current life time of the biosensor largely exceeds 100 h (expected life time ca. 200 h).

Implemented solutions (2)

The "air bubbles" problem was mitigated by reformulating the perfusion solution (via inclusion of a surface active agent).

GlucoMen®Day
Perfusion Solution

NaCl 8,00 g;
KCl 0,20 g;
KH_2PO_4 0,20 g;
Na_2HPO_4 1,15 g;
C_6H_5COONa 1,00 g;
Tween™ 80 0,50 g;
H_20 to 1000 mL



The full biocompatibility of the new solution was confirmed through extensive *in vitro* and *in vivo* tests performed at Research Toxicology Centre [RTC, Pomezia])

Biological Responses to Implantable Devices

Inflammatory Reaction

The main stages in this process include acute inflammation, chronic inflammation, and the formation of granulomatous tissue.

Foreign Body Reaction

A biomaterial implanted into the body induces a foreign body reaction.

The end stage of the foreign body reaction involves walling off the device by a vascular, collagenous fibrous capsule that is typically 50–200 mm in thickness.This fibrous wall confines the implanted device and prevents it from interacting with surrounding tissues (Fibrosis encapsulation)

Functional Loss of Glucose Sensor Due to Fibrosis Encapsulation

Materials currently utilized in the fabrication of implantable devices

Natural materials:

Collagen, chitosan, alginate, hyaluronan, and dextran

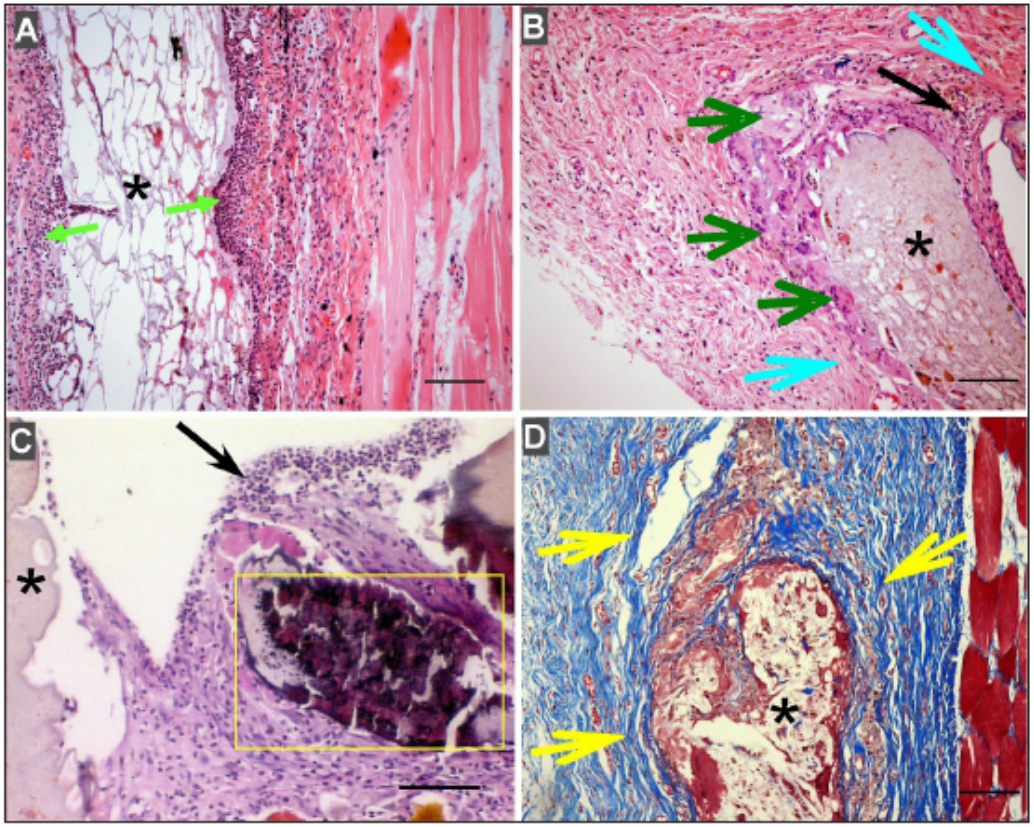
Synthetic polymers

poly(lactic acid)(PLA) and poly(lactic-co-glycolic acid)(PLGA), poly (ethylene glycol)(PEG),hydroxy ethyl methacrylate,and poly(vinyl alcohol)(PVA)
Polysulphone

Relatively biocompatible, but still biocompatibility issues, depending on the application

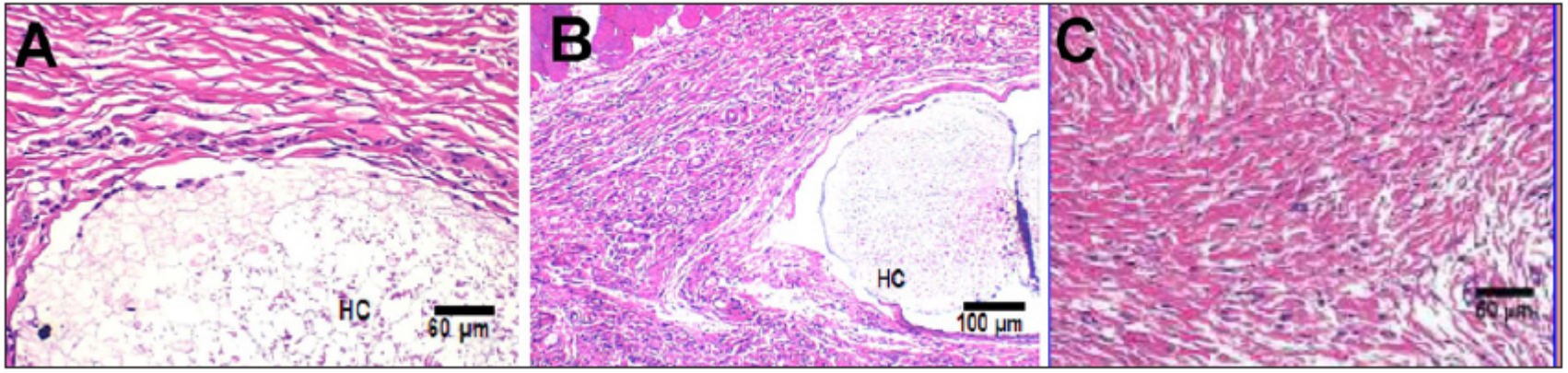
A material found to be safe in one application may not be safe in another application

Foreign body response to PVA hydrogel/PLGA microsphere composites (containing no drug) implanted into the subcutaneous tissue of rats. (A) Acute inflammation at day 3 after implantation (green arrow: neutrophils). (B) Chronic inflammation at day 30 after implantation (dark green arrow: multinucleate giant cells; light blue arrow: fibrosis; and black arrow: mixed inflammatory cells



(C) Mineralization (yellow box) around the implant at day 60. (D) Fibrosis around the implant (yellow arrows) stained with Masson's trichrome stain (collagen is stained blue). Bar: 100 μm.

Onuki, et al. J Diabetes Sci Technol2008;2(6):1003-1015



(A) Day 7 after implantation.

(B) Day 30 after implantation.

(C) Untreated normal tissue. Hematoxylin and eosin stains inflammation-mediating cells basophilic (purple) and subcutaneous connective tissue eosinophilic (pink).

Pharmacodynamic changes in representative tissue sections after subcutaneous implantation of PLGA microsphere/PVA hydrogel composites (HC) containing dexamethasone.

Long Term Glucose Sensor® (LTGS, MiniMed-Medtronic, Northridge, CA, USA)

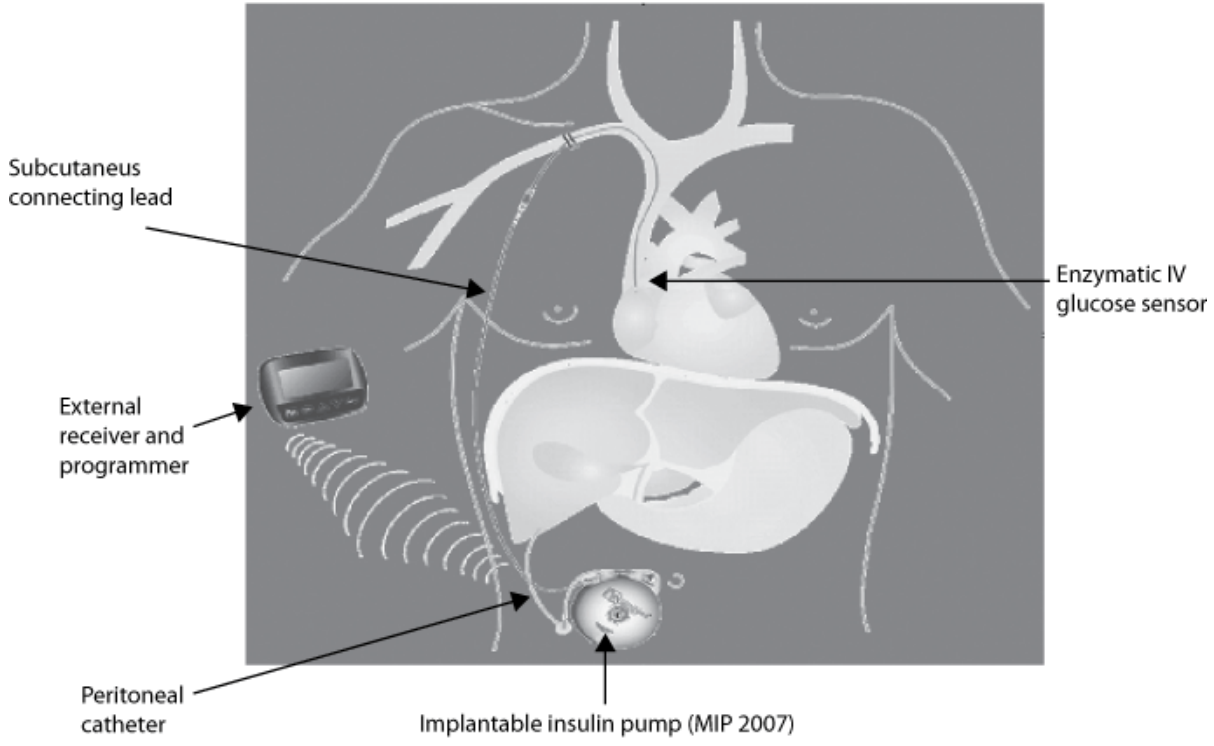
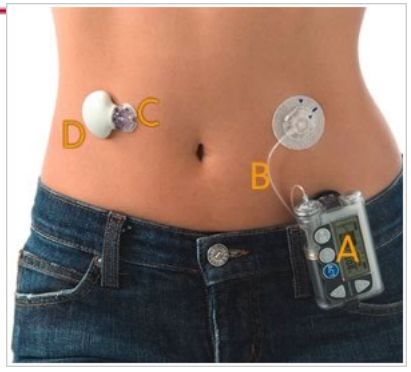


Figure 1. Scheme of human implantation of the Long-Term Sensor System® (LTSS, Medtronic-MiniMed), a prototype of implantable artificial beta-cell.

Feasibility of glucose control by the combined implantation of a pump for peritoneal insulin delivery and a central intravenous glucose sensor, connected physically by a subcutaneous lead and functionally by PID algorithms. It was performed in 10 type 1 diabetic patients from 2000 to 2007.

Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial

Roman Hovorka, Janet M Allen, Daniela Elleri, Ludovic J Chassin, Julie Harris, Dongyuan Xing, Craig Kollman, Tomas Hovorka, Anne Mette F Larsen, Marianna Nodale, Alessandra De Palma, Malgorzata E Wilinska, Carlo L Acerini, David B Dunger



Summary

Background Closed-loop systems link continuous glucose measurements to insulin delivery. We aimed to establish whether closed-loop insulin delivery could control overnight blood glucose in young people.

Methods We undertook three randomised crossover studies in 19 patients aged 5–18 years with type 1 diabetes of duration 6·4 years (SD 4·0). We compared standard continuous subcutaneous insulin infusion and closed-loop delivery (n=13; APCam01); closed-loop delivery after rapidly and slowly absorbed meals (n=7; APCam02); and closed-loop delivery and standard treatment after exercise (n=10; APCam03). Allocation was by computer-generated random code. Participants were masked to plasma and sensor glucose. In APCam01, investigators were masked to plasma glucose. During closed-loop nights, glucose measurements were fed every 15 min into a control algorithm calculating rate of insulin infusion, and a nurse adjusted the insulin pump. During control nights, patients' standard pump settings were applied. Primary outcomes were time for which plasma glucose concentration was 3·91–8·00 mmol/L or 3·90 mmol/L or lower. Analysis was per protocol. This trial is registered, number ISRCTN18155883.

Findings 17 patients were studied for 33 closed-loop and 21 continuous infusion nights. Primary outcomes did not differ significantly between treatment groups in APCam01 (12 analysed; target range, median 52% [IQR 43–83] closed loop *vs* 39% [15–51] standard treatment, p=0·06; ≤3·90 mmol/L, 1% [0–7] *vs* 2% [0–41], p=0·13), APCam02 (six analysed; target range, rapidly 53% [48–57] *vs* slowly absorbed meal 55% [37–64], p=0·97; ≤3·90 mmol/L, 0% [0–4] *vs*

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VeriChip Corporation Announces Phase II Development Of In Vivo Glucose-Sensing RFID Microchip With RECEPTORS LLC

VeriChip Human RFID Implant compared to long-grain rice

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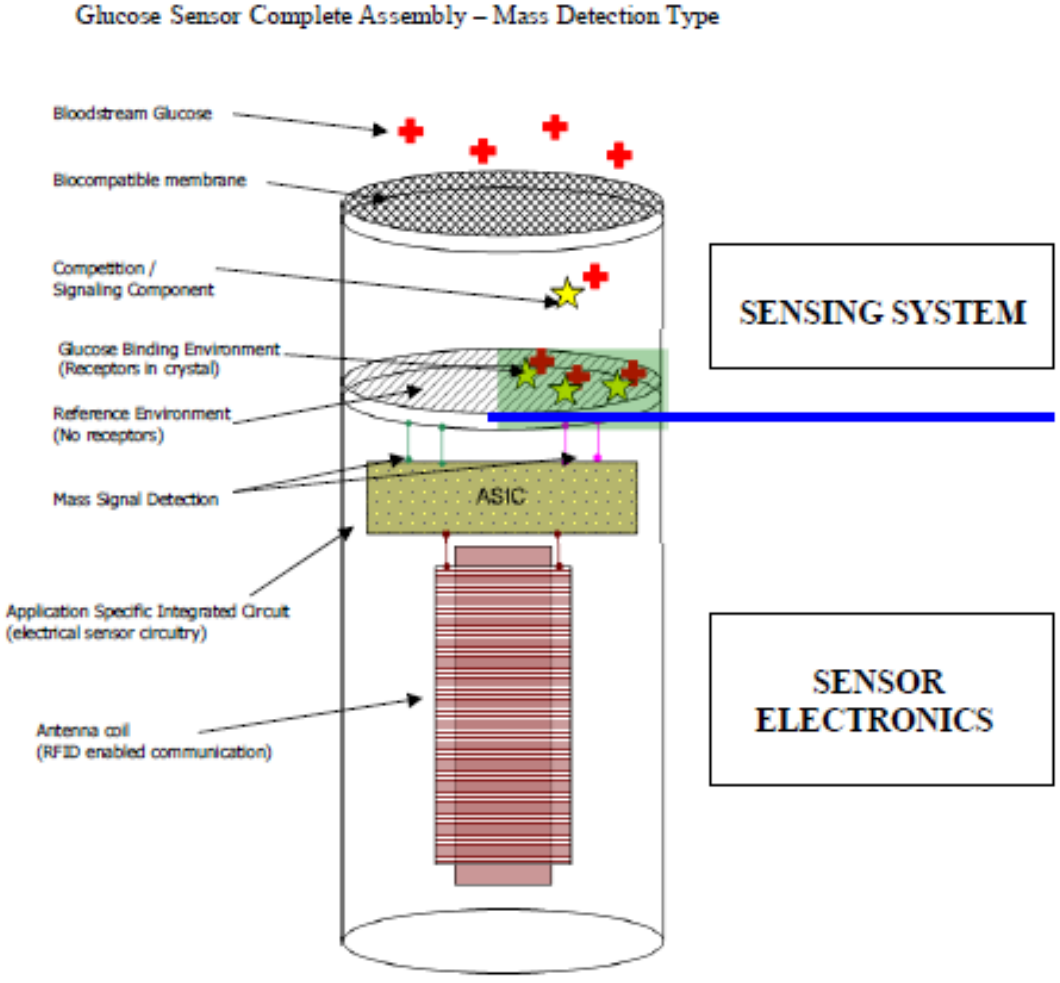
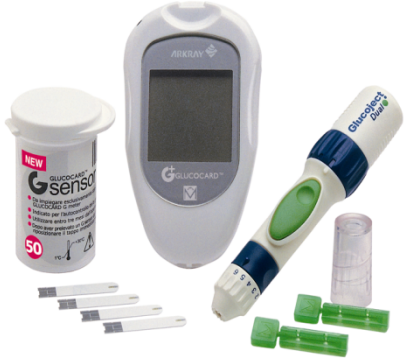


Bioengineer David Gough of UC San Diego and his colleagues have developed a sensor that uses two continuous oxygen monitors.

In a small chamber in the device, glucose from the blood is oxidized and the device measures the oxygen that is left behind. A second sensor measures the amount of oxygen in the blood. By subtracting the two readings, the device can tell how much glucose is in the blood. It then transmits the reading to a receiver that must be within 10 to 12 feet of the patient.

GlySens Inc. that is developing the sensor. Funding for his studies has been provided by the company, the National Institutes of Health and the Juvenile Diabetes Research Foundation

Next decade market expectations for Implantable Glucose Sensors



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