(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
1 July 2010 (01.07.2010)

PCT

(10) International Publication Number
WO 2010/072257 A1

(51) International Patent Classification:
C12N 11/14 (2006.01) *C12M 1/42* (2006.01)
C12N 13/00 (2006.01)

(21) International Application Number:
PCT/EP2008/068217

(22) International Filing Date:
23 December 2008 (23.12.2008)

(25) Filing Language: English

(26) Publication Language: English

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

(54) **Title**: METHOD, DEVICE AND SYSTEM TO CONTROL ADHESION, GROWTH AND/OR BIOFILM FORMATION OF PROKARYOTIC CELLS

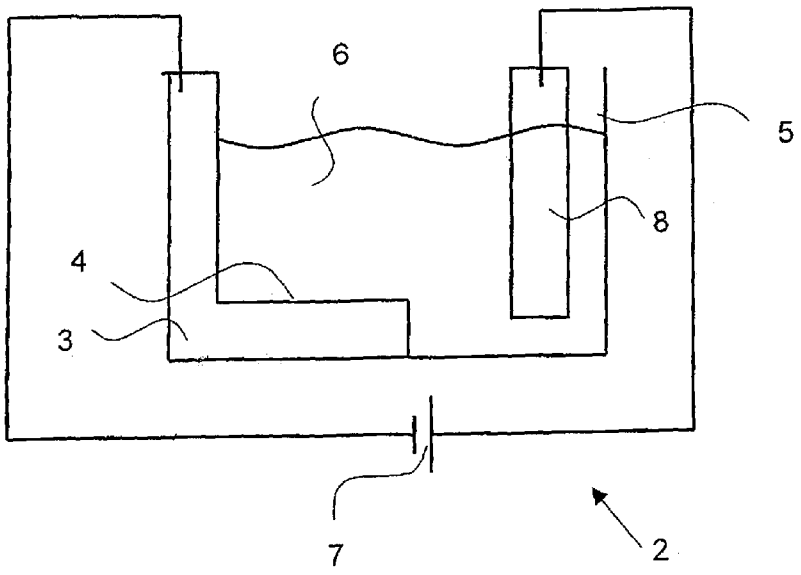

Fig. 1

(57) **Abstract**: A method to control adhesion, growth and/or biofilm formation of prokaryotic cells on a cell interaction surface of an electrochemically active element comprises bringing a medium comp rising prokaryotic cells into direct contact with the cell interaction surface, and providing an activation potential to the electrochemically active element.

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METHOD, DEVICE AND SYSTEM TO CONTROL ADHESION, GROWTH AND/OR BIOFILM FORMATION OF PROKARYOTIC CELLS

Technical field

The present document relates to a method, device and system to control,e.g. counteract or promote adhesion, growth and/or biofilm formation of prokaryotic cells on a surface.

Background

A biofilm is a structured community of microorganisms encapsulated within a self-developed polymeric matrix and adherent to a living or inert surface. Biofilms are also often characterized by surface attachment, structural heterogeneity, genetic diversity, complex community interactions, and an extracellular matrix of polymeric substances.

Bacterial biofilm formation is a serious problem in medical devices, industrial set up, antibiotic resistance and many other associated areas. Small amount of moisture and a surface allows the bacteria to form biofilm. Bacteria produce different matrix substances and many of the adhesion molecules to attach on a surface. Attachment could help the bacteria to re-infect or colonize the host. In other situations biofilm formation is beneficial. The polymeric matrix can be harvested and used as material for industrial and medical applications. It is hence desirable to control the adhesion, growth and biofilm formation of bacteria on a surface.

WO 2005/053836 disclosed a wettability switch that comprises an electrochemically active element having a wetting surface with switchable wetting properties. The electrochemically active element comprises an electro-active polymer and surface active molecules each having a lyophobic portion and a lyophilic portion. Each of said surface active molecules exposes

one of said lyophobic portion and a lyophilic portion towards the wetting surface depending on the electrochemical state of the polymer.

Summary

It is an object of the present disclosure, to provide an improved or alternative method and device to control adhesion, growth and/or biofilm formation of prokaryotic cells, on a surface.

The object is wholly or partially achieved by a method and a device according to the appended independent claims. Embodiments are set forth in the appended dependent claims, and in the following description and drawings.

According to a first aspect there is provided a method to control adhesion, growth and/or biofilm formation of prokaryotic cells on a cell interaction surface of an electrochemically active element. The method comprises bringing a medium comprising prokaryotic cells into direct contact with the cell interaction surface, and providing an activation potential to the electrochemically active element.

By ”cell interaction surface” is meant a surface to which the cells may adhere to, and grow or die or be prevented from adhering to, i.e. repelled or otherwise interfered with such that the cells do not adhere and grow on the surface.

Hence, the method may be used for promoting or counteracting bacterial growth, e.g. the formation of so called biofilm on various types of surfaces.

The electrochemically active element may comprise an electrochemically oxidizable and reducible and electrically conductive polymer.

The use of electro-active polymers or “conducting polymers”, may provide remarkable opportunities to electrically control cellular processes such as adhesion, growth and biofilm formation due to the unique properties of these materials. Conducting polymers are easy and relatively cheap to use, and therefore may provide an outstanding single-use analysis concept. The

conducting polymers may be processed from solution and their inherent physical and chemical characteristics make them suitable for all-printed and flexible electronic systems, such as paper-like displays, electronic tags and single-use analysis systems. The conductive polymers may be coated onto a wide range of devices and substrates and they may be selected to be biocompatible, and hence offers good use in cellular studies.

Different conducting polymers may provide different adhesion patterns for different types of cells, i.e. different cells may adhere more or less to different types of electro-active polymers. This may be used as a way of specifically controlling the adhesion of the cells or cell types both in quantitative and qualitative terms.

The polymer may be selected from a group consisting of polyacetylene, polyaniline, polypyrrole, polythiophene, poly(phenylsulfide), poly(phenylenevinylene), polysulfones, polyethylenedioxythiophenes, poly(p-phenylene), poly(p-phenylene vinylene), polypyridines, polyquinoxalines, polyanthraqinones, poly(n-vinylcarbazole) and derivates, copolymers and mixtures thereof.

The polymer may be doped with a dopant selected from a group consisting of anions, including halogenes (such as Cl^-, I^-, F^-, Br^-); ClO4-, S^{2-}, polyanions, such as polystyrene sulphonate (PSS^-); amphiphilic ions including octylbenzenesulfonte (OBS), dodecylbenzenesulfonate (DBS) tosylate, phosphates, sulfates, sulfonates, carboxylates, surfactants in general; charged biomolecules including proteins, artificially modulated proteins, drugs, amino acids, DNA, RNA, peptides, growth factors, hormones, proteoglycans, glycoproteins, glucose amino-glucans, neurotransmitters, or combinations and mixtures thereof.

By doping the electro-active polymer, or “conducting polymer” with a proper dopant increased conductive properties of the polymer may be achieved. To this effect the dopant may optionally be exchanged with different molecules and ions in the medium or remain bonded to the electro-active polymer.

Different dopants may provide different adhesion patterns for different types of cells, i.e. different cells may adhere more or less on different types of electro-active polymers doped with different types of dopants. This may be used to specifically control the adhesion of different types of cells to the surface.

The provision of dopants in the conducting polymer may be adjusted or controlled such as to counteract or promote the adhesion, growth and or biofilm formation of bacterial cells on various surfaces. The dopants may be released into the medium and hence may influence or disturb the normal cell signalling between the bacterial cells. The dopant may thus act as a blocking agent directed towards the bacterial cell signalling molecules. Alternatively the release of dopants from the polymer may allow for the bacterial cell signalling molecules to be electrochemically drawn into the polymer in a manner readily conceived by a person skilled in the art.

The electrochemically active element may comprise two electrode portions, wherein different electric potentials are provided to said different electrode portions.

Hence, there may be provided at least two surfaces, with different redox states, i.e. reduced and oxidized respectively, in contact with the same medium, this may allow for simultaneous studies of cells on both the oxidized and reduced surface, while undergoing the same experimental conditions.

The method may allow for the creation of functionalized cell culture systems that may be electrically biased, i.e. provided with an activation potential that causes different redox states of the electrodes, which gives great advantages in microbiology research. The biasing of the electro-chemically active elements may achieve a dynamic control of surface tension, chemistry and charge.

At least three different cell adhesion zones may be controlled to provide mutually different cell adhesion characteristics.

By “controlled to provide” is meant that the cell adhesions zones may be provided with different potentials, may comprise pre-treated materials,

such as electro-active polymers doped with specific dopants. This may e.g. provide for potential gradients in the zones.

At least two of the cell adhesion zones may be provided with different potentials.

By different potentials may also mean different redox states, such as positive, negative and zero.

By different potentials may also mean alternating potentials of different shapes, such as square, triangel or sinus wave and frequecies.

By the zones being provided with different potentials there may be provided a way to spatially control the adhesion of cells or to extract different types of cells to a specific zone.

At least two of the cell adhesion zones may be provided with substantially the same potential, but with different inherent cell adhesion properties.

By “inherent cell adhesion properties” is meant that the adhesion zones may comprise an electrochemically active element, or, in effect, a conducting polymer which has been doped with a particularly suitable dopant or otherwise pre-treated or coated. The material of the electrochemically active element, i.e. the conducting polymer itself may also exhibit properties which make it especially suitable for adhesion, growth and/or biofilm formation of specific cells or cell types. The material of the electrochemically active element, i.e. the conducting polymer itself may also exhibit properties which make it especially suitable to prevent adhesion, growth and/or biofilm formation of specific cells or cell types.

At least two of the cell adhesion zones may be provided with different potentials and with different inherent cell adhesion properties.

The prokaryotic cells may be selected from prokaryotic cells in different phases of growth.

Hence, it is possible to interact with bacterial cells at different phases, i.e. replicating planktonic or biofilm forming.

Hence the method may e.g. be used to select viable prokaryotic cells from dead cells.

The cell may be selected from transformed cells or in other ways genetically modified cells.

Hence, the method may, e.g. be used for selecting cells that have been successfully transformed.

The electrochemically active element may be coated onto a device or structure for cell culture.

Hence, the element may be coated onto e.g. a petri dish etc and thereby creating a “functionalized cell culture system”.

The electrochemically active element is coated onto a device or structure adapted for insertion or implantation into a human or animal body.

Thus, the device or structure may be selected from a group consisting of sutures, bone screws, nails, plates, tubes, sheets, stents, catheters, guide wires, sheaths, leads, outer tubings, inner tubings, trocars, stylets, embolic coils, part of a filter devices, parts of endoscopes, parts of gastroscopes, dilation balloons, knifes, needles, scissors, pliers, tweezers, guide wires, spheres and clamps.

By coating the electrochemically active element or in effect the conducting polymer onto e.g. a medical implant, such as a catheter, there may be provided a method for controlling the formation of biofilm on the medical implant. This may be advantageous due to the fact that bacterial biofilm formation is a major problem in medical care today, and a key cause of complications arising when implanting different devices.

The electrochemically active element may be at least partially coated onto a device or structure adapted for storage, transportation or immersion.

Adhesion, growth and/or biofilm formation of prokaryotic cells on the cell interaction surface may be promoted by providing said activation potential as a positive potential.

In the alternative, adhesion, growth and/or biofilm formation of prokaryotic cells on the cell interaction surface may be counteracted by providing said activation potential as a negative potential.

According to a second aspect, there is provided a device adapted for interaction with a medium comprising prokaryotic cells. The device may

comprise an electrochemically active element having a cell interaction surface, adapted for direct contact with the medium, and means for providing an activation potential to the electrochemically active element.

By this device it may be possible to control the adhesion, growth and/or biofilm formation of prokarytic cells on a cell interaction surface.

By this device it may be possible to control the adhesion or desorption of e.g. bacterial cells to a specific surface by bringing the medium, including prokaryotic cells in contact with the surface and providing an activation potential, thereby causing adhesion or repulsion of the desired cells. This may allow for a system which is easy and quick to use, which is essential in e.g. different cell studies and analysis methods, but also for counteracting or promoting growth of bacterial cells, or e.g. the formation of biofilms on various surfaces.

The prevention or promotion of bacterial cells may be advantageous in different clinical or industrial applications, e.g any system where water or other aqueous fluids, including emulsions, circulate or is contained. To this effect the system may both be organic, i.e. substantially within a human or animal body or a mechanical system transporting fluids. One example of a mechanical system may be the inside of the piping and tanks of a “dairy system”, where milk is transported in pipes from a cow to a collection tank and subsequently to a dairy or similar refining facility.

The electrochemically active element may comprise an electrochemically oxidizable and reducible and electrically conductive polymer.

At least two of the cell adhesion zones may be individually controllable.

By individually controlling the adhesion zones there may be a way of specifically controlling the cell adhesion in a specific zone.

In the alternative, or as a complement, at least two of the cell adhesion zones may be collectively controllable.

The cell adhesion zones may be arranged on an elongate substrate.

Examples of such elongate substrates may be e.g. a fibre, mesh, mat, grid, extracellular matrices both artificial and biological, catheter, needle etc.

The cell adhesion zones may be substantially co-planar.

The cell adhesion zones may face different directions.

The adhesion zones may e.g. be curved or comprise multiple facets etc. The adhesion zones may e.g. be arranged on the outside or inside of a tube.

At least one of the cell adhesion zones may present a cell adhesion surface which is at least partially curved.

At least two cell adhesion zones may present cell adhesion surfaces which are arranged in different planes.

The cell adhesion zones may be provided on a common substrate.

At least two of the cell adhesion zones may differ with respect to inherent cell adhesion properties.

By “inherent cell adhesion properties” is meant that the adhesions zones may comprise an electrochemically active element, or, in effect, a conducting polymer which has been doped with a particularly suitable dopant or otherwise pre-treated or coated. The material of the electrochemically active element, i.e. the conducting polymer itself may also exhibit properties which make it especially suitable for promoting or counteracting the adhesion of specific prokaryotic cells or cell types.

The electrochemically active element may be at least partially coated onto a device or structure adapted for cell culture.

To this end the element may be coated onto e.g. a petri dish or into a well of cell culture plate or plastic foil etc.

The electrochemically active element may be at least partially coated onto a device or structure adapted for insertion or implantation into a human or animal body. Such a device or structure may be selected from the group consisting of sutures, bone screws, nails, plates, tubes, sheets, stents, catheters, guide wires, sheaths, leads, outer tubings, inner tubings, trocars, stylets, embolic coils, part of a filter devices, parts of endoscopes, parts of gastroscopes, dilation balloons, knifes, needles, scissors, pliers, tweezers, guide wires, spheres and clamps.

Hence, the device may be coated onto a device adapted for insertion into an in vivo system, and hence may be used to prevent or promote biofilm formation on e.g. a catheter, which may be intended for prolonged use within the human body.

The electrochemically active element may be at least partially coated onto a device or structure adapted for storage, transportation or immersion.

To this end the device or structure may be a container or a tank for liquid or fluid material, or a tube for transportation of a liquid, such as cooling systems, radiators, pipe lines etc.. The device may further be an immersion heater or a stirrer.

According to a third aspect, there is provided a system for interaction with a medium comprising prokaryotic cells. The system comprises a device as described above, and a power supply, which is connectable to provide said activation potential.

Brief Description of the Drawings

Embodiments of the present solution will now be described, by way of example, with reference to the accompanying schematic drawings.

Fig. 1 shows a schematic cross-sectional view of one embodiment of a system to prevent or promote adhesion, growth and/or biofilm formation on a surface according to the invention;

Fig. 2 shows schematically the molecular structure of PEDOT;

Fig. 3a shows schematically the structure of dodecylbenzenesulfonate (DBS);

Fig. 3b shows schematically the structure of heparin;

Fig. 4 shows a schematic cross-sectional view an alternative embodiment of a system to prevent or promote adhesion, growth and/or biofilm formation on a surface according to the invention;

Fig. 5 shows a schematic cross-sectional view an alternative embodiment of a system to prevent or promote adhesion, growth and/or biofilm formation on a surface according to the invention;

Fig. 6 shows a schematic cross-sectional view of an alterative embodiment of system to prevent or promote adhesion, growth and/or biofilm formation on a surface according to the invention;

Fig. 7 shows a schematic cross-sectional view of an alternative embodiment of system to prevent or promote adhesion, growth and/or biofilm formation on a surface according to the invention;

Figs 8a and 8b show a schematic cross-sectional side view of two electrochemically active elements on a substrate;

Fig. 9 shows a schematic side view of an alternative embodiment of the electrochemically active elements;

Fig. 10 shows a schematic top and side view of an alternative embodiment of the electrochemically active elements;

Fig. 11a shows a schematic top view of one embodiment of the electrochemically active elements;

Fig. 11b shows a cross-sectional view of along the line A-A of Fig. 11a;

Fig. 12 shows a schematic top view of one embodiment of the electrochemically active elements;

Fig. 13 shows a schematic view of one embodiment of the electrochemically active elements.

Description of Embodiments

The terms electrochemically active element and electrode or “pad” will be used interchangeably throughout the description. A further description of the electrochemically active element will be given below in the materials and methods part.

In the below description the expression “device to control adhesion, growth and/or biofilm formation on a surface” has consistently been abbreviated to “the device” .or

The term “prokaryotic cells” have been abbreviated to “cells” or may be used interchangeably with the term bacterial cell(s).

The electrochemically active element 3 shown in Fig. 1 has a cell interaction surface 4, which is a surface onto which cells may adhere to;

adhere and die; or adhere and grow, or/and promote biofilm formation or be prevented from adhering to, or/and prevent biofilm formation under suitable conditions.

The term cell interaction surface and cell adhesion surface will however be used interchangeably throughout the description.

However, the cell adhesion surface 4 is controllable to control cell adhesion on the cell adhesion surface 4, i.e. the cell adhesion surface 4 has controllable cell adhesion properties. Thus, the adhesion of cells on the cell adhesion surface 4 may be controlled according to the invention. This will be further described and exemplified below.

The term “cell culturing” is herein intended to encompass all stages in cell culturing on a cell adhesion surface, i.e. adhesion, growth as well as release or desorption of cells. The term “cell adhesion properties” refers herein to properties of the cell adhesion surface 4 that influence cell adhesion on the surface 4, i.e. properties that influence the success of cell adhesion on the surface 4 and to what extent cell adhesion will be successful.

Furthermore, the term “control” of cell adhesion is herein intended to mean both to control, i.e. regulate or change, cell adhesion such that cell adhesion is counteracted or inhibited on a cell adhesion surface and to control or regulate cell adhesion such that cell adhesion is promoted on a cell adhesion surface. By the term “promote” adhesion, growth and/or biofilm formation of prokaryotic cells on the cell adhesion surface 4 it is herein meant that adhesion of cells to the cell adhesion surface 4 is promoted; that adhesion of cells to the cell adhesion surface 4 and growth of cells adhered to the cell adhesion surface 4 are promoted. By the term “counteract” adhesion of cells on the cell adhesion surface 4 it is herein meant that adhesion of cells to the cell adhesion surface 4 is counteracted or inhibited; that cells adhered to the cell adhesion surface 4 are repelled from the cell adhesion surface 4; or that cells adhered to the cell adhesion surface 4 are inhibited from growing or induced to die.

According to the first aspect of the present disclosure at least some of the cell adhesion properties of the surface 4 may be controlled. More

specifically, at least some of the cell adhesion properties may be controlled such that adhesion of a certain cell type on the cell adhesion surface 4 is promoted or counteracted. This will be further described below.

The cells or cell "types" that may be promoted or counteracted to adhere to the surface 4 will be discussed in more detail below under materials and methods.

Furthermore, the electrochemically active element 3 may comprise an electro-active polymer or a so called conducting polymer, which will be discussed in more detail below under materials and methods.

The molecular structure of one such conducting polymer, poly(3,4-etylenedioxythiophene), also denoted PEDOT or PEDT, is schematically shown in Fig. 2.

Optionally, the electrochemically active element 3 may also comprise dopants, which will be discussed in more detail below under materials and methods.

The dopant may be supplied to the electro-active polymer in many different ways, which will be described in more detail below, and some of which are also known to a person skilled in the art.

The dopants and the method for doping the electro-active polymer will be discussed in more detail below under materials and methods.

The structure of two such dopants, dodecylbenzenesulfonate (DBS) and heparin, is schematically illustrated in Figs 3a and 3b.

The electrochemically active element 3 may be adapted to receive an activation potential. Thus, the electrochemically active element 3 shown in Fig. 1 may, for example, be adapted to be connected to a potential source.

The electrochemically active element 3 shown in Fig.1 may be adapted to constitute an electrode being part of an electrochemical system.

Referring again to Fig. 1, the electrochemically active element 3 has cell interaction surface 4, which is adapted to be in contact with a medium, or "electrolyte" comprised in an electrochemical system. The term "electrochemically active element" is herein intended to mean an element susceptible to electrochemistry when exposed to an electric potential and in

contact with an electrolyte. The cell adhesion surface 4 may be adapted to interact with the medium.

As mentioned above, the cell adhesion surface 4 may have controllable cell adhesion properties. At least some of the cell adhesion properties of the cell adhesion surface 4 may be controlled or changed in order to promote or counteract cell adhesion on the cell adhesion surface 4, i.e. at least some of the properties of the cell adhesion surface 4 influencing the success of cell adhesion on the surface 4 may be controlled. As mentioned above, examples of properties that influence cell adhesion on the cell adhesion surface may be the surface roughness, chemical character, dipole character, wettability, surface tension and surface energy.

When the electro-active polymer in the electrochemically active element 3 is reduced or oxidized, at least some of the mentioned properties will be changed at the cell adhesion surface 4, whereby the cell adhesion on the cell adhesion surface 4 will be controlled. Thus, according to the invention, at least some of the cell adhesion properties are controlled or changed by changing the electrochemical state of the electro-active polymer, i.e. by changing the redox state of the electro-active polymer.

In one embodiment PEDOT may be utilized as the electro-active polymer, and heparin or dodecylbenzenesulfonate (DBS) may be utilized as the dopant and when the polymer is oxidized the properties of the surface may be changed such that adhesion and biofilm formation of bacterial cells is promoted. On the other hand in one embodiment PEDOT may be utilized as the electro-active polymer, and heparin or dodecylbenzenesulfonate (DBS) may be utilized as the dopant and when the polymer is reduced the properties of the surface may be changed such that adhesion and biofilm formation of bacterial cells is prevented. When the conjugated polymer, in one embodiment PEDOT, is in the oxidized (p-doped) state, the negatively charged counter ion, here the heparin or dodecylbenzenesulfonate (DBS), is ionically bound to the positively charged polymer chain. The oxidized state of PEDOT:heparin or PEDOT:DBS is highly conducting and has a light blue colour.

If the polymer is reduced to a neutral state, the counter ions are no longer bound to the polymer chain and free to interact at the surface interface. In this state the PEDOT:heparin or PEDOT:DBS has a poor conductivity and the colour is darker blue (violet).

Thus, the cell adhesion surface 4 may be controllable to control cell adhesion on the cell adhesion surface 4, i.e. the cell adhesion surface 4 may have controllable cell adhesion properties. The control depends on the electrochemical state of the electro-active polymer and/or the doping ion. For example, the cell adhesion control system 2 may be utilized to direct cells to feasible responses in time and space. Furthermore, the cell adhesion control system 2 may be utilized as substrate for cell adhesion. According to one embodiment the cell adhesion system 2 as shown in Fig. 1 may be comprised in a cell culture dish 5. In Fig. 1, the cell adhesion system 2 may be arranged to cover only parts of the bottom of the cell culture dish and parts of the sides of the cell culture dish 5. However the system 2 may be arranged to cover the complete bottom of the cell culture dish 5 and parts of the sides of the cell culture control device 5. In addition, the system 2 may be arranged to cover the complete bottom of the cell culture dish and essentially the complete sides of the cell culture dish 5, i.e. essentially the complete inside of the cell culture dish 5.

The system 2 shown in Fig. 1 further comprises a potential source 7 and may also comprise a counter electrode 8. A potential may be applied in any known way, e.g. by a battery, or a mains connection. In either case a converter or signal generator may be used to provide a desired signal or set of signals.

The cell culture dish 5 may be any known cell culture dish suitable to be utilized for cell culturing. For example, the cell culture dish 5 may be made of polystyrene.

The electrolyte 6 may be, e.g. a cell culture medium, i.e. a liquid that contains ions(salt) and molecules(nutrients) which promotes cell growth.

The cell culture medium may comprise compounds and ions well known to a person skilled in the art, such as essential amino acids, vitamins,

soluble salts, etc. The cell culture medium may be, for example, Luria broth. Thus, in the system 2 and in the method according to the invention, the cell culture medium works both as a cell culture medium for adhesion cells and as an electrolyte in an electrochemical system.

The cell culture medium may, according to one alternative, be selected based on which type of cells that is to be cultured. Selection of a cell culture medium that is suitable for a specific cell type and that is suitable to utilize as an electrolyte should be apparent for a person skilled in the art.

In order to provide rapid and accurate adhesion control using moderate control voltages, it is important that the electrochemical reactions are easily driven and controlled. Thus, the electrolyte 6 has preferably high ion conductivity. According to one embodiment, the electrolyte 6 may be Luria broth, which substantially comprises yeast extract, tryptone and NaCl.

Furthermore, the potential source 7 utilized in connection with the system 2 may be any suitable known potential source. The potential source 7 may be connected to the electrochemically active element 3 by means of any suitable connecting means. In addition, the counter electrode 8 may be any known electrode suitable to use as counter electrode. For example, the counter electrode may be an indium-tin oxide (ITO) electrode, a platinum electrode or a gold electrode, or CP electrode.

The electrochemically active element 3, the counter electrode 8 and the electrolyte 6 shown in Fig. 1 form part of an electrochemical system, which should be understood as a separate expression compared to the system 2. In the system 2, shown in Fig. 1, the electrolyte or, in effect, the medium 6 serves as an ion bridge between the electrochemically active element 3 constituting an electrode and the counter electrode 8. When applying an appropriate voltage between the electrodes 3, 8, electrochemical reactions occurs. All electric current flowing from one electrode to the other will be accompanied by corresponding electrochemistry in the electrode/electrolyte interfaces and by an ionic current in the electrolyte 6.

Fig. 4 shows a schematic cross-sectional view of an alternative embodiment of a cell adhesion system 2 according to the present disclosure.

According to this alternative embodiment the system comprises two electrochemically active elements 3, which each has a cell adhesion surface 4 with controllable cell adhesion properties. Each cell adhesion surface 4 of the second embodiment constitutes an electrochemically active surface adapted to be in contact with a medium or electrolyte comprised in an electrochemical system.

Furthermore, the two electrochemically active elements 3 may be physically separated from each other. In Fig. 4 the parts of the two electrochemically active elements 3 are shown to be arranged in a common plane, parallel with a bottom of a container, while other parts may be on wall portions of the container. However, in variants of the second embodiment the two electrochemically active elements 3 are not arranged in a common plane. For example, one element 3 may then be arranged at the bottom of a cell culture dish 5 and one element 3 may be arranged at one of the sides of the cell culture dish 5. The two electrochemically active elements 3 may be bridged by an electrically and electrochemically inert material in a space 9 between the two elements 3.

Furthermore, the two electrochemically active elements 3 may be adapted to constitute two electrically separate electrodes, whereby the two electrochemically active elements 3 may be adapted to receive different electric potentials, and hence display different redox states, and are adapted to be part of an electrochemical system together with an electrolyte.

The cell adhesion system 2 shown in Fig. 4 may, according to one alternative embodiment, be comprised within a cell culture dish 5. The two electrochemically active elements 3 and the space 9 between the two elements 3 may be arranged to cover the complete bottom of the cell culture dish 5, as shown in Fig. 4, or to cover only parts of the bottom of the cell culture dish 5. Furthermore, the two electrochemically active elements 3 may be arranged such that they cover parts of the bottom and at least parts of the sides of the cell culture dish 5, as shown in Fig. 4. Alternatively, the two electrochemically active elements 3 may be arranged such that they cover parts of the complete bottom and essentially the complete sides of the cell

culture dish 5 together with the space 9. The system 2 shown in Fig. 4 further comprises an electrolyte 6 and a potential source 7.

The cell culture dish 5, the electrolyte 6 and the potential source 7 may correspond to those previously described.

Thus, according to one alternative embodiment of the system 2 and the method according to the present disclosure, one of the electrochemically active elements 3 may be oxidized and the other electrochemically active element 3 may be reduced. According to the mentioned above, the cell adhesion properties of the two cell adhesion surfaces 4 are thereby changed such that the two surfaces 4 exhibit different cell adhesion properties. When PEDOT is utilized as the electro-active polymer and heparin or DBS is utilized as the surface active molecules in the system 2, the cell adhesion properties of the cell adhesion surfaces 4 may be changed such that adhesion and/or biofilm formation by bacterial cells may be promoted on the surface belonging to the element 3 being oxidized and such that adhesion and/or biofilm formation by bacterial cells may be counteracted on the surface 4 belonging to the element 3 being reduced.

Fig. 5 shows a schematic cross-sectional view of yet an alternative embodiment of a cell adhesion control system 2.

The electrochemically active element 3, according to this alternative embodiment, may have two electrode portions 10, 11 and one intermediate portion 12 comprising the cell adhesion surface 4. The cell adhesion surface 4 may constitute an electrochemically active surface. The two electrode portions 10, 11 may be physically separated by the intermediate portion 12. Furthermore, the electrode portions 10, 11 do not comprise a cell adhesion surface 4 adapted to be in contact with an electrolyte comprised in an electrochemical system. In addition, the electrode portions 10, 11 may be adapted to receive different electric potentials. For example, they may be adapted to be connected to a potential source.

The cell adhesion system 2 shown in Fig. 5 may, according to one embodiment, be comprised in a cell culture dish 5. The system 2 shown in Fig. 5 may further comprise an electrolyte 6 and a potential source 7. The cell

culture dish 5, the electrolyte 6 and the potential source 7 may correspond to those previously described.

When applying a voltage between the two electrode portions 10, 11, an electronic current will appear in the polymer. The electrolyte 6 will then experience a potential difference at the polymer interface, i.e. at the cell adhesion surface 4, whereby an ion current is induced in the electrolyte 6. Thus, resulting electrochemistry will occur at the cell adhesion surface 4. However, the electrochemistry is generally conditioned by the ion current in the electrolyte 6 complementing the electrical current in the electro-active polymer. Using an electrolyte with high ion conductivity and/or using an electro-active polymer that has a low electrical conductivity may thus intensify the electrochemical reaction. An advantage of using this type of structure is that the electrochemical reaction varies gradually across the electrochemically active element, resulting in a gradient of change of cell adhesion properties across the cell adhesion surface 4.

Due to the fact that the electro-active polymer element and the electrolyte are constantly in electronic as well as in ionic contact, the cell adhesion surface 4 will return, by varying speeds depending on the materials used, to its initial state upon removal of the drive potential.

Fig. 6 shows a schematic cross-sectional another alternative embodiment of a cell adhesion system 2. The system 2 may comprise three electrochemically active elements 3, 3, 3a physically separated from each other. As can be seen in Fig. 6, the system 2 may comprise two electrochemically active elements 3 adapted to constitute electrically separated electrodes and one intermediate electrochemically active element 3a. The two electrochemically active elements 3 adapted to constitute electrically separated electrodes are, thus, adapted to receive different electric potentials and may be connected to, for example, a potential source. Furthermore, each of the two electrochemically active elements 3 adapted to constitute electrically separated electrodes comprise an electrode portion 10 and a remaining portion 13 comprising the electrochemically active surface 4.

The intermediate electrochemically active element 3a may comprise a cell adhesion surface 4 and is not adapted to be connected to a potential source.

The cell adhesion system 2 shown in Fig. 6 may be comprised in a cell culture dish 5. The intermediate electrochemically active element 3a may be arranged to cover only parts of the bottom of the cell culture dish 5, as shown in Fig. 6, or to cover the complete bottom of the cell culture dish 5. The system 2 shown in Fig. 6 may further comprise an electrolyte 6 and a potential source 7. The cell culture dish 5, the electrolyte 6 and the potential source 7 may correspond to those previously described.

When a voltage is applied between the two electrodes 3, an ion current is thus induced in the electrolyte 6 and the intermediate electrochemically active element 3a experiences a potential difference at the electrolyte/polymer interface, i.e. at the cell adhesion surface 4. Electrochemistry thus occurs in the intermediate electrochemically active element 3a much like in the electrochemically active element 3 shown in Fig. 5.

However, the difference between the intermediate element 3a shown in Fig. 6 and the element 3 shown in Fig. 5 is that an ionic current in the electrolyte 6 induces an electric current in the intermediate element 3a rather than the reverse as is the case in the element 3 shown in Fig. 5. In the intermediate element 3 a gradient of change of cell adhesion properties across the cell adhesion surface 4 can be provided much like in the system 2 shown in Fig. 5. The embodiment shown in Fig. 6 is advantageous in that the intermediate element 3a provides a distinct cell adhesion surface. Actually, the electrochemically active elements 3 constituting electrodes need not exhibit changeable cell adhesion properties, since the intermediate element 3a alone can provide a sufficiently large cell adhesion surface 4.

Fig. 7 shows a schematic cross-sectional view of yet another alternative embodiment of a cell adhesion control system 2. The system 2 may comprise a plurality of electrochemically active elements 3, which are physically separated form each other. Each element 3 has a cell adhesion surface 4 with controllable cell adhesion properties and each cell adhesion surface 4 constitutes an electrochemically active surface adapted to be in

contact with an electrolyte comprised in an electrochemical system. In Fig. 7, the cell adhesion system 2 is shown to comprise five electrochemically active elements 3. However, in variants, the system 2 may comprise any suitable number of electrochemically active elements 3. The electrochemically active elements 3 may be bridged by electrically and electrochemically inert materials in spaces 9 between the elements 3.

Furthermore, the electrochemically active elements 3 may be adapted to constitute electrically separate electrodes, whereby any two of the electrochemically active elements 3 may be selectable to be part of an electrochemical system together with an electrolyte. For example, any two of the electrochemically active elements 3 may be selectable to be connected to a potential source.

The cell adhesion system 2 shown in Fig. 7 may be, according to one alternative embodiment, comprised of a cell culture dish 5. The system 2 shown in Fig. 7 further comprises an electrolyte 6 and a potential source 7. The cell culture dish 5, the electrolyte 6 and the potential source 7 may correspond to those previously described.

In Fig. 7, the two electrochemically active elements 3 selected to be connected to the potential source 7 and the electrolyte 6 may form part of an electrochemical system. In the system 2 shown in Fig. 7 the electrolyte 6 serves as an ion bridge between the electrochemically active elements 3 selected to be connected to the potential source 7. When applying a voltage between the two selected elements 3, electrochemistry is forced to occur since there is no electric contact between those elements 3. Rather, all electric current flowing from one selected element 3 to the other must be accompanied by corresponding electrochemistry in the electrode/electrolyte interfaces and by an ionic current in the electrolyte 6. Furthermore, the electrochemically active elements 3 not being connected to the potential source 7 experience a potential difference at their respective electrolyte/polymer interfaces, i.e. at their respective cell adhesion surfaces 4. Electrochemistry thus occurs in those elements 3 much like in the intermediate electrochemically active element 3 shown in Fig. 6.

In a variant (not shown) of the system 2, the system 2 may further comprise a counter electrode 8. Then any one of the plurality of electrochemically active elements 3 are selectable to be part of an electrochemical system together with the electrolyte 6 and the counter electrode 8. Thus, any one of the electrochemically active elements 3 and the counter electrode 8 may then be connected to the potential source 7.

Even though the cell adhesion control system 2 shown in Figs 1 and 4-7 is shown as being comprised in a cell culture dish 5, it may of course be arranged in any other suitable device or on any other suitable surface.

The system 2 may comprise a carrier substrate on which the electrochemically active element 3 may be arranged. The support can have many different shapes and can be formed out of a vast number of materials. One feasible support for the electrochemically active element 3 is polystyrene. Alternatively, the support may be glass. In case the cell adhesion system 2, or rather the electrochemically active element 3 is self-supporting, one or more of the components are rigid enough to carry the electrochemically active element 3 as an integral piece. This can be achieved by, for example, suitable choice of dimensions for the electro-active polymer.

According to one not shown embodiment the cell adhesion system 2 may instead of being comprised in a cell culture dish 5, be comprised a cell culture plate having at least two cell culture wells. Then at least one cell adhesion system 2 may be arranged in one or more of the wells. The system 2 may then correspond to any of the above described embodiments and the cell culture plate may be any known suitable cell culture plate. The cell adhesion system 2 may further also comprise one or more electrolytes 6, one or more potential sources 7 and one or more electrodes 8 working as counter electrodes of the previously described kind.

Furthermore, any of the above described embodiments of the cell adhesion system 2 may be arranged on a device or structure adapted for insertion or implantation into the human or animal body (not shown). Thereby, the cell adhesion on the surface of the device or structure may be controlled, i.e. the adhesion may be controlled and/or the adhesion and growth may be

controlled. The conducting polymer may e.g. be coated onto a medical implant such as a catheter. In addition, any of the above described embodiments of the cell adhesion system may be arranged on a surgical instrument (i.e. an instrument intended to be utilized in surgery) or on an instrument intended to be utilized for treatment of a human or animal body such as, for example, a catheter or a cannula shown in Fig. 13. Thereby, the cell adhesion and or biofilm formation on the surface of the instrument may be controlled, i.e. the adhesion may be controlled such that cells are inhibited from adhering to the surface or such that adhered cells are repelled. In addition, an instrument that is intended to be utilized for treatment of a human or animal body and that comprises at least one cell adhesion system 2 according to the invention on at least one surface is also within the scope of the invention.

A device or structure adapted for insertion or implantation into the human or animal body or a surgical tool sutures may be any one of bone screws, nails, plates, tubes, sheets, stents, catheters, guide wires, sheaths, leads, outer tubings, inner tubings, trocars, stylets, embolic coils, part of a filter devices, parts of endoscopes, parts of gastroscopes, dilation balloons, knifes, needles, scissors, pliers, tweezers, guide wires, spheres and clamps.

In the case of the system 2 being arranged on a device or structure adapted for insertion or implantation into the human or animal body or on a surgical tool the medium or, in effect, electrolyte may comprise a body fluid, such as blood, urine, saliva or any other mucous discharge, or a tissue, such as liver, spleen, heart, muscles, intestines a s o.

Fig. 8a shows a detail of a system comprising two electrochemically active elements 51a and 51b provided on a substrate 53. The substrate 53 may be (microscope slide) glass (objective glass), plastics such as PET, PS, petri dish, silicon or a silicon based device such as an integrated electronic circuit. This may be done on a plan/flat substrate or in different kinds of containers, such as a cell culture dish (not shown). The insulation between the pads/electrodes may be by physical separation 52, meaning that the electrodes 51a, 51b may be individually applied/assembled or material

between the electrodes may be removed by methods such as scraping, cutting, etching as are known to the person skilled in the art.

Fig. 8b shows an alternative method to separate the two electrodes compared to Fig. 8b. The insulation may be achieved by (electro-)chemical overoxidation, that is destroying the electronic conductivity of the conducting polymer at that part 54. The advantage with the (electro-)chemical overoxidation method is that no, or alternatively very small, topography differences are introduced between the two electrodes 51a and 51b.

Fig. 9 illustrates an alternative embodiment, wherein the electrochemically active elements 51 a-c isolated from each other by insulation 54. A potential may be applied to the elements 51a-c, such that they may be addressed as oxidized, reduced, and neutral. This gives the opportunity to investigate all three redox states at the same time. The non biased electrode/area may also work as a control area to the reactions at the redox electrodes.

Fig. 10 shows a schematic view of an alternative embodiment of the electrochemically active elements where the electrochemically active elements 51 a and 51b are deposited horisontally in a multiwell plate.

The electrochemically active elements can be deposited on flexible planar substrates and mounted on the multiwell plate in a subsequent step.

Figs 11a and 11b illustrate yet another embodiment of the system, in which the electrodes may be arranged as an array or matrix system 100 of cell adhesion zones.

The zones may comprise the cell adhesion surfaces. The system 100, may comprise electrochemically active elements or zones 101a-f, arranged in a matrix or array, insulation 102 and optionally a counter or auxiliary electrode 103. It may further comprise a reference electrode (not shown). The zones 101a-f may be mounted on a control unit 104, e.g. transistor matrix, such as an integrated circuit on a silicon chip, that may control each element individually or through another matrix addressing scheme such as is know the to person skilled in the art.

Fig. 11b only illustrates one alternative embodiment of the matrix/array system 100 showing 6 electrodes. It should be understood that the array/matrix system 110, 100 may comprise any number of electrodes.

Each zone, i.e. electrochemically active element 101a-f, may be individually controlled to result in a individual redox state of that electrode or pad, e.g., electrode 101a at 0V, electrode 101b at +0.5V, electrode 101c at +1.0 V etc.

Each surface, i.e. electrode or pad, may be fabricated of a different material, including different conducting polymers and different dopants. These pad/electrodes may then be addressed commonly, or in groups/rows etc or individually. According to one alternative electrode 101a may comprise PEDOT:PSS, electrode 101b PEDOT:heparin, electrode 101c PPy:DBS, electrode 101e PPy:ClO4 etc.

According to yet another alternative embodiment the electrodes may have different surface coatings.

Fig 12 illustrates an alternative embodiment of the array/matrix system 110, comprising multiple electrochemically active element 111e having a rounded shape. The system 110 may further comprise a counter electrode 113 and isolation 112, as described above.

The electrochemically active elements or zone may comprise any arbitrary shape or size.

Fig. 13 illustrates an alternative embodiment of the electro-active element where the electrochemically active elements are deposited inside and outside of a tube, i.e. the tube material constitutes the non-conducting gap 115 between the electrodes 114a and 114b. The tube can be submerged in an electrolyte to complete the circuit. The tube may be a urinary tract catheter in which case urine would be the electrolyte when the catheter is inserted into the bladder.

Materials and methods

Below a general description of materials and methods that may be used according to the present disclosure will be outlined. This is meant as an

exemplifying description of the materials and methods used and should in no way be limiting to the scope of the protection sought. After the general description of materials and methods more detailed examples will be given.

Electrochemically active element

The electrochemically active element may comprise an electro-active polymer (EAP). One class of EAP's are conducting polymers (CP). These expressions will however be used interchangeably throughout the description.

A further description of electro-active polymers can be found in WO2008113372.

Examples of such conducting polymers may be polyacetylene, polyanilin, polypyrrole, polythiophene, poly(phenylsulfide), poly(phenylenevinylene), polysulfones, polyethylenedioxythiophenes, poly(p-phenylene), poly(p-phenylene vinylene), polypyridines, polyquinoxalines, polyanthraqinones, poly(n-vinylcarbazole) and derivates, copolymers and mixtures thereof.

In one aspect, the CP material may be doped, by chemically or electrochemically oxidizing the polymer, with at least one of the following dopants:

Anions, including halogenes (such as Cl^-, I^-, F^-, Br^-); ClO4-, S^{2-}, acetate, polyanions, such as polystyrenesulphonate (PSS^-).

Amphiphilic ions, such as octylbenzenesulfonate (OBS), dodecylbenzenesulfonate (DBS), polystyrenesulfonate (PSS), tosylate, phosphates, sulfates, sulfonates, carboxylates, perchlorate, chloride surfactants in general, etc..

Charged biomolecules such as: proteins, artificially modulated proteins, drugs, amino acids, DNA, RNA, peptides, growth factors, hormones, proteoglycans, glycoproteins, glucose amino-glucans, neurotransmitters.

Doping the CP is a way of altering or even improving the conducting properties of the CP, in certain instances the conductivity may be increased a thousandfold.

As an example polypyrrole (PPy) can be electrochemically oxidized and reduced by applying an appropriate electrical potential to the material. The oxidation or reduction leads to a charge imbalance that, in turn, results in a flow of ions into or out of the material in order to balance charge. The oxidation and/or reduction reaction may also be accompanied by the transport of solvents (often water) into and out of the PPy. These redox reactions change the properties of PPy, such as the conductivity, morphology and water content. By electronically reducing or oxidizing conducting polymers a range of physical properties that are important for the interaction with biological systems are changed within the film as well as along its outermost surface. Such properties can be surface energy, conductivity, roughness and surface charge. Often several of these properties are affected.

PPy can be electrochemically or chemically synthesized from a solution of pyrrole monomers and a dopant as is known to those skilled in the art. After synthesis the PPy is generally present in an oxidized, or also called doped, state.

Poly-(3,4-etylenedioxytiophene (PEDOT) is one conducting polymer, which may be doped with heparin. PEDOT:heparin may throughout the present disclosure be taken as a non-limiting example of such a doped CP material.

The electro-active polymer may be fabricated according to the following non-limiting examples.

Electro polymerisation by applying a potential to the substrate submerged in a solution comprising the monomer form of the electro active material and a counter ion.

Chemical polymerisation by bar coating or by spin coating the solution comprising an oxidation agent (such as for instance iron tosylate), and preferably a strong base such as for instance pyridine and the monomer (for instance edot). Dependent of physical properties of the substrate (flat or dish for example) one of the two methods is used.

According to one embodiment the mixture of oxidation solution and monomer (preferably also a small volume of strong base may be added to

improve the conductivity of the resulting polymer) may be spread out on a flat substrate by moving a bar, i.e. “bar coated” in one direction over the substrate. After dispersion of mixture the coated substrate may be heated to favour polymerization and evaporation of solvents.

According to yet an alternative solution the solution comprising an oxidation agent (such as for instance iron tosylate), and preferably a strong base such as for instance pyridine and the monomer (for instance edot), as mentioned above, may be added to a substrate (flat or container (petri dish)) and then the mixture may spread over the substrate by spinning the substrate at a high (to achieve a thin film) speed, i.e. “spin coated”. After the solution has been spread and covers the substrate (bottom and edges of a dish) the substrate may be heated as mentioned above.

Electro-polymerisation, bar or spin coating may be used for flat/planar surfaces. Spin coating may even been used for coating inside containers, such as Petri dishes.

In the following one embodiment for preparation of a system according to the present disclosure, in this case a “surface developed to study biofilm formation control”, i.e. a plastic film surface provided with an electrochemically active element, i.e. an electro-active polymer doped with a dopant, will be given as a non-limiting example.

PEDOT was electro-polymerized using a three-electrode set up connected to a potentiostat. The working electrode consisted of PEDOT:PSS film(Orgacon™, available from Agfa-Gevaert Group), the reference electrode was Ag/AgCl and the counter electrode was a platinum net. For the PEDOT:DBS (PEDOT:heparin) film, a constant current of -200μA (-375μA) was applied for 1000 s (600 s). The concentration of the NaDBS solution was 0.1 M and for the NaHeparin solution approximately 0.4 mg/ml. Both solutions were made in dH_2O. To the electrolyte solution, 100 μl EDOT monomer was added, and the solution was bubbled with nitrogen before the polymerization started. The monomer-electrolyte solution was recycled a couple of times and stored in the refrigerator when not in use. The polymerized films were rinsed in dH_2O. As EDOT is not soluble in water, a surfactant is required to enable

some mixing. DBS is a surfactant itself, but with only heparin and EDOT present in water, no polymerization occurred. To solve this problem, Triton X-100, which is a neutral surfactant, was added, leading to film formation. As Triton is neutral, it should not be incorporated into the film to a large extent. The concentration of Triton was 0.1%.

A gradient was seen in the formed films, with a darker (and therefore thicker) layer of PEDOT:DBS (or PEDOT:heparin) closer to the connection to the potentiostat. The formation of a gradient is probably due to poor conductivity in Orgacon™, it was not observed on indium tin oxide (ITO) electrode surface. The gradient was less pronounced using constant current during electropolymerization compared to constant voltage.

Cyclic voltammetry was performed to test the electrochemical properties of the polymerized films. The experiment was performed using a potentiostat, with platina as the counter electrode and an Ag/AgCl reference electrode in 0.1 M NaCl (aq). The over-oxidation potential was investigated, as well as the reversible switching processes at lower voltages.

Films were cut in 2X3 cm. Two films were glued to the opposing sides within each well in the middle row of a 12 well cell culture plate. Sylgard 184 was used as glue because of its documented biocompatibility, optical properties and balanced strength. Curing was done at 37°C for 24h. Films were contacted using copper tape, which was applied so that the surfaces could be electrically addressed while the cell culture plate lid is on. For biofilm experiments 3ml Luria broth without salt was added to the wells. The liquid reaches to a little more than half of the height of the film. 300µl of bacterial overnight culture is added to each Luria broth containing well.

Cell types

Cell “types “concievable for use in the present disclosure includes prokaryotic cells including bacterial cells and blue green algea.

To this effect bacterial cells at different states, i.e. replicating planktonic or biofilm forming bacteria of different species may be utilized.

In the following will be given a non-limiting example of prokaryotic cell type that may be interacting with the system.

The genetic regulation and regulatory network of *Salmonella enterica serovar* Typhimurium ATCC1408 has been dissected for the last couple of years, the biofilm regulators and the matrices are known. *S. Typhimurium* may serve as an excellent model. But other biofilm forming bacteria such as *Pseudomonas aerginosa* and *Staphylococcus aureus* may also be used to see the global impact of biofilm on different polymeric surfaces designed with different morphologies and chemical composition for different purposes such as counteracting or promoting formation of biofilm.

Examples

The following examples are provided in order to exemplify the present disclosure.

Example 1

Prototypes were constructed using corning 12 wells plates were 6cm^2 pieces of PEDOT:heparin or PEDOT:DBS were glued to each side of the wall of the wells using Sylgard 184 curing for 24 hours at 37°C. In total two wells of PEDOT:heparin and two wells of PEDOT:DBS was prepared.

One surface of each was contacted using copper tape and 5.0V was delivered to the surface for 24 hours using a Hewlett Packard power supply. The wells without the polymer were used as positive and negative control with and without bacteria respectively.

After 24 hours cell culture and the culture media were decanted from the control wells. The wells were stained with crystal violet to investigate if the biofilm is formed at the air-liquid interface of the wells. After 24 hours incubation samples were stained with invitrogen LIVE/DEAD® BacLight™ bacterial Viability Kits and imaged with confocal laser scanning microscopy using 20X objective.

On DBS samples plenty of red, i.e. dead structures, can be seen in orthogonal section, and an increased density of the biofilm can be seen

closest to the polymer surface were the biofilm is formed and further away the cell density is gradually getting lower with more planktonic cells.

On two unactivated DBS surfaces and the oxidized DBS surface the red stain shows channelstructures. . On the reduced DBS no biofilm structures could be seen.

The heparin samples have less red staining than the DBS samples however on oxidized heparin both red and green staining can be seen. More biofilm is formed on the oxidized heparin surface than the reduced and unactivated.

Example 2

Prototypes were constructed using corning 12 wells plates were 6cm^2 pieces PEDOT:Heparin were glued to each side of the wall of the wells using Sylgard 184 curing for 24 hours at 37°C. In total two wells of PEDOT:Heparin was prepared.

One surface of each was contacted using copper tape and 0.5V was delivered to the surface for 24 hours using a Hewlett Packard power supply. The wells without the polymer were used as positive and negative control with and without bacteria respectively.

After 24 hours incubation samples were stained with invitrogen LIVE/DEAD® BacLight™ bacterial Viability Kits and imaged with confocal laser scanning microscopy using 20X objective.

On unstimulated PEDOT:Heparin indications of a immature biofilm was seen. On the oxidized electrode of PEDOT:Heparin a fully developed biofilm was present. On the reduced PEDOT:Heparin no biofilm was seen.

For some types of bacteria, it may be advantageous in promoting biofilm formation to provide access to oxygen, e.g. through electrochemistry at an anode, in gas form, reactions taking close to a liquid and oxygen-containing gas interface; or feeding oxygen in gas form to an area at or near an electrode. For other types of bacteria, access to oxygen may instead be detrimental. Hence, oxygen supply is optional, depending on what is intended to achieve and with what type of bacteria.

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CLAIMS

1. A method to control adhesion, growth and/or biofilm formation of prokaryotic cells on a cell interaction surface of an electrochemically active element, the method comprising:

bringing a medium comprising prokaryotic cells into direct contact with the cell interaction surface, and

providing an activation potential to the electrochemically active element.

2. The method as claimed in claim 1, wherein the electrochemically active element comprises an electrochemically oxidizable and reducible and electrically conductive polymer.

3. The method as claimed in claim 2, wherein the polymer is selected from a group consisting of polyacetylene, polyaniline, polypyrrole, polythiophene, poly(phenylsulfide), poly(phenylenevinylene), polysulfones, polyethylenedioxythiophenes, poly(p-phenylene), poly(p-phenylene vinylene), polypyridines, polyquinoxalines, polyanthraqinones, poly(n-vinylcarbazole) and derivates, copolymers and mixtures thereof.

4. The method as claimed in claim 2 or 3, wherein the polymer is doped with a dopant selected from a group consisting of anions, including halogenes (such as Cl^-, I^-, F^-, Br^-); ClO4-, S^{2-}, polyanions, such as polystyrene sulphonate (PSS^-); amphiphilic ions including octylbenzenesulfonte (OBS), dodecylbenzenesulfonate (DBS) tosylate, phosphates, sulfates, sulfonates, carboxylates, surfactants in general; charged biomolecules including proteins, artificially modulated proteins, drugs, amino acids, DNA, RNA, peptides, growth factors, hormones, proteoglycans, glycoproteins, glucose amino-glucans, neurotransmitters, or combinations and mixtures thereof.

5. The method as claimed in any one of the preceding claims, wherein the electrochemically active element comprises two electrode portions, wherein different electric potentials are provided to said different electrode portions.

6. The method as claimed in any one of the preceding claims, wherein at least three different cell adhesion zones are controlled to provide mutually different cell adhesion characteristics.

7. The method as claimed in claim 6, wherein at least two of the cell adhesion zones are provided with different potentials.

8. The method as claimed in claim 6 or 7, wherein at least two of the cell adhesion zones are provided with substantially the same potential, but with different inherent cell adhesion properties.

9. The method as claimed in any one claims 6-8, wherein at least two of the cell adhesion zones are provided with different potentials and with different inherent cell adhesion properties.

10. The method as claimed in any one of the preceding claims, wherein the prokaryotic cells are selected from prokaryotic cells in different phasesof growth.

11. The method as claimed in claim 10, wherein the cell is selected from transformed cells or in other ways genetically modified cells.

12. The method as claimed in any one of the preceding claims, wherein the electrochemically active element is coated onto a device or structure for cell culture.

13. The method as claimed in any one of claims 1-11, wherein the electrochemically active element is coated onto a device or structure adapted for insertion or implantation into a human or animal body and wherein the device or structure is selected from the group consisting of sutures, bone screws, nails, plates, tubes, sheets, stents, catheters, guide wires, sheaths, leads, outer tubings, inner tubings, trocars, stylets, embolic coils, part of a filter devices, parts of endoscopes, parts of gastroscopes, dilation balloons, knifes, needles, scissors, pliers, tweezers, guide wires, spheres and clamps.

14. The method as claimed in any one of claims 1-11, wherein the electrochemically active element is at least partially coated onto a device or structure adapted for storage, transportation or immersion.

15. A method as claimed in any one of the preceding claims, wherein adhesion, growth and/or biofilm formation of prokaryotic cells on the cell interaction surface is promoted by providing said activation potential as a positive potential.

16. A method as claimed in any one of claims 1-14, wherein adhesion, growth and/or biofilm formation of prokaryotic cells on the cell interaction surface is counteracted by providing said activation potential as a negative potential.

17. A device adapted for interaction with a medium comprising prokaryotic cells, the device comprising:

an electrochemically active element having a cell interaction surface, adapted for direct contact with the medium, and

means for providing an activation potential to the electrochemically active element.

18. The device as claimed in claim 17, wherein the electrochemically active element comprises an electrochemically oxidizable and reducible and electrically conductive polymer.

19. The device as claimed in claim 18, wherein the polymer is selected from a group consisting of polyacetylene, polyaniline, polypyrrole, polythiophene, poly(phenylsulfide), poly(phenylenevinylene), polysulfones, polyethylenedioxythiophenes, poly(p-phenylene), poly(p-phenylene vinylene), polypyridines, polyquinoxalines, polyanthraqinones, poly(n-vinylcarbazole) and derivates, copolymers and mixtures thereof.

20. The device as claimed in claim 19 or 20, wherein the polymer is doped with a dopant selected from a group consisting of anions, including halogenes (such as Cl^-, I^-, F^-, Br^-); ClO4-, S^{2-}, polyanions, such as polystyrene sulphonate (PSS^-); amphiphilic ions including octylbenzenesulfonte (OBS), dodecylbenzenesulfonate (DBS) tosylate, phosphates, sulfates, sulfonates, carboxylates, surfactants in general; charged biomolecules including proteins, artificially modulated proteins, drugs, amino acids, DNA, RNA, peptides, growth factors, hormones, proteoglycans, glycoproteins, glucose amino-glucans, neurotransmitters, or combinations and mixtures thereof.

21. The device as claimed in any one of claims 17-20, wherein the electrochemically active element comprises two electrode portions, wherein said electrode portions are arranged to receive different electric potentials.

22. The device as claimed in any one of claims 17-21, wherein the cell adhesion surface comprises at least three separate cell adhesion zones.

23. The device as claimed in claim 22, wherein at least two of the cell adhesion zones are individually controllable.

24. The device as claimed in claim 22, wherein at least two of the cell adhesion zones are collectively controllable.

25. The device as claimed in any one of claims 22-24, wherein the cell adhesion zones are arranged on an elongate substrate.

26. The device as claimed in any one of claims 22-25, wherein the cell adhesion zones are substantially co-planar.

27. The device as claimed in any one of claims 22-26, wherein the cell adhesion zones face different directions.

28. The device as claimed in any one of claims 22-27, wherein at least one of the cell adhesion zones presents cell a adhesion surface which is at least partially curved.

29. The device as claimed in any one of claims 22-28, wherein at least two cell adhesion zones present cell adhesion surfaces which are arranged in different planes.

30. The device as claimed in any one of claims 22-29, wherein the cell adhesion zones are provided on a common substrate.

31. The device as claimed in any one of claims 22-30, wherein at least two of the cell adhesion zones differ with respect to inherent cell adhesion properties.

32. The device as claimed in any one of claims 17-31, wherein the electrochemically active element is at least partially coated onto a device or structure adapted for cell culture.

33. The device as claimed in any one of claims 17-31, wherein the electrochemically active element is at least partially coated onto a device or structure adapted for insertion or implantation into a human or animal body and wherein the device or structure is selected from the group consisting of sutures, bone screws, nails, plates, tubes, sheets, stents, catheters, guide wires, sheaths, leads, outer tubings, inner tubings, trocars, stylets, embolic coils, part of a filter devices, parts of endoscopes, parts of gastroscopes, dilation balloons, knifes, needles, scissors, pliers, tweezers, guide wires, spheres and clamps.

34. The device as claimed in any one of claims 17-31, wherein the electrochemically active element is at least partially coated onto a device or structure adapted for storage, transportation or immersion.

35. A system for interaction with a medium comprising prokaryotic cells, the system comprising:

a device as claimed in any one of claims 17-34, and

a power supply, which is connectable to provide said activation potential.

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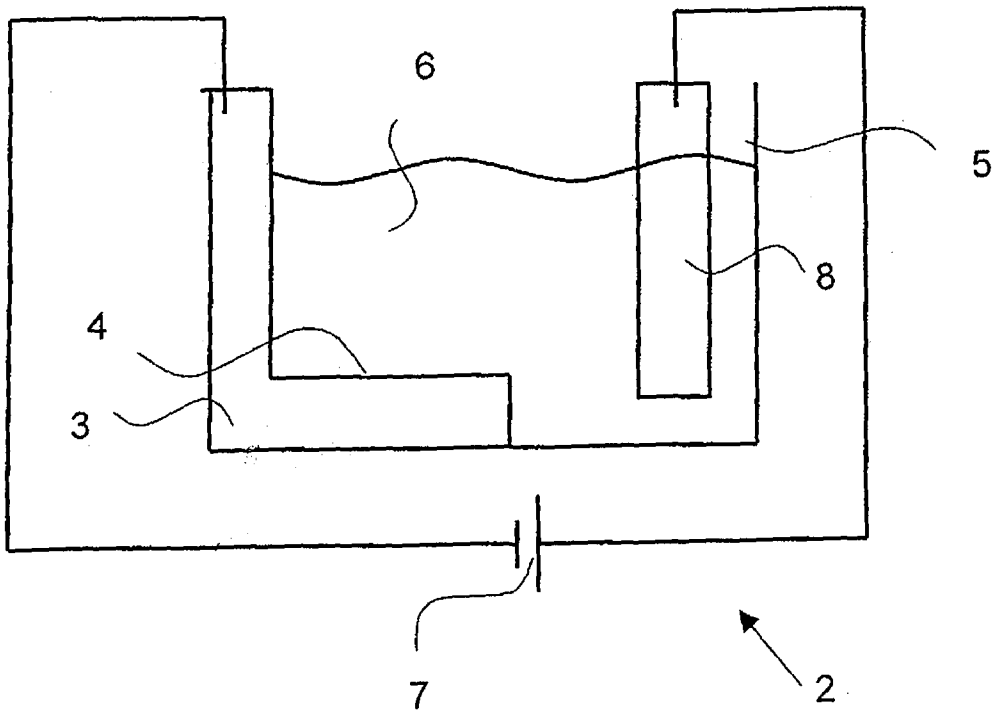


Fig. 1

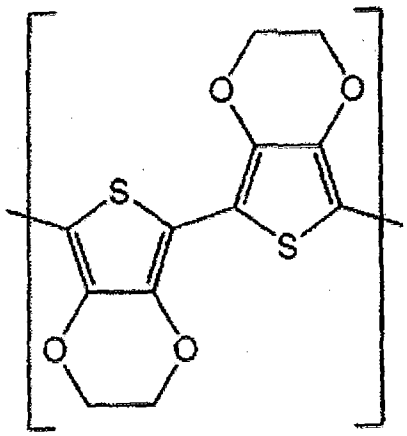


Fig. 2

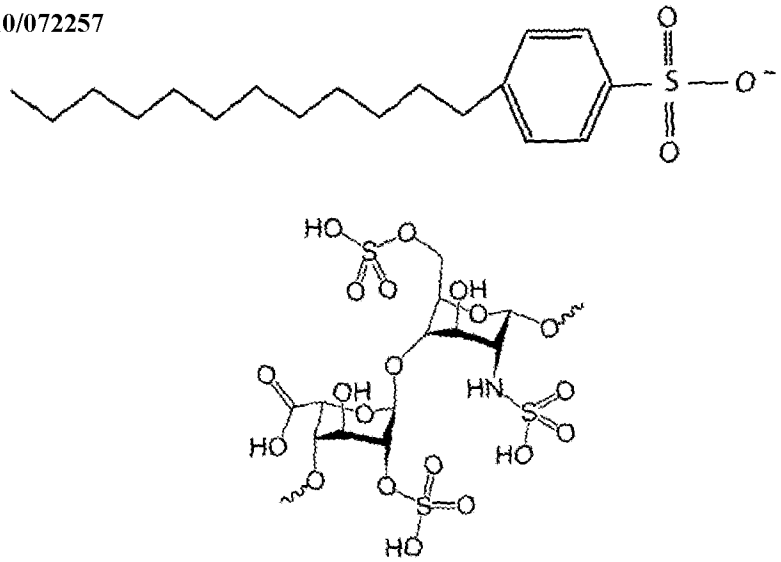


Fig. 3

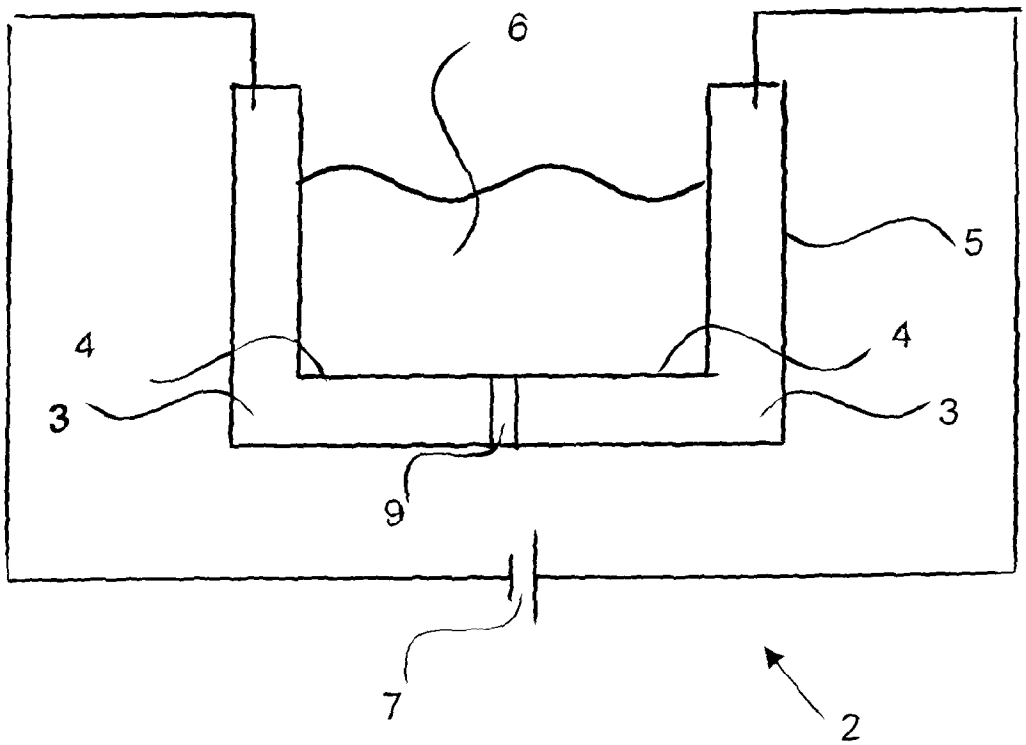


Fig. 4

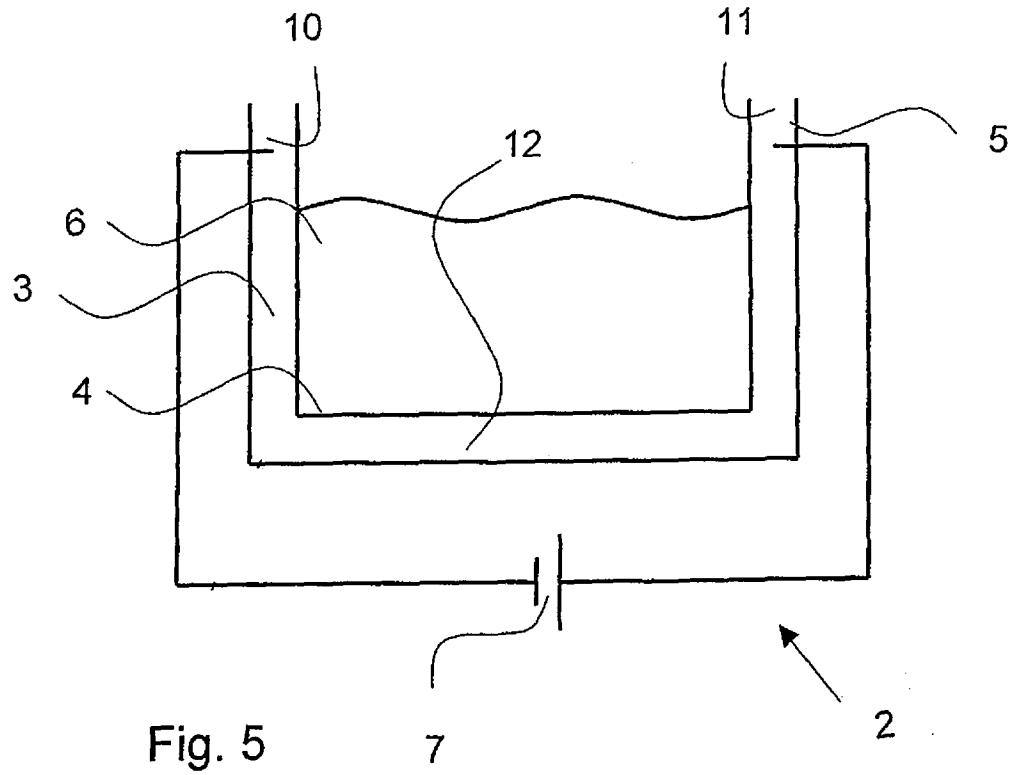


Fig. 5

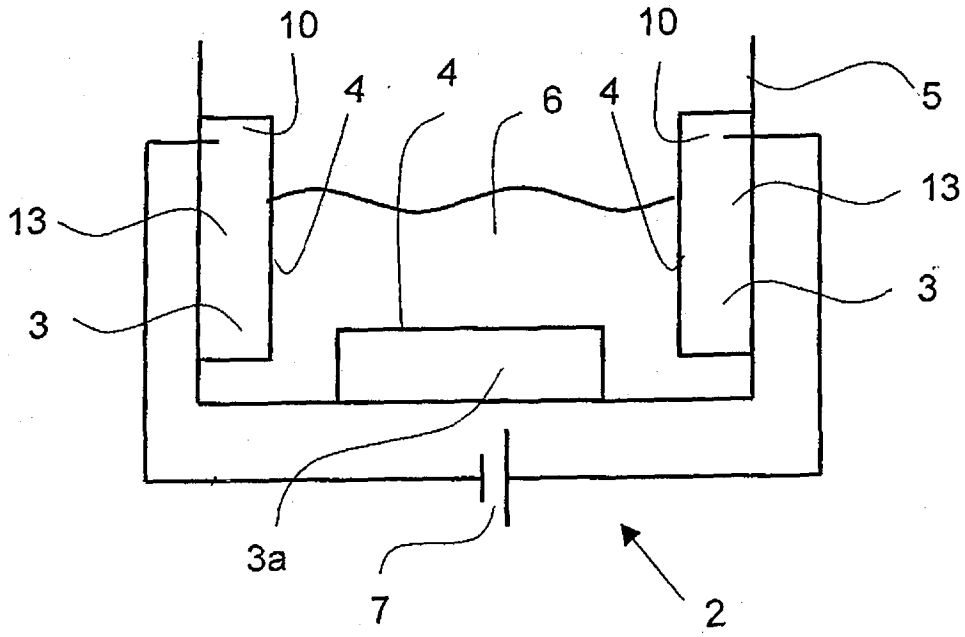


Fig. 6

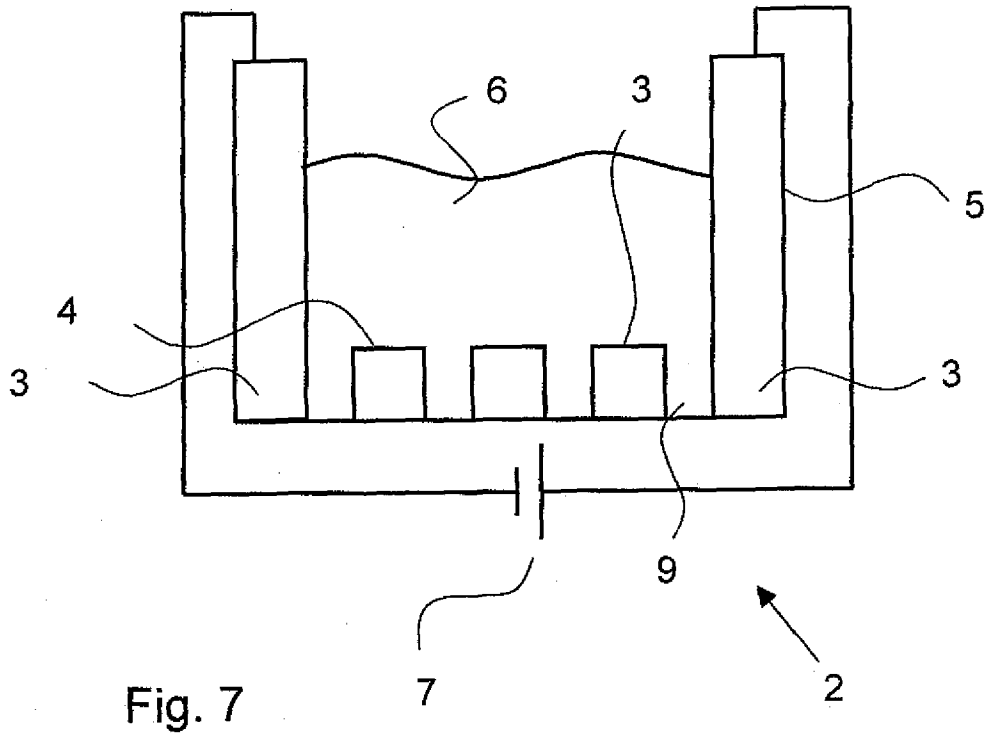


Fig. 7

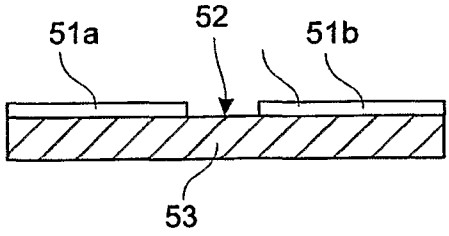


Fig. 8a

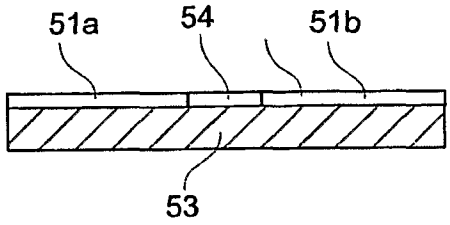


Fig. 8b

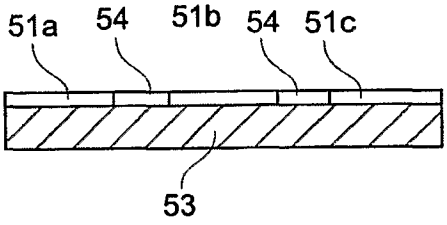


Fig. 9

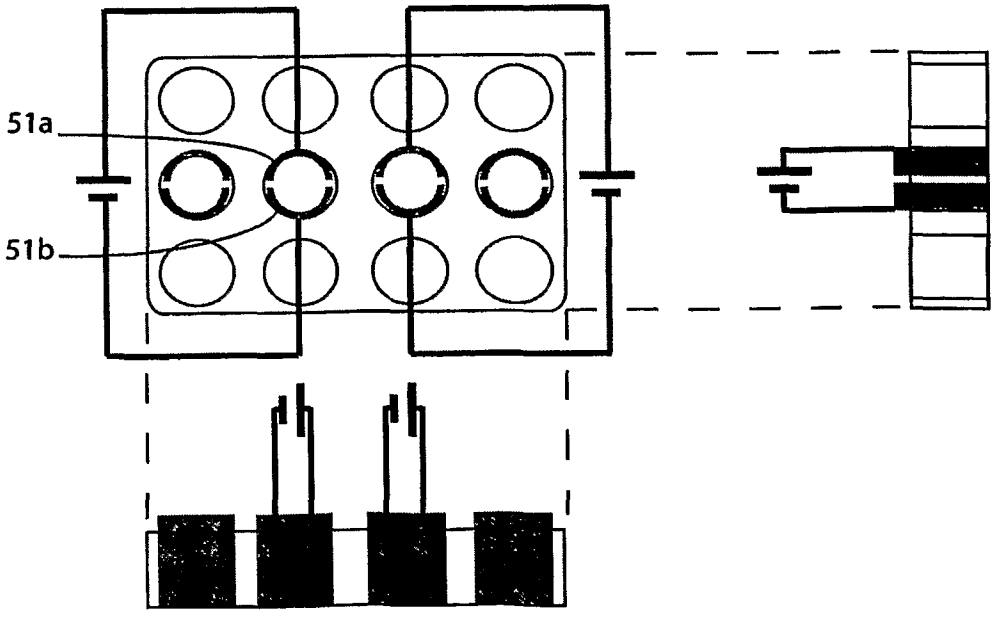


Fig. 10

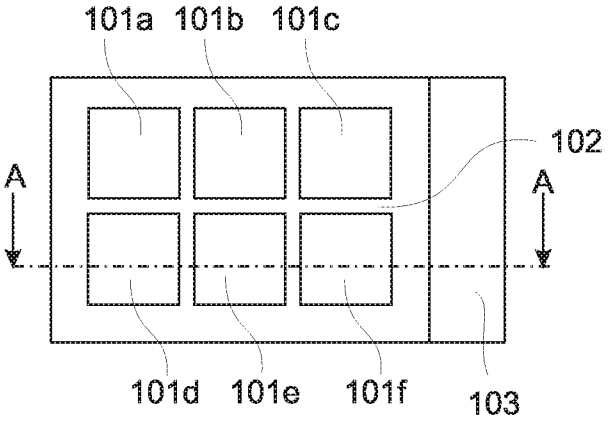
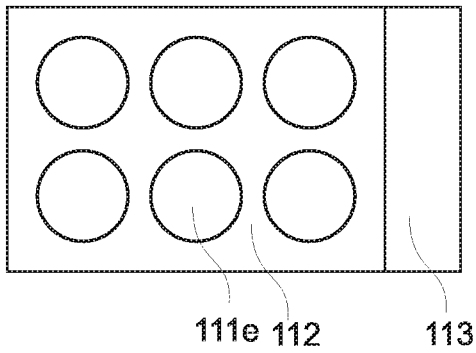


Fig. 11a



Fig, 12

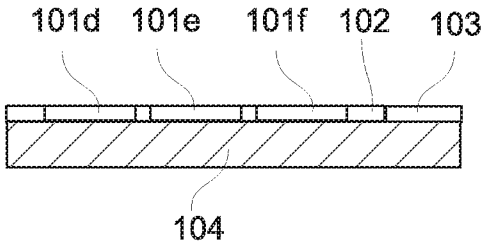


Fig. 11b

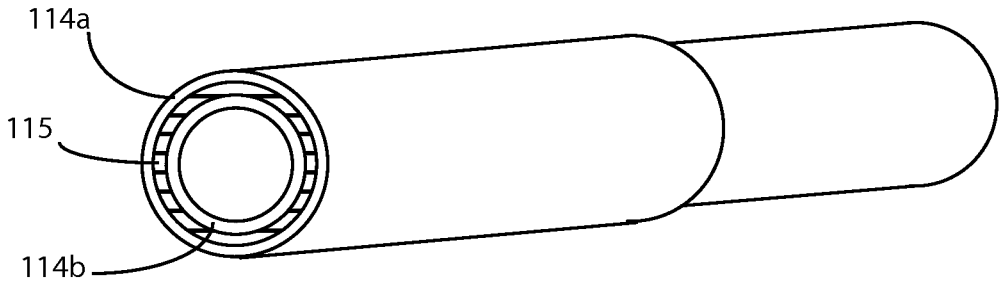


Fig. 13

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/068217

A. CLASSIFICATION OF SUBJECT MATTER
INV. C12N11/14 C12N13/00 C12M1/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C12N C12M

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DEL POZO JOSE L ET AL: "The electricidal effect: reduction of Staphylococcus and pseudomonas biofilms by prolonged exposure to low-intensity electrical current." ANTIMICROBIAL AGENTS AND CHEMOTHERAPY JAN 2009, vol. 53, no. 1, 27 October 2008 (2008-10-27), pages 41-45, XP002540812 ISSN: 1098-6596 abstract	1,16,17, 35
X	WO 92/19286 A (UNIV TECHNOLOGIES INT [CA]) 12 November 1992 (1992-11-12) abstract; example 1	1,16,17, 35

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2009	03/09/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	van Voorst, Frank

Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ODACI ET AL: "Use of a thiophene-based conducting polymer in microbial biosensing" ELECTROCHIMICA ACTA, ELSEVIER SCIENCE PUBLISHERS, BARKING, GB, vol. 53, no. 12, 6 January 2008 (2008-01-06), pages 4104-4108, XP022514184 ISSN: 0013-4686	1-3,12, 16-19, 32,34,35
Y	paragraph [02.3] paragraph [02.4] paragraph [02.5] abstract	1-35
Y	GROENENDAAL L ET AL: "OPTICAL, CONDUCTIVE AND MAGNETIC PROPERTIES OF ELECTROCHEMICALLY PREPARED ALKYLATED POLY(3,4-ETHYLENEDIOXYTHIOPHENE)S" SYNTHETIC METALS, ELSEVIER SEQUOIA, LAUSANNE, CH, vol. 118, 1 January 2001 (2001-01-01), pages 105-109, XP001012691 ISSN: 0379-6779 page 105	1-35
A	SHANKS ROBERT M Q ET AL: "Heparin stimulates Staphylococcus aureus biofilm formation." INFECTION AND IMMUNITY AUG 2005, vol. 73, no. 8, August 2005 (2005-08), pages 4596-4606, XP002540813 ISSN: 0019-9567	
A	NISHIZAWA MATSUHIKO ET AL: "Anisotropic growth of conducting polymers along heparin-modified surfaces." LANGMUIR : THE ACS JOURNAL OF SURFACES AND COLLOIDS 31 JUL 2007, vol. 23, no. 16, 31 July 2007 (2007-07-31), pages 8304-8307, XP002540814 ISSN: 0743-7463	
T	NOEMI ROZLOSNIK: "New directions in medical biosensors employing poly(3,4-ethylenedioxy thiophene) derivative-based electrodes" ANAL BIOANAL CHEM, 31 July 2009 (2009-07-31), XP002540811	

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2008/068217

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9219286 A	12-11-1992	AU 1672492 A	21-12-1992
		CA 2109084 A1	04-11-1992
		US 5312813 A	17-05-1994