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# REZUMAT TEZĂ DE DOCTORAT

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Dispozitive Electronice Mobile și Software Integrat pentru Aplicații Biomedicale

Mobile Electronic Devices and Integrated Software for Biomedical Applications

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**COMISIA DE DOCTORAT**

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**BUCUREŞTI 2023**

# Contents

# Chapter 1

# Introduction

The present work demonstrates the application of state-of-the-art methods in the field of image and signal processing, together with their specific optimizations, in completely new usage scenarios for ambitious biomedical applications of rapid diagnosis of bacterial meningitis and tropical diseases, ocular reconstruction and cell manipulation with microtweezers, the research projects in which I was involved.

Thus, a series of practical achievements involving hardware and software developments were included in this paper. The author developed software that integrates the methods available in the literature, managed to adapt them for the purposes proposed in each research project, carried out specific optimizations and indicated the choice of suitable combinations, algorithms and parameters, measuring sensitivity, specificity, accuracy and other properties of interest for the proposed prototypes.

These were compared with the results obtained by other authors or other partners in the project consortia, indicating at least similar or even improved results for the metrics of interest.

## 1.1 Presentation of the field of the doctoral thesis

The need to increase the quality of life at the global level has resulted in the definition of strategic objectives of the United Nations Organization that cover various fields from education to health and environmental protection. Ensuring the health of the global population involves, among other things, issues related to prevention, rapid diagnosis, treatment, and long-term follow-up of survivors. The use of modern technologies allowed the improvement of all the presented aspects, and thus a global phenomenon of research and development in the biomedical field was born. More and more rapid, point-of-care diagnostic devices have been developed for various diseases and for geographic locations where certain high-cost technologies are not available. Considering the increase in computing power and the versatility of electronics in the contemporary era, it is natural to look for methods as close to the patient as possible for diagnosis, treatment, and as useful as possible for treatment manufacturers to be able to efficiently and at low cost serve the demand global. Also, devices for handling biological materials, modern production through Computer-Aided-Design (CAD) and Computer-Aided-Manufacturing (CAM) techniques have also penetrated the medical sphere, being a real adjunct, together with the power of technologies 3D Printing, in serving specific needs in the biomedical field.

Developments in sensors and various methods of labeling specific antibodies and other specific identifiers for diagnostics have opened a gateway to the development of integrated devices. From gas sensors to high-resolution cameras, they can all benefit from the computing power of modern computers and mobile devices. Here we refer to the concepts related to signal processing, image processing, the application of reconstruction techniques, the implementation in manufacturing processes of elements from CAD/CAM and using materials with high biocompatibility in 3D printing processes, all are elements that have become components important aspects of the broader spectrum covered by the biomedical field.

Today's society is going through intense technologization, and the current process of globalization favors the collection and processing of data, against the background of the increase in the scope of sensor systems and the processing power of desktop and mobile devices. In this sense, numerous initiatives have been undertaken by today's researchers, but also by the institutions responsible for ensuring global health.

The use of modern technologies for biomedical applications has represented, represents and will represent an important pillar both at governmental, European and worldwide level. Thus, multiple projects were financed that demonstrated through the quality of the submissions, that they can solve real problems in an original way using the latest discoveries in various fields. The unification of these discoveries required multidisciplinary coverage and knowledge in multiple fields: biology, chemistry, physics, mathematics, electronics, signal processing, programming, hardware and software devices, materials science. The consortia of researchers in the mentioned fields (and not only) have succeeded in the development at the prototype level and even of marketable products, which have contributed massively to the achievement of the goal of ensuring the health of the global population. As part of these projects, I was privileged to contribute to this noble cause.

Thus, the projects presented in the following chapters pursued the use of modern image and signal processing techniques with dedicated software, starting from the acquisition hardware parameters with their optimization (LEDs and lenses for fluorescence highlighting and optical focusing, cameras photo-video CCD with or without HDR, gas sensors), or in other cases of manufacturing hardware and for precision measurements (Bioscaffolder 3D printing machines, biomedical microtweezers). Also, starting from the specific issue of each biomedical project, the aim was to optimize the collected parameters (determining the optimal concentrations for the exploitation of fluorescence for diagnostic purposes, determining the optimal parameters for obtaining biocompatibility for the purpose of modern eye implants), and achieving similar accuracy results ( the rate of false-negative/false-positive results for diagnostic applications, the standard deviation of measurement errors in the case of biomedical microtweezers) with those obtained in the literature in other issues addressed.

## 1.2 The purpose of the doctoral thesis

This paper aims to elaborate the results I had in the various research projects in which I was involved, all gravitating around the biomedical field, and being compiled under the aegis that represents the title of the paper. Considering the indicated direction, the current work presents various methods for identifying specific biomarkers, image and signal processing methods , their integration either in mobile devices or in modern desktop devices, 3D printing devices, or devices developed for specific purposes, such as the handling of biological materials, complementary hardware to be integrated into point-of-care devices for obtaining and improving the obtained signals, measurements and classification artificial intelligence algorithms for the purpose of rapid diagnosis with high sensitivity and specificity. Thus, a series of practical achievements that involved hardware and software developments were included in the present paper, all revolving around the addressed topic.

## 1.3 The content of the doctoral thesis

In **chapter I,** general notions are introduced, related to image processing techniques with applications in the biomedical field. Specific elements **of processing algorithms** and **commonly used formats for medical data are targeted for this purpose** . **Filters commonly used in various biomedical applications** are also presented , another important component of the performed processing, which are the basis for improving the quality of the results and **optimizing the signal/noise ratio** . Special attention is paid **to the methods of increasing the resolution of the optical signal from the fluorescent emission** , these elements representing the bases of the development of the mobile device in the concept presented in Chapter II.

Chapter **II** presents the concept of a mobile electronic system with integrated software for the detection of bacterial meningitis. This system incorporates **the hardware device for emission and fluorescence generation** , which is attachable to the capture system using **the camera of conventional mobile phones** . **The processing of images** collected using various samples is initially validated in a **desktop software application** developed in **MATLAB** . Methods for optimizing the functional model for the detection of cytokines on a solid substrate, by different methods, are subsequently presented, resulting in the validation of the optimal parameters for the exploitation of fluorescence and the improvement of the specificity and sensitivity of the system, resulting in a superior diagnostic capacity. Various simulations, including a **Monte-Carlo** simulation, are performed in order to optimize the functional model. The results of these simulations and the optimized parameters are then integrated into a **mobile application** capable of calculating the resulting **logistic curve , thus allowing the prototyped mobile device to decide whether the biological sample being tested contains the cytokines specific to a bacterial meningitis.**

Chapter **III** focuses on a different signal processing, coming from gas sensors, for the purpose of **diagnosing tropical diseases** by exploiting the specific volatile organic compounds present in the patient's exhaled gases, and by **algorithms of data characterization and classification** . An analysis of the most common tropical diseases and their impact in different countries is presented, together with the need to develop a non-invasive, mobile, low-cost method for their diagnosis, a true electronic **nose** . The collection and processing of data from various gas sensors and the signal spectrum obtained by **Fourier transformation** are optimized to facilitate the use of the system in real time on large volumes of data obtained through LabView. These optimizations are done in **MATLAB** which is the programming language of choice for this processing. The **Discriminant Function Analysis (DFA)** method is successfully used for classification, completing the concept of an **electronic nose** for the diagnosis of tropical diseases.

Related issues related to the use of image processing for ocular reconstruction are addressed in **Chapter IV .** In the first part, an innovative method from the category of **digital reconstruction is addressed** , which allows the customization of eye implants for each individual patient. The processing is semi-automatic and allows the production of a tessellated model ready to be inserted into **3D printing machines** . The configuration of the printing machine to obtain the structure with the required porosity, together with the use of materials specially developed for a high speed of tissue proliferation, are presented, together with the resulting prototype starting from computed tomography (CT) **images** .

Chapter **V** presents the personal contributions of the author of this thesis on another topic, namely the extraction of a clear, micrometric-scale image from an image with background noise for a method to characterize the opening of robotic micro-tweezers used in applications biomedical. This non-contact method uses **real-time tracking algorithms (Lucas-Kanade tracking)** and allows the characterization of the gripper opening distance according to the applied electrical voltage.

In **the last chapter , the global conclusions of this work** are presented and then the original contributions brought by the author to each chapter are highlighted, along with the list of the author's publications during the doctoral internship, concluding with some aspects of interest to be used in further **research** .

# Chapter 2

# Concept of a mobile electronic system with integrated software for the detection of bacterial meningitis

## 2.1 Realization of the mobile device for the diagnosis of bacterial meningitis

### 2.1.1 Realization of the mobile device for capturing images using the phone

As part of the MEDICY [W1] project, the team I was part of from the Politehnica University of Bucharest and the team of researchers from the Cantacuzino Institute made a sensor for identifying fluorescent elements on a smear, containing the sample taken from the cephalic fluid - spinal cord. The receptor element of the biosensor consists of Antibodies immobilized on the smear, sensitive to the cytokines that are released in the body of a patient, if he suffers from a bacterial infection. In this case, the specific Antigens in the tested liquid attach to the receptor Antibodies. If, in addition, the solution also contains a fluorophore substance, then the Antigens acquire fluorescent molecular tails, which can be highlighted under a microscope or even on images captured from a mobile phone. For the calibration of the mobile device, multiple smears were made with receptors from Antibodies specific to bacterial meningitis, in different concentrations. The purpose of the mobile device was to emit the radiation necessary for fluorescent loading and to detect it on different samples at different optimized concentrations for diagnostic purposes. The realization of the mobile device and the implementation of the related software were the elements developed by the ETTI project team, in which I also worked.

### 2.1.2 Software processing of the captured fluorescent image

Eliminating noise or improving the signal-to-noise ratio in fluorescence imaging of live cells on low-contrast media is an ongoing challenge. Thus, Yang et al report in 2012 a new method for fluorescent cell imaging in low contrast Signal/noise environments,

based on the PP (Particle Probability) concept, which estimates the critical visual characteristics of labeled cells, in a statistical manner, [17 ].
The detection of fluorescently labeled particles or cells proceeds through three main steps, [18]:
- removing noise from the image;
- emphasizing the useful signal;
- highlighting and establishing thresholds.

Often the first two steps are confused, but this is justified in imaging high-contrast media. But for low-contrast environments, such as today's cellular environments, removing noise from the image is an essential first step. The main concern in this first step is not to eliminate those weaker useful features, which cannot be recovered later, obtaining the so-called false negative detection. It can be circumvented by using the PP algorithm, which was applied to the grayscale mapping of the original image to distinguish the cellular regions of interest from the background. The probabilistic method of detecting a marked cell is based on the construction and then refinement of a PP image, after the entire captured image has been discretized as a grid, Fig. 2.3. PP image mapping is done after calculating the Haar feature in each pixel i(x,y) of the squares marked with gray tones in the original picture.

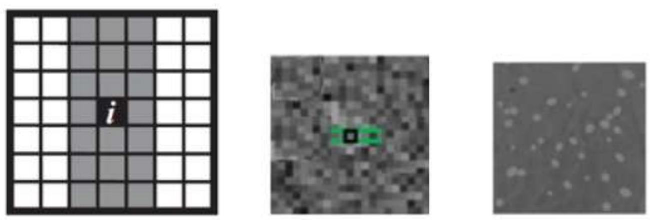



**Fig. 2.3** *A mapping of the captured image according to the Haar model, (image adapted from reference [19])*

At this stage, the segmentation of the estimated cell image can be applied, through similar methods of marking watersheds. The convention of maximum contrast per unit area is applied between small areas centered on the pixel and the surrounding environment. A weak threshold is then applied on the linear combination of these features to obtain a first distinction between cells and background.
The image refinement method starts from the FP-NLM (Feature Preserving - Non Local Means) filter, usually applied to low-contrast images, but applied to a PP-type image. The mathematical expression is of the FP-NLM filter but applied in a PP space [20]:

$$R(P)(i) = \sum_{j \in W_{1,i}} \omega(i,j) P(j) \qquad (2.1)$$

$$\omega(i,j) = \frac{1}{Z(i)} \cdot \exp\left( -\frac{\left\| F(\mathcal{N}_i) - F(\mathcal{N}_j) \right\|_{2,a}^{2}}{h^2} - \frac{\left\| P(\mathcal{N}_i) - P(\mathcal{N}_j) \right\|_{2,a}^{2}}{g^2} \right) \qquad (2.2)$$

where $R\ (\ P\ )(\ \boldsymbol{i}\ )$ is the output of the refinement filter, ω (i,j) are the weights on each pixel, $F(N_i)$ and $P(N_j)$ are the vectors taken from the neighborhood $N_{ij}$ on the FP-NLM images and PP respectively.
This algorithm leads to sharp images due to the robustness of the filter and avoids over-smoothing, a process that would otherwise remove useful areas from the cell.
Fluorescence microscopy techniques for live cell imaging must be adjusted so that sometimes one works at an extremely low SNR - Signal/Noise Ratio - for example 4 or below 2. In these situations, automatic detection of the fluorescent spot is a real challenge, [21]. Software-implemented algorithms were made based on synthetic image experiments of three different types. The results showed that for experiments with a very low SNR ratio (SNR ~ 2), the supervised method provides the best overall images. When the SNR is high, above 5, the difference in performance of all studied software extractors became insignificant.
Fluorescence microscopy is a basic tool today in visualizing living cells and their organelles. Here the target objects are labeled with fluorescent proteins and appear in the images as spots of fluorescent light, each occupying a few pixels, Fig. 2.4. [21]

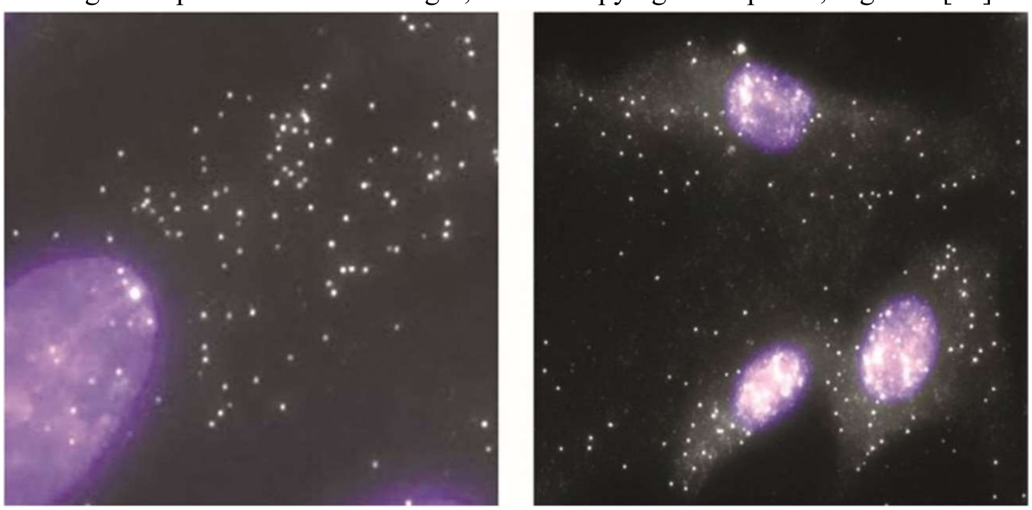


**Fig. 2.4** *Examples of cellular imaging for which image processing software techniques were subsequently developed: (a) Low-contrast "low SNR" fluorescence-labeled mRNA spots image; (b) "high SNR" type image, with high contrast. (image taken from reference [21] with permission)*

In Fig. 2.4 (a) the SNR ratio can reach the value of 6, while in Fig. 2.4 (b), the SNR reaches up to 2. The case of images with low SNR is frequent in the images of living cells in action, when a low intensity incident light is applied so as not to disturb the normal cellular activity, but also in our future experiments we could it still had a reduced light intensity, for other reasons but with the same approach. We will encounter low illumination, or lower than that under the microscope objective, for reasons of simplification of the experiment, and would be particularly interested in these low-contrast image processing. It is known that the resolution of even the best confocal microscopes is up to 100 nm, relatively unsatisfactory, if we refer to the dimensions of interest of sub-cellular structures - typically a few nanometers in diameter, resulting in

diffraction limitations. Consequently, it is also difficult for biologists to distinguish the desired object from the background or from an artifact or noise.
Modern detail detection algorithms, based for example on the Bayesian distribution, [22], describe the existence of objects in terms of the probability of some distribution functions. It is the difference between algorithms with brute thresholds - whether the object in a place exists or not is 1 or 0, and algorithms with a fuzzy estimate.

### 2.1.3 Mobile application for Android/iOS operating systems developed using Ionic frameworks and technologies, nodeJS – Cordova.

For the processing of fluorescent images on a mobile device, a mobile application was developed that uses different html/css javascript menus to navigate through. Calculation scripts are incorporated using low-level numerical processing methods. The main page of the application is shown in Figure 2.7. The top left button sends the user to the main application configuration menu (number of samples, camera color depth and image resolution – these can also be auto-populated after the image is loaded). [31]

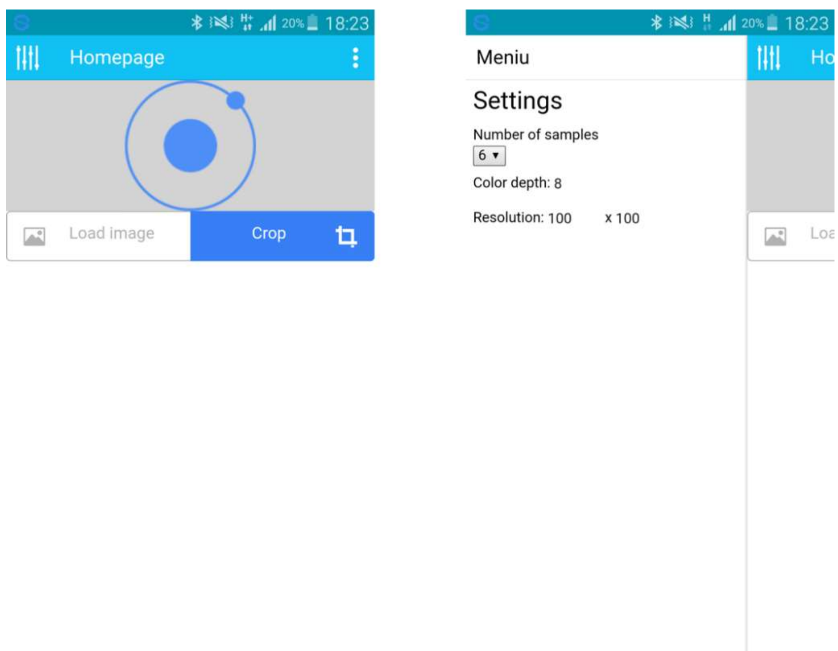



**Fig. 2.7** *The main page of the application (left) and the configuration menu (right).*

The load Image button will display the complete list of image files stored on the respective phone and the one with the fluorescent samples must be selected for loading (if the direct image is taken by the phone's camera, the invert step is not required), as shown in Figure 2.8. The images must be captured through another application that complements the phone's camera and has the role of creating an HDR image, such as the "Camera HDR Studio" application available on Android and iOS.

The Crop button will allow the user to touch-screen select the regions of interest (ROIs) and in this way the 6 samples will be loaded.

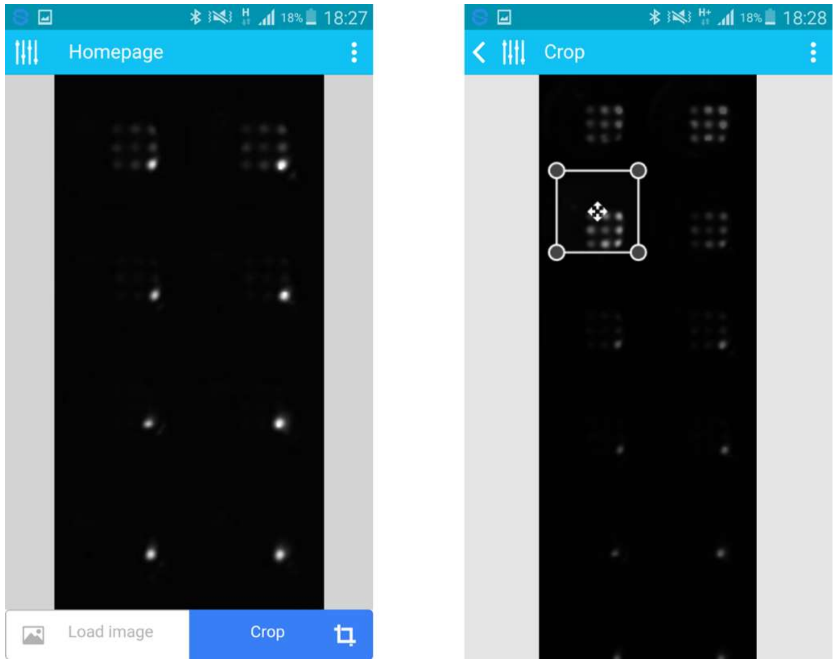



**Fig. 2.8** *The loaded image (left) and the cropping mechanism (right).*

After selecting the 6 samples you can opt for the recrop option if there was a human error during the crop or you can decide, if they are selected correctly, the start of the processing that will automatically calculate the histograms, will determine the intensity values of fluorescence, will interpolate the logistic curve and display its parameters, as described in Figure 2.9 and published in [31].

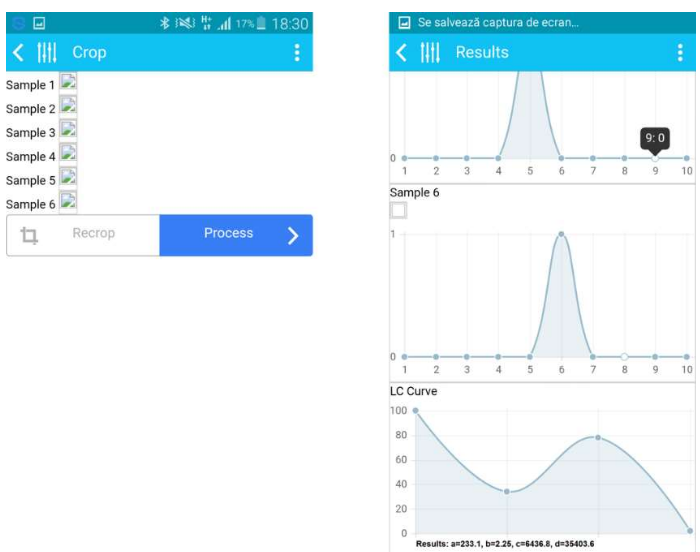



**Fig. 2.9** *Menu with selected samples (left) and measurement results (right).*

Thus, together with the developed hardware device, the application on the phone manages to complete the concept of a mobile electronic system, data collection and processing, fully autonomous, low cost, and high diagnostic capacity.

## 2.2 Functional model optimization for solid substrate cytokine detection

### 2.2.1 Monitoring the sAUC parameter

To optimize the results obtained, the parameter sAUC (area under the curve for the solution, dimensionless) is monitored according to the cytokine concentration applied to the matrix, in two cases: curves of TNFa and MCP-1 dilutions applied in a mixture over the antibody matrices, Fig .2.10. The choice of the mathematical model - the logistic curves with 4 or 5 parameters, as well as the processing of the data in Fig. 2.10, were initially performed in the R programming environment using the calibFit package, with which the analytical detection parameters were calculated (minimum detectable concentration – MDC, definite detection limit – RDL, limit of quantification – LOQ). The meaning of the sAUC parameter comes from its calculation mode: the scaling of the binding curve between the values of 0 and 1, the modeling with the relationships inside Fig. 2.10 of the binding curves, integrating the curve and finding the area under the AUC curve and scaling it to the average fluorescence intensity, obtaining the scaled curve - sAUC.

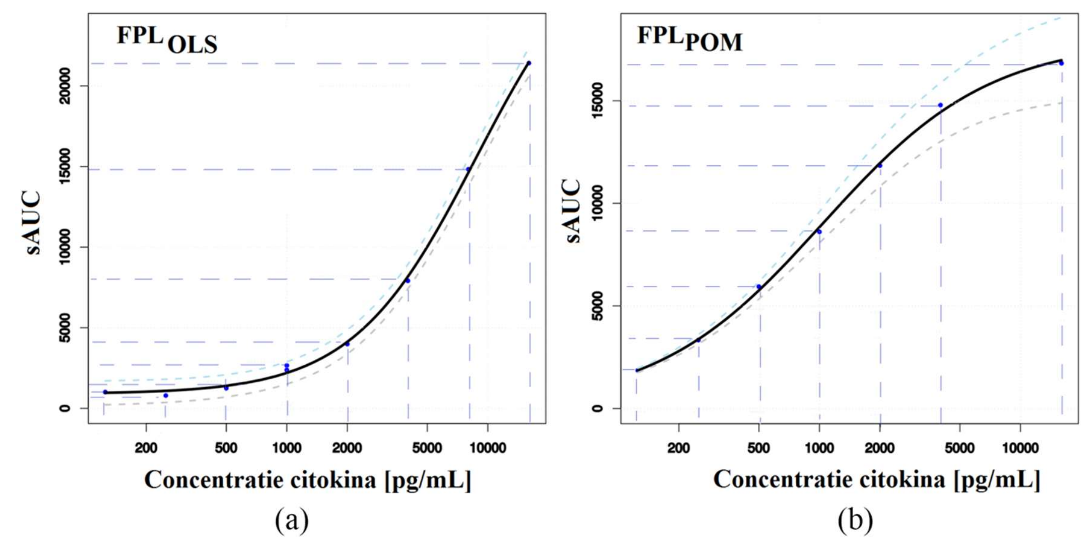
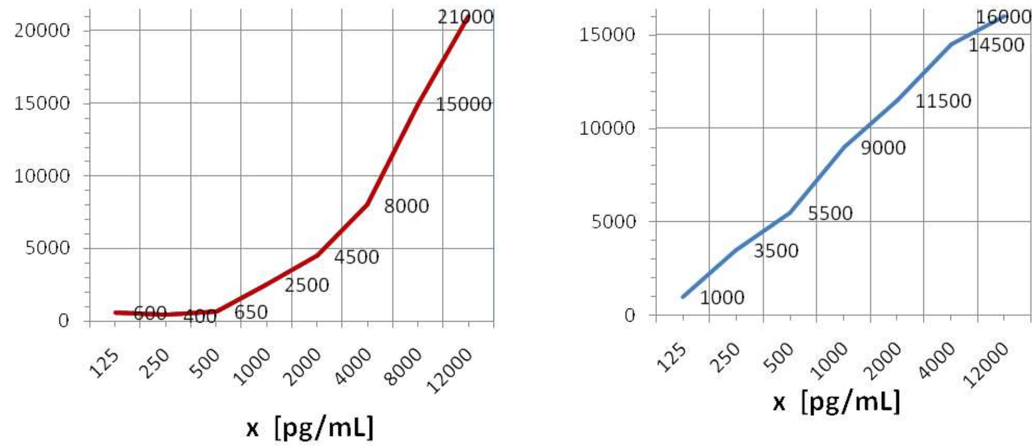



**Fig. 2.10** *The dependence of the sAUC size on the cytokine concentration in pg/ml, for: (a) MCP-1 – left, for which we define the FPL $_{OLS\ curve}$; (b) TNFa – right, for which we define the FPL $_{POM\ curve}$.*

### 2.2.2 Graphical method

The optimization of the solution concentrations was also done by the graphic method by which the experimental points (x,y) were extracted from each of the FPL **OLS** and FPL **POM curves** in Fig. 2.10. These points, by interpolation with spline functions, generate the following graphs in Fig. 2.11. In the following, we will consider these to be the true, reference curves against which we must calibrate our subsequent analytical models.




(a) (b)

**Fig. 2.11** *Experimental interpolation curves, yx, where y=sAUC and x represents cytokine concentration in pg/ml, for: (a) FPL $_{OLS\ curve}$; (b) FPL $_{POM\ curve}$.*

## 2.2.3 Analytical method

A more controlled algorithm was also proposed for extracting the parameters of the logistic curve, so that the model of the logistic curve is as close as possible to the experimentally measured points in Fig. 2.11. For this purpose, a function will be constructed to minimize the mean squared error between each measured point and point calculated with the logistic function - chosen in the form of equation (2.11). This function F will have as variables exactly the parameters to be extracted, i.e. it will be a function of 4 variables for the logistic curve with 4 parameters (β1, β2, β3 and β4) or it will be a function of 5 variables for the logistic curve with 5 parameters (β1, β2, β3, β4 and σε). For example, this error minimization function, F1, for FPL **OLS** will have the compact expression, in the 8 measurement points:

$$F1 = \sum_{k=1}^{8} \left[FPL_{POM,calc}(x_k) - FPL_{POM,masurat}(x_k)\right]^2 \qquad (2.13)$$

## 2.2.4 Numerical methods

The deterministic Monte Carlo method was implemented to determine the global minimum, which will indicate the global optimum with an error given by the step chosen in varying the parameters, with the disadvantages of a high complexity of the algorithm given the number of parameters to be determined. On the other hand, the other indicated methods show a lower running time but do not guarantee the detection of the global optimum.

Monte Carlo simulation uses random sampling and statistical modeling to estimate mathematical functions and mimic the behavior of complex systems, with applications in the generation of random numbers that follow specific probability distribution functions. Common examples are uniform, exponential, normal, and Poisson distribution.

## 2.2.5 Results of the Monte Carlo algorithm

The space of mean squared errors for each run of the algorithm (combination of 4 parameters) is shown in Fig. 2.16, with the iteration that resulted in the smallest error highlighted:

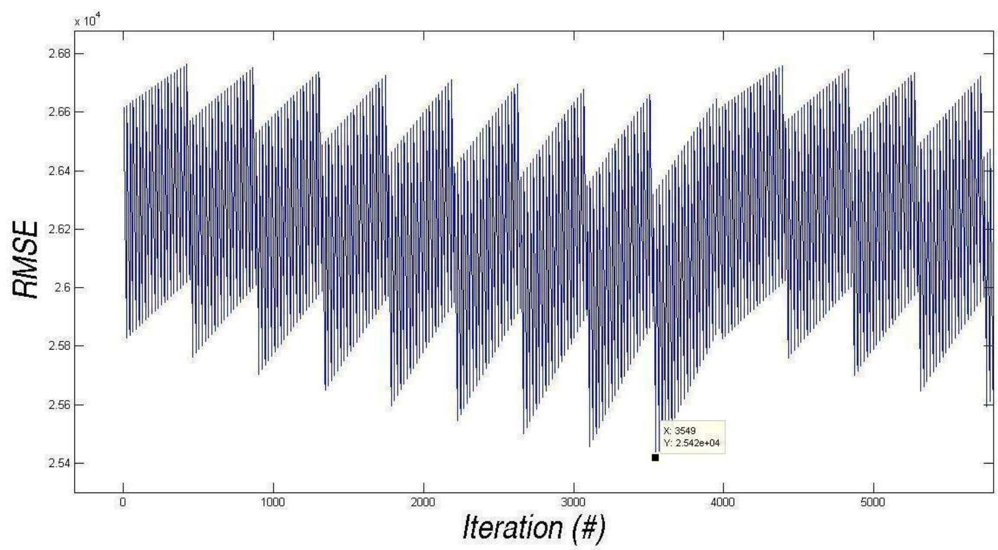



**Fig. 2.16** *Error space per generated iteration – combination of 4 parameters*

The logistic curve with the parameters (b1,b2,b3,b4) that resulted from the minimum rmse is represented in blue and the initial points to be interpolated are in red in Fig. 2.17.

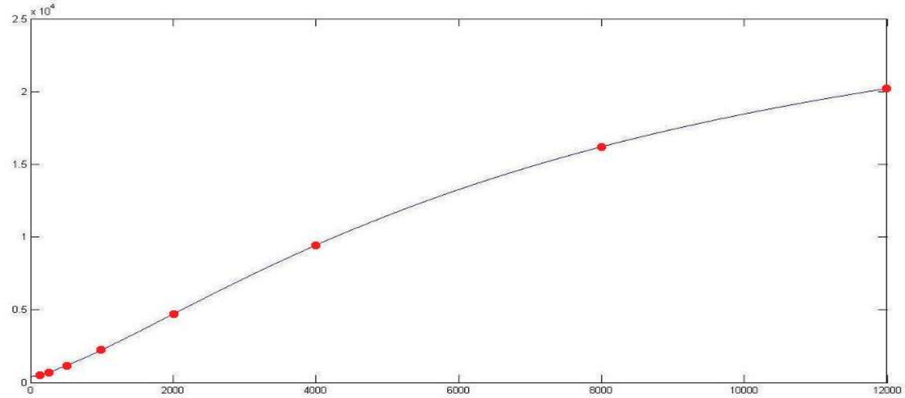



**Fig. 2.17** *Logistic Curve with parameters resulting in minimum rmse*

The resolution and accuracy with which the parameters are determined can be controlled by the step of the parameter generator, with a smaller step for varying the parameters resulting in a longer running time of the algorithm.

### 2.2.6 Conclusions, optimization and implementation in the mobile application

The original contributions of the author of this thesis to this chapter concerned the development/optimization of the functional model for the detection of cytokines on solid substrate. Analytical and numerical methods were applied based on fundamental principles of optimization, interpolation, fitting, using various Software tools and related Hardware support.

# Chapter 3

# Realization of the experimental model for a mobile device for the diagnosis of tropical diseases

## 3.1 Study on tropical diseases

### 3.1.1 Introduction to common tropical diseases

Within the European TROPSENSE project [W3] we aimed to demonstrate the feasibility of a non-invasive, safe and patient-friendly methodology for rapid on-site diagnosis of tropical diseases.

### 3.1.2 Breath sampling and the electronic nose concept

To identify common biomarkers of tropical diseases investigated in the TROPSENSE project and without considering the differences between populations with different genetic and lifestyle characteristics, volunteers from three different geographical locations (Europe. South America and the Maghreb) were included in this study. Volunteers provided several breath samples for analysis. The collection of breath samples followed a standardized procedure used by the research team in previous experiments, which ensures the collection of air samples deep inside the lungs while avoiding external training [44].

## 3.2 Analysis of collected data

Due to the large amount of data that was acquired by the different partners and the diversity of data formats used by each partner in the project, a common data format / data conversion tool was first developed as a prerequisite for data processing. To enable efficient interaction between the panels, a platform was selected for cloud storage and exchange of data obtained at different sites. Data analysis focused on detection algorithms that provide classification results and high confidence values. Samples were classified into recognized disease classes from control patients, along with unclassified samples.

## 3.3 Prototype portable instrumentation for tropical disease detection

Also, the analytical performance of QCLs combined with integrated hollow waveguides was determined and compared to the chemical analysis of VOCs in exhaled breath.

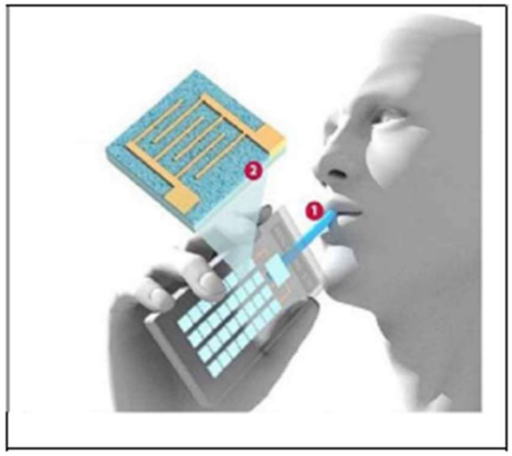


**Fig. 3.3** *Schematic representation of the breath sample collection device*

The portable system that was designed and manufactured comprises: an attachable preconditioning unit provided with heating capability for preconditioning the breath samples (here the sorbent tube with the stored breath sample is heated by applying an appropriate heating pulse and the breath VOCs made of the absorbent material are transferred to a preconditioning chamber for the homogenization of the volatile mixture): an exposure chamber housing the detection devices; electronics required to control, acquire and process sensor readings, software for data analysis and interpretation incorporating the developed pattern recognition model; and a display for viewing diagnostic results. This portable prototype is to be field tested on new patients and control volunteers at the end of this project.

## 3.4 Optimization of Matlab algorithms for the characterization of detected frequencies

Power Spectral Density (PSD) is the measure of the power of a signal as a function of frequency. PSD is used to characterize in-band signals obtained from different sources, in this case gas sensors. The PSD amplitude is normalized by the spectral resolution used to digitize the signal. The application of a Hanning filter served to better differentiate the frequencies of interest, an increased resolution in the frequency spectrum, and for its real-time capabilities. In Fig. 3.4 shows an example of PSD obtained by measurements obtained from gas sensors for air and formaldehyde at a concentration of 7 ppm.

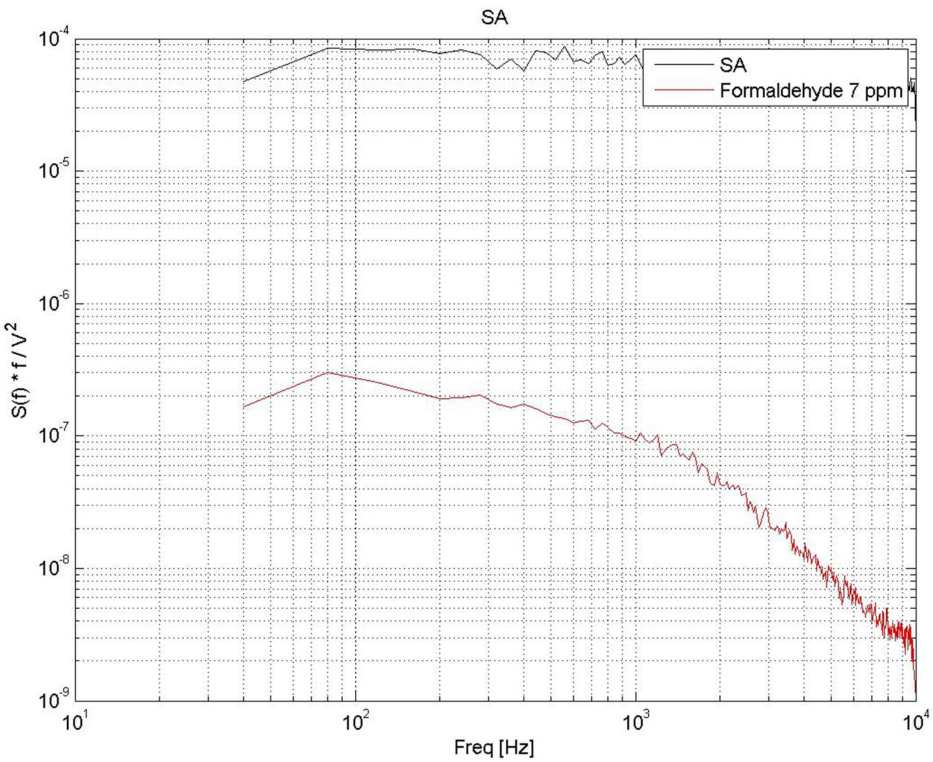



**Fig. 3.4** *PSD spectrum of frequencies for synthetic air and formaldehyde. Significant differences are observed for DFA at specific frequency values [40Hz, 320Hz, 1000Hz, 5000Hz]. [62]*

The steps of processing the signals from the sensors involve the processing of .lvm (LabView measurement) files:

- Data recording at a high frequency - 5 kHz (Tab. 3.1)
- Large data processing - 2 minutes of recording
- Memory and CPU optimization
- Optimization of processing time for PSD calculation
- Delivering graphs and consolidating them for DFA analysis

The main code optimizations are as follows:

- Using cellfun to vectorize data from lvm/csv format
- Data cleaning: data integrity validation and partial data integration
- Using cell2mat to improve performance on matrix operations
- Using regular expressions to optimize data extraction
- Memory preallocation of structures to optimize memory and processing time
- Using optimized Discrete Fast Fourier Transform (Cooley-Tukey) FFT algorithms, by segmenting data into a power-of- 2 cardinality and zero-padding mechanisms for edge vectors
- Improved error logging and telemetry mechanisms

The data collected at high frequency is read by the optimized processor lvm, and the Discriminant Function Analysis (DFA) of the PSD on the frequencies chosen as representative (40Hz, 320Hz, 1000Hz, 5000Hz from Fig. 3.4 [62]) is performed. The result is shown in Fig. 3.8.

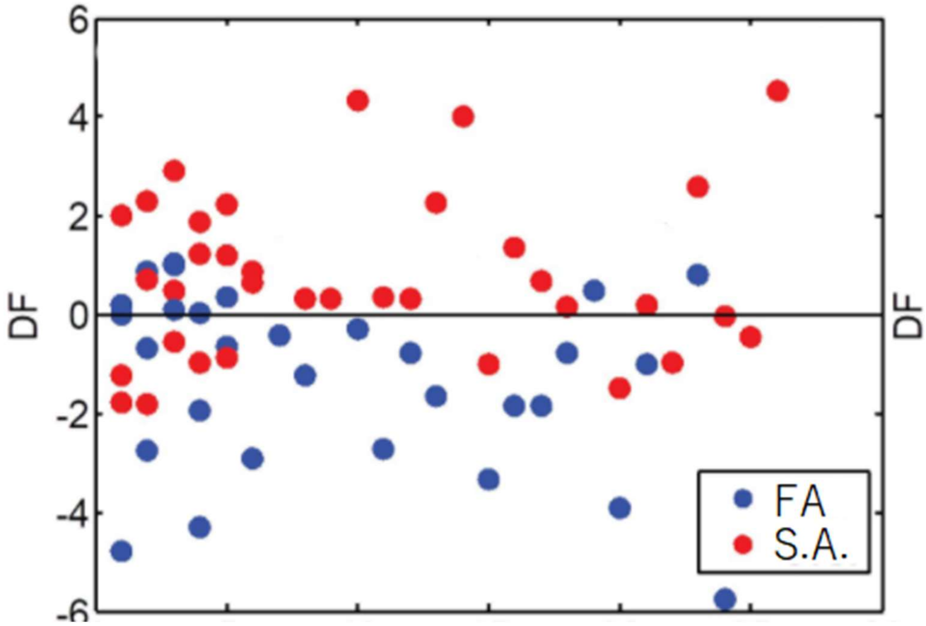



**Fig. 3.8** *DFA between selected frequencies from the PSD of synthetic air (SA - red) and formaldehyde at a concentration of 7ppm (FA or F7- blue) at different measurements made. DF represents the line of demarcation with a 95% confidence interval*

## 3.5 Conclusions

In this thesis chapter, personal contributions to the creation of a rapid, non-invasive and inexpensive breath test for the diagnosis of the most common tropical diseases were presented.

# Chapter 4

# Using image processing for ocular reconstruction

## 4.1 Realization of the experimental model of an eye implant through the 3D bioprinting technique

In this thesis chapter, another software application integrated with design tools is presented, which aims to create an artificial eyeball. Image processing allows the reconstruction of custom-sized organs, starting from medical images obtained, commonly, by computed tomography. Personal contributions in this direction were made within the ORBIMPLANT project [W6]. The target was to create a customized eye implant, starting from CT images, using 3D printing techniques and biocompatible materials specially developed to allow a high rate of tissue proliferation.

## 4.2 DICOM image processing

DeVide reconstruction software was used for the first time in such an application (ocular implantology) with an original network and optimization of specific parameters. The final network is shown in Fig. 4.8 and the final result in Fig. 4.9.

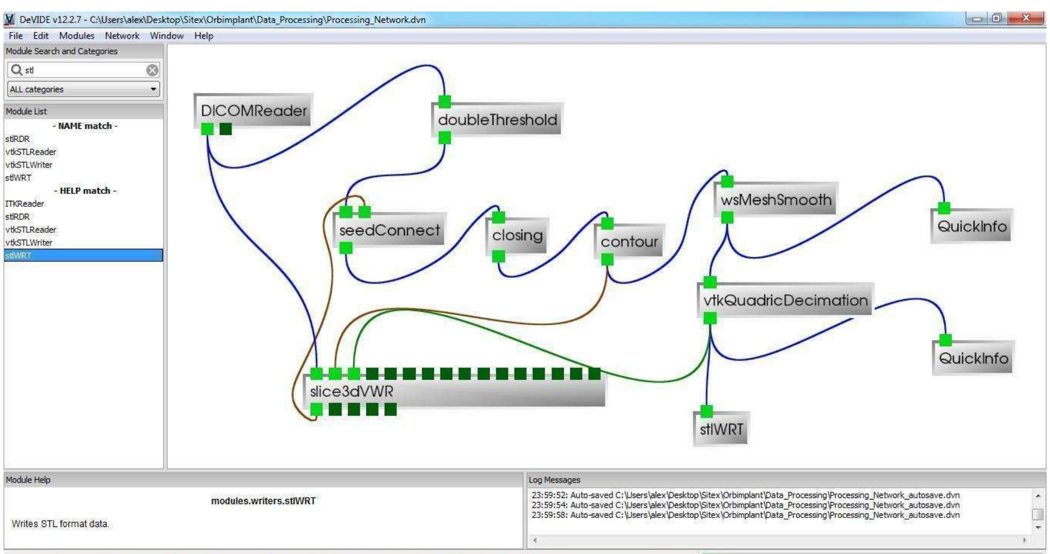



**Fig. 4.8** *The DeVide network for the implementation of the processing algorithm that performs the extraction of the tessellated model (.stl).*

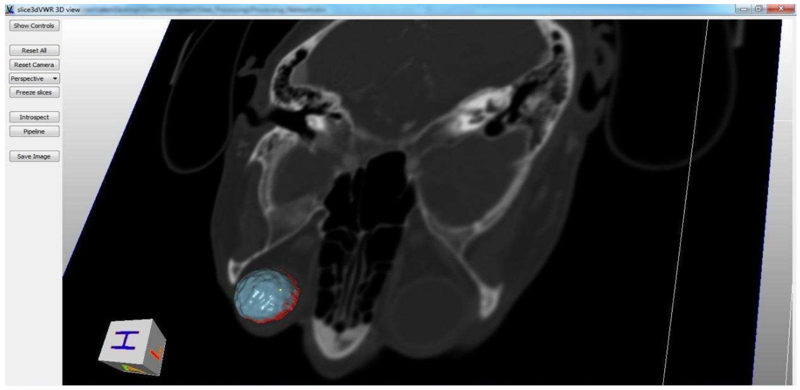



**Fig. 4.9** *The tessellated model (.stl) of the region of interest, in the present case the eyeball*

## 4.3 Realization and exploitation of the experimental model

In order to make the experimental model and the fabrication of the porous structures required for the ocular implant, it starts from the result of the 3D reconstruction modeling and simulation by software/image processing methods. The result of the image processing step was a semi-automatic software method of obtaining the .stl model, the model to be loaded as such into the bioscaffolder type printing machine, production model SYSENG - BioScaffolder Software Vers. 3.0-USB with a configuration specific to the application and the materials used, in order to obtain controlled porosity, honeycomb structures are used. In the case of honeycomb structures, the walls are between 100 and 200 microns thick and the pore diameter between 200 and 400 microns, different arrangements of such cells [65] . The result of the printing is the actual implant, shown in Fig. 4.18

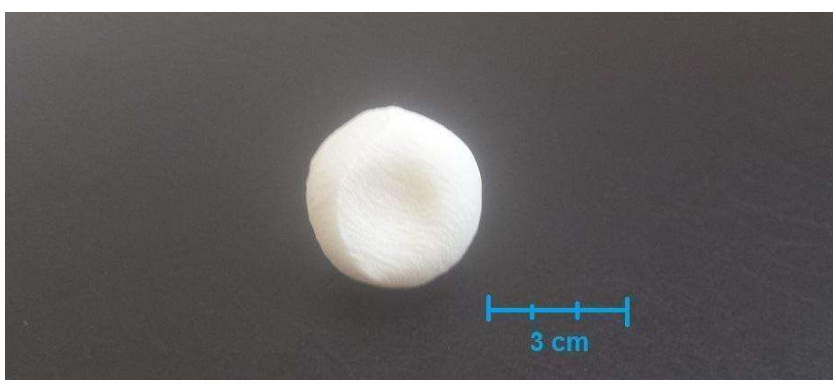



**Fig. 4.18** *Experimental eye implant model [66]*

The feasibility of using 3D printing techniques using biocompatible materials has also been demonstrated, starting from medical imaging (CT) and using image processing techniques for implant customization. The results were published [66] and a patent was granted to the contributors for these results [67]. The modernity and innovation brought by this technique was awarded the silver medal at the Geneva International Exhibition of Inventions in 2018 [W10] and at the Euroinvent 2018 (10th edition) Exhibition for Inventions with Applications in Medicine [W11].

# Chapter 5
# Precision measurements of biomedical microtweezers

## 5.1 Characterization and measurement of the opening of MEMS microtweezers for biomedical applications

The main goal of the ROBOGRIP project [W12] of which I was a team member was to develop a robotic system for micro-manipulation consisting of micro-tweezers with integrated position/force sensors for cell manipulation. To achieve this goal, a series of micro-tweezers with electro-thermal actuation have been developed, to perform different functions (positioning, push-pull, grasping), and to be integrated into a robotic micromanipulation system. The effectors were designed at the system level due to their interdependence in operation, also considering the manufacturing technology and component materials.

## 5.2 Developments of the real-time tracking technique

A tracking algorithm that gives good results in many circumstances is the Lucas-Kanade algorithm [16], widely used in computer vision applications. The algorithm aims to identify and track "Harris" type points that can be defined as inflection points, having a high response on both the vertical and horizontal gradient. The algorithm works under the assumption that these points maintain the same properties within a (small) movement from one frame to the next.

Under the high precision circumstances that are required in the present application, a correlation-based algorithm that aims to track regions of interest (gripper arms) as distinctive elements in the image can be used. The algorithm consists of the following main steps:

1. Reset: Load the video to be analyzed, set some parameters, and choose the distinctive templates (gripper arms) to track from frame to frame.
2. Pre-filtering (optional): applying different filters to reduce noise and improve signal-to-noise ratio, highlight certain elements in the image, edge detection of gripper arms/edge detection, etc., using convolutions with different specific kernels (Gaussian, Sobel, etc.)
3. Frame-by-frame analysis: at each frame, templates are correlated in a certain neighborhood (search area) of their last detected position, and the best identification

(global minimum in correlation) will be reported as the new position. The templates will be updated accordingly.

In this context, the correlation between template A and region image B is defined as the Frobenius norm between matrices A and B:

$$\|A - B\|_F$$

The Frobenius norm of a matrix C of dimensions mxn being defined as:

$$\sqrt{\sum_{i=1}^{m}\sum_{j=1}^{n}|c_{ij}|^2}$$

An example of tracking between frames 1 and 2 is shown in Fig. 5.3.

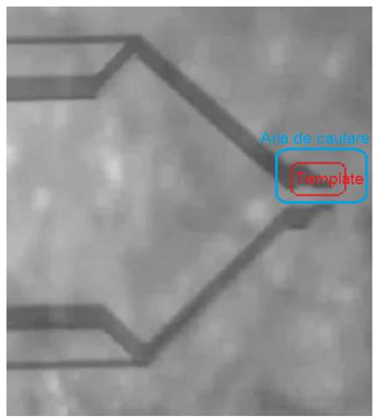



**Fig. 5.3** *A distinctive template (red) and the search area around it (blue)*

Calculating the results of the correlation between the templates and the search area, the values shown in Fig. 5.4.

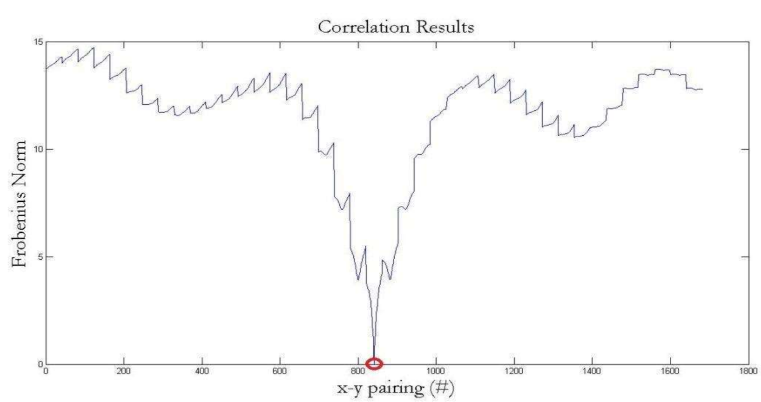



**Fig. 5.4** *Results of correlation between templates and search area for different xy positions in the search area. The minimum point indicated in red.*

After loading the video obtained with the CCD camera focused on the microtweezers, the Matlab application developed for the project is used and various configurations have been tried. The best results are given by applying a binary transformation to which the threshold value can be configured . With a threshold of 140 the following results are obtained which reveal a clear separation of the gripper arms (which thus become completely black) from the background (which thus becomes completely white [69]), Fig. 5.11.

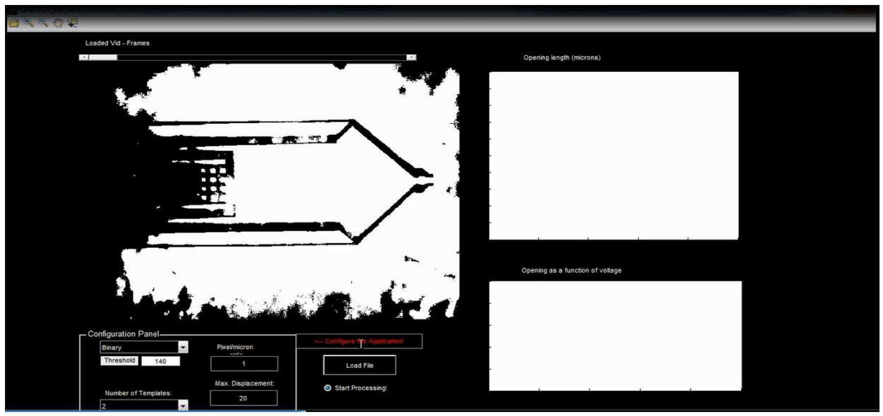



**Fig. 5.11** *Configuration with a threshold of 140*

When you press the "Start Processing" button, automatic tracking will start on the gripper arms that are selected in advance. At each frame, the distance between the arms recorded in both pixels and microns (using the scaling factor configured in the "Pixel/micron" field) will be displayed in the plot type graphics on the right.

We can see the removal of the arms (marked by the red and green circles) recorded as higher values in the plot on the right (maximum 85 pixels up to the current frame), Fig. 5.12.

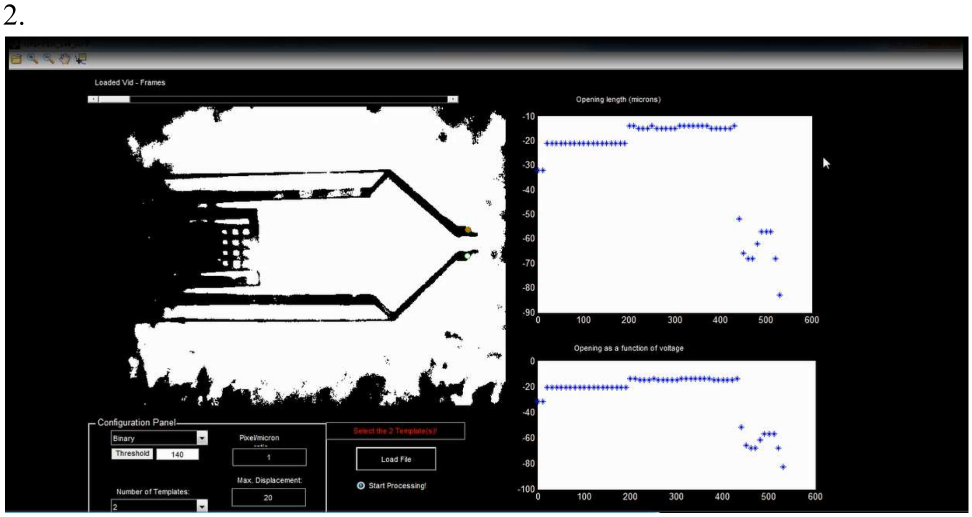



**Fig. 5.12** *Commencement of processing based on established configuration*

Continuing the processing over several frames further spacing of the arms is observed - recorded as larger values in the right plot (maximum 140 pixels to the current frame), Fig. 5.13.

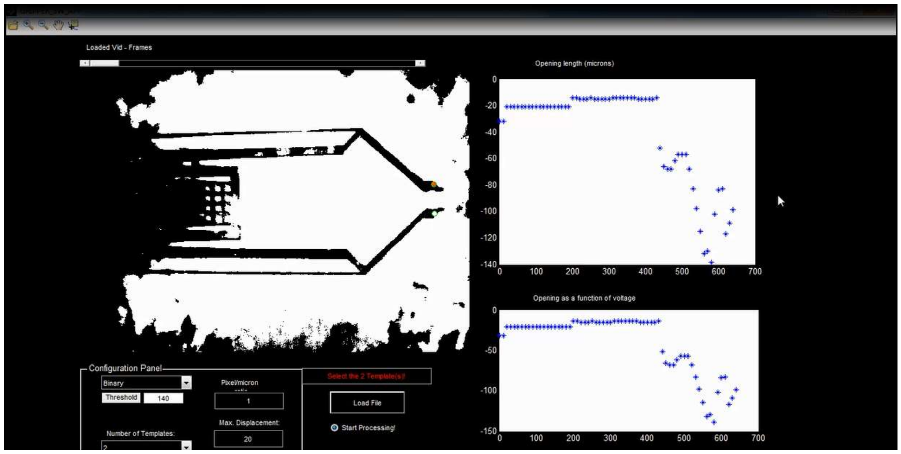



**Fig. 5.13** *Results obtained based on the established configuration*

The results show that the model can be validated along with a faithful description of the opening characteristic of the arms as a function of the applied electrical current/voltage. Fine-tuning elements allow continuous improvement of the model.

The validation of the proposed system was done using as a source of truth the measurements made with the system developed by the partner in the consortium - the Technical University of Cluj-Napoca, the results being summarized in Table 5.1. It can be seen that even sub-pixel accuracy can be achieved, similar to literature results for other applications [70].

| Opening (microns) | 16 | 20 | 60 | 80 | 100 | 120 | 140 |
|---|---|---|---|---|---|---|---|
| Frame1 | 16 | 20 | 58 | 80 | 100 | 120 | 140 |
| Frame2 | 17 | 20 | 62 | 81 | 102 | 118 | 138 |
| Framework 3 | 16 | 20 | 62 | 81 | 101 | 119 | 139 |
| Frame4 | 16 | 20 | 61 | 81 | 100 | 118 | 140 |
| Frame5 | 16 | 19 | 60 | 78 | 100 | 120 | 139 |
| Frame 6 | 15 | 20 | 62 | 79 | 97 | 121 | 139 |
| Frame7 | 16 | 20 | 60 | 81 | 100 | 118 | 138 |
| Frame8 | 17 | 19 | 61 | 80 | 101 | 119 | 140 |
| Mediate | 16,125 | 19.75 | 60.75 | 80,125 | 100,125 | 119,125 | 139,125 |
| Standard deviation | 0.599479 | 0.433013 | 1.299038 | 1.053269 | 1.363589 | 1.053269 | 0.780625 |
| Accuracy | 0.125 | -0.25 | 0.75 | 0.125 | 0.125 | -0.875 | -0.875 |
| **average std** | **0.940326** | | | | | | |
| **Average accuracy** | **0.446429** | | | | | | |

**Tab.** Eroare! În document nu există text cu stilul precizat.. **1** *Results of measurements by the adapted Lucas-Kanade algorithm compared to measurements of the reference system*

# Chapter 6

# ConCluSIonS

In this paper, a demonstration is made both at a theoretical level, but especially at a practical level, of the use of image processing and signal processing techniques, without however being limited to them, within specific applications in the biomedical field.

## 6.1 Results obtained

Chapter II presents the results obtained in the development of an innovative concept for the diagnosis of bacterial meningitis - the MEDICY project. A hardware device with a fixture on the mobile phone and an optical system for simulating fluorescence, capturing it in focus, and enabling image recording using standard mobile device cameras was made. An implementation in MATLAB (desktop application) and an implementation based on the IONIC framework running on Android and iOS mobile phones have been made. The algorithms implemented in these programs have been optimized for diagnostic logistic curve processing. The optimization of the functional model for the detection of cytokines on a solid substrate was carried out using a series of methods, using the results obtained from the Monte Carlo simulation performed in MATLAB that gave the most accurate results, in the final implementation of the software related to the mobile device. The final product is mobile, low-cost, minimally invasive, does not require microscopy, and uses mobile devices with integrated software for a high diagnostic rate.

In chapter III, signal processing techniques from gas sensors are illustrated, in a prototype of an electronic nose built for the purpose of diagnosing the most common tropical diseases, both bacterial and viral - the TROPSENSE project. An analysis of their impact and the present diagnostic difficulties was made. Contributions related to the realization of the experimental breath sample collection device, a device simulated by computer-aided design techniques, were delivered. The device made is made of modular parts, and allowed the attachment of both Tenax tubes and gas tanks and cylinders present in the laboratory to facilitate the simulations performed. The gas introduction pumps in the measurement chamber where the Bosch sensors were mounted were controlled using the LabView software, through which the data measured by the sensors was also collected. Data processing by FFT and optimization of processing time to allow the analysis of large volumes of collected data are the main contributions of the author in the thesis. Also, an important contribution is the implementation of the DFA classification algorithm that allows a clear separation between the different volatile organic compounds, essential metabolomic elements for diagnosis using the prototyped electronic nose. The classification and diagnosis algorithm has a similar accuracy to the results obtained for gastric diseases in other electronic nose research.

In chapter IV, image processing techniques were used for ocular reconstruction within the ORBIMPLANT project. An important contribution of the author is the development of ocular reconstruction software using DeVide software. Thus, eye implants can be customized for each individual patient who requires such a prosthesis. The result of the reconstruction is finished and ready to be fed into modern 3D printing machines. Another important contribution is the configuration of the printing machine and the production of the experimental model with a honeycomb structure to facilitate a high tissue proliferation rate. All these elements, combined with the developments of biocompatible materials for the 3D printing machine, led to the filing of a Patent for all contributors to the proposed concept, and a silver medal at the Geneva Invention Salon.

Chapter V presented software methods for performing precision measurements in order to characterize the microrobotic microtweezers developed within the ROBOGRIP project. An alternative to characterize the opening of the microtweezer arms as a function of the applied current/voltage was made, using mechanisms for optimizing the collected images and real-time tracking (Lucas-Kanade) correlation algorithms. The proposed method was presented as a viable alternative to the more sophisticated system with lasers proposed for measurement by the team from the Technical University of Cluj, partner in the project. Thus, an estimated 80% cost reduction of the measurement system can be achieved. The proposed measurement solution has an increased accuracy, at the level of other adaptations of the algorithms used in applications different from the one presented.

## 6.2 Original Contributions

In this paper, the elements that constitute original contributions are represented by the proposals regarding the use of certain image and signal processing techniques in very specific biomedical applications and mobile devices where appropriate. For the realization of the proposed concepts and the experimental models, the hardware development component dedicated to each individual application was also achieved, to facilitate the collection of the signal of interest, images collected or numerical data collected by using different parameters of the sensors of interest. Optimizing the models and choosing the right algorithms for each case, together with the combination of traditional and modern techniques, represent the most important contribution of the author, within the present work and the projects in which he was involved.

Deep knowledge and high-level use of MATLAB enabled the optimization of the processing and classification algorithms in the tropical diseases project, opening up the possibility of processing the large volume of data collected, which would not have been possible without the optimizations implemented by the author . Determining the frequencies of interest from the PSD for the input of the classification algorithm was thus possible, and the classification algorithm has an accuracy similar to that obtained in the literature for other pathologies. I mention that the company Sitex 45 also subsequently filed a patent application for the solution proposed in the project.
We contributed, using DeVide software, to the programmable reconstruction of the custom implant, producing a model of the reconstruction compatible with 3D printing machines. The customized eye implant is a novelty in the biomedical field, the use of controlled porosity and materials with high biocompatibility for automatic reconstruction mechanisms being purely innovative elements. Obtaining a valid model ready for modern 3D printing techniques, as well as approaching the printing machine study in order to achieve the honeycomb structure with the materials developed dedicated to the project, necessary for tissue proliferation and high biocompatibility, were also essential contributions , which allowed the author to be co-author of an Invention Patent and winner of a silver medal at the Geneva Inventica Salon in 2019 and at the EuroInvent salon (Iași 2018).

Another original contribution is the development of an alternative method for characterizing the opening of the arms of a microtweezer developed for biomedical applications. Here the author managed to process the images and apply algorithms mainly used in the field of computer vision, managing to achieve precision measurement and characterization performances, similar to the more sophisticated and expensive methods proposed by the consortium. .

## 6.3 List of original works

**Articles in ISI Journals, area Q4.**

[1] A. Voina, **A. Topor** , G. Alecu, C. Voina, F. Babarada, D. Manuc, "Integrated Sensors Network into an Acquisition Platform for the Air Quality Monitoring", ISI Journal *Rev. Rome. Sci. Techn. – Electrotechn. et Énerg* , vol. 3, pp. 305-310, **WOS:000414507000015** , 2017, FI=0.777
https://www.researchgate.net/publication/320539775_Integrated_sensors_networks_into_an_acquisition_platform_for_the_air_quality_monitoring

[2] **Topor Alexandru** , Ulieru Dumitru, Ravariu Cristian, Babarada Florin, "Development of a new one eye implant by 3D bioprinting technique", *Rev. Rome. Sci. Techn. – Electrotechn. et Énerg* ., vol. 68, no. 1, Bucharest, 2023, WOS pending.

[3] **Topor Alexandru** , Voicu Rodica Cristina, Ulieru Dumitru, Ravariu Cristian, Babarada Florin, "Image processing algorithms for characterization of MEMS type micro-tweezers aperture", JOAM-RC- Journal of Optoelectronics and Advanced Materials, 16, 11-12 , December 2022, pp. 505-508 WOS pending.

**Articles published in Conference Proceedings indexed by ISI or IEEE**

[1] **A. Topor** , C. Ravariu, F. Babarada, I. Caras, B. Patrichi, "Fast fluorescence detection in optical bio-systems", Proceedings of 39-th IEEE-ISI Int. Conference of Semiconductor CAS, Sinaia, Romania, ISBN 978-1-5090-1207-7, pp. 45-48, Oct. 10-12, 2016, **WOS:000391323300007** .

[2] **A. Topor** , C. Ravariu, F. Babarada, S. Malin, A. Salageanu, I. Caras, D. Manuc, B. Patrichi, "Hardware and Software Contributions for Optimized Detection of Fluorescent Labeled Cytokines", in Proc. of 40th edition of IEEE International Semiconductor Conference CAS'2017, October 11-14, Sinaia, Romania, pp. 267-270, **WOS:000425844500059** , 2017, https://ieeexplore.ieee.org/document/8101221

[3] **A. Topor** , S. Malin, F. Babarada, C. Ravariu, A. Salageanu, I. Caras, D. Manuc, B. Patrichi, "Applications of Images Processing Algorithms for Bacterial Meningitis Diagnosis", ECAI International Conference – 9th Edition Electronics, Computers and Artificial Intelligence, 29 -30 June 2017, Targoviste, Romania, Young Researchers session, **WOS:000425865900063** , 2017, https://ieeexplore.ieee.org/document/8166447.

[4] Ravariu C., **Topor A.,** Mihaiescu DE, Manea E., "Bioelectronics and Green Electronics for a clean Environment", Conference CEST2021, Paper ID: cest2021_00345, Topic: Electric and electronic waste, https://cest. gnest.org/e/cest-2021?room_id=3&date=2021-09-02%2000%3A00%3A00

**Publications in the form of Chapters in Books at International Publishers**

[1] **Alexandru Topor** , Cristian Ravariu, Florin Babarada, Aurora Salageanu, Iuliana Caras, Bogdan Patrichi, "Mobile electronic device and integrated software for cytokines fluorescence detection", Chapter 6-th in the book: New trends on monitoring and diagnosis for health sciences, Editors Mihaela Badea, Laura Floroian, published by LAMBERT Academic Publishing, trademark of OmniScriptum GmbH & Co. KG, Germany, ISBN 978-3-659-77699-1, pp. 95-112, 2015, https://www.amazon.com/trends-monitoring-diagnosis-health-sciences/dp/3659776998.

[2] **Alexandru Topor** , Cristian Ravariu, Florin Babarada, Dumitru Ulieru, "Development of a Mobile Prototype for Diagnosing Tropical Diseases Through

University-industry Cooperation", in Proceedings of REV International Conference of Remote Electronic Virtual, accepted, in press in 2023.

**Presentations at International Conferences, present in the Conference program or in the Abstract Book**

[1] **A. Topor** , C. Ravariu, "Novel performances of a diamond nano-device with vacuum tunnelling conduction", 15th European Vacuum Conference (EVC-15), Geneva, Switzerland, 17-22. June 2018. EVC-15 Abstract book, pp. 116-117

[2] **A. Topor** , C. Ravariu, F. Babarada, D Manuc, B. Patrichi, "Novel performances of a diamond nano-device with vacuum tunnelling conduction", 27th International Conference on Diamond and Carbon Materials, Le Corum, Montpellier , France, 4-8 Sept 2016, P13.16, pp. 18-18, Indexed Elsevier,
https://www.researchgate.net/publication/307464203_Novel_performances_of_a_dia
mond_nano-device_with_vacuum_tunnelling_conduction.

[3] D. Ulieru, Oana-Maria Ulieru, Xavi Vila, **Alexandru Topor** , "Developing and implementation of a new generation of nanosafety assessment tools", EURONANOFORUM 2019 Conference, 12-14 June 2019 Paper H04, Bucharest Parliament Palace, Romania.
http://www.olidigraph.com/stagetwo.php

[4] D. Ulieru, Oana-Maria Ulieru, Xavi Vila, **A. Topor** , F. Babarada, "Development of non-invasive early diagnosis of tropical diseases", TROPSENSE
BioNanoMed 2019 Conference 15/17 April 2019, Book of Abstract, Graz, Austria, https://phantomsfoundation.com/NANOBIOMED/2018/Abstracts/NanoBioMed2018
_ULIERU_DUMITRU_43.pdf

[5] D. Ulieru, Xavi Vila, Oana-Maria Ulieru, **A. Topor** , "The human eye protection by application of optical limiter devices", MedTec Exhibition 23-25 May 2019, Nurnberg, Germany.
http://www.olidigraph.com/stagetwo.php

[6] D. Ulieru, OM Ulieru, X. Vila, **A. Topor** , The Modern Concept of Microsensors/Microsystems Integration at Wafer Level by High Accuracy Micromanufacturing Processes, 4M/ICOMM 2015, 09, http://rpsonline.com.
sg/proceedings/9789810946098/html/sess5.html

[7] **A. Topor** , C. Ravariu, F. Babarada, A. Salageanu, I. Caras, "Enhanced Fluorescence Detection Based On Simple Electronic Devices", 2nd Edition of Internat.Confer. New Trends on Sensing- Monitoring- Telediagnosis for Life Sciences, Brasov, Romania - September 03-05, 2015, Oral Presentation, Book of Abstract, Lux Libris Publishing House, ISBN 978-973-131-328-3. pp. 118-119, code KN.4.2.

**Patents and Medals**

[1] Popescu LM, Piticescu RM, Motoc AM, Voinea LM, Gradinaru Istrate S, Ulieru D, **Topor A** , Gradinaru ISL, "Three-dimensional structures used for ocular implants comprises spray-dried hybrid powder comprising hydroxyapatite and polyurethane diol prepared by hydrothermal process, water soluble binders solution, and extrusion bioprinting solution", Patent Number(s): EP3366319-A1 ; RO132753-A2; RO132753-B1; EP3366319-B1, 2019, 2020, Derwent Primary Accession Number: 2018-675525.

[2] Popescu LM, Piticescu RM, Motoc AM, Voinea LM, Gradinaru Istrate S, Ulieru D, **Topor A** , Gold medal: Euroinvent Salon 2018 (10th edition), organized between 17-19 May 2018, at Iasi, Romania, where they obtained 2 gold medals for inventions with applications in medicine (eye implants).

[3] Popescu LM, Piticescu RM, Motoc AM, Voinea LM, Gradinaru Istrate S, Ulieru D, **Topor A** , Silver Medal: 46th International Exhibition of Inventions Geneva, Apr 2018 http://www.icpe-ca.ro/icpe-ca/eng/activity-reports/annual-report-2018.pdf

# 6.4 Prospects for further development

further development are motivated by solving some problems faced by society at a global or regional level, always constituting the motivational element behind all the actions undertaken by the author. As one of the most pressing problems is health, the desire to apply the accumulated knowledge and research methods to solve some of the most interesting problems in the medical field using modern technologies was the element around which the contributions were built the projects mentioned above and this work.

The above projects and detailed contributions are perfectable. Also, these projects are at different stages of development, standing at different points between the theoretical model and the finished product available on the market to help patients. Specifically, for the concept presented in Chap. II, the further development of the hardware device, the mobile application and the improvement of the diagnostic capacity, allowing a precise calculation of the sensitivity and specificity of the proposed method, would represent the next step towards the production of this concept, being elements of interest for a potential future research project performed so far.

Also in this field, the comparative study of the different methods applied, as well as of the newly appeared methods in the area of image and signal processing, would be of interest. In some of the applications, the author used the intuition developed in previous experiences, and sometimes did not analyze the full spectrum of existing ways and implementations for solving a specific problem. A qualitative and quantitative comparative analysis of the available methods will be able to solve the problem of

finding and deciding the best solutions and combinations of solutions, together with the related optimizations, to give the expected results in each individual case.
A case study can also be done on ocular reconstruction and subsequent network development in the DeVide app, along with new releases made available by the app's developers. Currently, widespread ocular implants are still standard sizes, and are not built to the patient's profile, resulting in high rejection rates, in addition to aesthetic inconveniences.
It is also aimed at continuing the development of the GRIPPER_SW_APP.exe application, proposed at the prototype level in Chapter 4. It is aimed at the possibility of scaling the application and its use in order to ensure the quality and conformity of the microtweezers at the time of their industrial production. By enriching the image processing methods available in the application, higher accuracy can be reached, thus becoming a powerful alternative to consider to perform gripper characterization.
**The realization, in a broad sense, on a larger scale of the concepts, prototypes, and experimental models presented is also desirable. As some biomedical applications are relatively recent and new information on complementary concepts is published from year to year, keeping them at the cutting edge of technology will be an ongoing effort over time.**

# Bibliography

[16] Chang Che-Han, Chun-Nan Chou and Edward Y. Chang, "CLKN: Cascaded Lucas-Kanade Networks for Image Alignment", 2017 IEEE Conference on Computer Vision and Pattern Recognition (CVPR), Honolulu, HI, USA, 2017, pp. 3777-3785, doi: 10.1109/CVPR.2017.402.

[17] Lei Yang, Zhen Qiu, Alan H. Greenaway, and Weiping Lu. "A New Framework for Particle Detection in Low-SNR Fluorescence Live-Cell Images and Its Application for Improved Particle Tracking", IEEE Transactions on biomedical engineering, vol. 59, no. 7, 2012, pp. 2040-2050.

[18] R. Parton, R. Hamilton, G. Ball, L. Yang, C. Cullen, W. Lu, H. Ohkura, and I. Davis, "A PAR-1-dependent orientation gradient of dynamic microtubules directs posterior cargo transport in the Drosophila oocyte", J. Cell Biol., vol. 194, no. 1, pp. 121–135, 2011.

[19] L. Yang, R. Parton, G. Ball, Z. Qiu, AH Greenaway, I. Davis and W. Lu, "An adaptive non-local means filter for denoising live-cell images and improving particle detection", J. Struct. Biol., vol. 172, no. 3, pp. 233– 243, 2010.

[20] Jensen KA, Gaudet VC, Levine PM, "Noise analysis and measurement of integrator-based sensor interface circuits for fluorescence detection in lab-on-a-chip

applications", 22nd IEEE International Conference on Noise and Fluctuations (ICNF) , 2013, pp. 1-4.

[21] Mabaso Matsilele, Withey DJ and Twala Bhekisipho, " Spot detection methods in fluorescence microscopy imaging: A review. Image Analysis & Stereology", 2018, v. 37, pp. 173, doi: 10.5566/ias.1690.

[22] I. Smal, K. Draegestein, N. Galjart, W. Niessen, and E. Meijering, "Particle Filtering for Multiple Object Tracking in Dynamic Fluorescence Microscopy Images: Application to Microtubule Growth Analysis", IEEE Transactions on Medical Imaging, pp. 789 – 804, doi: 10.1109/TMI.2008.916964

[44] U. Tisch, I. Schlesinger, R. Ionescu, M. Nassar, N. Axelrod, D. Robertman, Y. Tessler, F. Azar, A. Marmur, J. Aharon-Peretz, "Detection of Alzheimer's and Parkinson's disease from exhaled breath using nanomaterial-based sensors", Nanomedicine, 8, 2013, 43-56.

[65] Sumantu Iyer, Maen Alkhader, TA Venkatesh, “Electromechanical Response of Piezoelectric Honeycomb Foam Structures”, 2013, doi: 10.1111/jace.12699.

[66] Topor Alexandru, Ulieru Dumitru, Ravariu Cristian, Babarada Florin, "Development of a new one eye implant by 3D bioprinting technique", Rev. Rome. Sci. Techn. – Electrotechn. et Énerg. Vol. 61, Bucharest, 2022.

[67] Popescu LM, Piticescu RM, Motoc AM, Voinea LM, Gradinaru Istrate S, Ulieru D, Topor A, Gradinaru ISL, "Three-dimensional structures used for ocular implants comprises spray-dried hybrid powder comprising hydroxyapatite and polyurethane diol prepared by hydrothermal process, water soluble binders solution, and extrusion bioprinting solution", Patent Number(s): EP3366319-A1 ; RO132753-A2; RO132753-B1; EP3366319-B1, 2019, 2020, Derwent Primary Accession Number: 2018-675525.

[69] Topor Alexandru, Voicu Rodica Cristina, Ulieru Dumitru, Ravariu Cristian, Babarada Florin, "Image processing algorithms for characterization of MEMS type micro-tweezers aperture", JOAM - Journal of Optoelectronics and Advanced Materials.

[70] Roberts Timothy, Mckenna Stephen, Wuyts N, Valentine Tracy and Bengough Anthony, "Performance of Low-Level Motion Estimation Methods for Confocal Microscopy of Plant Cells in vivo", 2007, IEEE Workshop on Motion and Video Computing, WMVC 2007, two: 10.1109/WMVC.2007.32.

**WEB addresses:**

[W1] Project PN-II-PT-PCCA (2014-2016) led by INCDMI Cantacuzino, partner in the ETTI/DCAE/ERG consortium, represented by Mr. F. Babarada, ETTI/DCAE/ERG research team composed of F. Babarada and **A. Topor**
[W3] MSCA RISE Horizon 2020 project (2015-2017) led by Uppsala University Sweden, partner in the Sitex45 consortium, represented by Mr. D. Ulieru, the Sitex45 research team composed of D. Ulieru and **A. Topor**
http://h2020.tropsense.icmpp.ro/en/index_en.php
[W6] National Project (2015-2016) led by UMF Carol Davila, partner in the Sitex45 consortium, represented by Mr. D. Ulieru, the Sitex45 research team composed of D. Ulieru and **A. Topor**
https://umfcd.ro/cercetare-si-dezvoltare/proiecte/proiecte-nationale/proiect-orbimplant/
[W10] "46th International Exhibition of Inventions Geneva", Apr 2018
http://www.icpe-ca.ro/icpe-ca/eng/activity-reports/annual-report-2018.pdf
[W11] Euroinvent 2018 (10th edition), organized between May 17-19, 2018, in Iasi, Romania, where it won 2 gold medals for inventions with applications in medicine (ocular implants) - https:// fundatiadanvoiculescu.ro/euroinvent-2018/
[W12] ERA-MANUNET-II ROBOGRIP project (2014-2016) led by IMT Bucharest, partner in the Sitex45 consortium, represented by Mr. D. Ulieru, the Sitex45 research team composed of D. Ulieru and **A. Topor**