FPGA based system for automatic cDNA microarray image processing

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**A B S T R A C T**

Automation is an open subject in DNA microarray image processing, aiming reliable gene expression estimation. The paper presents a novel shock filter based approach for automatic microarray grid alignment. The proposed method brings up significantly reduced computational complexity compared to state of the art approaches, while similar results in terms of accuracy are achieved. Based on this approach, we also propose an FPGA based system for microarray image analysis that eliminates the shortcomings of existing software platforms: user intervention, increased computational time and cost. Our system includes application-specific architectures which involve algorithm parallelization, aiming fast and automated cDNA microarray image processing. The proposed automated image processing chain is implemented both on a general purpose processor and using the developed hardware architectures as co-processors in a FPGA based system. The comparative results included in the last section show that an important gain in terms of computational time is obtained using hardware based implementations.

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1. Introduction in cDNA microarray technology

Measurement of gene expression can provide clues about regulatory mechanism, biochemical pathways and broader cellular function. Molecular biology and bioinformatics are using microarray technology in order to identify genes in biological sequences and to determine their functionality and their expression levels under different conditions. Genes are known as portions of DNA molecule that encode for a type of protein. By gene expression we understand the transformation of gene's information into proteins. The informational pathway in gene expression is as follows: DNA → mRNA → protein. The protein coding information is transmitted by an intermediate molecule called messenger ribonucleic acid, mRNA. This molecule passes from nucleus to cytoplasm carrying the information to build up proteins [1]. This mRNA acid is a single stranded molecule from the original DNA and is subject to degradation, so it is transformed into stable cDNA (complementary DNA) for further examination. Microarray technology is based on creating cDNA microarrays which represents gene specific probes arrayed on a matrix such as a glass slide or microchip [2]. Usually, samples from two sources (cDNA from target sample and cDNA from reference sample) are labelled with two different fluorescent markers (cyanine 3–Cy3 and cyanine 5–Cy5, respectively) and hybridized on the same array (glass slide). The hybridization process represents the tendency of two single stranded DNA molecules to bind together. After hybridization, the array is scanned using two light sources with different wavelengths for each marker (red and green) to determine the amount of labelled sample bound to each spot through hybridization process. The light sources induce fluorescence in the spots which is captured by a scanner and a composite image is produced [2] (Fig. 1). In this way, microarrays compare genes from normal cells with abnormal or treated cells, determining and providing information for understanding the genes involved in different diseases [3]. The microarray technology is used also in toxicological research and monitoring environmental effects on different genomes.

Classical genomic microarray experiments involve complex steps including slide production and scanning. A brief description of a microarray experiment can be summarized as follows:

1. Generation of array ready cDNA (selecting specific cell material and using Polymeric Chain Reaction for DNA amplification);
2. cDNA selection and microarray slide printing;
3. Selection of specific cell material from target tissues to be tested and fluorescent labelling;
4. Hybridization of the target material on the microarray slide;
5. Microarray image scanning;
6. Image filtering and spot detection;
7. Intensity extraction in order to evaluate gene expression;
8. High order processing (Clustering and interpretation, gene regulatory network estimation).

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Steps 1–5 are carried out by companies producing microarray slides and special laboratory conditions need to be met in order to be accomplished. Regarding steps 6 and 7, they represent a chain of image processing techniques integrated in existing software platforms (e.g., Agilent Feature Extraction software, GenePix Pro etc.). The classical flow of processing a microarray image is generally separated in the following tasks: pre-processing, for improving image quality and enhancing weakly expressed spots, addressing, segmentation and intensity extraction [4]. Addressing associates logical coordinates to each spot of the image and segmentation classifies pixels either as foreground, representing the DNA spots, either as background. The last step calculates the intensities of each spot and also estimates background intensity values. Following all these steps information regarding the array layout, spot sizes and shapes, spot intensities and background intensity values, is obtained for further interpretation.

The main disadvantage in microarray image processing is user intervention which brings up the need of a workstation with a costly processing platform which will slow down the process of microarray analysis if a large number of subjects is involved. Besides that, the equipment is not portable and cannot be used in field applications where a fast decision on a specific analysis result may be crucial, as in embarked crews and remote areas, or where e-health is an objective [5]. In this context, we design a shock filter-based approach for image addressing, within a complete microarray image processing system, robust and independent of operator last time adjustments. The proposed automatic image addressing method is compared with existing approaches in terms of computational complexity and accuracy in the presence of artefacts. Moreover, to validate the proposed image processing techniques, we compare our results with results taken from the Gene Expression Omnibus, a public functional genomics data repository containing microarray image processing results delivered by software platforms like Agilent Feature Extraction, GenePix Pro [6] and Affymetrix [7]. The last mentioned software platforms provide raw-data with microarray image characteristics which are used further on in high order analyses like clustering and gene regulatory network estimation. An example of raw-data information delivered by Agilent Feature Extraction software as a result of a microarray experiment is described in Fig. 1, where each information line corresponds to a microarray spot which has a precise location and represents a specific gene.

For each of the proposed microarray image processing techniques, using FPGA technology and taking advantage of its parallel computation capabilities, we designed application specific hardware architectures. All together they describe an FPGA based system for fast and automated microarray image processing and acquisition. The proposed system can be either integrated into the microarray scanner to automatically deliver results or into another device designed for remote microarray scanning and processing.

2. Automatic image processing techniques for cDNA microarray images

Spot detection and intensity extraction, included in a microarray experiment workflow, are fulfilled using image processing techniques. Recent research developed several microarray image processing methods specific to cDNA microarray analysis which provide grid alignment, spot segmentation and spot intensity extraction. This section details each step of cDNA microarray image processing by presenting the state of the art and also our proposed image processing techniques. The novel shock filter based approach for automatic image addressing is compared regarding the computational complexity to the state of the art approaches. Moreover, the accuracy of the proposed method in the presence of artefacts is illustrated compared to SVM and OMTG approaches reported in [8] and [9] respectively. In order to validate our results in terms of accuracy and reliability of spot detection, GEO (Gene Expression Omnibus), a MIAME compliant database was used to provide for comparison between different microarray images and the correspondent results delivered by existing software platforms for microarray image processing.

2.1. Microarray image enhancement

A well-known characteristic of microarray images delivered by existing scanners is the low level of expression for microarray spots, determined by their pixel intensity. Thus, the microarray image processing workflow commonly starts with a point-wise nonlinear transformations, used in order to improve image quality and to enhance weakly expressed spots [5,10]. One can use a logarithm transformation as shown in Eq. (1). The output, for a microarray image $I(x,y)$ with $(x,y)$ denoting the coordinates of a pixel and $n$ the number of bits for luminance/chrominance function representation, is described by:

$$I_n(x,y) = \frac{\ln[I(x,y) + 1]}{n \ln 2} 2^n$$

Alternatively, an arctangent hyperbolic based transformation can be used for image enhancement [11]. In case of such a nonlinear transformation only foreground (spot) information is selectively enhanced.

2.2. Automatic microarray image addressing (grid alignment)

The first operation performed on microarray image is known as addressing or grid alignment. This operation aims registering a set of horizontal and vertical lines which describe a two-dimensional array of spots. The existing software platforms for microarray image analysis together with late research impose two approaches for grid alignment, template-based and, respectively, data-driven methods [12]. Currently available software like GenePix Pro (Molecular
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