Microelectronic Engineering 144 (2015) 23–26

Contents lists available at ScienceDirect

Microelectronic Engineering

journal homepage: www.elsevier.com/locate/mee

Non-ideal biological layer deposition effects on membrane surface stress based biosensor performance

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ARTICLE INFO

Article history:
Received 29 October 2014
Received in revised form 10 January 2015
Accepted 21 January 2015
Available online 30 January 2015

Keywords:
Biosensors
Finite element analysis
Surface stress
Micromembrane

ABSTRACT

Depending on the deposition method used for the immobilization of biomolecules on the surface of a biosensor, spot misalignment and spot inhomogeneity may occur. The biological layer's homogeneity also depends on the functionalization protocol and the potential presence of surface sites with significantly different chemical affinities. These non-ideal situations influence the performance of surface stress based biosensors. Their effects on membrane based sensors are investigated in this work by exploiting finite element analysis (FEA). In the FEA models, the biological layer deposition faults are expressed as non-central deposition of the biological layer and both clamped and simply supported membranes are studied. To simulate the effect of inhomogeneity, several FEA models have been developed, in which voids in the biological layer resemble areas with low chemical affinity. The performance differences between flat membranes and membranes partially in contact to their substrate are also discussed. The FEA results have provided information for explaining experimental issues, such as low reproducibility and signal variations in the same sensor array.

1. Introduction

The stress induced by the biological layer of a surface stress based biosensor is of crucial importance for the device performance. The effectiveness of stress transfer to the sensing element depends on the coverage of the sensor surface by the biological layer and the functionalization method that has been used. Surface stress based biosensors comprise structures of microcantilevers or micromembranes with optical, piezoelectric or capacitive readout [1]. Capacitive readout is facilitated when using micromembranes and is preferable compared to the other detection methods since it enables simpler structures with higher potential for integration into arrays and microfluidic total analysis systems (μTAS). The optimization of the geometry parameters for micromembrane based surface stress biosensors is usually accomplished using finite element analysis (FEA) [1–3]. Typically the sensing layer is considered ideal and thus it is assumed that the stress is effectively transferred from the biological layer to the membrane, without considering alignment errors and spatial stress variations.

It has been proven, both experimentally and through FEA, that partial coverage of flat membranes is better than full coverage in terms of sensitivity [2–4]. Therefore, the need for precise coverage and miniaturized sensing elements leads to the use of controllable deposition techniques. These are mainly contactless techniques such as inkjet printing and laser based techniques [5,6] due to the fact that the sensitive mechanical structures used as the sensing elements of surface stress based sensors are susceptible to break. The alignment errors caused by the deposition methods are in the range of a few μm. The spot misalignment effect is studied in the present work though Finite Element Modeling (FEM).The reduction in the sensor sensitivity is discussed for the cases of simply supported and clamped membranes.

The second effect that is considered in this study is the spot inhomogeneity, as a result of non-ideal deposition or non-ideal immobilization of the receptor molecules. The immobilization of the biomolecules, their grafting density and distribution on the biosensor's surface are important for the effectiveness of stress transfer on the sensor's surface. The consequence of spot inhomogeneity is the formation of surface sites with significantly different chemical affinities and thus variable surface stress values over the sensing area [7–10]. Therefore, the effect of a non-uniform biological layer is investigated in the FE models through the addition of voids in the biofilm. Furthermore, the corresponding results for flat and non-flat membranes are compared, revealing the importance of the initial morphology of the sensing elements.

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http://dx.doi.org/10.1016/j.mee.2015.01.025
0167-9317/

2. Methodology

The sensor that is studied typically comprises a 1 μm thick Si membrane covered by a low temperature SiO_2 (LTO) of 0.5 μm thickness that serves as functionalization and passivation layer [11,12]. The membrane radius is 100 μm and the biological layer above the flexible Si/SiO_2 structure is designed in different patterns depending on the simulation models. A cavity of 0.5 μm depth separates the flexible membrane from its fixed substrate (Fig. 1). A thin SiO_2 layer on the fixed substrate protects the device from short circuit in case of contact between the membrane and the substrate. The fabrication process of the simulated structure involves silicon fusion bonding between two wafers. Typical fabrication processes are described in [12,13]. The simulation results are generalized since the sensitivity values are compared. The sensitivity is defined as the capacitance change after the exertion of the surface stress divided by the initial capacitance of the biosensor ((C–Ci)/Ci). The surface stress applied by the biological layer is considered compressive and equal to 50 mN/m. The stress is expressed as temperature difference [3], according to the following equation that correlates the surface stress (σ_s) and the temperature variation (ΔT) on the thin film of the biological layer:

$$\Delta T = \sigma_s / E \cdot \alpha \cdot t$$

where E and t correspond to the Young's modulus and thickness respectively, whereas α corresponds to the thermal expansion coefficient of the thin film.

In the FEA models the deposition alignment errors are expressed as off-center deposition of the biological layer and the corresponding reduction in sensitivity is calculated for misalignment of a few micrometers. To estimate the effect of spot inhomogeneity, several FE models were developed, where voids in the biological layer were used to emulate different cases of inhomogeneity.

In the case of full coverage or central deposition, the sensor structure is axisymmetric and can be simulated by simple 2D-axisymmetric models. However, in the presence of a deposition fault, the symmetry is lost and 3D models are required. Therefore, the following analysis used 3D FEA models only. The use of 3D models, however, is demanding in terms of computational cost, thus in order to simplify the problem, the supporting SiO_2 layer was omitted and the membranes were considered fixed at their rim.

Furthermore, two types of membrane support were studied: simply supported at the membrane lower edge and clamped membranes fixed at their peripheral boundary. The sensor response practically ranges between these two extreme cases and, depending on the width of the rim over the supporting oxide, is closer to the simply supporting (small rim) or the clamped case (large rim). Both cases of clamped and simply supported membranes are studied for spot misalignment. The comparison between them reveals when the biosensor is more susceptible to deposition faults. Nevertheless, according to the fabrication of the presented biosensors, the sensor structure resembles more the clamped condition [14], thus for the inhomogeneity study clamped membranes are simulated aiming to reveal qualitative results.

Apart from the surface stress applied by the biological layer, additional mechanical forces are also present. These forces include the initial stresses exerted on the membrane such as the stress due to the deposition of the LTO layer and the intrinsic stress of the Si membrane, or forces related to the fabrication conditions such as a difference between the ambient pressure and that in the cavity. For thin membranes and small cavity depth, the membrane deformation due to the above mentioned factors can be larger than the cavity depth thus forcing it to become partially in contact to the fixed substrate. To investigate the performance of the biosensor when the membrane touches the substrate, the substrate is simulated by an extra domain that restricts the downward deflection of the membrane and the consequent results' variations in terms of sensitivity are considered.

3. Results and discussion

3.1. Effect of spot misalignment

In Fig. 2 the FE model of a misaligned biological layer deposited on the membrane surface is presented. The radius of the biological layer spot is 70% of the radius of the membrane since previous FE and experimental results have shown that this is the optimum surface coverage for flat membranes ideally spotted [3,4]. The form of a membrane with the biological layer spotted in the center of its surface and a membrane with the biological layer spotted off-center are depicted in Fig. 3a and b, respectively.

The results for the two extreme cases of the membrane support (clamped and simply supported) are presented in Figs 4 and 5. Fig. 4 shows the differences in the way that the membrane is deflected. The simply supported membranes are deflected more than the clamped ones, as theoretically expected. Since the sensitivity of simply supported membranes is higher than that of clamped ones, in Fig. 5 the normalized to unity values of (C–Ci)/Ci are compared. It is observed that the sensitivity reduction is more pronounced for clamped membranes and large alignment errors indicating that the clamped membranes are more vulnerable to spot misalignments.

Taking into account that the spot alignment error due to the deposition method can be practically less than 5 μm [5,6], the sensitivity reduction for 70% radial coverage can be less than 2%. However, these results show that signal variations between similar sensors in the same array may be attributed to spot misalignment.

3.2. Effect of inhomogeneity of the biological layer

To study the effect of spot inhomogeneity, FE models with voids in the biological layer were developed. The specific conditions

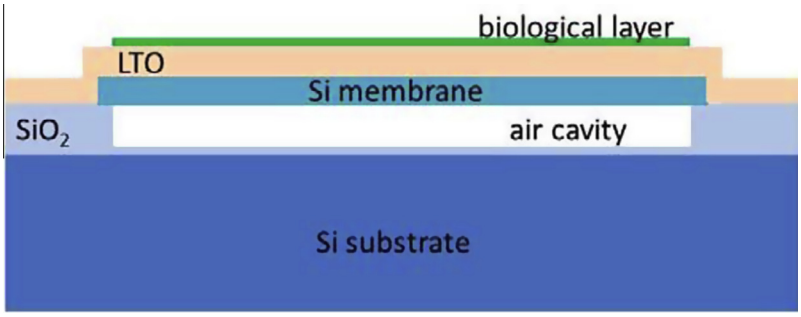

Fig. 1. Cross-section of the biological sensor's structure.