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For the benefit
of the Patient.

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International Organization for Medical Physics
IOMP

The International Federation for Medical and Biological Engineering, IFMBE, is a federation of national and transnational organizations representing internationally the interests of medical and biological engineering and sciences. The IFMBE is a non-profit organization fostering the creation, dissemination and application of medical and biological engineering knowledge and the management of technology for improved health and quality of life. Its activities include participation in the formulation of public policy and the dissemination of information through publications and forums. Within the field of medical, clinical, and biological engineering, IFMBE's aims are to encourage research and the application of knowledge, and to disseminate information and promote collaboration. The objectives of the IFMBE are scientific, technological, literary, and educational.

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Olaf Dössel · Wolfgang C. Schlegel (Eds.)

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Micro- and Nanosystems in Medicine, Active Implants, Biosensors

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Preface

Present Your Research to the World!

The World Congress 2009 on Medical Physics and Biomedical Engineering – the triennial scientific meeting of the IUPESM - is the world's leading forum for presenting the results of current scientific work in health-related physics and technologies to an international audience. With more than 2,800 presentations it will be the biggest conference in the fields of Medical Physics and Biomedical Engineering in 2009!

Medical physics, biomedical engineering and bioengineering have been driving forces of innovation and progress in medicine and healthcare over the past two decades. As new key technologies arise with significant potential to open new options in diagnostics and therapeutics, it is a multidisciplinary task to evaluate their benefit for medicine and healthcare with respect to the quality of performance and therapeutic output.

Covering key aspects such as information and communication technologies, micro- and nanosystems, optics and biotechnology, the congress will serve as an inter- and multidisciplinary platform that brings together people from basic research, R&D, industry and medical application to discuss these issues.

As a major event for science, medicine and technology the congress provides a comprehensive overview and in–depth, first-hand information on new developments, advanced technologies and current and future applications.

With this Final Program we would like to give you an overview of the dimension of the congress and invite you to join us in Munich!

Olaf Dössel
Congress President

Wolfgang C. Schlegel
Congress President

Preface

Welcome to World Congress 2009!

Since the first World Congress on Medical Physics and Biomedical Engineering convened in 1982, medically and biologically oriented engineers and physicists from all continents have gathered every three years to discuss how physics and engineering can advance medicine, health and health care and to assess the clinical, scientific, technical and professional progress in their fields. In the tradition and the mission of our professions, which are the only ones involved in the whole loop of health and health care from basic research to the development, assessment, production, management and application of medical technologies, the theme of WC 2009 is "For the Benefit of the Patient". Thus, in addition to scientific aspects, the Congress will focus on all aspects of safe and efficient health technology in both industrialized and developing countries, including economic issues, the perspectives that advanced technologies and innovations in medicine and healthcare offer for the patients and the development of societies, the progress of MBE and MP, including health policy and educational issues as well as the need for the regulation and classification as health professionals of those biomedical/clinical engineers and medical physicists who are working in the health care systems.

The World Congress as the most important meeting of our professions, bringing together physicists, engineers and physicians from all over the world, including the delegates of the 138 constituent organizations of the IUPESM representing some 140,000 individual members, is the best place to discuss these issues, thereby contributing to the advancement of the physical and engineering sciences, our professions and thus to global health.

It gives me great pleasure to welcome you to this important event. I wish you a rewarding and enjoyable congress and a most pleasant time in Munich, the ‘metropolis with heart’ that has so much to offer.

Joachim H. Nagel
President of the IUPESM

Preface

Let's talk!
Is our level of communication between Medical Physics, Biomedical Engineering, Clinical Engineering, Medical Informatics, Tissue Engineering, etc. and Medicine good enough? We would like to answer: yes, we are quite good, but not good enough! There is a lot of room for improvement. Let' start right on the spot - on the World Congress on Medical Physics and Biomedical Engineering 2009. And please remember: communication is 50% talking and 50% listening.

Let's work together!
Do we have a perfect level of collaboration in our field? OK, we are quite good, but we can do better. Just to give an example: there should be no funded project in Medical Physics or Biomedical Engineering where there is no medical partner. And vice versa: medical doctors should join their forces with physicists and engineers if they are aiming at improvements on medical devices or healthcare systems. Let's start right here in Munich, September 2009, with innovative projects and innovative ways of cooperation.

Let's get to know each other!
It's known for more than thousand years: people who know each other personally and from face to face can talk with better mutual understanding, collaborate with less friction losses, are much more successful ..... and have much more fun. Plenty of chances to make new friends and to refresh old relations on World Congress on Medical Physics and Biomedical Engineering 2009!

And here are the numbers:
More than 3000 scientists working in the field of Medical Physics and Biomedical Engineering meet in September 2009 in Munich. They come from more than 100 nations. They submitted about 2800 contributions. 10 plenary talks and 46 keynote lectures bring us to the top level of science in our field. 75 companies show their latest achievements in the industrial exhibition. It's definitely the largest market place of ideas and innovations in Medical Physics and Biomedical Engineering of the year 2009.

August 2009 Olaf Dössel

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Silicon Eye

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Silicon eye can be otherwise called as a complete eye implant. The project overview is given in brief by the description of main components.

Here in the silicon eye, a biconcave gel lens is used in connection with a micro controller. A porous silicon nano photodiode is placed before the gel lens. This specially designed transparent diode will help in identifying the intensity of light receiving in the beginning of the processing chain. An effective drainage system (with the help of two valves) will control the working of gel lens. All these components together form the primary circuit to enable the process of auto focusing. The micro controller is connected with all main components of the system. The primary circuit is connected to a secondary circuit which consists of an artificial silicon retina and a chemical synapse. By the combined and co-ordinate working of both these will enable vision. The power supply, which all the electrical components here need is given by a series of nano paper batteries placed beneath the retinal layer (carbon nano tubes can also be implemented instead or along with it). The converted electrical impulses (from intensity of light received) will be carried to the visual area of brain through optic nerve by the effective interaction with a number of artificial chemical synapses.

Finally this silicon eye will be an effective implant for the damaged eye. And we are sure that this will be a great breakthrough in the modern medicine.

MATERIALS AND METHODS WITH DESCRIPTION

A. *Lens*

This is one of the main parts of the silicon eye. We believe that this is the main thing that we have thought in a different way from the existing technologies.

The lens is made of a special gel. We prefer this gel to be ideally transparent and also it shouldn't decrease the speed of light that passes through it. Silicon hydro gel is a suitable substance. Because it is a substance which is having high oxygen permeability. The substance used for making the contact lenses can also be tried.

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The preferred lens is made almost in a biconcave shape. We are designing the lens in such a way that, there are two pin holes on the lens; one at the top and one at the bottom. Now we are going to discuss about the drainage that used for the auto focusing of the gel lens.

The ductless lachrymal gland is connected to the top of the lens through a tiny tube. Thus we are making the ductless lachrymal gland to a ducted gland. The excess fluid after use is drained to the eye through another tube from the lower part of the lens. This will enable the eye to keep wet every time for the easy movement of eye lids. Now we are going for the explanation for the process of auto focusing,

As we have already explained above there is a drainage system using two tubes through which the fluid flows in out of the lens.

Now consider, the person wearing silicon eye is looking at an object; the porous silicon nano photo diode* will identify the intensity of light and it will create a specific electrical impulse and send that information to the micro controller**.

B. **Porous silicon nano photo diode(P.S.N.P.D);*

A specially made photo diode uses silicon. The need of this device here is, it will identify the intensity of light and pass information to a micro controller. As it name indicate this is porous in nature. I.e. it will pass the light without much difficulty. That's what we need too.

C. ***Micro controller(M.C);*

It is type of micro processor. In this device specific data will be encoded. The function of this is that, when a specific intensity of light is identified by the P.S.N.P and will send a particular electrical impulse to this M.C. Now this impulse is processed in M.C as follows;

- The intensity of light is identified.
- The system verifies and compares the pre coded data with the received intensity.
- Acquires the data with respect to the intensity of light received.
- Produces a new impulse for transmission to the valve system at the opening of the lachrymal gland.

Drainage system;

The drainage system is for, the working of auto focusing lens i.e. the process of focusing with respect to the object distance. Let us consider an object at a certain distance from the lens, the microprocessor sends a specific coded data to the first valve (let it be valve 1). The opening of this valve is related to the intensity of light falling on the porous silicon nano photo diode. If the intensity is high (or low), the valve 1 will regulate the secretion.

Thus a certain quantity of fluid enters the lens, which will result in the change of shape of lens from concave to convex or vice versa. That means the rays of light will converge or diverge in accordance with the intensity of light falling on the gel lens to take place the process of auto focusing.

I. *Working of the valve system*

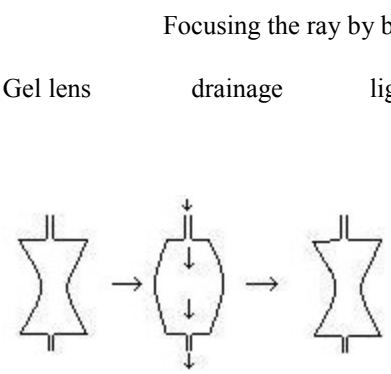
As we have early pointed out there are two tiny tubes used in the drainage. A group of valves that are controlled by several controlling units' (microcontroller) controls the flow of the lachrymal secretion through the tiny tubes. The detailed description of these valves is given below;

1. *Valve 1:*

This first valve is placed at the opening of lachrymal gland. Its function is to regulate the flow of fluid from the gland. It will work according to the data received from the micro controller. That means, when a small intensity of light is identified by the micro controller it will send specific information to the valve 1 and a respective process takes place vice versa too. Thus, the valve may open with respect to the impulse received from the M.C. The working means, opening and closure of the valve. Thus, it will help in the filling of the lens with the fluid. Moreover, in that way only, the process of auto focusing takes place. It is because of the reason that when fluid fills inside the lens, the previously made concave lens will slightly transform its shape to almost a convex shape. Thus, the light rays may diverge or converge with respect to the distance of the object observing the person.

2. *Valve 2:*

The second valve is placed at the bottom of the gel lens. The main function of this valve is to regulate back flow of the glandular secretion in gel lens and it will act as the outlet for the fluid from lens. The working of this valve 2 is controlled by the special sensors placed on the valve it self. The sensor at the valve 2 is a specially designed to identify the secretion level. Its function is to identify the level of secretion inside the gel lens.



A Rough diagram of the process of focusing

Power supply

For the uninterrupted power supply for the proper working of the entire system, we are taken the following measures

1. Nano paper battery

The nano paper battery will act as the primary source energy. This specially designed nano, power producing device is completely made of cellulose. Therefore, there will not be any problem of biocompatibility. As the name implies, this setup is like a paper only. So we can place this battery in between the choroid and sclera without much difficulty.

The main advantages of using this type of battery is that,

The most important thing is its nano size.

- Surgery can be done easily, since it is having only that much size.
- Due to its biocompatibility, we can use two or more batteries as supply according to the need.
- It can be easily replaced, if needy.

WORKING OF THE SILICON EYE

Here we are developing a lens, which is made up of silicon hydro gel. The gel should be ideally transparent and it will not reduce the intensity and speed of light considerably. A suitable gel substance is silicon hydro gel. This gel substance is coated with a transparent metal alloy, which is made up of indium tin oxide (ITO). This must be flexible i.e. it bears a sort of elasticity. We will enclose the gel inside ITO in almost a biconcave shape. For that purpose we are making some layers of ITO, it can be directly vaporized. However, at the top and bottom surface of the concave lens is solidified with a suitable metal alloy. Then we give drainage through the gel lens by using a tiny tube, which is connected to lachrymal gland. The tube must be hollow with opening at both ends and flap at mouth. The microcontroller controls Opening and closure of the flap.

The light through the pupil incident on the porous silicon nano photo diode, which is placed just before the gel lens and this, will identify the intensity of light and passes the information to the micro controller. If the object is near to us then the intensity of light will be high and vice versa. If the light intensity is high (or low) then the flap will open in accordance with that. This process of focusing takes place continuously. As a result, the biconcave lens will bulge out and it will become convex. This way the focusing will take place. To give power for the system we will use nano paper battery. The secretion going out through the drainage should be lesser than the secretion comes into the lens. All required program to control the opening and closure of the flaps are coded in the micro controller.

After the process of focusing, the light will fall on the artificial silicon retina. This will convert the received intensity of light to a specific electrical impulse. This impulse is traveled through the artificial chemical synapse to reach the area of vision in brain. Then brain enables the vision.

ADVANTAGES:

- The whole system is easy and convenient to carry.
- Most effective conduction process is employed.
- Simple power production from body fluids itself.
- For the additional power needed, a compact nano paper battery is used in extra.
- The clarity of the picture is almost near to, a normal man’s vision. Nevertheless, the persistence of vision will be somewhat higher than in a normal eye.

CONCLUSION:

Nowadays no such devices are available which have the ability to provide the vision to the blinds. This is an effective one and without much time delay a blind can enjoy the beauty of vision.

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Automated Assembly of Dynamic Micro-Bead Arrays Using a Multi-arm Laser Manipulator with Computer Vision

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Abstract— **Dynamic microarrays have great flexibility and potential as tools for advancing research in diagnostics and biomedical fields. In contrast with static microarrays such as DNA-chip using micro-spots of the bio-molecules, dynamic microarrays use a mobile substrate, usually micro-beads coated with bio-molecules. To realize the dynamic microarray, micro-bead handling techniques are essential, allowing us to transport the selected bead, and immobilize them for signal detection. Laser manipulation, known as optical tweezers, is one of the most suitable techniques for arranging and handling micro-beads. We have developed a multi-arm laser manipulation system with an excellent user-interface and real-time image processing functions. In this paper, we report a new approach for fully-automated assembly of a versatile dynamic micro-bead array. The beads, dispersed in a pipetted liquid on a cover glass, can be simultaneously trapped and sorted into a desired order, using multiple optical tweezers to transport the beads along collision-less paths guided by both computer vision and knowledge database techniques. Two typical examples are demonstrated. One is the fully-automated assembly of a 3x3 micro-bead array and its handling in 3D space. The other is the collision-free sorting of an array's elements. We also describe the experimental apparatus used in these demonstrations.**

Keywords— **Optical tweezers, Micromanipulation, Dynamic microarray, μTAS, Hough Transform.**

I. INTRODUCTION

Micro/Nano systems for biomedical fields, such as the so-called Lab-on-a-Chip and bio-MEMS, is currently an area of intensive research. DNA-chips, using micro-spots of bio-molecules, represent a widely-used group of static microarrays for basic studies in biomedical fields, diagnostics, drug discovery, etc. Compared with static microarrays, dynamic microarrays using mobile substrate, usually micro-beads coated with bio-molecules, have several advantages as tools for advancing research in biomedical fields [1]. To realize the potential of dynamic microarrays, micro-bead handling techniques allowing us to transport the selected beads and immobilize them for signal detection are necessary. Laser manipulation, also known as optical tweezers [2, 3], is one of the most suitable techniques for manipulating and handling micro-beads. To achieve fully-automated manipulation for assembling micro-bead arrays, we developed a multi-arm laser manipulator based on the Time-Sharing Synchronized Scanning (T3S) approach for generating multiple laser trapping positions [4]. The multi-arm laser manipulator has an excellent user-interface and real-time image processing functions. In Section II, we propose a new approach for automated assembly of versatile dynamic micro-bead arrays. The system configuration is also described in this section. In Section III, we demonstrate two typical examples based on the proposed approach. One is the fully-automated assembly of a 3x3 micro-bead array and its handling in 3D space. The other is the collision-free sorting of an array's elements.

II. PC-CONTROLLED DYNAMIC MICROARRAYS

A. Approach using laser multiple-trap techniques

For assembling dynamic microarrays, several approaches including hydrodynamic [1], dielectrophoresis [5], and mechanical [6, 7], have been demonstrated. Laser trapping is one of the most suitable approaches and has several advantages: (i) no physical contact means we can manipulate the beads in a closed space such as Lab-on-a-Chip, and since no adhesion between manipulator and beads occurs, we can achieve more precise positioning; (ii) we can simultaneously manipulate multiple beads using single laser source; (iii) it is not necessary to redesign hardware configurations, namely, mechanical and fluidic parts, for handling beads of different size and number (a reusable platform can greatly reduce the cost of operation); (iv) an objective lens can be used as both a manipulating and an observing apparatus. We can control both operations under the same coordinate system, which makes using computer vision techniques for fully-automated applications easier when compared with competitors' systems. Figure 1 illustrates our approach for assembling dynamic bead arrays using laser multiple-trap techniques. Our approach consists of three control stages: Stage 1, image recognition and automated trapping; Stage 2, automatic transportation; and Stage 3, automatic sorting by color/size. First, in Stage 1, beads with specified properties are recognized, and then all

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the beads are trapped simultaneously. Secondly, in Stage 2, all the trapped beads are transported simultaneously to latticed positions along the collision-less path. Finally, in Stage 3, the beads are sorted to arrange in the specified order under the collision-free interchange algorithm based on group theory.

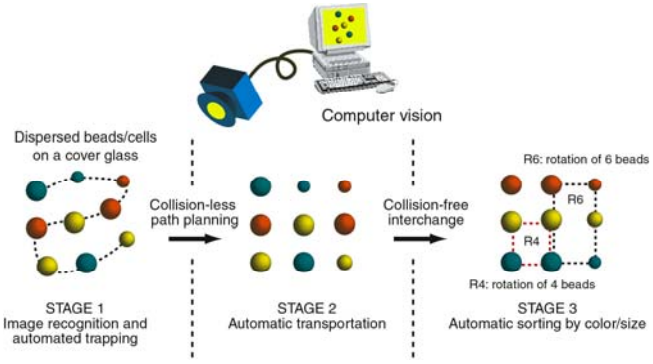

Fig. 1 Scheme of automated assembly of a dynamic beads array

B. *Experimental system*

To manipulate many micro-beads using laser multiple-trap techniques, we have used Time-Sharing Synchronized Scanning (T3S) Optical Tweezers [4]. This additional optical structure is linked to a commercially-available inverted microscope. Figure 2 schematically shows the experimental setup. The focal positions of the time-shared beam on the XY-plane are controlled by the 2-axis steering mirror. This mirror can tilt at a considerable rate just as a piezoelectric mirror can. The Z-coordinate is controlled by the lens L1 mounted on a PC-controlled linear stage, which can be moved parallel to the optical axis.

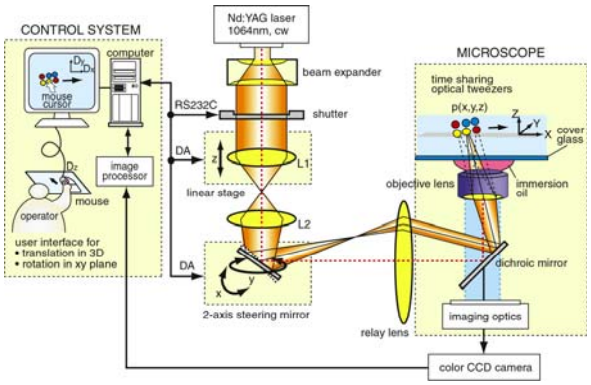

Fig. 2 Schematic of experimental setup

Thus, an assembled bead-array can be translated in 3D and rotated in XY-plane at a specified Z-coordinate using a PC 3-button mouse. An image processor digitizes the images from a color CCD camera in real time for feature recognition. Developed software for image processing and device control is executed by a personal computer (PC).

III. DEMONSTRATIONS

A. *Fully automated assembly of dynamic bead array*

Here, we demonstrate the fully-automated assembly of a 3x3 micro-bead array using computer vision techniques in order to explore the future possibilities for a laser-controlled, flexible microarray chip, or so-called "dynamic microarray". Figure 3 is a sequence of images recorded with the CCD camera showing the result of the fully-automated assembly of the dynamic array. First, the positions of the micro-beads dispersed in the pipetted water on a cover glass were detected by the circular Hough transform technique [8]. Nine beads nearest to the center position, o, were simultaneously trapped at the initially detected position of each bead using the T3S optical tweezers (Fig. 3(a)). Second, nine trapped beads were simultaneously transported to pre-designated destinations, where the beads formed a 3x3 array, along the collision-less paths (Fig. 3(b)). After forming the 3x3 array, the array could be translated in XY-plane (Fig. 3(c)), rotated (Fig. 3(d)), lifted off/down the cover glass (Fig. 3(e)), and expanded (Fig. 3(f)) using the PC 3-button mouse.

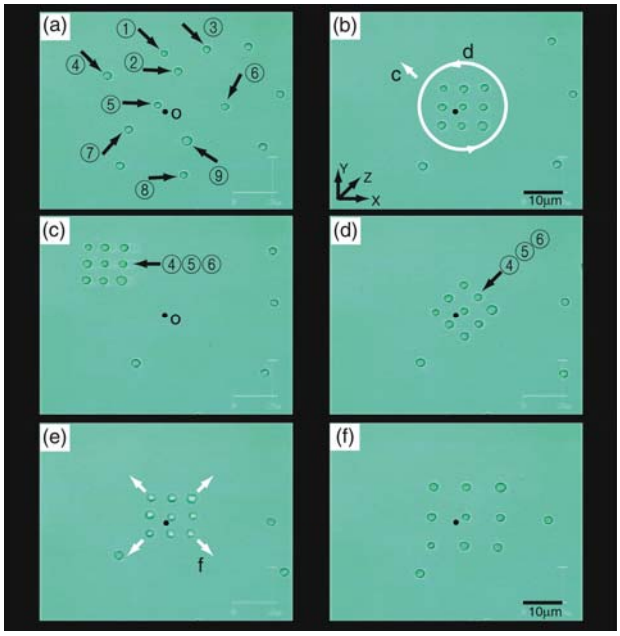

Fig. 3 Automated assembly of a 3x3 array and its translations in 3D space

B. Collision-free sorting of the array's elements

Rearrangement of the beads at arbitrary lattice positions is important for signal analysis applications of dynamic microarrays. Here, we demonstrate the automatic sorting of an array's elements by size. Figure 4 is a sequence of images recorded with the CCD camera showing the result of automated assembly of a 3x3 array and subsequent automatic sorting by size. First, nine beads were detected and transported to form the 3x3 array in a manner identical to Subsection A (Fig. 4(a), (b)). Next, the successive rotations of 4/6 beads at lattice position (R4/R6 in Fig. 1) were carried out, like solving the Rubik's Cube puzzle, in order to interchange the array's elements under the collision-free paths (Fig. 4(c)-(e)). Note that a mathematical proof based on the group theory shows that the procedure of rotations, R4 and R6, can exchange two beads at arbitrary lattice positions. This procedure continued until the sorting was completed (Fig. 4(f)).

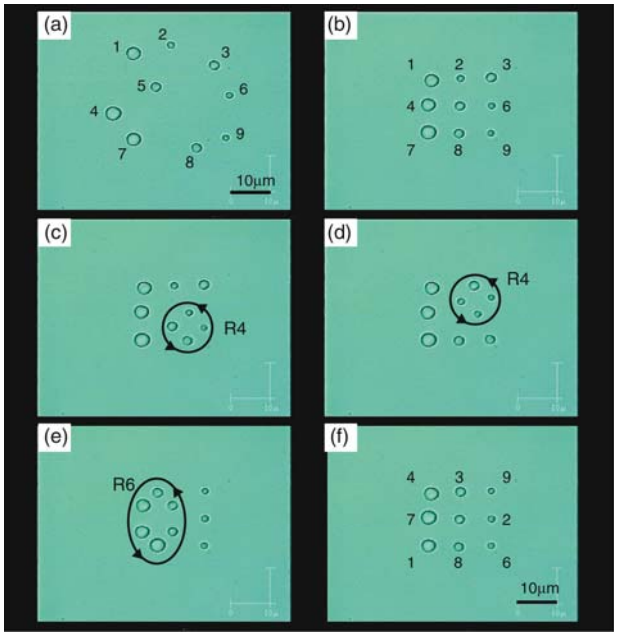

Fig. 4 Automated assembly of a 3x3 array and its sorting by size

IV. Conclusions

We have proposed a new approach for automated assembly of PC-controlled dynamic micro-bead arrays, and demonstrated two typical examples of fully-automated assembly. Although the demonstrations performed are indeed simple, laser-controlled dynamic arrays have great flexibility and potential as research tools in various fields, including biomedical applications. Furthermore, multi-arm laser manipulators combined with visual-feedback control or knowledge-database control may not only enable the assembly of dynamic micro-beads array, but also be applied to other biomedical and industrial fields.

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A Nano-porous Aerogel Biochip for Molecular Recognition of Nucleotide Acids

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Abstract—**A nano-porous aerogel was produced in regular atmospheric conditions using the sol-gel polymerization of tetraethyl orthosilicate (TEOS) to build a three-dimensional (3D) structure for recognizing nucleotide acids. The Fourier transformation infrared spectroscopy and Brunauer-Emmett-Teller instrument had been used to characterize this 3D aerogel and concluded that it had a high porosity and large internal networking surface area to capture nucleotide acids. The functionality of molecular recognition on nucleotide acids was demonstrated on human gene ATP5O.**

Keywords— **Aerogel, molecular recognition, DNA detection. 3D biochips.**

I. Introduction

Silica aerogel is a material with high porosity, large surface area, low density, and low thermal conductivity. These unique characteristics guarantee this advanced material in the applications of thermal insulation, electrical batteries, nuclear waste storage, catalysis, acoustic insulation, and adsorbents [1]. In addition, silica aerogel also holds promises as biocompatible scaffolds to be applied on virus detection [2], protein entrapment [3], protein incorporation [4], hybridization array [5, 6], and building potential matrices in the further design of biosensors. The modern exciting application on capturing comet dust further pushed this material into the outer space (www.nasa.gov).

Unlike the traditional supercritically-dried technique [5], this contribution adopted a process to prepare the aerogel in the regular atmospheric condition. We also demonstrated the functionality of molecular recognition on detecting a sequence-specific deoxynucleotide acid (DNA) target and compared the results with those using traditional planar slides.

II. Exeperimental

A. Materials

The networking precursor of the aerogel, tetraethyl orthosilicate (TEOS), the solvent, methanol, and the surface modifying reagent of aerogel, 3-Glycidoxypropyltrimethoxysilane (GLYMO), were all obtained from Acros Company. The DNA targets were PCR (Polymerase Chain Reaction) products amplified from the human gene ATP5O in total RNA. Table 1 lists its gene information and the primers participating in the PCR process. Both probe and primer sequences are listed in Table 1. The conformations of DNA probe immobilization and probe-target hybridization are shown in Fig. 1.

Table 1 Genetic information of materials

ATP5O	
Length	313 bases
Definition (NCBI gene bank)	ATP synthase, H+ transporting, mitochondrial F1 complex, O subunit (oligomycin sensitivity conferring protein)
ATP5Oc (probe)	
Sequences	amine-C_6-5'(GTGATTGGACGCGGTGA)-(GTCTTGACAGACATGTCAACATATTTCTCGCCAATGCGCACAATCATTCCACCCAAGATT)3'
PCR Primers	
ATP5O-F1	TTCTGCTGCATCAAAACAGAAT
ATP5O-R1	ATGGCAGAAAACCAACACTTTT
cy3-ATP5O-F2	CGATTAAGCA CAAGGAG ATACC

B. Instrument

Fourier transformation infrared (FTIR, BIO-RAD-FTS-7) spectrometer was used to verify the removal of the template from the aerogel. The BET specific surface area and the pore volume of the as-prepared aerogels were deter-

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mined from the nitrogen adsorption/desorption isotherm by the Barrett-Joyner-Halenda (BJH) method using a Micrometrics ASAP 2020 analyzer. PCR was performed on GeneAmp_PCR, System 9700. The microarray scanner (GenePix 4000B, Molecular Devices) was used to excite and read the labeling fluorescence.

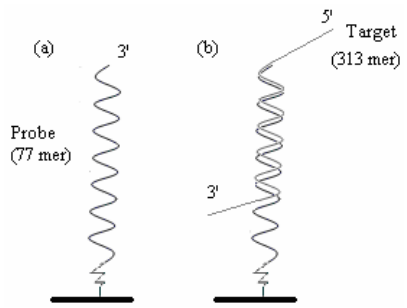

Figure 1. The Conformations of DNA Probe Immobilization and Probe-Target Hybridization. (a) To compare with experimental results, the 77-mer probe, ATO5Oc, was immobilized on both planar slide and aerogel surfaces. (b) The upper 60-mer of the probe was designed specifically to recognize the DNA sequence of the target. The lower 17-mer provided a space to prevent the target-substrate interface from a steric hindrance.

C. Procedure

The silica-aerogel was prepared in the sol-gel process by mixing TEOS, methanol, network template, and water. It was then cured at the ambient temperature for 1 week. The as-prepared silica aerogel was finally obtained by freeze drying, and Fourier transformation infrared (FTIR) analysis was utilized to confirm the removal of the ionic-liquid template. To capture the NH_2-modified DNA probe, the aerogel product was grained into powder and stirred in 5% GLYMO solution for 1 hr to modify the surface from -OH to epoxy functional group. The internal volume and porosity using Brunauer-Emmett-Teller (BET). The results were compared with those obtained prior to modification.

The epoxy-modified aerogel was dropped onto slides in the array aligned by a grid paper placed underneath. The slides were then baked at 100°C for 90 minutes and ready for DNA-probe immobilization.

The oligonucleotide probe was dropped on both commercial and aerogel slides in 1 µl. The slides were then incubated in a humid box at 30°C for 16-17 hours to immobilize the probes on the planar slides or aerogel. A wash step was conducted to remove the free probes in 0.5% SDS by shaking at 80rpm for 15 minutes. The slides were then immersed in the blocking buffer at 60°C for 45 min and finally rinsed with ddH_2O and spun to dry. DNA target was mixed with 1X hybridization buffer to the final concentrations of 40, 60, 80, and 120 nM. One micro-liter of the target solutions were dropped onto planar slides and aerogel dots at the previously-immobilized probes. All chips were then enclosed in a humid box and incubated at 50°C for 16-17 hours and then washed. They were initially immersed in 2X SSC/0.2X SDS at 42°C at 80 rpm for 10 min, then changed to 2X SSC in the same condition, and finally 0.2X SSC at room temperature. After rinsing with ddH_2O and spun to dry, the slides were scanned for fluorescence analysis.

III. Results and Discussion

Figure 2 shows the FTIR spectrum for the as-prepared silica aerogel before and after template removal. The characteristic template band was found to be absent revealing that the template was entirely removed from the wet aerogel by our extraction process.

Figure 3 shows the nitrogen adsorption/desorption isotherm of the silica aerogel product. The measurement indicated that its specific surface area was 813 m^2/g, pore volume was 0.78 cm^3/g, and the average pore-diameter was 4.2 nm. Its large surface area granted the assurance that the detection signal of the captured biological samples on the surface can be tremendously intensified.

As shown in Figure 4, ATP5Oc-immobilized aerogel was utilized to recognize the target human gene ATP5O and compared the results side-by-side with commercial planar slides. The positive control on the leftmost bottom of aerogel was the brightest over those on planar slides and the flat surface reached its accommodation saturation for target molecules; whereas the aerogel still kept capturing DNA targets.

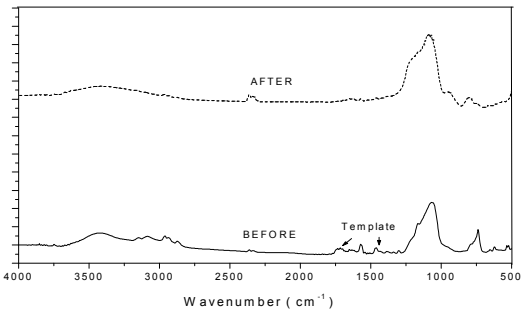

Figure 2. FTIR analysis of the aerogel product before and after template removal. The disappearance of the characteristic peaks in the spectrum indicates that the template was successfully removed.

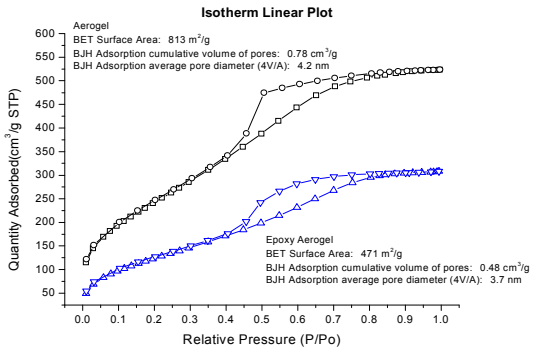

Figure 3. Nitrogen Isotherm of the Silica Aerogel Product. The specific surface area was 813 m^2/g, pore volume was 0.78 cm^3/g, and average porosity was 4.2 nm.

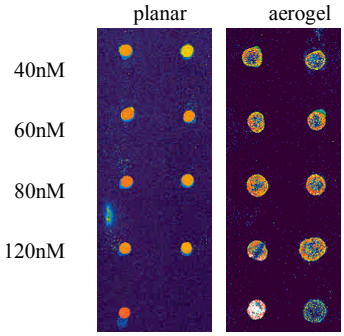

Figure 4. Molecular Recognition Test of ATP5O on Aerogel. Human gene ATP5O (313b) was recognized on the aerogel surfaces over various target concentrations

IV. Conclusions

In this study, mesoporous aerogels are prepared at room temperature by the sol-gel polymerization. The as-prepared aerogel was characterized and concluded that it had a high porosity and large internal networking surface area. The as-prepared aerogel was further arrayed onto slides and successfully recognized a short-size human gene ATP5O by an immobilized oligonucleotide probe on the aerogel surface.

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Biodegradable Polymeric Implants as Drug Delivery Systems for Brain Cancer Therapy

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Abstract— **Brain cancer therapy has been a challenging task due to its fatal outcome and limited accessibility. Recent advance in DDS leads to the utilization of polymers for the local delivery of anticancer agents directly to brain tumors. Polymer has received a growing attention as a material for drug delivery systems (DDS), especially brain cancer because of its biodegradable and biocompatible properties. Ease of polymer synthesis makes it possible to tune polymer properties to provide different drug release profiles and degradation mechanisms. This review aims to provide the information concerning biodegradable polymeric implants. The main focus is on systems that currently reach the *in vivo* study or are using in clinic.**

Keywords— **Polymer, implant, drug delivery system, brain cancer, tumor.**

Tremendous efforts have been made to create drug delivery systems that can deliver therapeutic agents to brain tumor and increase chemotherapeutic efficacy while reducing the negative side effects. In the late 19th century, Paul Ehrlich, the German scientist, originated the concept of "Magic bullet" for the targeted drug delivery from his experience in bacteria research.

Several great reviews on drug deliverys for brain cancer therapy have been reported. [1-3] This review aims to provide not only updated success and application of polymer implantation for brain cancer therapy but also the insight information on the design, problem and consideration that must take into account for the future development. First, obstacles in drug delivery to brain will be reviewed, followed by the in-depth summary on the utilization of polymers as drug delivery systems with the emphasis on Gliadel® wafers.

Even though many kinds of drug delivery systems have been developed for brain cancer therapy, for example, polymeric implants, liposomes and nanoparticles, little success have been accomplished. This is because brain cancer chemotherapy encounters very challenging obstacles: 1) *Drug elimination*: small molecules are secreted by kidney without any restriction. Chang et al.[4] reported that the renal elimination in a rat model of low molecular weight dextrans with a radius lower than 2.0 nm (Mw ~10 kDa) occured without any molecular restriction. On the other hand, the renal clearance of larger dextrans gradually decreased and approached zero at a radius higher than 4.4 nm (Mw ~40 kDa). For example, carmustine (BCNU) has a short elimination half-life (15 minute) [5]; 2) *Side effect*: side effect is the major obstacles for cancer treatment, especially chemotherapy. For example, 7-Ethyl-10-hydroxy-camptothecin (SN-38) has the side effect in category 3 (severe) and 4 (life threatening) as categorized by the National Cancer Institute Common Toxicity Criteria, USA. The symptom is such as severe diarrhea [6,7] and neutropenia.; 3) *Physiological barriers*: drugs are required to pass many physiological systems. For brain cancer, drugs must travel through the blood brain barrier (BBB). Inside the brain tumor, drugs will encounter the interstitial hypertension [8-11] which is the elevated pressure inside tumors. Due to this effect, the diffusion through the brain tumor will be dramatically limited. BBB is formed by tight junctions of endothelial cells in the central nervous system (CNS) which can inhibit the access of therapeutic agents to the brain. Many attempts have been made to overcome these problems but unfortunately end with the failure to successfully treat the brain cancer. Therefore, there is a need to develop drug delivery systems that can overcome these obstacles and efficiently deliver drugs to the brain. The ideal design of drug delivery system to use for brain cancer chemotherapy would be one that is able to directly deliver anticancer drugs in the brain, i.e. intracranial delivery.

The well known advantages of drug delivery over conventional chemotherapy are lowering the adverse effects and prolonging blood circulation time of therapeutic agent in body. Polymers have emerged as widely used delivery carriers for different kinds of anticancer drugs and have been successfully used as materials for a variety of drug delivery systems, for example, polymer implant[12,13] and microparticles for brain cancer therapy. Besides unique properties such as thermoplastic property, viscoelastic, biocompatible and adjustable thermal properties, polymers should be biodegradable. These polymers can be hydrolyzed and eventually decomposed. Therefore, there is no need to remove them after all of drugs diffuse out. Each polymer has different hydrolysis rate as the following sequence: polyanhydride > polyorthoester > polyester > polycarbonate > polyamide > polyurethane > polyurea.

POLYANHYDRIDE

Polyanhydride is successfully used for brain tumors therapy. Its fast hydrolysis rate produces a different degradation mechanism (surface erosion) from a common diffusion-controlled mechanism. The steady drug concentration is achieved from the controllable degradation rate of the polymer matrices and can be controlled by the copolymer

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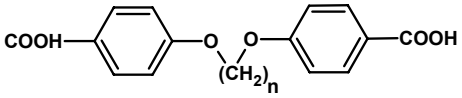
ratio of monomers. Polyanhydride can be made by polymerization of the two carboxylic acid containing monomer.

A) Aliphatic monomer

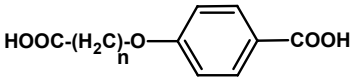
$HOOC\text{-}(CH_2)_4\text{-}COOH$ = adipic acid

$HOOC\text{-}(CH_2)_8\text{-}COOH$ = sebacic acid

B) Aromatic monomer

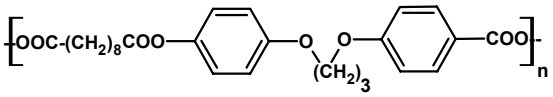


n = 1; bis(*p*-carboxyphenoxy)methane
n = 3; 1,3-bis(*p*-carboxyphenoxy)propane
n = 6; 1,3-bis(*p*-carboxyphenoxy)hexane



n = 1; *p*-carboxyphenoxy acetic acid
n = 4; *p*-carboxyphenoxy valeric acid
n = 8; *p*-carboxyphenoxy octanoic acid

C)



sebacic acid 1,3-bis(*p*-carboxyphenoxy)propane

Fig. 1 Chemical structure of A) aliphatic andydride monomers; B) aromatic anhydride monomers; and C) poly[1,3-bis(carboxyphenoxy) propane-*co*-sebacic-acid] (PCPP-SA).

Poly(bis(*p*-carboxyphenoxy)propane-sebacic acid) (pCPP:SA = 20:80) is used as a material for Gliadel®, a polymer wafer approved by the US food and drug administration in 1996 for the brain tumor treatment.[14-16] This system can be placed inside the brain cavity after brain surgery and can release drug within 2-3 weeks. It has a disc-shape with 1.4 cm in diameter and 1 mm in thickness. Gliadel wafers are prepare by spray drying pCPP-SA microspheres with BCNU-polymer solution.[12] The final formulation contains 3.85% BCNU which are homogenously distributed and within the pCPP-SA matrix. BCNU was found to stay as a solid solution form in the polymer matrix. This is confirmed by the presence of the single melting peak at 58 ^{o}C between that of pCPP:SA = 20:80 (approximately 65 ^{o}C) and BCNU (32 ^{o}C).[17] The fast hydrolysis of pCPP:SA leads to the surface eroding mechanism (the hydrolysis occurs simultaneously to the diffusion of water into the polymer surface as shown in Figure 2).

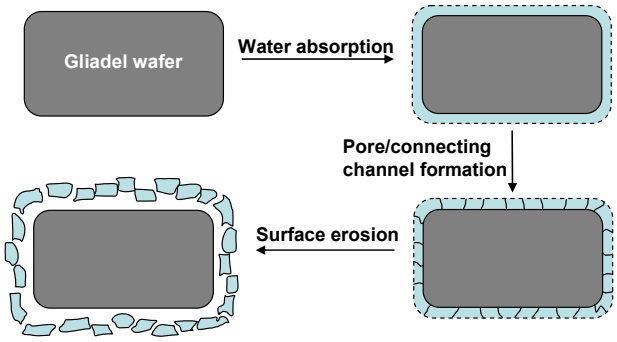


Fig. 2 Mechanism of surface erosion.

Westphal et al. [18] conducted a 30-month trial in two hundred forty patients and reported that the median survival time for the BCNU wafer and the placebo are 13.9 and 11.6 months, respectively. The BCNU wafers provide 29% risk reduction (P = 0.03) for the Gliadel® group against the placebo. These results are in agreement with results from the long time study (2-3 years) in which the median survival time for the BCNU wafer and the placebo are 13.8 and 11.6 months, respectively and 27% risk reduction. Even though the promising brain cancer therapy, Gliadel® were found to cause adverse effects such as CSF leak (5% vs. 0.8% for BCNU wafer vs. placebo) and intracranial hypertension (9.1% vs. 1.7% for BCNU wafer vs. placebo). Other adverse effects are seizures, brain oedema, healing abnormalities and intracranial infection.[18-20]

Recently, Gliadel® was reported as a contraindication when it is conducted in conjunction with the large opening of the ventricle.[21] The fatal consequences were found in three patients with glioblastoma multiforme whom were implanted with Gliadel®. The lateral ventricles of these patients were opened and wafers were hold in the resection cavity by the fibrin glue. Patients then had severe hydrocephalus and subsequently death possibly due to the obstruction of ventricular system. This report raises the concern on the use of fast hydrolysis polymer as a material for brain implantation. Therefore, it is very interesting to investigate how the slower hydrolysis polymer, i.e. polyester behaves once implanted into a brain.

Besides pCPP:SA, another polyanhydride, fatty acid dimer-sebacic acid (FAD-SA) copolymer, has been developed to deliver hydrophilic agents such as 4-hydroperoxycyclophosphamide (4HC) [22,23] and platinum drugs.

POLYESTER

Polyester is one of the most used materials for drug delivery systems. Generally, polyester can be made by ring

opening polymerization which can efficiently control the degree of polymerization and produce a narrow molar mass distribution.

This polymer does not have very fast hydrolysis as a result it is degraded by the bulk eroding mechanism (Figure 3). For this mechanism, the degradation takes place simultaneously through out the sample. Generally, drugs can be released from polyester by diffusion-based drug release.

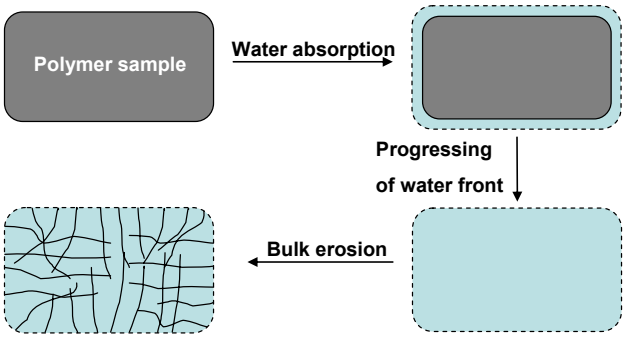


Fig. 3 Mechanism of bulk erosion.

The degradation of polyester has the characteristic mechanism so-call "autocatalytic effect" in which an acid, by product, can accumulate inside the sample and causes the inside out degradation as shown in Figure 4.

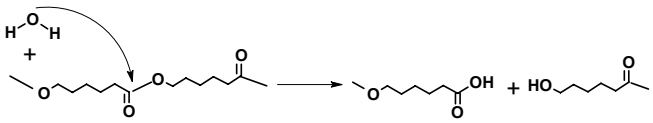


Fig. 4 Hydrolysis of polyester. An acid, by product of polyester degradation, can accumulate inside the sample and causes the inside out degradation so-call "autocatalytic effect".

Poly(lactic-co-glycolic acid) (PLGA) is the most widely used polyester for drug delivery systems, especially for cancer therapy because of its well-known biocompatible and biodegradable properties. [24-26] PLGA is a random copolymer of lactic acid and glycolic acid. Chemcial properties such as hydrophilicity, degradation rate, crystallinity can be controlled by the copolymer ratio between lactide (decrease hydrophilicity and degradation) and glycolide.

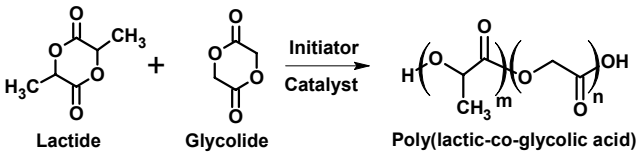


Fig. 5 Chemical structure of poly(lactic-co-glycolic acid) (PLGA). Its property can be controlled by the copolymer ratio between lactide and glycolide during the polymerization.

Similar approach has been performed to produce BCNU wafers from PLGA. Antitumor efficacy study in subcutaneous rat tumor model showed that this BCNU-PLGA wafer can delay the tumor growth. Nevertheless, tumors started to grow after 25 days. [27,28] There has been no report on PLGA wafers behavior and safety in the brain. A long term study in animal should be carried out to address this issue.

A variety of drug delivery systems for brain cancer therapy have been developed from polymers as shown in Table 1. Among them, PLGA microparticles have gained considerable attention with the ease of administration and great cancer treatment. Their microscale structure should be able to avoid the blockage of ventricles as reported in macroscopic systems such as wafers.

Table 1 Drug delivery systems for brain cancer

Formulation	Polymer	Drugs	*In vitro* study	*In vivo* study	Ref
Gliadel® (Wafer)	CPP: SA	BCNU	-	- Sprague-Dawley rats - Fisher 344 rats - Human	[12], [17], [18-20]
Disk	FAD-SA	4HC	-	- F98 & 9L gliomas in rat	[22,23]
Wafer	PLGA	BCNU	9L gliosarcoma cells	9L gliosarcoma cells in F 344 rats	[27,28]
Microparticle	PLGA	5-fluorouracil	-	- Phase II - C6 glioma in rats	[32] [33]
Micro/ nanofibers	PLGA	Paclitaxel	C6 glioma	-	[34]
Microparticle	PLGA	Temo-zolomide	C6 glioma	-	[35]
Microparticle	PLA/ PLGA	Cisplatin	C6 glioma	-	[36]

Conclusion

Rational designs as mentioned in this review must be considered to produce efficient drug delivery systems for brain cancer therapy. Antitumor activity in parallel with safety of the systems must be seriously considered.

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CH_2-Symmetric/CH_2-Antisymmetric Stretch Ratio Sensor for Cell Analysis

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Abstract— **Here we report on a novel infrared sensor system for measuring the CH_2-symmetric/CH_2-antisymmetric stretch ratio of cell samples. Based on IR absorbance spectra of healthy and malignant breast [1], blood [2] and brain [3] cells found in literature we hypothesized the possibility of disease stage cell discrimination by only comparing a few absorbance peaks in the lipid absorbance wavelength region between 3 and 4 µm. By comparing the lipid CH_2-symmetric and CH_2-antisymmetric stretch ratios (with baseline correction and normalization) of three defined epithelial kidney cell lines, healthy MDCK and carcinoma A-498 and Caki-1 with the developed sensor, significant stretch ratio differences have been found between healthy and tumor cell types (and even between the two tumor types). The developed LED-photodiode based infrared absorbance sensor could be used for quick pre-screening of biopsy samples which, compared to labeling and staining techniques, does not require highly trained personnel and is much cheaper than liquid nitrogen cooled FTIR spectroscopes.**

Keywords— **Infrared absorbance sensor, Label-Free, Cell analysis**

I. Introduction

In recent years cancer is becoming the number one disease of dead causes [4]. The development of diagnostic tools plays an important role in understanding the fundamentals of tumor development and in selecting the proper treatment. Normally the screening of biopsies for possible malignant cells is done by visual inspection of slides with labeled or stained cells. The labeling and staining techniques are expensive and the visual inspection is time consuming, performed only by highly trained personnel and also results in false positives and negatives (e.g. for cervical tumor screening the interobserver reproducibility is very low [5]).

Infrared spectroscopy, IR absorbance due to specific molecular vibrations, is an interesting diagnostic tool without the need of added labels with the ability to analyze cell components such as DNA, RNA, proteins and lipids. By comparing the IR absorbance spectra of healthy and malignant cells, published in literature (e.g. in breast [1], blood [2] and brain [3]), we hypothesized a new concept to distinguish cell types. It concerns a few-wavelength based cell type discrimination concept in the wavelength region between 3 and 4 µm. In this region specific lipid absorbance peaks [6] can be found (CH_2-and CH_3-symmetric and antisymmetric stretch).

To test the few-wavelength hypothesis we recorded and compared our own data set of healthy (MDCK) and carcinoma (A-498 and Caki-1) epithelial kidney cell lines with a Fourier transform infrared (FTIR) spectroscope. The IR absorbance ratio CH_2-symmetric/CH_2-antisymmetric stretch (3.51/3.42 µm) differs between the cell types. This ratio is increased in the carcinoma cell lines compared to the healthy MDCK cell line (Fig. 1). This confirms that it is possible to distinguish between healthy and carcinoma epithelial kidney cell lines by only measuring the IR absorbance at a few wavelengths. To compare the lipid CH_2 stretch ratio of different samples baseline correction and normalization is required. This is normally done with the software package supplied with the IR spectroscope. Instead of recording the whole IR spectra between 2 and 20 µm with an expensive FTIR spectroscope, comprising of an liquid nitrogen cooled detector, we developed a smaller, faster and cheaper sensor system based on LED light sources, narrow bandpass filters and a room temperature operable photodiode detector which could be used to discriminate between healthy and tumor cell types.

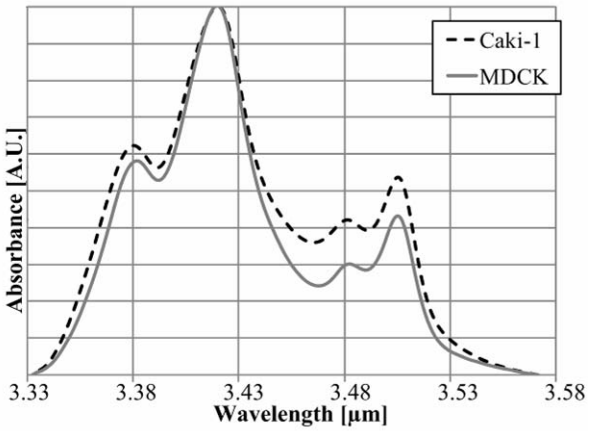

Fig. 1 Normalized and baseline corrected IR Absorbance spectra of epithelial kidney cells MDCK and Caki-1 recorded with a Bruker Equinox 55 spectrometer (240 scans per spectrum, 4 cm-1 resolution and 1 mm beam diameter). The absorbance peak at 3.51 µm is increased in the Caki-1 carcinoma cell line compared to the healthy MDCK cell line.

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