Automatic Measurement of Skin Wheals Provoked by Skin Prick Tests

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Abstract

Skin prick tests (SPT) represent the standard method for the diagnosis of type-1 allergies. The skin wheals provoked by the SPTs are considered positive above certain cut-off diameters, usually 3 mm. At present their size is mostly estimated by measuring the diameter with rulers. Since the shape of wheals usually is not circular, the measurement of diameters leads to imprecise results. Therefore, we developed an algorithm for precisely measuring the wheals' area in mm^2 automatically. The average deviation of the automatic measurement on a test set achieved with the developed algorithm was 6.9 %. Compared to the maximum standard deviation of 6.59 % when measuring the manually redrawn outlines, the automatic method works sufficiently well.

Keywords:
Allergy, urticaria; Skin prick test; Mathematical morphology; Computer-assisted diagnosis; Methodology

1. Introduction

For the diagnosis of type-1 allergies, skin prick tests (SPTs) are applied to the patient's volar forearm. As a preparation, the forearm is marked with a skin-marking pen corresponding to the number of allergens to be applied. After applying the allergens dissolved in aqueous solution onto the skin, each drop is pricked with a standardized, sterile metallic lancet through the drop to provoke a specific dermal reaction described as wheal or hive. The wheal appears as a circumscribed edema of the skin with a characteristic reddened adjacent area. Since it can also be provoked by urticaria stinging, it is also termed an urticarial lesion. After leaving the allergenic solution on the skin for 15 to 20 minutes, the drops are wiped off. The outline of the possibly provoked skin wheals are marked with the skin-marking pen. A standard translucent adhesive tape is sticked onto the marked outline and pulled down again. This way the marker is transferred to the tape. Finally the tape is put on a documentation form.

The wheal size has been demonstrated to correlate with activity of allergic diseases. The measurement of wheal size has therefore been applied in a lot of study settings [1-3]. At present only the wheals' diameter is measured. Some physicians determine the average of the maximum and minimum diameter for estimating the allergic reactions [4].

There has been done some work on determining wheal sizes automatically already [5-7]. These works proved that measuring wheals automatically is an adequate method. We intended to develop an easy-to-use tool for the precise calculation of wheal sizes. The tool

should easily integrate into the usual SPT flow of work and should be based on standard computer equipment. Therefore, we decided to use the common skin prick test procedure of outlining the wheals' border with a blue coloured pen and transferring the borders' shape to a form. We implemented an application which scans the documentation form and automatically detects wheals, strokes and empty SPT areas and measures the wheals' area in mm^2.

2. Material and Methods

For the development of the algorithm we used the Khoros Pro 2001 development environment for image analysis applications developed by Khoral Incorporated. Khoros has been installed on a standard 800 MHz Linux PC[1]. The algorithm was based on methods of mathematical morphological image analysis operations [9] and therefore, the MMach-package for Khoros was used [10]. The forms were scanned with a resolution of 200 dpi on a standard HP ScanJet 7400 C.

2.1. Documentation form

For being able to automatically detect the wheals provoked by the various allergens we decided to design a new documentation form onto which all adhesive tape stripes with the transferred wheals' outlines have to be put on (***Figure 1***). Since usually the form is not positioned precisely upright onto the scanner (***Figure 2***) we attached two black dots to the form at the upper left and the lower right corner. These dots are automatically detected by our algorithm after the scanning process. The form is moved and rotated correspondingly to obtain a precisely upright positioned form necessary to for further processing (***Figure 3***). The small boxes at the lower right corners of the SPT-areas are used for marking the clinical relevance of the allergic reaction.

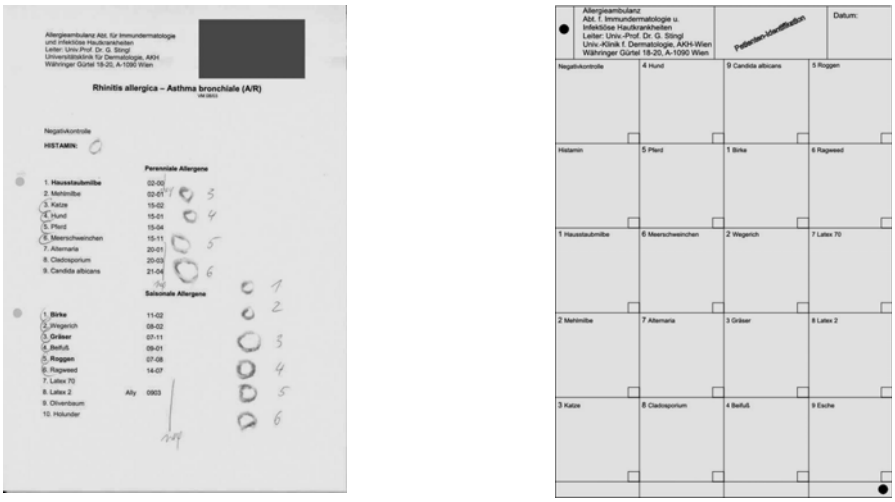

Figure 1 - Old versus newly designed form. The old form shows a "chaotic" order of wheal outlines making it impossible to perform measurements automatically. On the new form the outlines are put on at predefined areas. Two black dots were attached for being able to position the form exactly after the scanning process. The small boxes at the lower right of the SPT areas are used to mark the test's clinical relevance.

[1] In the meantime Khoros has been taken over by Accusoft Corporation and has been renamed to VisiQuest [8].

The two black dots at the form's upper left and lower right corner are detected by their shape and size. By eroding and subsequently conditionally dilating the image with a circular structure element all dots larger resp. smaller than the structure element are removed. Only the two marker dots remain visible. The angle between the connection of the detected dots' centres and a vertical line is measured. The form is rotated by the difference between the ideal angle and the measured angle. Afterwards the position of the upper left dot is redetected and the entire form is relocated to the ideal position. As long as both marker dots are visible on the scanned image the algorithm is able to ideally reposition the form.

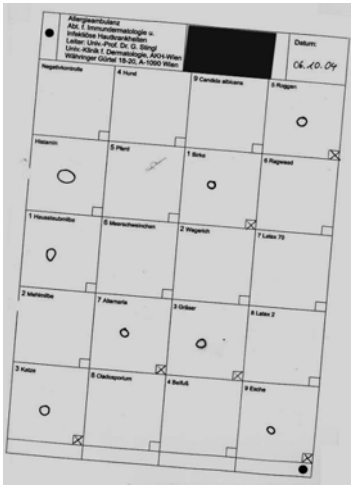

Figure 2 - The form has been put onto the scanner imprecisely.

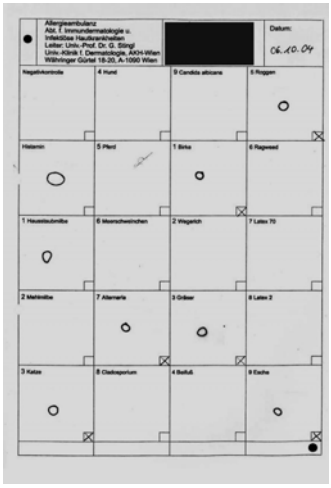

Figure 3 - By detecting the black dots the algorithm is able to correct the position of the form to obtain a precisely upright positioned form.

Extraction of SPT areas

After positioning the form exactly the individual SPT areas are extracted via their well known coordinates (***Figure 4***). The outlines of the wheals have been marked with a blue coloured marking pen. Thus, by extracting the blue channel of the SPT area images, the black coloured area contours including the small box at the lower right are excluded (***Figure 5***).

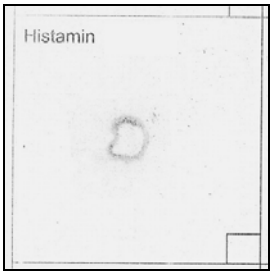

Figure 4 - An SPT-area has been extracted. The border of the area and the small box at the lower right are still visible.

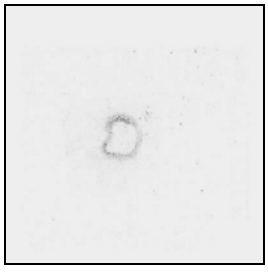

Figure 5 - The SPT-area's blue colour channel has been extracted. The black borders around the SPT area and the label have disappeared.

Detection and Measurement of wheals

The extracted SPT-areas are inspected one after the other. The area to examine is limited to the wheal's actual extension by detecting the wheal's minimum and maximum coordinates.

These coordinates are extended by a safety margin to be sure not to cut off the wheal's outer border (***Figure 6***). The wheal's border is condensed by a mathematical closing operation. Thus, fine gaps are closed (***Figure 7***). To be able to close larger gaps the border is watersheded to obtain the wheal's middle contour (***Figure 8***). The middle contour is dilated and superimposed on the closed border (***Figure 9***). By applying this procedure large gaps in the wheal's border contour are appropriately reconstructed. A threshold has to be found dynamically to obtain a closed binary border contour. This is achieved by increasing the threshold stepwise starting from a minimum value until a closed border emerges (***Figure 10***). Since the wheal's outer border has been outlined on the patient's arm the inner contour of the border resembles the actual wheal's area. The inner contour is extracted by dilating the border and subtracting the dilated border from the thresholded border. The resulting contour is smoothed to remove peaks which do not resemble manually drawn outlines (***Figure 11***).

The number of pixels inside the extracted contour is measured and converted to mm^2 by considering the scanning resolution.

Figure 6 - The actual area of the wheal (ROI) has been extracted.

Figure 7 - A mathematical closing operation has been applied to the original wheal border.

Figure 8 - The closed wheal border is watersheded to obtain the wheal's middle contour.

Figure 9 - The wheal's dilated middle contour is superimposed on the closed wheal border to fill larger gaps of the wheal border.

Figure 10 - The resulting grey level border is dynamically thresholded to obtain a closed wheal border.

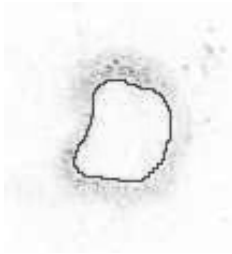

Figure 11 - The inner contour of the border is extracted and smoothed.

When an allergen is not applied to the patient's skin a blue coloured stroke from the lower left to the upper right is manually drawn into the assigned SPT area directly on the form (***Figure 12***). Our algorithm is able to detect these strokes automatically and indicates that the corresponding test has not been applied. The detection of the stroke is started by extracting the stroke's blue coloured pixels. The regression line of these pixels is calculated and the angle between the regression line and the horizontal line is measured. Regression lines with angle values between 10° and 80° meet the requirements for strokes. The length of the stroke has to be at least 300 pixels and the average distance of the stroke's pixels to the regression line has to be less than 5 pixels. If a set of pixels meet these requirements the test is classified as not applied.

Allergens which do not provoke any allergic reactions to the patient's skin are indicated by leaving the corresponding SPT area empty (***Figure 13***). The algorithm also detects empty SPT areas and indicates that there has been no allergic reaction to the allergen.

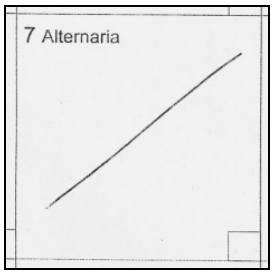

Figure 12 - A manually drawn stroke in a form's SPT area indicates that the corresponding test has not been applied.

Figure 13 - An empty SPT area indicates that there has not been any reaction to the allergen.

3. Results

For evaluating the accuracy of our application we formed a test set of 12 test persons who were treated on both inner forearms with 5 distinct concentrations of histamine ranging from 1:1 to 1:100. Histamine is the main mediator secreted by skin mast cells after activation with allergen and causative for the dermal reaction described as wheal. For each skin prick test, it is used as a positive control to demonstrate skin reactivity that can be hampered by inadvertent intake of drugs with antihistaminic side effects such as antidepressants. We preferred histamine to real allergen for the evaluation of this system, because it produces reproducible wheals also in non-allergic subjects. The overall number of provoked wheals was 111. To obtain the actual wheals' area the outlines were manually redrawn and measured with the image processing software ImageJ [11]. Each wheal was redrawn 3 times by the same physician. The average of the 3 measurement was taken. The standard deviation of the areas derived by the manual outlines was up to 6.59 %. The average deviation of the automatic measurement on the originally scanned forms was 6.9 %. We observed a few runaways with deviations above 20 % which nevertheless resembled the actual outline sufficiently well. Thus, the average deviation of the automatic measurement was only slightly higher than the maximum average deviation of the manual measurement. Similar to [5] we observed higher deviations from the actual size at small wheals < 5 mm^2. We achieved some improvement by enlarging these wheals by a factor of 1.5 to 3.0 for the reconstruction of their border and reducing them again for measuring their size.

The application was also applied to a set of 126 prick tests with allergens in allergic individuals at which the wheal outlines were manually redrawn with a blue coloured pen directly on the form. Only slight parameterizations had to be made to achieve excellent detection and measurement results of these outlines.

The algorithm behaves very stable on varying contrasts and varying intensities of the blue coloured contour on the adhesive tape. By using mathematical morphological operations even larger gaps in the contour are reconstructed very well.

4. Discussion

The accuracy and the stability of our algorithm are very promising and are appropriate for applying it to the routine SPT. The algorithm provides an objective and reproducible

method for measuring wheals. So far we have developed a prototype of the application. The processing speed of the wheal detection procedure has to be improved. The overall processing of an entire form with 20 SPT areas takes about 20 minutes on a standard 800 MHz PC.

5. Conclusion

We have presented an algorithm for processing SPTs automatically which works without any interaction by the user. Wheals, strokes and empty SPT-areas are detected automatically. The area of wheals is measured precisely. The algorithm is appropriate for being integrated into the routine process of performing SPTs. The results of the measurement can easily be transferred to medical documentation systems and thus, provides a completion of the patient history concerning treatment of skin allergies.

6. References

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