A Comparative Study of Robust Feature Detectors for 2D Electrophoresis Gel Image Registration

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Abstract: In this study we consider the performance of different feature detectors used as the basis for the registration of images from two-dimensional gel electrophoresis. These are three spot detectors also used to identify proteins, and two domain independent keypoint detectors. We conduct a case study with images from a publically available data set which are synthetically distorted using thin plate splines. The performance is assessed by the repeatability score, the probability of an image structure to be detected in original and distorted images with reasonable localization accuracy.

1 Introduction

Two-dimensional gel electrophoresis is a well established approach for separating proteins in cell samples, and along with mass spectrometry one of the key technologies for comparative proteomics [Spe04]. To assess protein quantification and differences from varying experimental conditions and technical or biological replicates, it is essential to account for variations and distortions between gels and resulting gel images due to the experimental procedure. To ease this analysis, and especially with increasing amount of gel data available, the automatic analysis of gel images is of large interest. Typically, a first step in this process is the registration of pairs of gel images [DDY03].

Due to the global and local characteristics of deviations between gel images non-rigid transformations have to be applied. Registration techniques can be distinguished in feature-less and feature-based approaches, where also combinations were proposed [ZF03]. The first category directly exploits the intensity information of the images [WGP08]. In contrast, the latter one first detects features in both images which are subsequently matched and used to guide the computation of a suitable transformation for registration. Results and quality of feature-based registration obviously depend on the amount, spatial distribution, and localization accuracy of features used for matching.

For registration of gel images, protein spots have typically been used as features within feature-based registration methods (e.g. [P$^+$99, R$^+$04, SK08]) as they are detected anyway to identify proteins. However, for the registration process there is no need to restrict potential types of features to spots. In this work we aim at assessing the appropriateness of five feature detectors as basis for subsequent matching and registration of gel images. Among these are three spot detectors, namely the Laplace, Ring, and Meaningful Boundaries detector. We contrast these with two keypoint detectors, SIFT and SURF, which are widely used for various image analysis tasks, however, have not been applied to gel images. We expect our results to give guidance to select suitable feature types and detectors for robust and precise registration algorithms.

The remainder of this paper is organized as follows. After reviewing related work in Section 2 we briefly review the feature detectors evaluated. The test data and our evaluation strategy are detailed in Sec. 4, and the results are presented in Sec. 5.

2 Related Work

Over the years various techniques for automatically registering pairs of 2D electrophoresis images have been published. Regardless of whether the registration method is exclusively based on feature correspondences, or if it is a combined feature-based and feature-less technique, the quality of the registration result is directly linked to the quality of the correspondences provided. The more robust these matches are, the more uniformly distributed over the entire image area and the less outliers they contain, the better the registration will work. A large number of correct matches is especially important with regard to the domain of gel image registration, since here *non-rigid* image transformations have to be applied, requiring much more parameters than rigid ones and, thus, more correspondences for robust transformation estimation (cf. Sec. 4). In addition, common statistically robust estimators, like RANSAC, are not applicable for these transformations due to the high-dimensional parameter space and a high computational effort.

An indispensable prerequisite to determine robust correspondences for pairs of images is the detection of stable *features* in each single image, which are then matched for correspondence selection. Given the domain of gel images it is straight-forward to extract such features by explicitly detecting the most striking image patterns, i.e., protein spots. Common techniques for detecting those are, e.g., Laplacians [R$^+$04], watersheds [P$^+$99], morphological operators [CP92] or parametric spot models like 2D Gaussians [PF89]. Also more complex algorithms have been proposed, e.g., based on Markov Random Fields [Bak00]. However, spot-like structures in gel images are only one possible choice for stable features.

In various other computer vision applications, like camera motion recovery [HZ04], mosaicing [Cap04] or robot navigation [GZBSV03], also robust features for correspondence extraction are indispensable. In these scenarios usually no assumptions about specific image contents or structures can be made. Thus, for feature detection flexible keypoint detectors have been devised that yield stable features independent of a certain image domain or application context, and also under severe image deformations and degradations.

In [MS04] a thorough analysis of various general keypoint detectors is presented. Most of them are either based on image derivatives, i.e., Hessian or moment matrices. One of the most prominent ones is probably the Harris corner detector [HS88]. Alternative approaches, e.g., rely on evaluation of local image intensity patterns [SB97]. More recently a new class of scale invariant detectors, the Scale Invariant Feature Transform (SIFT) [Low04] and Speeded-Up Robust Features (SURF) [BTvG06], became popular. Compared to explicit spot and local feature detectors these have the advantage that they also detect more and other meaningful image structures. In particular, their scale invariance allows for extraction of characteristic intensity configurations on larger scales, e.g., striking intensity distributions in the images, which yields a larger flexibility in feature extraction.

3 Feature Detection for 2D Gel Image Registration

Our aim in this paper is to provide a thorough performance evaluation of common gel image specific spot detectors, and in particular, to compare those to more general keypoint detectors in the domain of 2D electrophoresis gel images. In detail, we will analyze the robustness of different techniques with regard to non-rigid image deformations and non-uniform image structure distributions as they are typical for gel images. Below, different approaches for feature detection included in our case study are discussed in more detail.

3.1 Spot Detectors

Laplace Detector One of the most simple and fast techniques for spot detection in gel images is given by Laplacian detection (e.g., [R$^+$04, RG07]). Spot centers are modeled as image locations with significant local curvature, detectable in terms of significant values in 2nd order derivatives. The spot detection itself is done by smoothing the image applying a Gaussian mask and then simply thresholding the Laplace images ∂_x^2 and ∂_y^2:

$$f(x,y) = \begin{cases} 1, & \text{if } \ (\partial_x^2(x,y) > t_L) \wedge (\partial_y^2(x,y) > t_L) \ \text{ with } \ t_L = 0 \\ 0, & \text{otherwise} \end{cases}$$

As detected spot locations are usually not isolated, connected components are extracted from the binary image f, and only their mass centers are kept as valid locations (Fig. 2).

Ring and Ellipse Operators The ring operator proposed in [WTN97] for spot detection is based on the assumption that spots usually show a circular or elliptical shape, with the inner parts of the ellipse being darker than the outer ones. Related structures are detected by initially smoothing the gel image with a Gaussian mask, and then applying Otsu thresholds to the original image intensity values, and also to local gradient magnitudes.

In the resulting two binary images all pixels (x,y) that show a low intensity and lie in homogeneous image regions are further analyzed. The main idea is to search for spot-specific intensity distributions given two sets of pixels, $C_{x,y}$ and $R_{x,y}$, for each (x,y):

$$\begin{aligned} C_{x,y} &= \{(u,v) | (u-x)^2 + (v-y)^2/\alpha^2 \leq r_M^2\} \\ R_{x,y} &= \{(u,v) | r_m^2 \leq (u-x)^2 + (v-y)^2/\alpha^2 \leq r_M^2\} \end{aligned}$$

$C_{x,y}$ includes all pixels lying in an elliptical region (specified by α) around pixel (x,y) with distances up to r_M to the center pixel (x,y), while $R_{x,y}$ contains only the pixels of $C_{x,y}$ with a distance of at least r_m to the center. The ring detector itself is then given by

$$h(x,y) = \min_{(u,v)\in R_{x,y}} I(u,v) - \min_{(u,v)\in C_{x,y}} I(u,v).$$

For final spot detection, h is thresholded with $t_H = 0$, connected components are labeled in the resulting binary image, and spots are extracted as the components' centers of mass.

Level Lines and Meaningful Boundaries The concept of meaningful boundaries defines a measure of meaning for closed curves based on the Helmholtz principle [A$^+$07].

The level lines of the lower gray level sets are extracted from a 2D gel image and examined for their meaning to derive meaningful level lines and by this detect spots. The meaning of a level line is determined by its length and the probability of occurence of a contrast in the image, which is larger than the minimal contrast on the level line. Meaningful level lines are reduced to one contour per spot, and the enclosed area determines the position of the spot by its center of mass (Fig. 2, right clip).

3.2 Image Content Independent Feature Detectors

If no assumptions about image contents and structures can be made, feature detectors independent of such knowledge are needed. Optimally, these are invariant against scale and transformations. Recently, two such scale invariant keypoint detectors were published, the Scale Invariant Feature Transform [Low04] and Speeded-Up Robust Features [BTvG06]. Both are quite robust against affine transformations and gained large importance due to their proven general applicability in various scenarios. In the context of our study we evaluate their robustness with regard to the domain of 2D gel images, and regarding non-rigid transformations which has not been done systematically until now.

SIFT - Scale Invariant Feature Transform The basic concept of SIFT [Low04] is a thorough analysis of image characteristics in scale space. Different scales are acquired by downsampling the input image $I(x, y)$ applying Gaussian convolution kernel functions $G_\sigma(x, y)$ of specific standard deviation σ:

$$I_\sigma(x, y) = G_\sigma(x, y) * I(x, y)$$

Combining different scales of an image into a continuous function of scale yields the image *scale space*. Between neighboring scales σ is varied by a constant factor k. Keypoints are then given by local extrema in the difference images $D_\sigma(x, y)$ between two subsequent scales:

$$D_\sigma(x, y) = I_{k\sigma}(x, y) - I_\sigma(x, y)$$

For extrema detection, the difference value $D_\sigma(x, y)$ of each point (x, y, σ) in scale space is compared to all neighbors in a $3 \times 3 \times 3$ neighborhood. By fitting a 3D quadratic function to the local point the extremum can be localized with subpixel accuracy (Fig. 2, left).

SURF - Speeded-Up Robust Features More than SIFT the SURF approach is tuned for efficiency, but the features nevertheless show a high stability [BTvG06]. The main idea is given by an analysis of local Hessian matrices $H(x, y, \sigma)$ over various scales:

$$H(x, y, \sigma) = \begin{bmatrix} L_{xx}(x, y, \sigma) & L_{xy}(x, y, \sigma) \\ L_{yx}(x, y, \sigma) & L_{yy}(x, y, \sigma) \end{bmatrix},$$

where $L_{..}$ are the results of convolving the input image with 2nd order Gaussian derivatives in xx, yy, xy and yx direction, respectively. However, for efficiency reasons the entries of the matrix are calculated only approximately applying discrete box filters as approximations to the Gaussian derivative kernels. Convolutions with box filters can quite efficiently be calculated given integral images. In addition, in contrast to usual scale space approaches, the images are not resampled within a pyramid, but detection results for various scales are produced by simply applying differently sized filters to the input image.

In SURF robust keypoints are defined by maximal determinant values of local Hessian matrices. Accordingly, detection is done by searching for maximum determinants. Initially a non-maximum suppression in a $3 \times 3 \times 3$ neighborhood of each point is performed, and maxima locations are interpolated in scale and space, like in the SIFT approach (Fig. 2).

4 Experimental Evaluation

Evaluating the efficiency of spot and keypoint detectors, respectively, is a difficult task. The main problem is usually a lack of ground truth data with known corresponding feature point locations. Accordingly, one common approach is to generate synthetically deformed images from a given reference image by applying a known transformation so that correspondences can be calculated directly (e.g. [MS04, BTvG06]). Before and after transformation features are then detected in the test images applying different detectors. To assess quality and robustness of the various detectors, meaningful quality measures are used.

Dataset For testing the various feature detection techniques we used a selection of gels from the LECB 2-D PAGE Gel Images Data Sets [LLL84], freely available for public use[1]. In detail we selected 45 images from the Human leukemias data set, each image sized 512×512 pixels in 8-bit GIF format. All images were converted to PGM format and automatically cropped given the annotated valid spot areas within the gels as specified in the complementary description files. Since not all area specifications were accurate and sometimes artefacts remained at the border of images, 10 images were manually post-processed afterwards (cropping, filling of spurious white regions with local background color) to also remove these artefacts and prevent detectors from selecting spurious features.

Categorization of Images The images of the dataset show a wide variety of complexity, ranging from bright images with very few spots to very dark images with lots of structure. To enable a thorough comparison, the gels were manually classified into 4 different complexity classes, where each class contained 7 to 15 images:

- C_0 gels with only some few spots;
- C_1 gels with a moderate number of spots;
- C_2 gels with lots of spots;
- C_3 gels that were quite dark and spot segmentation quite difficult in large areas.

Synthetic Image Deformations using Thin Plate Splines The deformation of 2D electrophoresis gel images is often modelled applying bilinear transformations [SA$^+$02] or thin plate splines [Ped02]. Since thin plate spline (TPS) transformations [Boo89] can take full advantage of the information provided by landmark points [DDY03] we choose this model for our experiments. 25 basis functions were applied to model local and global deformations. For each image, the centers for the 25 basis functions were uniformly sampled in the image domain. For each basis function a displacement vector was drawn from a Gaussian distribution with standard deviation σ_D and zero mean. The standard deviation σ_D was varied to simulate different amounts of distortion of the 2D gels. A global affine transformation was added to these displacements, which again was randomly

[1] http://www.lecb.ncifcrf.gov/2DgelDataSets/

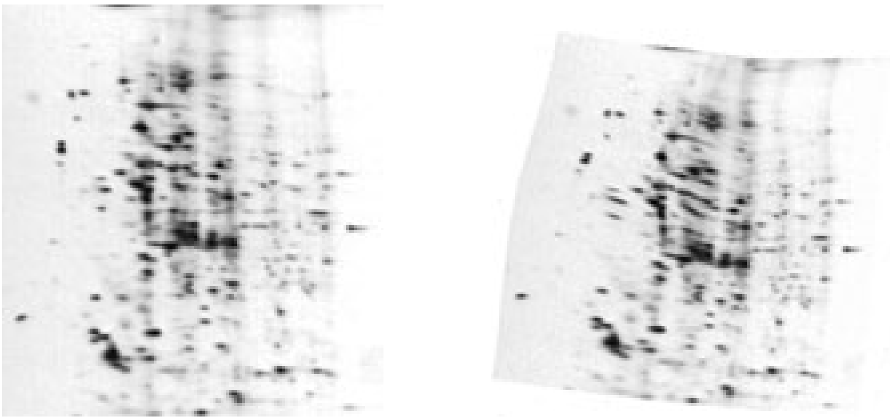

Figure 1: A sample gel from class C_2, undistorted (left) and deformed with $\sigma_D = 4$ (right).

sampled. The rotation was uniformly drawn from the interval $[-10°; 10°]$, the shearing axis uniformly from $[-90°; 90°]$ and the two scale factors uniformly from the interval $[0.9; 1.1]$. Given the resulting displacements for the centers, a TPS transformation was determined and the original image transformed accordingly. To simulate variations in the gray value structure, white noise was added to the interplolated intensities which was sampled independently from a Gaussian distribution with standard deviation 5. For each $\sigma_D \in \{1, 2, 3, 4, 5\}$ we generated 10 randomly distorted images for each original image. This results for each σ_D in an evaluation set of $45 \times 10 = 450$ distorted images. For an example of a distorted gel image see Fig. 1. All images with one distorted image for each distortion level and detected features are available as supplemental material on our server[2].

Performance Measure Comparing the robustness and efficiency of feature detectors is an important task in computer vision, and various performance measures exist. With regard to the topic of this paper we are particularly interested in the *repeatability score* Rs_r of a certain detector (cf. [MS04]). It quantifies the probability of a feature in an undistorted image I to be re-localized in a deformed version I_T of the same image with accuracy r:

$$\mathrm{Rs}_r(I, I_T) \;=\; \frac{|P_T|}{|P_I|} \;\text{ with }\; P_T = \{\, p_t \mid r > \| \, p_i - TPS(p_t) \, \| \} \tag{1}$$

P_I is the set of features p_i detected in the undistorted original gel image, and P_T is the set of features p_t detected in the transformed image, that have a distance not bigger than r to their initial counterparts in the original image after TPS transformation. For the evaluation in this work we used $r = 1.5$ pixels. This value has already proven its suitability in evaluating feature detectors for non-rigid registration, allowing for convenient registration results given the robustness and flexibility of up-to-date feature descriptors (cf. [MS04]) .

Obviously the overall number of final correspondences not only depends on the initially detected features, but also on the subsequent matching process where suitable feature descriptors have to be applied. In this work, we concentrate on robust detection of features as an indispensable prerequisite and fundamental precondition for any matching process.

[2] http://www2.informatik.uni-halle.de/agprbio/AG/Publication/OnlineMaterial/GCB_2008/Gels

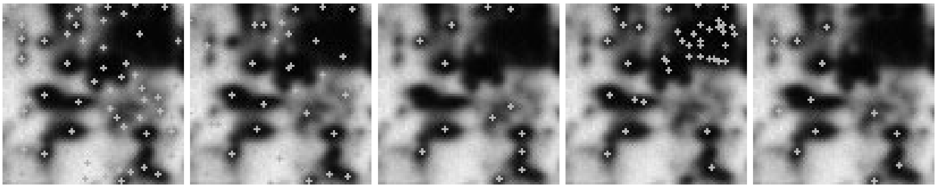

Figure 2: Prototypical detection results for SIFT, SURF, the ring operator, Laplacians and the meaningful boundaries (from left to right) for an image of class C_3. Green crosses mark spot centers.

5 Results and Discussion

Five different spot and keypoint detectors, respectively, were included in our study, i.e., Laplacians ('laplace'), the ring detector ('ring'), meaningful boundaries ('level'), SIFT ('sift'), and SURF ('surf'). For SIFT and SURF we used publicly available software packages, i.e., the free C++ implementation of SIFT by A. Vedaldi[3] and the original SURF library provided by its authors[4]. All other detectors were re-implemented by ourselves.

Each of the detectors was applied to all original images within the four complexity classes and all images within the five distortion levels. All detectors were initially run with standard parameter settings as specified in related publications. The only exception is for the Laplacian detector adopted from [R$^+$04] where the number of spots to be detected was explicitly specified manually. The authors select the 400 most intense spots from their gel images. However, for images in our experiments this number appeared too high, especially for image categories with few spots. The detector is enforced to extract spots even from more or less homogeneous background regions. Hence we chose more suitable spot numbers for each complexity class in our test dataset (Tab. 1).

Detector	C_0	C_1	C_2	C_3
Laplace	100	150	275	300
Ring	13	33	87	226
Level	45	101	153	158
SIFT	247	534	826	1100
SURF	43	148	330	573

Table 1: Avg. number of features detected with standard parameter settings for the gel images in each complexity class C_0 to C_3.

First it is noted that the number of features detected on average in undistorted images varies significantly for different detectors (see Tab. 1 and Fig. 2 for an example of detection results from a clipped section of one gel image). SIFT and SURF almost always extract significantly more keypoints than the spot detectors. The ring operator yields less than 100 spots for classes C_0 to C_2, which is well below the counts for the other spot detectors. As a large number of correspondences and, thus, features is required for precise registration, the keypoint detectors show superior compared to the spot detectors regarding this aspect.

Of course, the total number of features detected is not sufficient for high detector quality. As important is the repeatability score of the detector, i.e., the number of initially detected features that are expected to be re-localized in deformed and degraded images. The repeatability score as defined in Equ. (1) in Sec. 4 relates the number of re-detected features to the number of features detected initially. Accordingly, it is normalized with regard to the

[3]http://vision.ucla.edu/~vedaldi/code/siftpp/siftpp.html
[4]http://www.vision.ee.ethz.ch/~surf/

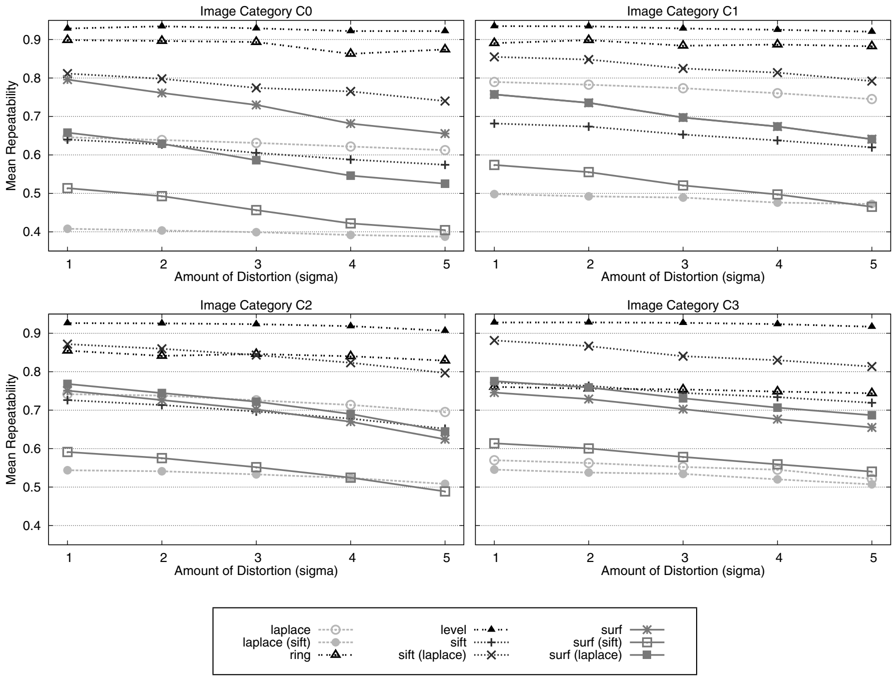

Figure 3: Average repeatability scores per class for various detectors applied to all four complexity classes for varying distortion levels σ.

total number of features. As a consequence, the repeatability scores achieved for different detectors are only comparable if approximately the same number of features was detected. To this end we have performed additional evaluation runs where the parameters for SIFT, SURF and Laplacian detectors were adjusted to yield approximately the same number of features. The ring detector and meaningful boundaries were not included since there is no reasonable way to adapt them for detecting comparable numbers of features.

The results of our experiments are summarized in Fig. 3. For each class the mean repeatability scores for each detector are plotted, calculated by averaging the detection results for all images of a class with a given distortion level. The graphs 'sift', 'surf', 'laplace', 'ring' and 'level' give results for experiments with standard parameter settings. For SIFT, SURF and Laplace there are additional curves in each plot, related to non-standard parameter settings. For 'sift(laplace)' and 'surf(laplace)' both detectors were adjusted to detect the same number of keypoints as the Laplace does for its standard settings. Likewise 'laplace(sift)' and 'surf(sift)' give the results for both detectors parameterized to yield the same high number of features that SIFT detects with default settings (cf. Tab. 1 for exact numbers).

For standard parameters, the meaningful boundaries give a repeatability of about 90% for all configurations, the ring operator yields also about 90% for categories C_0 and C_1, which drops to about 75% for C_3. SIFT and SURF show performances in the range of about 60% to 80%. The standard repeatability score of Laplace for categories C_0 to C_2 is comparable to the ones of SIFT and SURF, and drops to $55-50\%$ for category C_3.

Adjusting SURF to detect the same number of feature points as SIFT, which results approximately in doubling the number of keypoints, reduces its performance significantly to about $45 - 65\%$. Accordingly, considering both the total number of detected features and the repeatability score, SIFT appears to have advantages over SURF, independent of the image category. For the Laplace detector, the repeatability goes down to about $40 - 55\%$, particularly for images with little structure as in categories C_0 and C_1. This is not surprising, but underlines the superiority of standard SIFT in these classes. It becomes obvious that the Laplace detector is by no means suitable for detecting large numbers of features.

Restricting the feature number of SIFT to the smaller number of the Laplace detector yields significant improvements of the repeatability which increases by $\approx 15 - 20\%$ in each category. In contrast, if SURF is restricted to the same number of features its repeatability remains more or less unchanged except for category C_0, where it declines significantly[5].

In general, our evaluation results show that the image category has little influence on the repeatability scores of the various detectors, but mainly yields significant differences in the total number of detected feature points. Increasing the amount of distortion has also little influence for the meaningful boundaries and ring detector, but decreases the performance for the others of about 10%. If only the repeatability is considered, the meaningful boundaries and ring detector yield the highest scores and the largest robustness. Contrary, if a large number of robust features is required general scale invariant detectors, in particular SIFT, appear favorable compared to explicit spot detectors. Given their repeatability scores they form a suitable foundation for extracting a large number of robust feature correspondences essential for high-quality feature-based gel image registration.

6 Conclusion

In current approaches for feature-based registration of gel images, correspondences are almost always based on protein spots as domain inherent features. The first contribution of this paper is a novel systematic quantitative analysis of various commonly used spot detectors. It allows for an objective evaluation of the detectors with regard to stability and repeatability. Secondly, we propose the application of more general keypoint detectors for feature extraction, i.e., SIFT and SURF. Compared to explicit spot detectors a significantly larger number of features per image is extracted on average with a likewise higher repeatability. Since large numbers of stable features yield an important basis for robust correspondence detection and also high-quality image registration, SIFT and SURF show advantages over conventional techniques and should no longer be ignored in this field.

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