Dynamic Modeling of the Hydrogel Molecular Filter in a Metamaterial Biosensing System for Glucose Concentration Estimation

T. Teutsch[1], M. Mesch[2], H. Giessen[2] and C. Tarín[1]

***Abstract*— We present a novel concept for ophthalmic glucose sensing using a biosensing system that consists of plasmonic dipole metamaterial covered by a layer of functionalized hydrogel. The metamaterial together with the hydrogel can be integrated into a contact lens. This optical sensor changes its properties such as reflectivity upon the ambient glucose concentration, which allows in situ measurements in the eye. The functionalization of the sensor with hydrogel allows for a glucose-specific detection, providing both selectivity and sensitivity. As a result of the presented work we derive a dynamic model of the hydrogel that can be used for further simulation studies.**

I. INTRODUCTION

In the last decades new techniques have been employed to develop noninvasive devices for blood glucose monitoring, especially to enhance diabetes management [1]. To overcome their shortcomings, alternative approaches have been developed to measure glucose concentration in accessible body fluids in order to subsequently estimate blood glucose by using mathematical models. Tear fluid offers great advantages to develop non-invasive monitoring of physiological indicators, including glucose.

Ophthalmic glucose sensing has been developed since the 1930s through different technologies [2]. Many reports state a correlation factor between tear glucose and blood glucose concentration [3], [4]. Integrating a glucose sensor into a contact lens enhances patient comfort even for continuous measurement. Holographic hydrogels, fluorescent indicators and polarimetric lens-based sensors have been presented [5], [6], [7]. The deficiencies lie in resolution and sensitivity, as well as safety problems arising from harming substances that may be released from the lens into the eye.

In this contribution we present a new concept for tear glucose measurement that is based on the use of metamaterials, i.e., artificial materials with special electromagnetic properties that do not occur naturally [8]. The main advantage of metamaterials for this particular application is that they are able to detect even minute changes in the dielectric properties of their environment. Selectivity to a particular type of molecule (glucose in this case) is added by covering the metamaterial with a sensitive hydrogel. As this design is transparent in the visible and near-infrared range it can be designed as contact lens to be inserted into the patient's eye. The readout is carried out by an external light emitting diode (LED) in the infrared (eye-safe range). As depicted in Fig. 1, measured signals are conditioned to estimate the tear glucose levels via an developed inverse model of the system consisting of metamaterial, hydrogel, LED, photodiodes and disturbances.

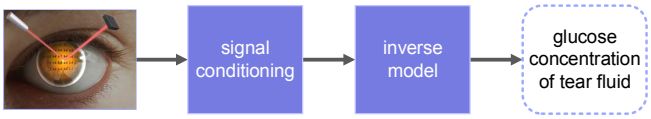

Fig. 1. Glucose concentration estimation of tear fluid via an inverse model of a biosensing contact lens that consists of plasmonic dipole material with functionalized hydrogel.

The main reasons why this new method has the potential to be extremely successful are its selectivity to glucose, guaranteed through the hydrogel; further its sensitivity in the physiological range that is accomplished by the metamaterial; its biocompatibility due to the characteristics of the noble metals of the metamaterial, and its non-degrading during the lifetime of the sensor [9], [10].

In this contribution we are especially focusing on the modeling of the hydrogel acting as molecular filter when embedded in the tear fluid, which is absolutely necessary to guarantee glucose selectivity. For this reason, we feed the real warrant value of the glucose level, i.e., the *ground truth*, into the signal processing stage for the modeling process. In the results the derived dynamic model of the hydrogel, with identified parameters, is presented.

II. METAMATERIALS FOR GLUCOSE SENSING

A. Metamaterials

The metamaterial structures used in these experiments are simple gold nanoantennas, with a single resonance in the near-infrared. They are fabricated by electron beam lithography. Therefore, a positive photo resist is spin-coated on top of a 10×10 mm^2 quartz substrate, allowing the desired structures to be defined by an electron beam. The following development step removes the resist where it had been exposed. Next, 30 - 40 nm of gold are deposited using electron-beam evaporation. At last, the residual resist is removed in a lift-off process, leaving the gold structures on the glass substrate.

B. Biosensing

Commonly, broadband electromagnetic radiation in the optical domain is used to investigate the respective properties

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[1]Institute for System Dynamics, University of Stuttgart, 70569 Stuttgart, Germany, contact: tanja.teutsch@isys.uni-stuttgart.de

[2] 4th Physics Institute, University of Stuttgart, 70569 Stuttgart, Germany, contact: giessen@pi4.uni-stuttgart.de

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of nanostructures in sensing applications. One possibility is the recording of transmittance or reflectance spectra which exhibit characteristic dips and peaks. Due to the localized electric field in and around the metallic pattern, the resonance positions are highly sensitive to changes of the electric permittivity or the refractive index, respectively, in their nearest vicinity. Exploiting this fact allows to monitor for example the concentration of pure solutions on top of the structure by evaluating the shift of a distinct spectral feature [9].

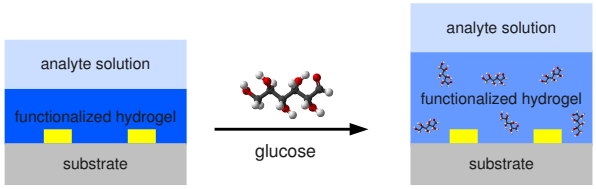


Fig. 2. The principle of sensing with a functionalized hydrogel. The dielectric environment of the structures is changed by the swelling and the induced decrease of the hydrogel refractive index.

Unfortunately, such gold structures are not able to detect specific substances naturally. To realize a chemically selective sensor, one has to assure that the changes in the refractive index are exclusively caused by the desired analyte. For biological sensing, the existence of molecule pairs with strong affinity can be beneficial. One of the molecules can be fixed to the gold and therefore ensure that the other one, the desired analyte, will specifically be attached in the vicinity of the sensitive elements. Ranking among the strongest non-covalent interactions known in nature, the biotin-streptavidin complex, for example, is a commonly used system for proof of concept experiments [11].

From a conceptual point of view, the method of embedding the functionalization into a hydrogel is similar. Hydrogels are polymer networks that, due to their hydrophilic properties, absorb a considerable amount of water which causes substantial swelling. Lee et al. have shown, that replacing several sites in the polymer chains with a molecule, which will form a charged complex with a glucose molecule, establishes a relation between the swelling of the hydrogel and the glucose concentration in the surrounding water [12]. As those changes in volume also imply a varying refractive index, they again are subject to detection by the metamaterial structure.

C. Experimental setup

We use a Bruker Vertex 80 Fourier-transform infrared spectrometer to determine the properties of our samples. The system is extended by a Hyperion 2000 microscope with a computer-controlled 2D translation stage, to allow for exact positioning of the structures. Transmission measurements are carried out with incident light polarized along the long wire axis. The liquids are handled by a custom-made microfluidic system. The flow cell provides a channel with a shape optimized for laminar flow and a height of $50\,\mu$m. Therefore, the absorption of water in the near-infrared region can be reduced to a suitable level. Furthermore, the design enables the easy exchange of samples, retaining constant measurement conditions.

III. Modeling of the Hydrogel Molecular Filter

A. Simulation model

The simulation model as depicted in Fig. 3 consists of block I, the eye-lentil simulator (sample: substrate, metamaterial with surrounding hydrogel, tear fluid equivalent liquid with glucose concentration g_t), block II, the IR spectrometer that provides measurement data on the optical properties of the sample, and block III, a post processing stage relating the transmitted and reflected intensity $I(\lambda_s, t)$ to the glucose concentration in the hydrogel $g(t)$.

The eye-lentil unit (I) is simulated using scattering matrix theory to calculate reflectance, transmittance, extinction and absorption spectra of metallic structures [10]. Additionally, information about the electric and magnetic field distribution can be obtained. For each time step t during a simulation, the IR spectrometer (II), consisting of a IR source and an IR sensor, provides the transmitted and reflected intensities $I(\lambda_s)$ between the optical wavelengths $\lambda_b = 1000\,\mathrm{nm}$ and $\lambda_e = 2500\,\mathrm{nm}$ with $\lambda_{s,i} = \lambda_b + i \cdot \delta\lambda$, for $i = 1, ..., 3111$. The post processing stage (III) contains the methods to determine the glucose concentration in the hydrogel including spectral signal interpolation, centroid calculation, and mapping as further described in subsection III-B.

B. Signal processing

The aim of the post processing stage of the model is to estimate the glucose concentration by the analysis of the optical properties of the sample (see Fig. 3). In order to gain an analytical expression of the spectra for the post processing stage, a high-degree polynomial fit to the spectral data $I(\lambda_s)$ is performed. As illustrated in Fig. 4 the transmittance spectra exhibit a dip, which will be influenced in position and shape by the optical properties of the sample. The analytical expression is used to determine a *characteristic wavelength* [13] that exhibits either a high reflection coefficient or a low transmission coefficient.

Four different methods (see Fig. 4) are applied to obtain the characteristic wavelength in order to compare their performance:

a) Minimum transmittance value: The minimum transmittance value of the spectrum is computed by finding the minimum of the polynomial fit. The fitting helps to avoid falsification due to noise effects.
b) Constant transmittance T_{max}: The centroid is determined from the area between a defined and constant maximum transmittance value T_{max} and the transmittance spectral data.
c) Constant wavelength span $\Delta\lambda$: The centroid is determined from the area of transmittance spectral data up to a transmittance value such that the spectral span $\Delta\lambda$ is held constant.
d) Constant area A: The centroid is determined from the area of transmittance spectral data up to a transmittance value such that the area A is held constant.

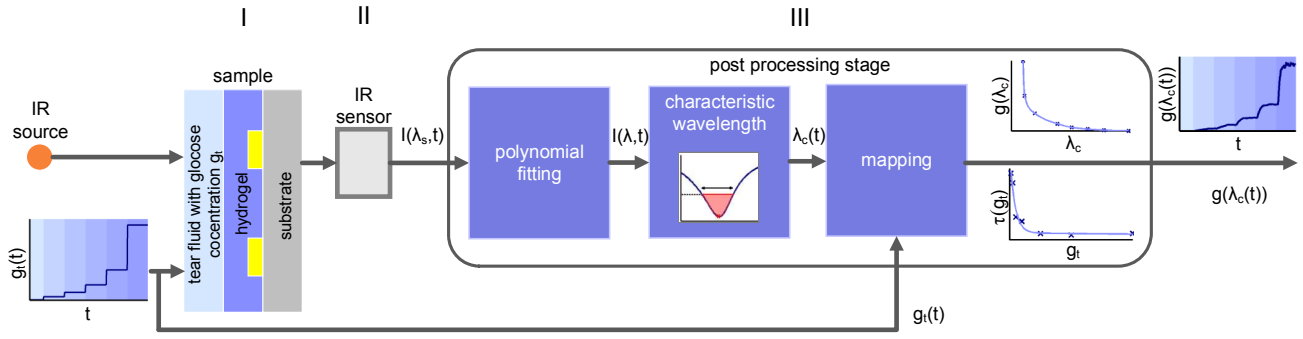


Fig. 3. Block diagram for the estimation of the glucose concentration including a defined glucose solution and with hydrogel functionalized metamaterial.

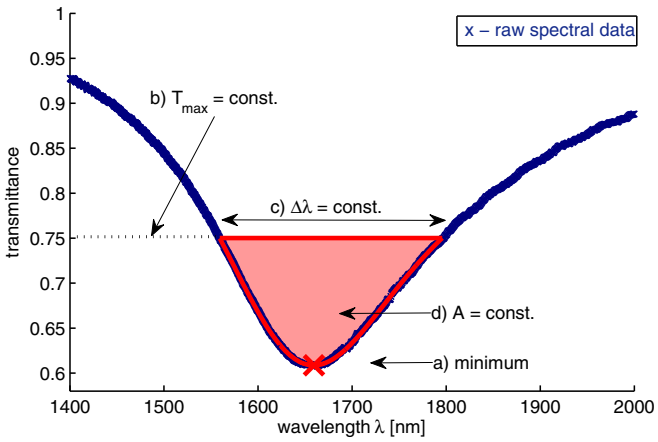


Fig. 4. Four different methods to evaluate the characteristic wavelength: (a) Minimum transmittance value; (b) constant transmittance; (c) constant wavelength span; (d) constant area.

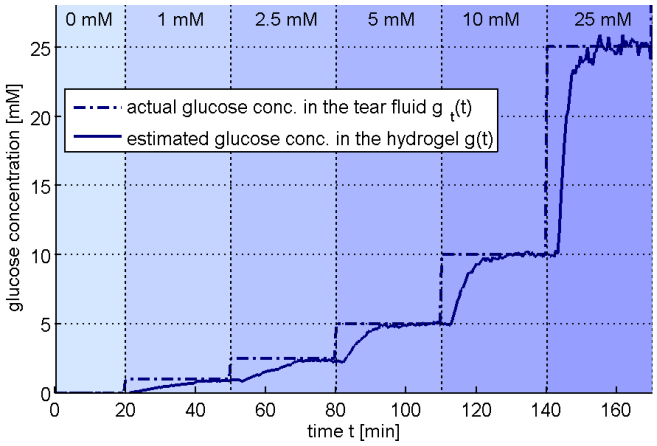


Fig. 5. Temporal course of glucose concentration $g_t(t)$ in tear fluid and estimated temporal course of the glucose concentration $g(t)$ in the hydrogel from the dynamic model.

In the last step of the post processing stage, a mapping of the characteristic wavelength $\lambda_c(t)$ to the glucose concentration in the hydrogel $g(t)$ is conducted. The determination of the mapping from measurement data is described in the following section IV.

IV. EXPERIMENTAL RESULTS AND DISCUSSION

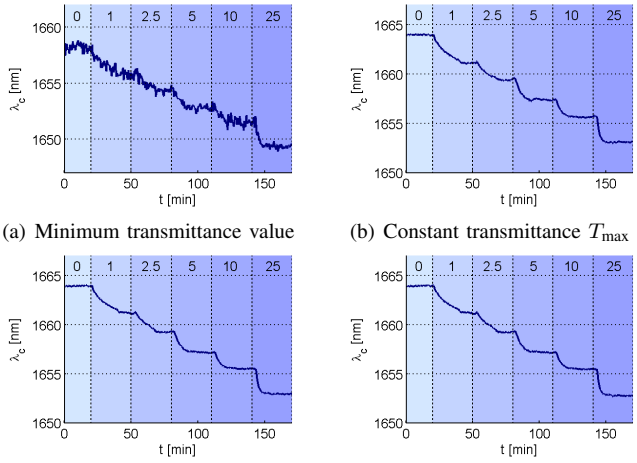
In order to determine the relationship between the glucose concentration g_t in the tear fluid and the characteristic wavelength λ_c steady state measurements are conducted. The glucose concentration of the tear fluid is stepwise increased from 0 mM to 25 mM as illustrated in Fig. 5. All of the used concentrations lie in the physiological range of tear glucose. The duration of each step is 30 minutes, such that the steady state for the system is achieved, i.e., the glucose concentration in the hydrogel is allowed to saturate completely. A transmittance spectrum is taken every 30 seconds to evaluate the temporal behavior of the system. A significant part of raw data obtained using the IR spectroscopy is exemplarily depicted for a glucose concentration of 0 mM in Fig. 4. The data is fit to a polynomial of order 20 by applying least squares to enhance the spectral resolution and to obtain an analytical expression.

At each time step the characteristic wavelength is evaluated and the temporal course of the characteristic wavelength λ_c is shown in Fig. 6 for each of the presented methods a)-d) of section III. Methods b)-d) show similarly smooth signals, which is due to the fact that all of these methods rely on an integration of the spectral signal which obviously eliminated jitter due to noise. Therefore, it is highly recommended not to use only one single frequency for measurement devices but instead use a broadband light source together with a number of photodiodes in the range of interest. The further results of the model are exemplarily shown for method d).

The result of the temporal course of the characteristic wavelength $\lambda_c(t)$ in Fig. 6 shows that the relationship between $\lambda_c(t)$ and the glucose concentration in the tear fluid $g_t(t)$ can be described as a first order model of the following form

$$\tau(g_t(t)) \cdot \dot{\lambda}_c(t) + \lambda_c(t) = K(g_t(t)) \cdot g_t(t). \qquad (1)$$

The glucose concentration dependent time parameter $\tau(g_t(t))$ and the gain $K(g_t(t))$ are identified by the measurement data in a least square sense. Assuming that the dynamic behavior of the glucose concentration in the hydrogel $g(t)$

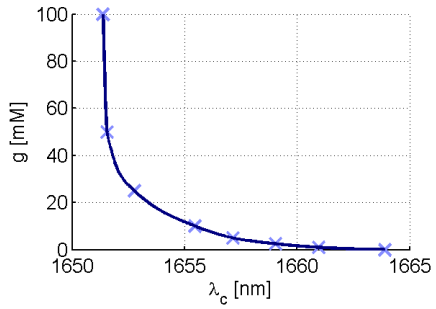


(a) Minimum transmittance value (b) Constant transmittance $T_{\max}$

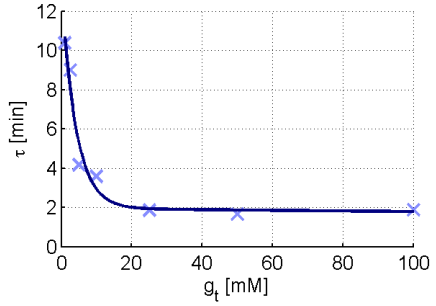
(c) Constant wavelength span $\Delta\lambda$ (d) Constant area A

Fig. 6. Temporal course of the characteristic wavelength $\lambda_c(t)$ determined by methods a)-d).

is equivalent to the dynamic behavior of the characteristic wavelength $\lambda_c(t)$ and that in the steady state the glucose concentration in the hydrogel g is equal to the glucose concentration in the tear fluid g_t, a mapping for the determination for $g(t)$ can be established. The results of the mapping are illustrated in Fig. 7. The developed overall model describes the relationship of the measured IR spectra $I(\lambda_s, t)$ and the glucose concentration in the hydrogel $g(t)$ and leads to the output shown in Fig. 5.



(a) λ_c vs. $g(\lambda_c)$



(b) g_t vs. $\tau(g_t)$

Fig. 7. Determined relationship between a) the glucose concentration in the hydrogel g and the characteristic wavelength λ_c; b) time parameter τ and the glucose concentration in the tear fluid g_t.

V. CONCLUSIONS AND FURTHER WORK

A novel method for tear glucose measurement that is based on the use of metamaterials is presented in this contribution. Using these metamaterials it is possible to quantify physiological glucose concentrations even in the presence of disturbing substances due to the fact that metamaterials are able to detect even minute changes in the dielectric properties of their environment. Glucose selectivity is achieved by covering the metamaterial with a sensitive hydrogel, which acts as molecule filter when embedded in the tear fluid.

The present work is focused on the dynamic modeling of the hydrogel attached to the metamaterial that guarantees glucose selectivity. The real value of the glucose level, i.e., the *ground truth*, is fed into the signal processing stage for the modeling process, which includes, amongst other signal processing stages, the estimation of an equivalent wavelength using different methods in order to estimate the equivalent refraction index of the hydrogel. The obtained results show that a first order dynamic system shows excellent approximation of measured data.

In future investigations this dynamic model will be used to simulate the system under different conditions, such as e.g., glucose concentrations, perturbing substances, metamaterial configuration, LED and photodiode characteristics. Simulated results will be verified through experimental data.

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