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BioMEMS for Processing and Testing of Hydrogel-Based Bio-Interfaces

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Abstract

A BioMEMS platform for development, processing and testing of hydrogels is presented. It is based on standard silicon micromachining including smart assembly and interconnection techniques. Hydrogel materials can be brought into the device by several methods. Material tests and functionalizations of the hydrogels can take place in the system as well as cell cultivation for biotests. First results are promising for easy and parallel testing of several materials / samples and for further biomedical applications.

1 Introduction

Hydrogels on solid material surfaces offer a wide range of applications in biomedical devices, mechanical implants with enhanced functionalities, sensors in biosystems and sensors for biochemical processes. However, they have to be applied to the surface of a carrier material, covalently attached and ideally patterned in 3D to gain maximum performance. All these processes are challenging due to the swelling behaviour of most hydrogels. We present a microfluidic system for development, processing and testing of hydrogels.

2 Methods

The combination of hydrogel materials and BioMEMS components requires new ways of implementation as most micromachining processes are not compatible to fragile polymer components or their functionalized surfaces.

2.1 BioMEMS

Basically, the BioMEMS platform is the housing for hydrogel carrier components. It is based on standard micro fabrication technology with silicon substrates (100 mm diameter). The silicon wafer gets dry etched on front and backside to generate trenches, chambers and holes for the microfluidic functionalities. Then there is a special dry etching step on the backside of the wafer, the so called 'Black Silicon Process' which leads to areas with nanostructured surfaces. Needle-like features enable several smart assembly processes to connect the devices to the microfluidic environment. Assembly with polymer adaptors as direct adhesive-free tube connections realizes low dead volume and particularly biocompatibility.
The front side of the substrate is covered with a glass wafer (Borofloat®) by anodic bonding to allow optical access and to close to the microfluidic chambers and channels. As said before, additional silicon components can be plugged into the microsystem from the backside via Velcro®-like interface areas, see also [1]. They have got two functionalities. On the one hand they serve as a carrier to allow the implementation of 3D hydrogel structures or pre-cultured cells on polymeric scaffold structures [2].
On the other hand they form a plug to seal the system securely. Figure 2 shows a front view of the microfluidic device with four tube connectors (Luer) assembled and a carrier/plug.

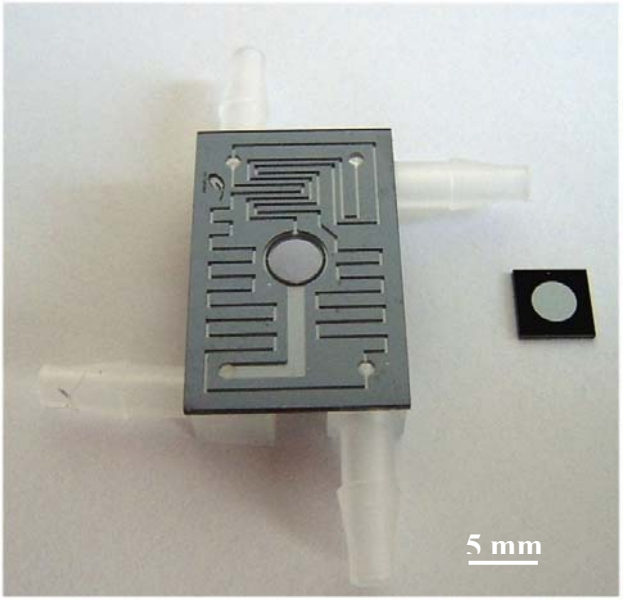

Image 1 modular microsystem with tube connector (left) and a modular carrier/plug (right)

Free flowing polymer components are moved randomly inside the chamber by fluidic forces, so online monitoring is a challenge.
There are two ways of permanently localizing the hydrogels: utilizing surface morphologies with dramatically increased adhesion and/or nanostructures with undercuts, fixing can be combined in order to employ both mechanical and physical fixation. On the other hand, a chemical modification of the carrier surface for a covalent bonding of hydrogels is always favorable, if possible. If the carrier

is inserted into the BioMEMS chamber, the following experiments are possible:

- Flow-through / cross-flow of substances (incl. automated layer-by-layer coatings)
- Mechanical loading / testing (hydrostatic, sheer forces, deformation)
- Chemical stability tests / long term stability
- Temperature control / temperature ramp experiments
- Online-monitoring, and simplified biocompatibility testing

2.2 Coating of scaffolds and hydrogels

An easy and scalable way of functionalizing scaffolds or hydrogels is a coating. Functionalities targeted span antibiotic drug delivery to avoid inflammation, growth initiating factors for faster body incorporation, coatings preventing encapsulation and rejection of the implants, cell adhesion promoters as well as bio repellents (to prevent clogging or biofilm growth). We use a Layer-by-layer approach to generate multiple coatings.

Beside the shown microsystem three syringe pumps VP9101 (STRATEC Biomedical Systems AG, Birkenfeld, Germany) with 5 ml syringes are components of the entire system. One pump is for distilled water, one for high molecular weight carboxymethyl dextran (CMD) and one for high molecular weight aminodextran (AMD). They are operated by a PC with custom-tailored, LabView®-based control software. UNF tube fittings for tight connection and guiding and 1/16 inch Teflon® tubes are used to connect pumps, microsystem and waste container. Image 2 shows a scheme of the system configuration and image 3 the real experimental setup.

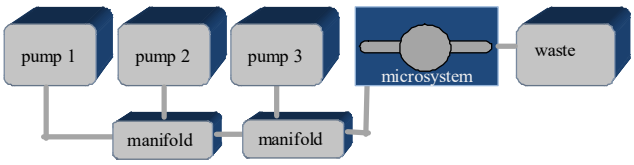

Image 2 scheme of system configuration for layer-by-layer coatings

2.2 Analytics

After the testing / handling of the hydrogels inside the BioMEMS some subsequent evaluation of the hydrogel structures and the biointerfaces can be of great interest. For quantitative analysis such as ellipsometrical measurements, x-ray photoelectron spectroscopy (XPS) and auger electron spectroscopy (AES) etc. free access to the coated surface is required for the beams to get in direct contact with the surface. For completely closed microstructures (as in most cases) this can be only done by destruction of the system. Our approach offers a soft removing of the implemented polymer components by simply pulling out the silicon plug (carrier).

Image 3 experimental setup from left to right: distilled water in a reservoir on a hot plate, three pumps, tubes, manifolds, reflected-light microscope, connected microsystem, trash bin and PC in the background

3 Results

We have manufactured and implemented BioMEMS into standard lab procedures and fluidic setups. Image 4 shows a polymer scaffold implemented into a BioMEMS via an orifice in the backside which is sealed by a silicon plug.

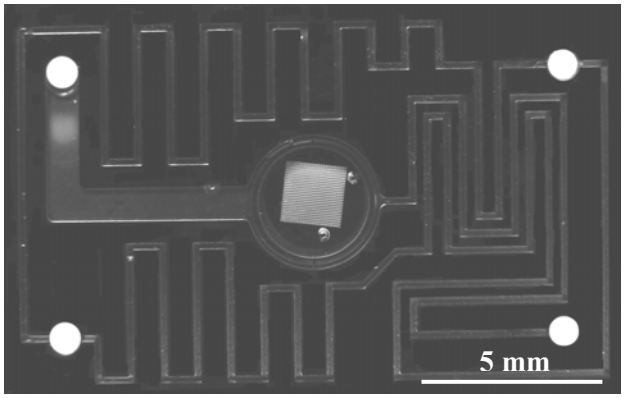

Image 4 hydrogel scaffold in a filled BioMEMS for cell culture

First experiments with an automated layer-by-layer coating on silicon plugs (3 mm in diameter) were successful. Image 5 shows a stack of 12 layers (CMD, AMD, …) with a total thickness of about 36 nm, measured by ellipsometry. Thus, an individual average thickness of the layers was estimated to be 3 nm. These results correspond to conventionally dipcoated single layers which have a layer thickness between 3 and 5 nm [3].

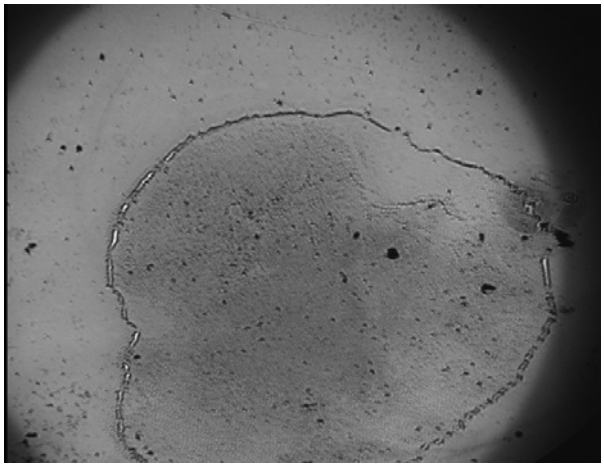

Image 5 image of the multilayers recorded by ellipsometry (circular structure in the right lower region)

4 Conclusions

BioMEMS for processing and testing of hydrogels on solid state surfaces are a useful tool for biomedical and biochemical research. Modern implants can be improved, sensors can attain higher sensitivity and a many product surfaces can be made bio-compatible or bio-inert, all by using differently functionalized hydrogels. Our microfluidic microsystems will be able to facilitate the entire manufacturing process, including functionalization and some of the primary testing.

5 References

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