Sensors and Actuators B 137 (2009) 781–788

Contents lists available at ScienceDirect

Sensors and Actuators B: Chemical

journal homepage: www.elsevier.com/locate/snb

Microfluidic imaging: A novel concept for pixelation of chemical and biological samples

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ARTICLE INFO

Article history:
Received 14 September 2008
Received in revised form 11 January 2009
Accepted 18 January 2009
Available online 30 January 2009

Keywords:
Pixelation
Droplets
Compartmentalisation
Imaging
Tissue

ABSTRACT

We propose and experimentally demonstrate a novel concept to spatially resolve the chemical composition of complex biological samples by pixelation within a micro total analysis system (μTAS) platform. The device we developed images samples of interest by discretising targeted areas into droplets suspended in a two-phase microflow. These droplets are transferred from parallel to serial mode for data readout in a similar fashion to a CCD camera, thus referred as "microfluidic imaging". Three major process steps are conducted within the device: (i) parallel pixelation and uptake of the sample (ii) sample transfer from parallel to serial mode into a microchannel for individual analysis and (iii) image generation. This microfluidic pixelation method is a technique suitable for obtaining non-averaged data from heterogeneous specimen. The concept attempts to reduce arduous preparation steps, allowing high throughput while retaining the spatial information.

1. Introduction

The μTAS concept, which aims to engineer miniature devices to carry out analytical processes for chemical and biological reactions, has dramatically evolved since its beginning back in 1990 [1,2]. The capability of miniaturised devices to provide more precise spatial control over samples and reagents handled, to attune and integrate exactly to the experimental requirements, and to fabricate biocompatible microenvironments, has driven many bioanalytical scientists towards μTAS [3,4]. Within this established field, microfluidics plays a significant role as it bears the potential to handle, meter and create defined small liquid volumes.

The first experimental demonstrations of the usefulness of the μTAS concept focussed on electrophoretic separation of DNA or protein mixtures on simple planar microchips comprising microchannels with crossed- or double-T-junction designs [5,6]. While the time required for electrophoresis was dramatically reduced in such systems (down to <5 s) compared to commercially available systems of that time (20–40 min), the devices only provided the possibility for serial analysis, i.e., for various sample mixtures, injection and separation were performed one after the other. In this configuration, high throughput screening of large sample library is limited. However, one of the main advantages of miniaturisation is the high level of parallelisation accessible on chips. An example presented by Manz and co-workers [7,8] is a microfluidic chip design, where a conversion of serial to parallel sample analysis takes place by using up to 80 separation channels, all of which were filled at once for simultaneous homogeneous sample separation. In principle, the number of parallel analyses could be increased as much as desired, but aspects concerning simultaneous injection of various sample as well as the readout process set limit to the applicability of this approach.

In recent years, highly parallelised and extraordinary efficient separation devices have been developed. High throughput analyses are realised for parallel multiple sample electrophoresis, for example, by the use of I-shaped microchannel [9], or in radial chip designs [10,11]. However, these studies involve aqueous sample or suspended cells and are not directly transferable if immobilised species with a heterogeneous distribution has to be analysed. In other words, these studies are mainly for batch homogeneous samples and are unsuitable for differentiating and retaining spatial information from an immobilised sample.

In this work, we propose a device that is able to image specific areas of biological samples like cells, tissues, organs or biofilms [12]. It can be used to isolate, analyse and screen samples, allowing determining heterogeneity of these biosystems and hence, increasing our understanding of stochastic behaviour expected on a cellular or on a given systems' level. Moreover, the method is suitable for systematic studies of cellular responses in tissues. In the following, we

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doi:10.1016/j.snb.2009.01.032

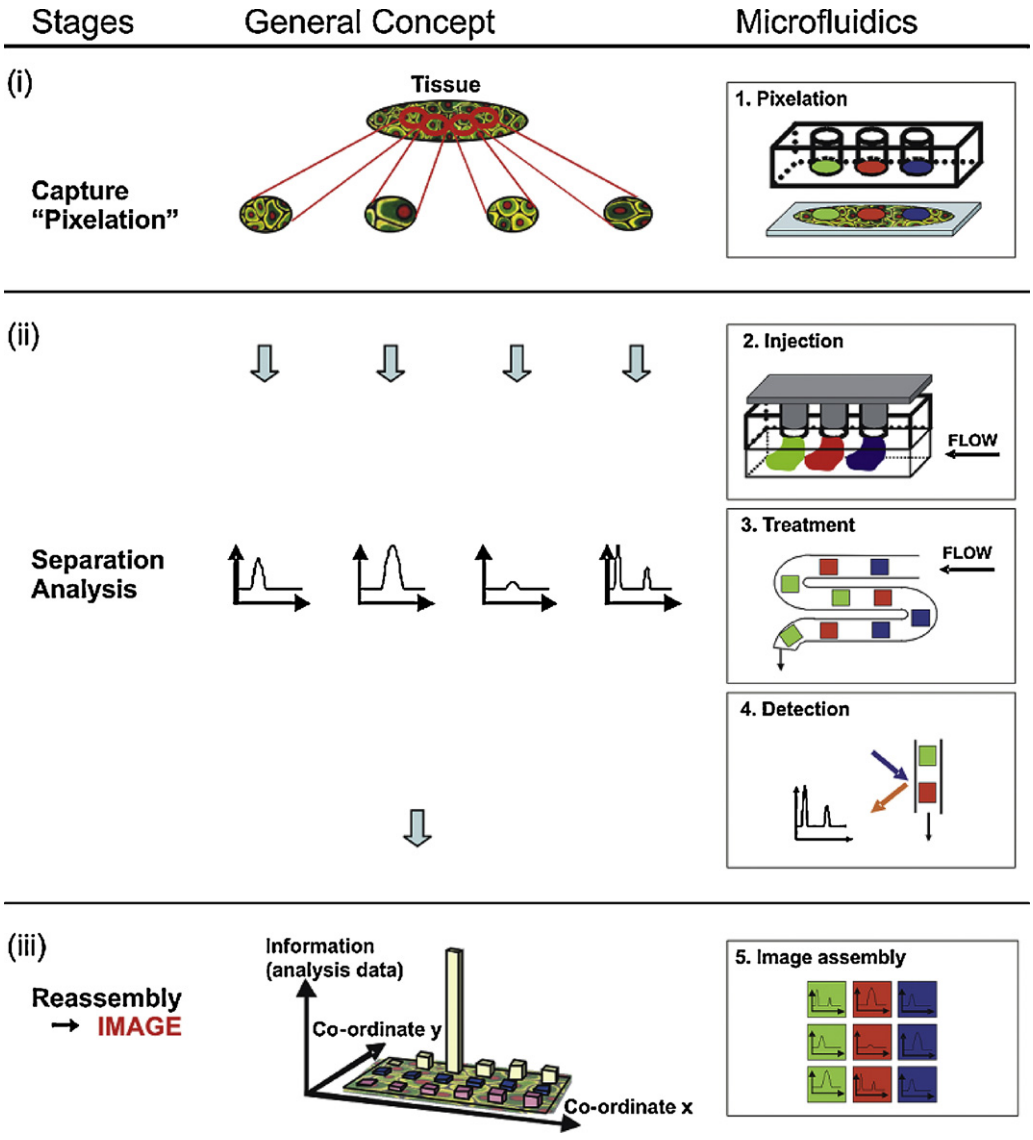

Fig. 1. A conceptual flow diagram depicting the "microfluidic imaging" concept. This three-step concept comprises (i) sample capture and pixelation, (ii) transfer and analysis steps, and (iii) reassembling of the image. During pixelation (1. Pixelation), discretisation of complex sample into smaller units (pixels) takes place. In step (ii), simultaneous sample injection into linear microfluidic channel (2. Injection), individual sample treatment e.g., cell lysis, PCR (3. Treatment) and the detection of individual pixel (4. Detection) are carried out. In the final step, the pixel information is mapped to original sample position (5. Image assembly) as post-processing.

introduce the concept and support its fundaments with the results obtained from the proof-of-principle tests.

2. The concept of microfluidic imaging

The microfluidic chip we devised, the concept of which is illustrated in Fig. 1, shall index the sample into individual pixels similar to a fluorescence imaging system with a CCD camera to compose an image [13–15]. In a standard CCD chip, images are optically projected onto the parallel array that acts as the image plane. The device takes the scene information and partitions the image into discrete elements that are defined by the number of "pixels". The resulting rows of scene information are then shifted in a parallel fashion to the serial register that subsequently shifts the row of information to the output as a serial stream of data. The image is then reconstructed as given by the system. On a microchip platform, we apply the digital analogy to biological samples and substitute the image plane with heterogeneous constituents, e.g., tissues and membranes. To realise this, the sample is partitioned in an irreversible and mechanical manner and uptaken as small volumes ("pixels"). Each of these separated volumes represents a μTAS in its own, and can be processed and analysed along a fluidic network afterwards. For this reason, we named the novel concept "microfluidic imaging".

The procedure of imaging consists of three steps, i.e., (i) sample capture, (ii) transfer and analysis steps, and (iii) reassembling of the image. First, the sample is pixelated and discretised into smaller addressable units (pixels). Using a stamp-like device made of hard material that embeds perforations, the targeted area is partitioned into smaller units and, at the same time, captured into perforations of the device. Second, the segmented sample is transferred into a microchannel for individual analysis. For the transfer step, micropillar manifolds are the key feature in allowing simultaneous sample injection into a serpentine channel that is positioned underneath. The emerged droplets can be transported afterwards along the channel in a stream of hydrophobic or gaseous carrier. Sample treatment steps can be implemented before the droplets are delivered to a stationary detection window, for data readout and serial collection. Finally, the information obtained from each pixel (in this study: the fluorescence intensity) is assembled as an image of the