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Studying pharmacodynamic effects in cell cultures by chemical fingerprinting – SIA electronic tongue versus 2D fluorescence soft sensor

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ABSTRACT

The viability of cells for drug screening purposes is usually tested with a variety of colorimetric/fluorescent methods In this work, two alternative ways of assessing toxic effect in cell cultures: sequential injection analysis (SIA) electronic tongue and soft-sensor based on 2D fluorescence have been evaluated and compared as novel, rapid techniques for cell culture monitoring. It is shown, that the proposed non-selective methods, which are based on sample fingerprinting, are capable of cytotoxic effect detection and incubation time estimation in a model experiment considering the treatment of various cell lines with a model drug – diclofenac. It affected the metabolic activity of the cells in a concentration- and time-dependent manner resulting in varying amounts of necrotic, early apoptotic and late apoptotic cells. These phenomena could have been revealed with the use of both non-selective analytical systems based on the extraction of useful information from sample fingerprints by multivariate data analysis procedures. This proves that the proposed methods can be used for fast and reliable cell culture monitoring which potentially can be also non-invasive.

1. Introduction

Current laborious preclinical trials for novel therapies rely on combination of in vitro cell culturing protocols and in vivo animal models [1,2]. Animal testing has inherent complexity involving many ethical issues as well as its use may cause difficulties with the proper interpretation of the obtained results. Beside those matters, animal models are not physiologically accurate to most of human organs functions, diseases and response to medical treatment [2]. The high utility of human cell culturing assays for biomedical applications, such as anticipation of biological activity of substances (e.g. potential toxic effects) has been demonstrated. It was possible due to facility of controlling the specific microenvironment where cellular proliferation and functionality are easily observed and tested [2,3]. The critical issue of therapeutically active molecules development is a possible mechanism of their action – one of the most successful strategy for drug and potential anti-cancer agents' discovery is targeting critical regulators of apoptosis with the goal of inducing apoptosis in cells [4]. Therefore, rapid, easy to use and low-cost analytical tools for the studies of the type of cellular death (apoptosis or necrosis) induced by examined active molecules are required.

For most investigations in cell biology, the determination of cell count and the evaluation of cell viability is essential. The ability to measure cell viability is important for applications that include the measuring effect of drugs and basic physiologic studies of cell metabolism. The ideal method of measuring cell viability would not be toxic to the cell, allowing continuous or repeated measurements; would have a range of sensitivity that allows measurement of degrees of viability; would not be dependent on cell division; and would be convenient and save [5]. For this purpose, a variety of assays have been developed, e.g. assays that rely on membrane integrity, metabolic activity, proliferation rate or protein content of the cell population [6]. Viable cells could be measured by using any of several staining methods but it is preferred to avoid any washing steps that would increase processing time and sample variation. One popular assay is the MTT-assay measuring the activity of mitochondrial dehydrogenases colorimetrically [7]. However, the assay procedure leads to cell death. An alternative indicator of the cellular redox state is the Alamar Blue™ dye, which is reduced from a non-fluorescent form to a fluorescent product due to metabolic activity of the cultured cells. When additional information about cells are necessary, flow cytometry is used. This system is a laser- or impedance-based, biophysical technique employed in cell counting, determining the cells viability, apoptotic cells detection or biomarker detection by suspending cells in a stream of fluid and passing them by an electric

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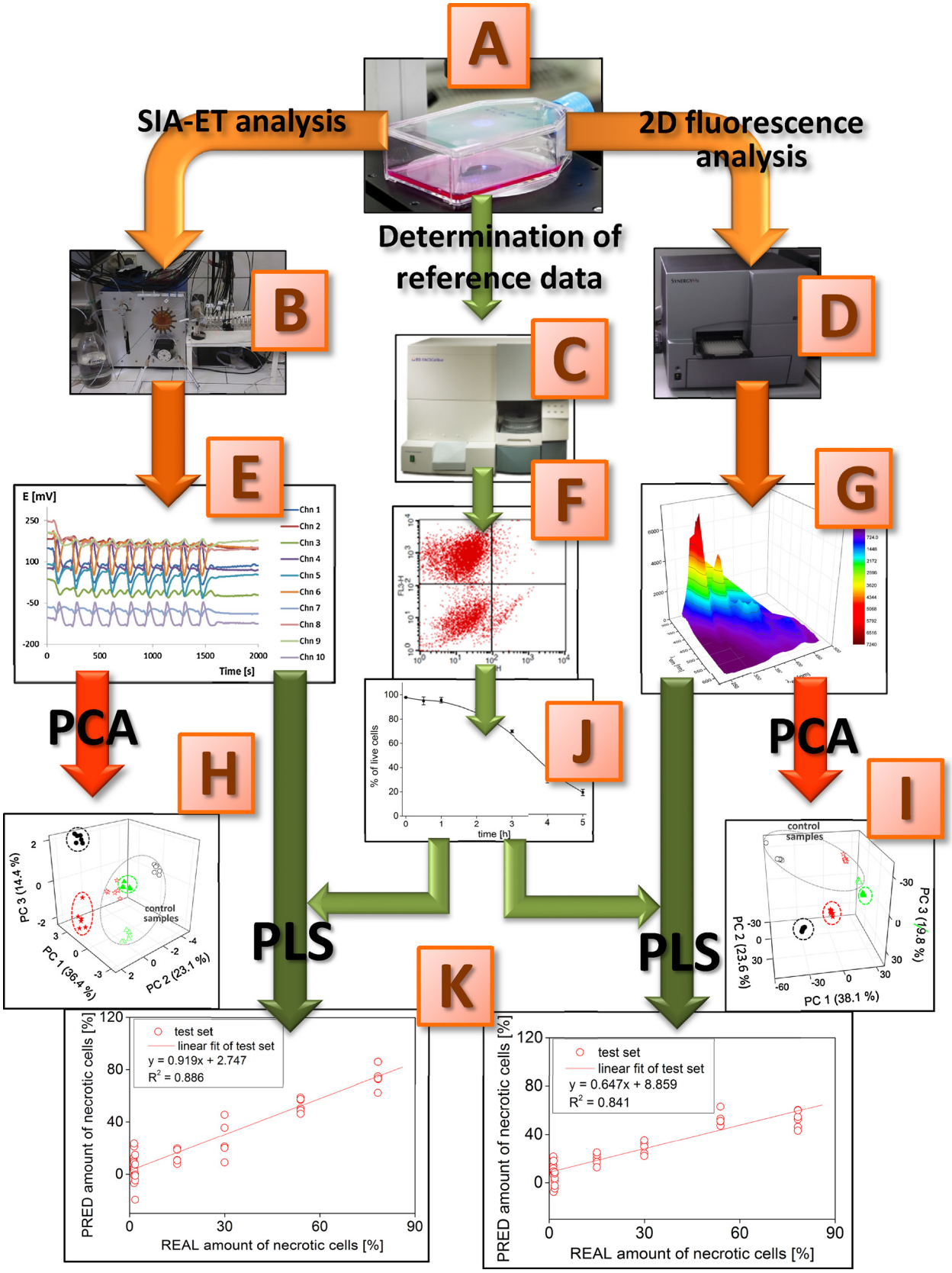

Fig. 1. Experimental set-up: (A) cell culture; (B) SIA system for potentiometric and spectrophotometric measurement (SIA-ET); (C) flow cytometer for classical determination of reference parameters; (D) multiwall plate reader for 2D fluorescence measurements; (E) dynamic responses of potentiometric sensor array; (F) flow cytometry analysis (G) 2D excitation-emission fluorescence map; (H, I) PCA score plots of data; (J) classical determination of cell culture parameters; (K) PLS analysis (for target matrix reference data.