Optimized optical glucose reader for transcutaneous glucose measurements

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1 Abstract

Aim: The development of a single-port closed-loop system for **type 1 diabetic patients** aims for continuous glucose monitoring, insulin dose calculation and continuous insulin infusion as an "all-in-one" artificial pancreas system. The glucose sensor is based on two luminescent dyes with different excitation wavelengths grafted on standard insulin infusion sets, showing a glucose-sensitive and O_2-sensitive luminescence, respectively. Here we present an optimized optical reader for reliable transcutaneous read-out of the sensors.

Methods: The system is divided into an integrated optoelectronic reader that is located on the skin over the infusion set with the optical sensor layers and a separate signal processing unit. This design allows miniaturizing the reader for maximum convenience of the patient. Bright SMD LEDs with custom collimating optics and large area photodiodes are combined with optical interference filters for spectral discrimination between the glucose and the reference O_2 channel.

Results: The reader's dimensions are only Ø25mm at 7mm height, allowing convenient continuous wearing.

The sensor can be integrated in standard 90° infusion sets with 0.4mm steel cannula. The reader is characterized in terms of signal intensity, channel crosstalk, optical background and signal to noise ratio. Interstitial glucose and O_2 in animal models are compared to blood values.

Conclusions: The optimized optical glucose reader shows promising performance valuable for the further development of the innovative single-port artificial pancreas system.

2 Functional description

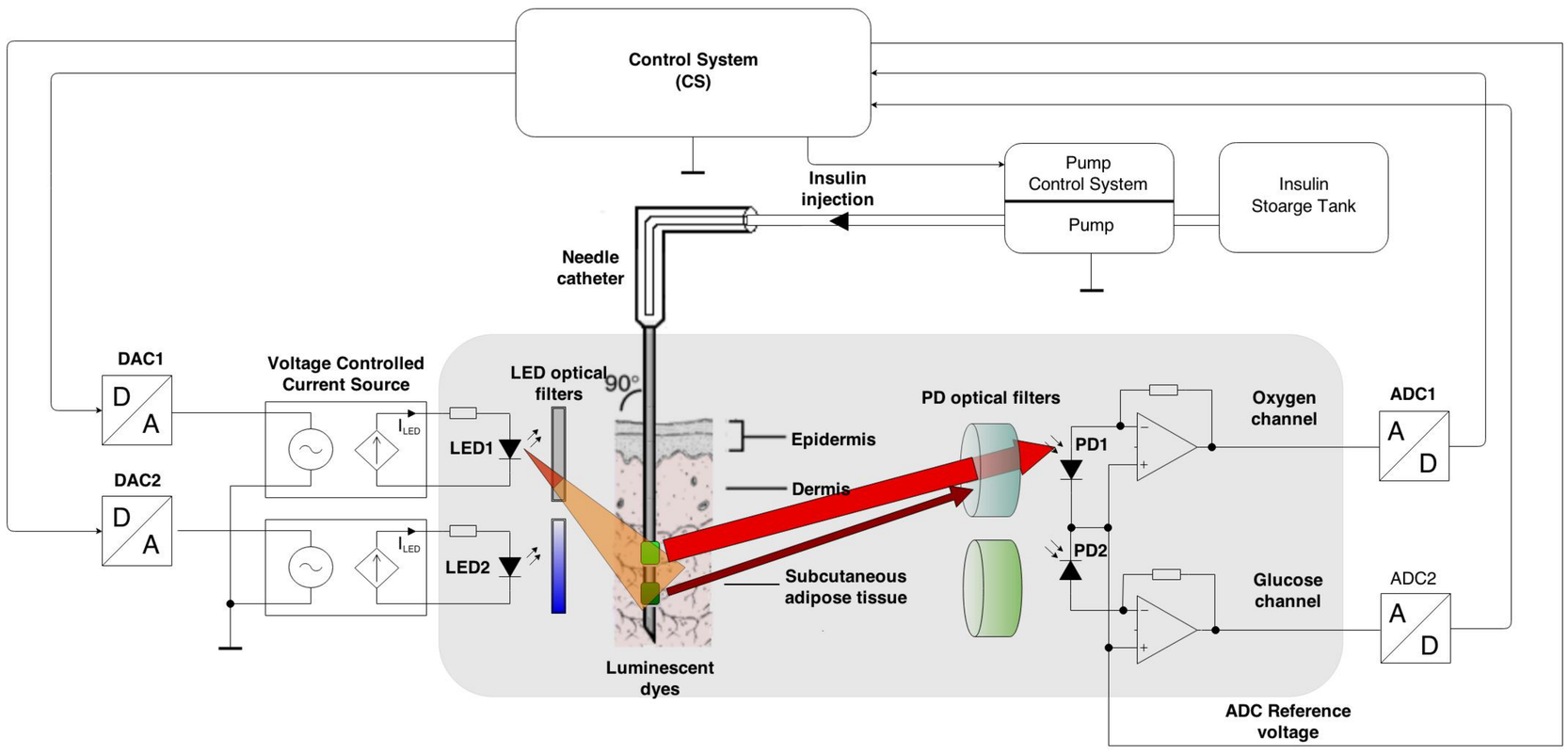

Fig. 1. Functional diagram of the system.

Structurally the device is composed of three parts: (1) optical reader positioned on the skin, (2) glucose and reference sensors grafted on the needle catheter and (3) a control system module. The gray rectangle encloses the components related to the reader as well as the needle with both sensors grafted on it. The second function of the needle catheter is insulin delivering. That is why it is connected to an insulin pump and an insulin storage volume.

Schematically, a structure of the sensor system is shown on the Fig. 2.

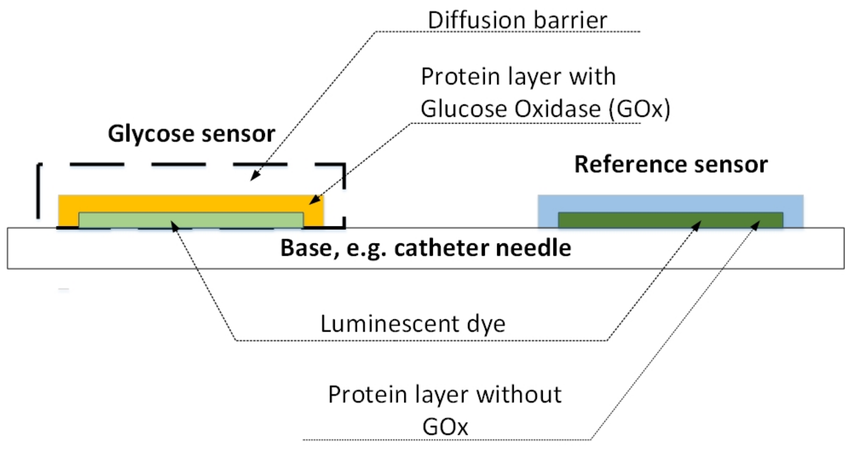

Fig. 2. Sensor system.

Luminescent dye is an oxygen-sensitive phosphorescent layer. It changes its lifetime as a function of oxygen partial pressure, pO2.

Glucose oxidase (GOx) layer composed of Bovine serum albumin (BSA) with a clamped GOx ferment which is aimed to catalyze glucose oxidation reaction according to the equation 1:

$$\beta - D - glucose + O_2 + H_2O \xrightarrow{GOx} D - Glucono - \beta - lactone + H_2O_2 \quad \textbf{(1)}$$

Diffusion barrier is a hydrogel matrix above the sensor. Ideally it is transparent for oxygen but limits the amount of glucose molecules that can reach GOx layer to avoid saturation of the sensor. Apart from that it brings stability of luminescent particles and biocompatibility.

Important steps for the calculation of glucose concentration are:

1. Both sensors get excited one after another with intensity – modulated light of specific wavelengths. Sensors' emitted light mimics the shape of the excitation signal but with a certain delay or phase shift.
2. For each sensor the device measures an amplitude, offset and a phase shift of the emitted light and calculates the lifetime of the respective luminescent sensor dye.
3. Based on the lifetime of both sensors, the amount of oxygen consumed only by the GOx layer within the glucose sensor can be deduced using the Stern-Volmer equation, which let us calculate the glucose concentration (equation 1)

Why the reference sensor is used?

Lifetime of both sensors depends on physiological changes in oxygen partial pressure, pO2. Additionaly the lifetime of the glucose sensor changes due to activity of GOx .

An oxygen sensor next to the glucose sensor is therefore used to correct for physiological changes in pO2. Substraction of the signals from both sensors yields a luminescence signal that depends only on GOx activity and not influenced any more by the varience in pO2 due to physiological processes.

Additionally, each LED and photodiode is equipped with customized optical interference filters ensuring a minimized optical crosstalk between the oxygen and the glucose measurements.

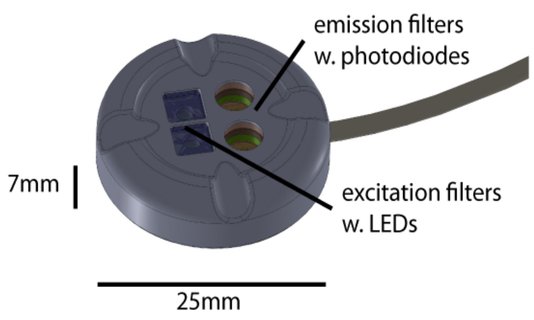

Fig. 3. The reader (bottom view).

3 Background and crosstalk compensation

Along with the "true" signal from the proper sensor, the photodetector(PD) measures additional disturbing components; main of which are presented on the Fig.4.

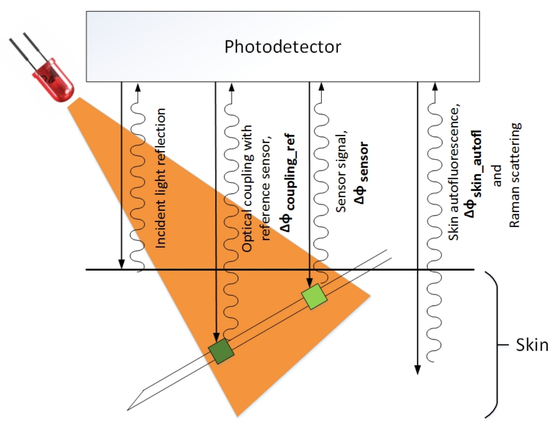

Fig. 4. Factors influencing "true" signal

These additional disturbing components include:

1. Electromagnetic coupling between LED-drivers and PD-amplifiers on printed circuit board (not shown on the Fig.4).
2. Skin autofluorescence and Raman scattering;
3. Optical crosstalk between the two luminescent sensor dyes.

These disturbing components have influence on the measured phase shift and intensity and they decrease the signal-to-noise ratio.

Components 1 and 2 can be compensated manually by a so called "background compensation" with a measurement on a blank skin (before introduction of the sensors).

4 In-vivo proof - of - concept

The proof-of-concept pig trial was done in [1] using 1-st generation reader on a pig model.

The pig was under general anesthetics, maintained with artificial lung ventilation machine. Blood glucose concentration varied during the trial by infusion medical glucose solution intravenously in a range from 23 mg/dL to 287 mg/dL. Blood pO2 was controlled with breath rate adjustment. Every 5 minutes control blood sample was taken from the pig and measured with a blood analyzer. The reader device was measuring phase shifts of glucose and reference sensors.

The results are presented on Fig.5 a,b. Where "blood glucose" and "blood pO2" are the data from blood analyzer machine.

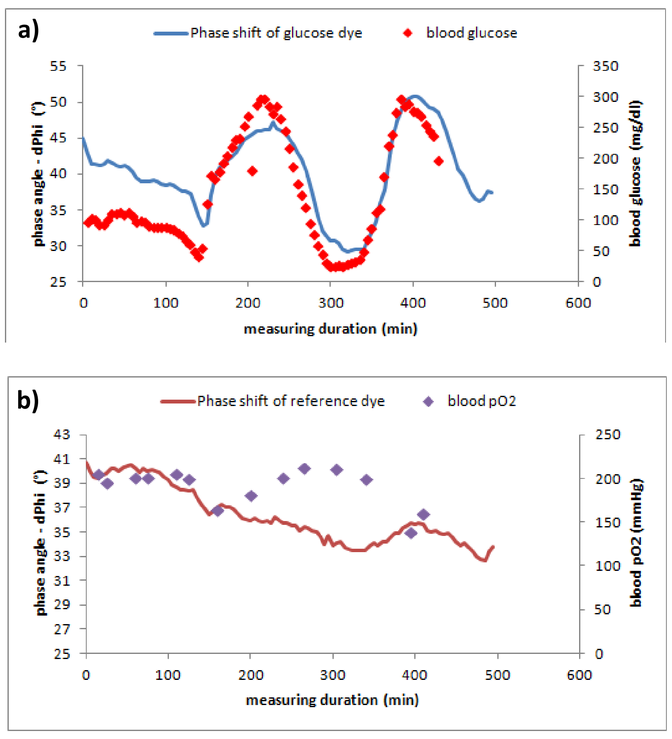

Fig. 5. Phase shift measurements for both fluorescent dyes

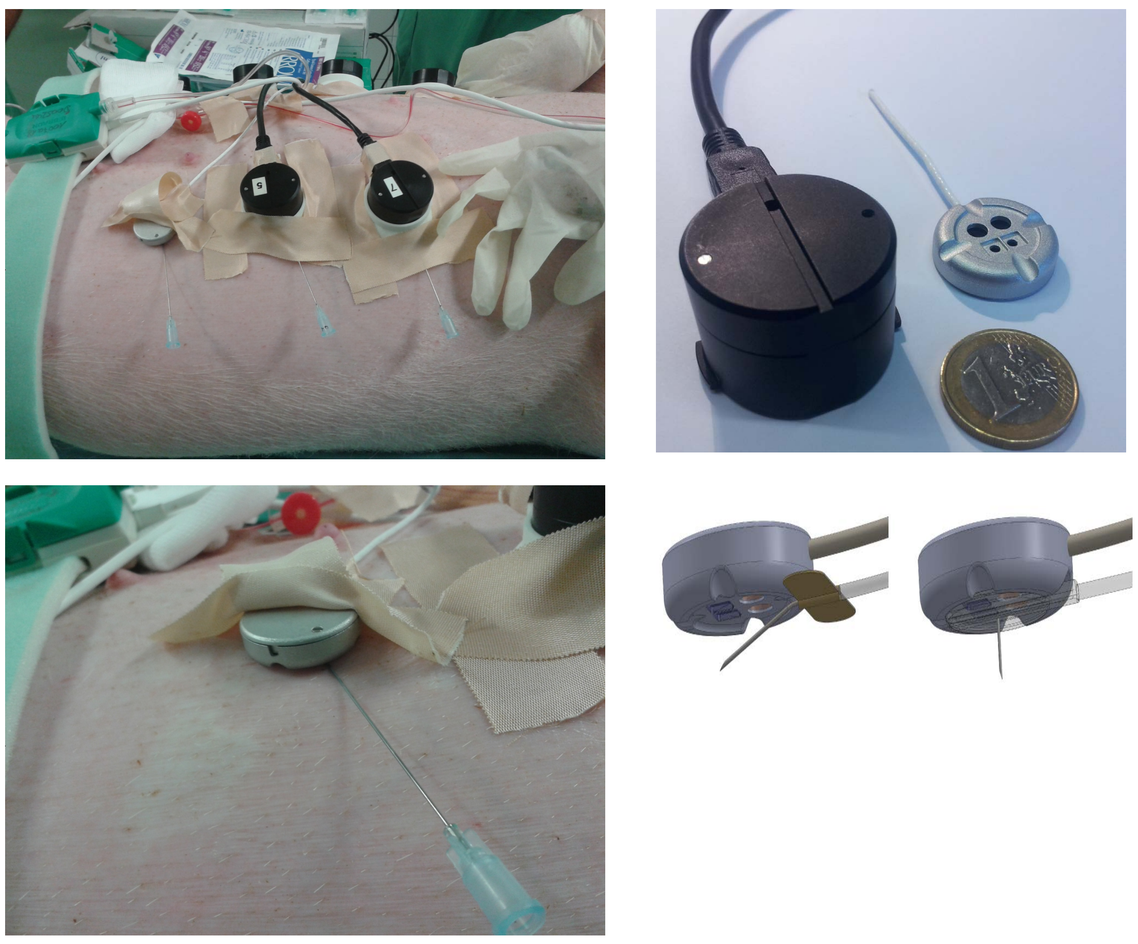

Fig. 6. In-vivo pig trials with the readers of 1st and 2nd (smaller one) generation .

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1. Nacht, B., Larndorfer, C., Sax, S., Borisov, S.M., Hajnsek, M., Sinner, F., List-Kratochvil, E.J.W., Klimant, I.
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