The Microchips for Alzheimer Disease Diagnosis

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ABSTRACT

The modern micromachined chip conception dedicated for Alzheimer disease has been presented in this paper. Additionally the simplified amyloid plaque recognition and micromachined micro-zoom has been superficial demonstrated.

Keywords: Alzheimer disease, *BSE, CJD*, diagnosis microsystems, micromachined micro-zoom.

1 INTRODUCTION

The Alzheimer, BSE[1] and CJD[2] diseases belongs to a group of neurodegenerative diseases characterised by an accumulation of extraneuronal filamentous material consisting of β-sheet proteins of various biochemical properties. Clinically, these diseases manifest as dementia is permanent state of losing cognitive functions like: a memory, an orientation, a visual spatial abilities etc. Until now, the silver impregnation techniques (e.g. according to Bielaschovsky or Yamamoto) have been used to their diagnosis. They are extremely difficult to reproduce and not specific, therefore the novel techniques free from these disadvantages and based on immunochistochemistry (using anti-PrP or anti-Aβ antibodies) have been applied [2]. Unfortunately until now the diagnostics of these diseases are limited to selected laboratory centres, where the lack of quantitative diagnosis criteria is substituted by the experts' experience.

The research presented in [2][3][4] and especially in [5] allows to describe the protein recognition model and quantitative diagnosis criteria based on dependencies between amyloid plaques and their graphical representation (see Figure 1). The obtained results have allowed elaborating the laboratory place, where the diagnosis can be made automatically. The diagnosis can be made using the standalone expert system or Internet portal facilities [5].

Proposed approach can be also effectively implemented and integrated in the single microchip, eliminating in this way expensive microscope equipment (see Figure 2). Unfortunately the dimensions of the amyloid plaques (3.6÷27μm) and a currently manufactured CCD cell sensor (5÷14μm) are comparable. This inconvenient can be eliminated using micromachined micro-zoom system proposed in the next part of this paper (Figure 4).

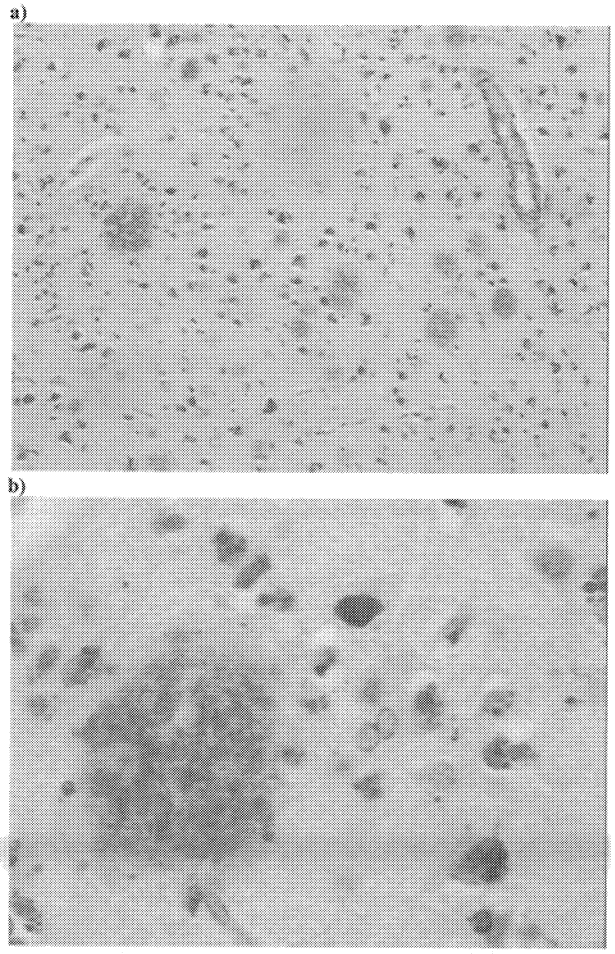

Figure 1 Exemplary microscope section of a *hipokamp* brain (visible amyloid plaques and dye precipitation) reproduced using immunochisto-chemistry process for different microscope magnification: (a) 132.5:1 and (b) 530:1.

[1] BSE - *Bovine Spongiform Encephalopathy*, know as *MadeCow diseases* has now been transmitted to cattle, mice, sheep, and goats both orally and by inoculation, and to pigs, marmoset monkeys but not hamsters merely by inoculation [1].

[2] CJD - *Creutzfeldt-Jakob Disease*, was first described in 1920/21 when it was known as *spastic pseudosclerosis* or *subacute spongiform encephalopathy'* [1].

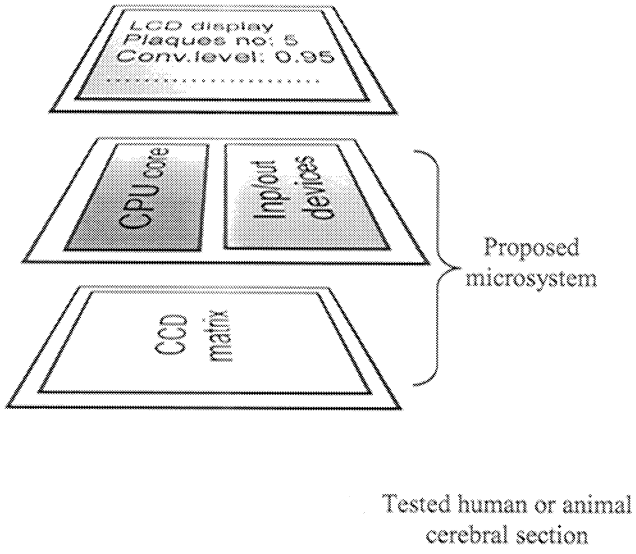

Figure 2 Proposed solution.

2 OBJECT RECOGNITION

The microscope object recognition has been performed in several steps (Figure 3). In order to eliminate the microscope image distortion it should be ameliorated using homomorphic filtering. Firstly the threshold image segmentation is applied using developed amyloid colour model. The hypothetical amyloid plaques are detected using morphogical object properties and selected applying the fuzzy logic Madamie model. The number of detected amyloid plaque per image area is the final diagnosis criteria [5].

3 MICRO-ZOOM SYSTEM

The detection of microscope object (e.g. amyloid plaques) can be realized using proposed bellow micro- mechanical micro-zoom system. The rays emitted by the light source have been successively transmitted via the microscope section, microchip protection glass and translucent thin plate (Figure 4). The rays are deflected via the translucent

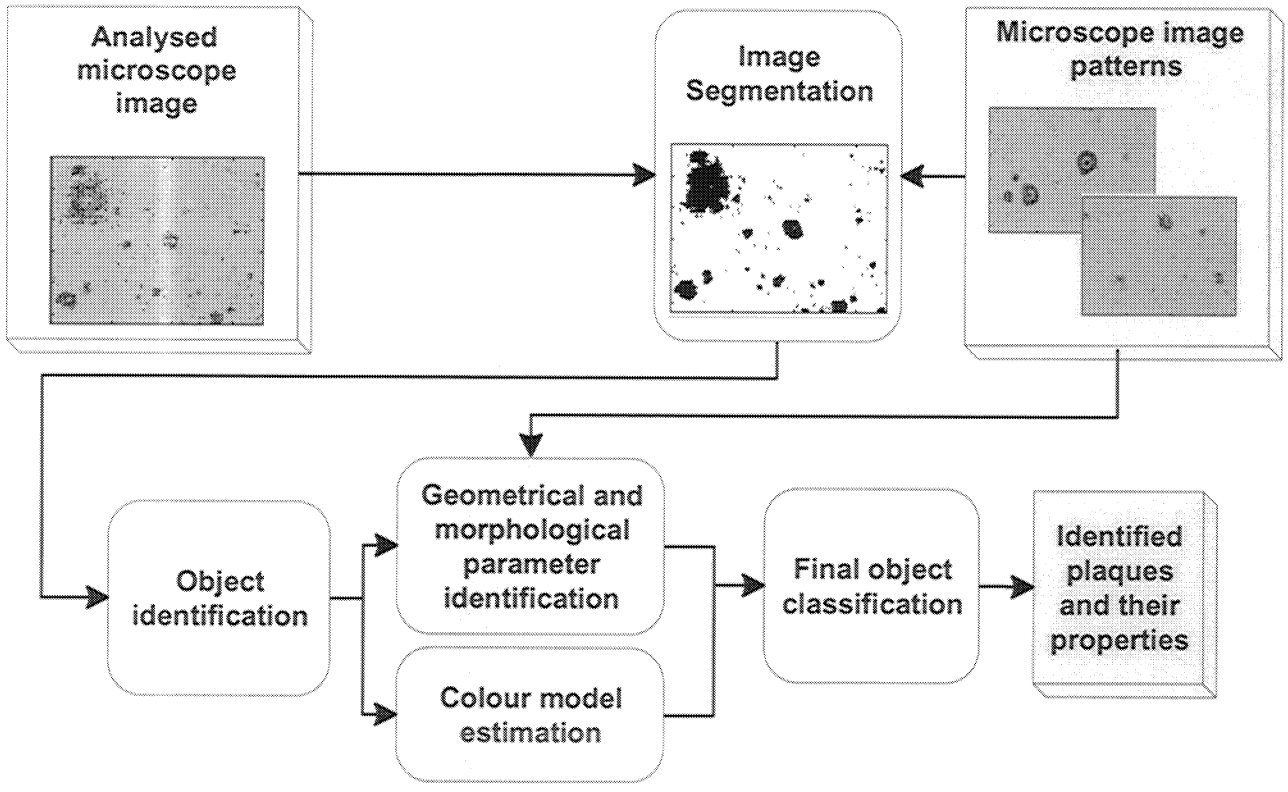

Figure 3 The filtering process of amyloid plaques.

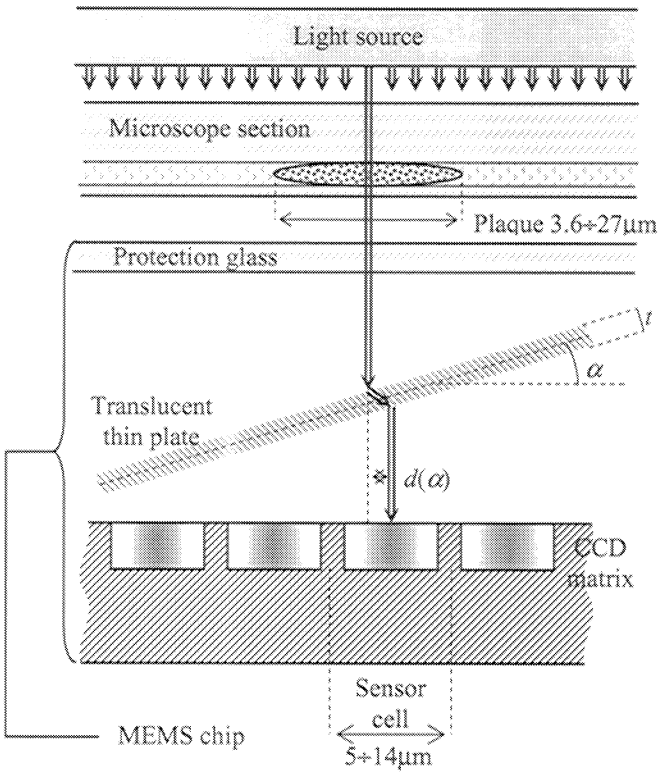

Figure 4 The simplified micro-zoom operation principle.

thin plate in accordance with W. Snell van Royen law (1).

$$\frac{\sin\alpha}{\sin\gamma}=\frac{n_{plate}}{n_{air}} \qquad (1)$$

where α – the slope between the translucent thin plate and CCD matrix; γ - primary ray deflection; n_{air}, n_{plate} – air and plate relative deflection coefficient.

In our case the magnetic permeability $\mu_r \cong 1$,hence the relative plate deflection can be preliminary estimated for $n(\lambda)$=idem by the following equation:

$$n_{plate}=\sqrt{\varepsilon_r \mu_r} \cong \sqrt{\varepsilon_r} \qquad (2)$$

where ε_r – the relative permittivity of the translucent thin plate.

In the next part of this article will be assumed: $\varepsilon_{rSi}=11.7$, $\varepsilon_{rSiO_2}=4.6$, $n_{r\,Sapphire}\cong 1.78$, $n_{r\,Glass}\cong 1.51$ and $n_{air}=1.0003$.

After some transformation the primary ray shift coefficient can be written as the follow:

$$d(\alpha)=t\frac{\sin(\alpha-\gamma)}{\cos\gamma} \qquad (3)$$

where t – the thickness of the translucent thin plate.

The translucent thin plate can be fabricated from the different materials. In this paper, the solution

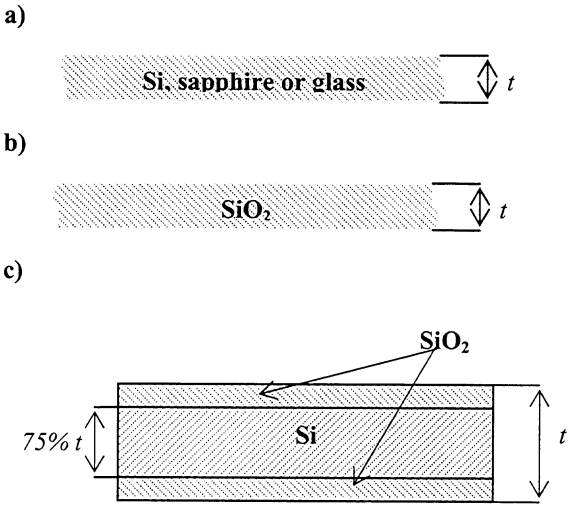

Figure 5 Exemplary translucent thin plate construction: a) Si, sapphir or glass b) SiO_2 c) 1xSi t75%+2xSiO_2 t12.5%.

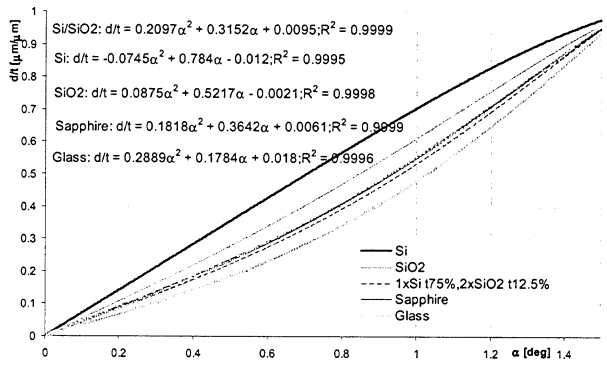

Figure 6 The primary ray shift coefficient (*d*/*t*) vs. translucent thin plate slope (*α*).

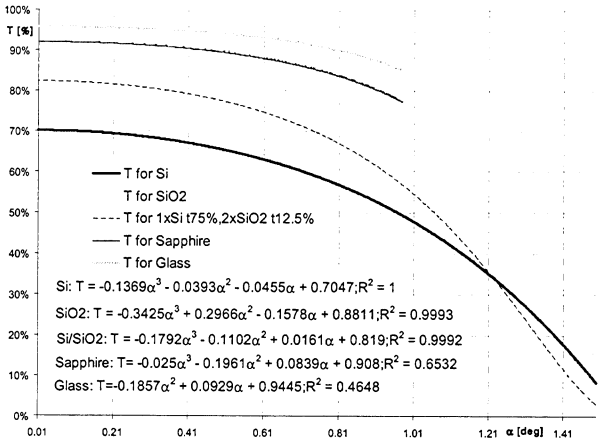

Figure 7 The Fresnel tranfer coefficient of the primary ray electric field intensity (*T*) vs. transluced thin plate slope (*α*).

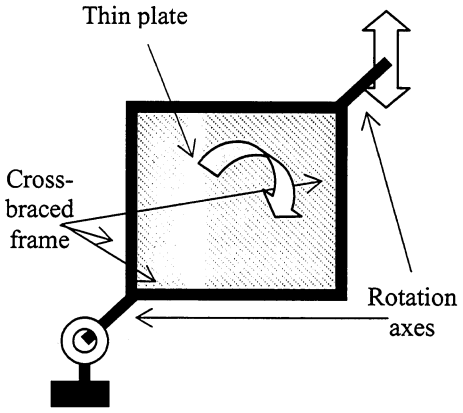

Figure 8 The exemplary translucent thin plate fastening.

with silicon, silicon dioxide and presented on Figure 5 theirs joins will be taken into account. The obtained for theses materials primary ray shift coefficients have been shown on the Figure 6. As it can be seen the sufficient deflection can be obtained for these materials taking into consideration: the plate thickness, the operating thin plate slopes (Figure 7), the material absorption (equation (4)) and plate rigidity. Fortunately the small material transparency and plate rigidity can be compensated by increasing the source light intensity, CCD sensor sensitivity and additional cross-braced frames.

$$\frac{I(l)}{I(0)} = \exp(-a \cdot l) \tag{4}$$

where l - optical path; $I(l), I(0)$ - light intensity; a - absorption coefficient, which for dielectric medium depends on wavelength in the following way $a(\lambda) = 4\pi n_2(\lambda) c / \lambda \neq \text{idem}$; $n_2(\lambda)$ - imaginary relative plate deflection coefficient ($n_2(\lambda) \ll n_{plate}$); c - light velocity in the free space; λ - vacuum wavelength.

To obtain the image zoom the additional software computation is required. In our approach the magnify image can be calculated using deconvolution of the source image for the different slope optical images using linear and rotational motors (see Figure 8).

$$\begin{aligned} m_{d_1,d_2}(x_1,x_2) &= s(x_1-d_1, x_2-d_2) \otimes t(x_1,x_2) \\ &= m_{0,0}(x_1,x_2) \otimes \mathcal{F}^{-1}\left\{e^{-j(\omega_1 d_1 + \omega_2 d_2)}\right\} \end{aligned} \tag{5}$$

where $s(x_1,x_2) = \mathcal{F}^{-1}\{S(\omega_1,\omega_2)\}$ - source microscope section image; $m_{d_1,d_2}(x_1,x_2)$ - registered images for different slopes d_1, d_2; $m_{0,0}(x_1,x_2) = s(x_1,x_2) \otimes T(x_1,x_2)$ - estimated magnify image; $t(x_1,x_2) = \mathcal{F}^{-1}\{T(\omega_1,\omega_2)\}$ - optical transfer function (including aperture etc.).

4 CONCLUSIONS

In this paper the one of the possible applications of the developed amyloid plaque recognition has been presented. In the proposed approach the model recognition has been implemented in the single microchip solution. As the result the protein searching and diagnosis process has been automated. Proposed microsystem architecture can be used in the portable system with possibility to work in the field and make the diagnosis independent of human subjectivity. The mass scale fabrication of proposed chip with micro-zoom can decrease the price of the product.
Presented in this paper solution can be also used for diagnosis other neurodegenerative diseases like CJD, BSE and Kuru disease.

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