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### Two-dimensional gel electrophoresis image registration using block-matching techniques and deformation models



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#### ABSTRACT

Block-matching techniques have been widely used in the task of estimating displacement in medical images, and they represent the best approach in scenes with deformable structures such as tissues, fluids, and gels. In this article, a new iterative block-matching technique—based on successive deformation, search, fitting, filtering, and interpolation stages—is proposed to measure elastic displacements in two-dimensional polyacrylamide gel electrophoresis (2D–PAGE) images. The proposed technique uses different deformation models in the task of correlating proteins in real 2D electrophoresis gel images, obtaining an accuracy of 96.6% and improving the results obtained with other techniques. This technique represents a general solution, being easy to adapt to different 2D deformable cases and providing an experimental reference for block-matching algorithms.

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Proteomics is the study of protein properties in a cell, tissue, or serum aimed at obtaining a global integrated view of disease, physiological and biochemical processes of cells, and regulatory networks. One of the most powerful techniques used to analyze protein mixtures extracted from cells, tissues, or other biological samples is two-dimensional polyacrylamide gel electrophoresis (2D–PAGE).<sup>1</sup> With this method, proteins are separated by molecular weight and isoelectric point using a controlled laboratory process and digital imaging equipment [1].

2D–PAGE images represent 2D patterns of proteins derived from a sample that appear in the images as dark spots and where the sizes of the spots depend on the amounts of protein. In association studies, a pair of images is compared to find differences between proteins of interest. For this purpose, it is necessary to register the images and find the spots' correspondence.

The analysis of 2D gel images is a bottleneck in proteomics research due to potential displacements, appearance changes between proteins, or differences in protein expression and experimental conditions [2,3]. Over the years, several works studied this problem [4–6], but the correspondence between proteins problem is still far from a standard solution.

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In this work, a block-matching technique is proposed to be used as a pair of 2D electrophoresis gel images considering the test image as a deformation of the reference image so that the correspondence between the different proteins of the pair is estimated by analyzing the deformation. Block-matching techniques calculate the displacement of points  $(x_i, y_i)$  defined in a source image *I* by comparing the region or block around them with candidate blocks defined in a destination image *I'*, representing each candidate block with a possible displacement of the original region, and selecting the block in *I'* centered at  $(x'_i, y'_i)$  with the largest similarity value with the original one.

Over time, several works have focused on block-matching techniques, and important contributions were made. To increase accuracy, sub-pixel estimation using parabola fitting over three points was used in several works [7,8]. In addition, multiresolution approaches were widely proposed [9–11]. A related contribution is the adaptive reduction of the search area [12,13]. Another important contribution was the analysis of displacements in the frequency domain using fast Fourier transforms (FFTs) to increase performance [8,14].

Based on early iterative image registration principles [15], some new methods have been proposed to explicitly include deformation in the search process [16]. In these techniques, dense fields are calculated iteratively by interpolating the block displacement field. Some examples of these techniques are based on the use of B-spline interpolation [17], first-order bidimensional Taylor series [16], and radial basis functions (RBFs) [9,18].

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<sup>&</sup>lt;sup>1</sup> Abbreviations used: 2D-PAGE, two-dimensional polyacrylamide gel electrophoresis; RBF, radial basis function; RSS, residual sum of squares; L-M, Levenberg-Marquardt; EP, endpoint.

In addition, some works have used different approaches to improve the obtained flow. Some examples include the use of the particle swarm optimization technique [19], the inclusion of edge analysis [20], the use of feature information [21,22], and the use of Markov random fields (MRFs) [23].

The main advantages of block-matching techniques are simplicity, flexibility, robustness, and locality. However, these techniques are limited due to the block concept itself. Because a block has a size and shape defined a priori, this leads to wrong measurements near discontinuities in the motion field [24,25].

Several works have attempted, with some success, to reduce this problem by using a multilayer approach [26], pairwise affinities based on boundaries [24], adaptive shape windows [27–32], adaptive support weight windows [33], barycentric corrections [34], feature matching methods [35], and stereo analysis of cost volumes [25]. But the question is still far from having a standard solution.

Currently, it can be assumed that block matching might not be appropriate when analyzing a scene with different objects moving with different motions. However, it is one of the most robust methods for extracting the displacement field of a surface without reference points such as corners and edges. Therefore, block matching has been applied in several fields such as in analysis of flows [16] and deformable materials [36]. In medical imaging, its general application was studied in Refs. [37] and [38], and the use of block matching in rigid medical image registration was shown in Ref. [17] where a B-spline technique was visually tested with different examples of medical images. More concrete works have applied block matching to ultrasound images [39,40], echocardiography images [41–43], and magnetic resonance imaging (MRI) brain images [44,45].

Current block-matching algorithms are created for each problem [17], usually using traditional noniterative and nondeformable techniques [36]. In this work, a general solution for the 2D scenario is provided. This approach has the advantage of being easily adaptable to different problems, allowing comparison with different motion algorithms.

The main contributions of this article are as follows:

- A block-matching algorithm is proposed to solve the medical problem of matching proteins in images of 2D electrophoresis gels, defining a methodology to conduct and evaluate assays and improving the performance and accuracy of available state-of-the-art techniques.
- The proposed algorithm uses a multiresolution iterative process integrated with several deformation models that can be used as restrictions to guarantee the smoothness and freedom of the flow and to interpolate a dense flow for each pixel from an arbitrary set of points, allowing the registration of a warped image.

• A new methodology to conduct and evaluate experiments with 2D electrophoresis gels has been carried out.

#### Materials and methods

The 2D–PAGE image registration problem involves correlating the same protein in two 2D electrophoresis gel images from the same tissue but from different patients and obtained in different conditions (Fig. 1). The proposed technique was applied to the problem, assuming that one image can be mapped in the space of a reference image through a process of deformation.

Because there are no published datasets with ground truth data in this field, and a standard methodology to conduct experiments or evaluate protein-matching algorithms does not exist, eight samples (grouped into four pairs) of 2D gel electrophoresis images were selected from the dataset of Yang and coworkers [4]. These images have been used in several publications [46,47], and they correspond to an experiment where the effect of a plant extract on the protein expression of IBR3 human dermal fibroblasts was investigated. Both control and candidate samples were taken from homogeneous cell cultures grown in the laboratory where the candidate samples were treated with the plant extract.

The conducted tests correspond to intergroup comparisons with  $1024 \times 1024$  8-bit images, and 2D protein separation patterns were visualized by silver staining using standard protocols [48,49].

The defined methodology to evaluate the proposed registration technique on the dataset uses the following steps. First, the ground truth data are obtained from a pair of images by selecting proteins with Beads [50], a software program for spot detection in 2D gel images using surface information, and then correlating the detected spots using the criterion of experts. Then, the accuracy is measured for every point corresponding to a protein detected by Beads and taking into account only proteins expressed in the two images.

#### Proposed technique

The proposed technique divides the image into regular regions called blocks and solves the correspondence problem for each block (Fig. 2). To this end, it uses an iterative approach with different stages.

The main steps of the algorithm to analyse the displacement between two frames are as follows:

(1) The displacement field from the previous iteration is used to update the search area. Then, a deformation model is applied to change the shape of the block.



Fig.1. A pair of 2D electrophoresis silver-stained gel images that will be compared. Left: Reference image. Right: Test image.

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