Cells Modeling Approaches for Microfluidic Biodevices

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Abstract – **in this paper concept of approach for the detection and measurement in the biomedical analisys device based on cells deflection is presented.**

Keywords – **bioanalysis, image processing, microfluidics**

I. Introduction

Microfluidic devices are widely used in biological and chemical research, as they provide rapid analysis, are portable, require less reagents, samples and are sensitive. The Lab-chips for biomedical analysis often utilize ultrasensitive optical detection method of biological cells.

Cell state is often assayed through measurement of biochemical and biophysical markers. Although biochemical markers have been widely used, intrinsic biophysical markers, such as the ability to mechanically deform under a load, are advantageous in that they do not require costly labeling or sample preparation. However, current techniques that assay cell mechanical properties have had limited adoption in clinical and cell biology research applications.

One of the newest method of bioanalysis is the analysis based on mechanical properties of cells. cytophysiological and cytopathological processes. The study of elastic properties allows to obtain new knowledge about biological cells and also is of clinical interest. Mechanical properties of intact cells are associated with different cell events such as locomotion, differentiation and aging, physiological activation and electromotility, as well as cell pathology. Such approach is new and it needs new research techniques to be developed.

II. Problem description

The main idea of bioanalysis mentioned before is to detect diseases using only mechanical properties of cells. Modern techniques in most cases use chemical analysis which makes further reuse of the samples impossible due to it pollution by chemical reagents. New method allows researcher to reuse samples for further analysis steps.

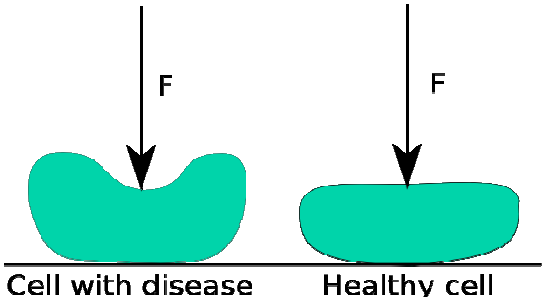

Figure 1Healthy and unhealthy cells deformation under the same load

Biological cells have different mechanical properties not only depend on their type but also depend on their conditions [2]. For example cells which are harmed by disease are much less elastic than healthy cells (Fig. 1).

There is growing evidence that cell deformability (i.e., the ability to change shape under load) is a useful indicator of changes in the cytoskeleton and nuclear organization and may provide a label-free biomarker for determining cell states or properties such as metastatic potential, cell cycle stage, degree of differentiation, and leukocyte activation. Clinically, a measure of malignancy and metastatic potential in tissues or biological fluids could guide treatment decisions, or a measure of degree of differentiation could prevent transplantation of undifferentiated, tumorigenic stem cells in regenerative therapies. For drug discovery and personalized medicine, a simple measure of cytoskeletal integrity could allow screening for cytoskeletal-acting drugs or evaluation of cytoskeletal drug resistance in biopsied samples. Additionally, measures of leukocyte activation are strong predictors of disease prognosis and response to treatment in persons with HIV-1 infection or rejection of allografts.

A wide variety of platforms have been engineered to perform mechanical measurements on cells (11). Generally, these techniques can be divided into two categories based on the samples they act on: bulk and single cell (12). Bulk platforms, such as microfiltration, tend to have high-throughput, but they yield one endpoint measurement and do not take into account heterogeneity or size differences within the sample population of cells. Disease may develop from abnormalities in a single cell or smallsubset, such that accurately detecting rare events or small populations is important, and bulk measurement may result in misleading average. Single-cell platforms that can assay this heterogeneity include micropipette aspiration , atomic force microscopy (AFM), magnetic bead-based rheology, microfluidic optical stretching, and microfluidic cell transit analyzers. In particular, microfluidic single-cell mechanics assays have been promising, yielding more automated measurements through microscopically observed cell transit through microchannels or pores. In these approaches the transit time at a constant pressure is indicative of mechanical properties; however, cell size and adhesiveness also can contribute to the measurement, which is especially relevant when dealing with heterogeneous cell solutions. In general, current approaches, usually optimized for biophysics research, operate at rates from 1 cell per min

(AFM and optical stretching) to approximately 1–5 cells per s (microfluidic cell transit analyzers, electroporative flow cytometry; ref. 18).

Mechanical properties of cells are defined by Young modulus E and Poisson's ratio ν. These properties are measured by atomic force microscopy (AFM) which is a modern technology [1,3]. Such procedure is complicated and expensive.

Using of microfluidic devices makes mechanical analysis much easier and cheaper. Structure of device is shown on Figure 2.

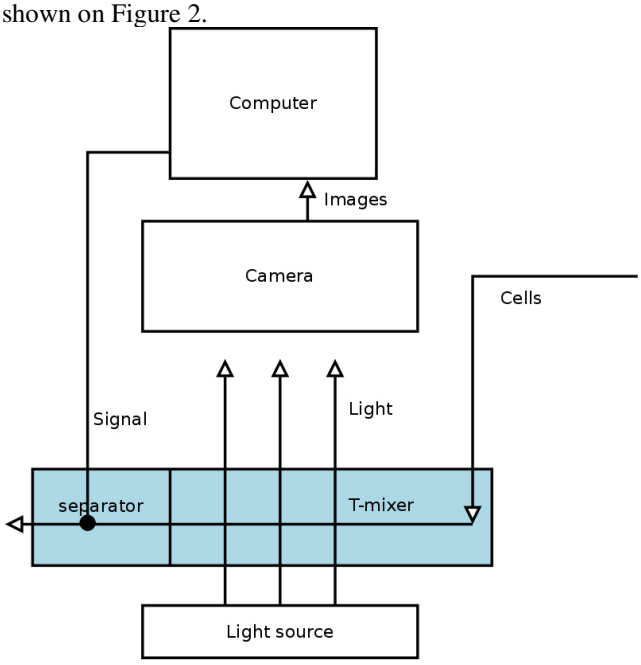

Figure 2. Structure of the analysis system

There is four types of microfluidic manipulations of cells (Figure 3):

Constricted geometry

Advances in microfabrication enable the fabrication of structures on the microfluidic platform to be used for deformation studies on single cell. Various forms of customized structures for example wedge/funnel shape, vertical gap, long channel, hyperbolic shape and cross road allows for single cell deformability measurement along with parameters to characterized intrinsic cell properties.

Aspiration induced

This particular technique mimicked the concept of micropipette aspiration (MA) as explained previously (Figure 4B). suction pressure. Generally, by performing cell deformation measurements similar to MA using standard PDMS microchannel surely imposed several challenges due to rectangular cross section. For examples; the driving fluid might get leaked along the edges, issue on cell conformity since rounded shape of cell cannot accommodate sharp edges of PDMS channel and hard to determine shear force due to presence of additive flow in microfluidic. Nevertheless, the rectangular channels do exhibit several advantages such as ease of fabrication and easier for cell-surface observation under optical microscopy. Compared to other techniques, micropipette aspiration has a number of well-established mathematical models for Young's modulus assessment.

Fluid induced

Another way to deform cell using microfluidic involves the generation of converging streamlines. This dynamic fluid equilibrium effect produces converging streamlines that able to distinguish, sort and enrich any cells in the fluidic free flow. Specifically, this technique target the cell at the center between two converging streamlines and characterized the deformation index experienced by the cell instead of direct contact with the microstructures (Figure 4C). Deformation index is defined as ratio of both axis of cross sectional area of a deformed cell has been linked with cell deformability and was proved to be an efficient biophysical marker for cell state

Electrically Induced

Mechanical manipulations involving electrically induced microfluidic has started ever since the Coulter principle was established (Figure 4D). The principle states that any particle moving through an orifice along with electric current should produce a change in impedance. By this means, the impedance changes are due to displacement of electrolytes caused by the particles movement. Vast areas emerged as a result for example electroporation, electrodeformation, electrorotation, dielectrophoresis, microelectrical impedance spectroscopy (μ-EIS) and impedance based flow Cytometry (IFC). Electroporation is referred to swelling or expansion in cell size whenever a cell experiences an externally applied electric field.

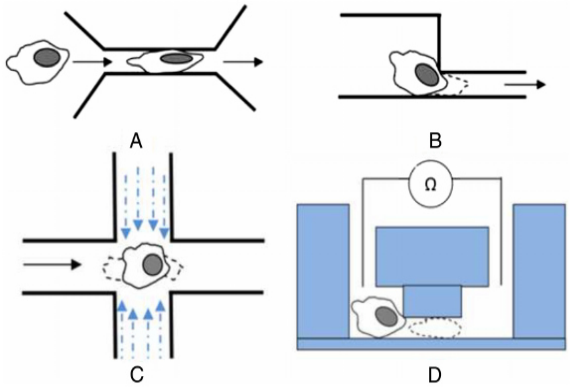

Figure 3. Microfluidic manipulations (A) Constricted Geometry (B) Aspiration Induced (C) Fluid Induced (D) Electrically Induced.

The considered design is a combination of fluid and aspiration induced approaches to manipulate and deform cells with advantages and disadvantages (e.g. touching the corner of the channel by cell's shell).

Under pressure created by two flows of fluid cells deflect on the corner of the channel junction (Fig 3). Then they are pictured by camera with microscopic optical system. Obtained images are processed by effective image processing algorithms which calculate such properties as eccentricity, relative size and others by using contour detection algorithms. These results are then compared to previously made data by statistic techniques.

Based on processing results the specific signal is sent to separator unit which divides cells on two groups: healthy and sick.

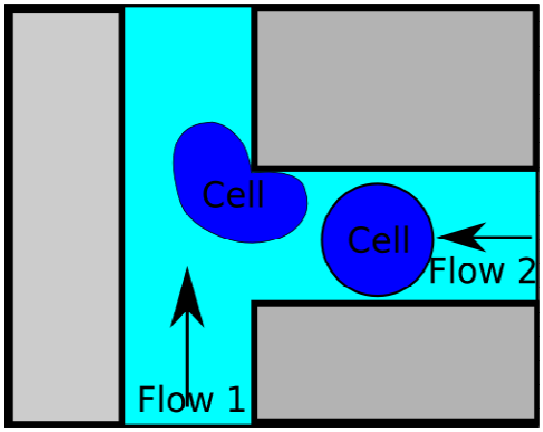

Figure 3. Cells inside T-mixer

The problem is to find specific distinction in shape between healthy and not healthy cells and design T-mixer in a way that provides the best possibilities to measure such distinctions.

III. Considering solutions

The idea is to model cell bending inside the T-mixer. Modeling results will be used to generate contour patterns of bended cell and to design channels of T-mixer in a proper way. Images taken from the camera will be matched with these patterns to detect ill cells.

There should be chosen a specific way of modeling. There are two approaches. The first one is to model a single cell as a piece of homogeneous material with defined mechanical properties, measured earlier. The second one is to consider a cell as a elastic shell with liquid inside it [1] (Fig. 4). Where the relation for determining the deflection of the shell is:

$$h = \frac{Pl^2}{2\pi D}(-kei(x) - k_R \times$$

$$\times\left[(1+\nu)(\frac{\pi}{2}Y_0(c\sqrt{2k_R}) + \ker(x)) + \frac{1}{2}c\ker'(x)\right] +$$

$$+(\eta - \varepsilon)\ker(x) + \frac{t}{4}c\ker'(x))$$

where

$$D = \frac{Et^3}{12(1-\nu^2)}; l = \frac{\sqrt{rt}}{\sqrt[4]{12(1-\nu^2)}}$$

$$k_R = \frac{l^2}{r^2}; \varepsilon = \frac{\nu t^2}{10(1-\nu^2)l^2}$$

$$\eta = \frac{t^2}{5(1-\nu^2)l^2}$$

E - Young's modulus of the sample, Pa; ν - Poisson's ratio of the sample; R - radius of the AFM tip, m; h - the difference between the coordinate tip contact point and the coordinate of separation when the AFM tip withdraw from the surface (moving at material stretching), m; P - applied load, N; r - radius of the shell, m; t - thickness of the shell, c' - the contact area, m^2; l - characteristic size; c - dimensionless quantity, equals to c = c' / l ; kei (c) - Thompson function; k = l^2 / R^2 - coefficient characterizing the thickness of the shell.

The first method is simpler but the second is more precise and allows to model a complex phenomenon at the microchannels corners while cell is being bended between liquid flows (Figure 3).

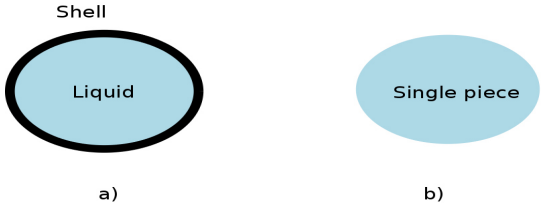

Figure 4. Difference between modeling approaches

Shell modeling has also one significant advantage – it enables an ability to check if cell's shell is broken or not. If shell is broken cell is no more appropriate for further analysis. Furthermore in real experiments the remains of broken cell are spoiling the channels and can cause different measurement errors.

IV. Conclusions

In this paper were considered possible solutions for design of software and mathematics subsystems of bioanalysis device. Was chosen approach to model cell's deflection inside microfluidic system.

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