33rd Annual International Conference of the IEEE EMBS
Boston, Massachusetts USA, August 30 - September 3, 2011

# Investigation on the Use of Deformable Registrations in Lymph Node Tracking Over Time

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***Abstract*—Evolutionary features of lymph nodes such as change in size over time are decisive descriptors to assess disease progression in cancer patient. Other than study at one point in time, it is more useful to derive temporal analysis on structures of interest. The paper presents the use of deformable registration in lymph node tracking, particularly in the context of disease progression. We found that the extent of disease progression plays an important role in determining the performance of deformable registration in aligning up small anatomic structures, such as lymph node. Both Demons and B-spline registrations have their own advantages in different medical context.**

## I. Introduction

The accurate assessment of lymph node involvement is crucial in making clinical decisions regarding staging and therapy response of lung cancers [1]. While study at one point in time is important, it is more useful to monitor its progression over time. In longitudinal CT (Computed Tomography) scans, evolutionary features of lymph nodes such as change in size over time are decisive descriptors to assess the status of the disease, be it stable or progressive [2]. Under the newly revised Response Evaluation Criteria In Solid Tumors (RECIST) guidelines [2], pathological lymph nodes with a short axis greater than 15 mm are treated as target lesions, unidimensional measurement should be carried out to assess tumor burden. Given the large medical imaging data acquired for a single patient and due to lack of tools, comparison of these studies is currently limited to a visual examination of representative images or simple two axes measurements. Thus it calls for an automated analysis tool which could not only assist the measurement in an accurate and consistent manner, but also provide additional information, e.g. volume, shapes, etc. Toward development of such an integrated temporal analysis system, it requires establishing structural correspondence between images over time so that structures of interest can be tracked and analyzed. In particular, tracking of corresponding lymph node in follow-up images needs to be succeeded to allow subsequent feature analysis and comparison.

In this work, we extend the previous work [3] and take a detailed examination on the use of deformable registration in tracking of small structures in medical images, particularly in the context of disease progression. The results obtained using Demons and B-spline registrations are compared as well.

This work was supported in part by Singapore National Medical Research Council (NMRC) under Grant number NMRC/NIG/1033/2010.

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## II. Methods

Image registration is the process of overlaying two images taken at different times, from different view points, or by different sensors [4]. It can be used to establish a spatial relation between corresponding structures at baseline and follow-up scans. For medical images taken over time, there are several factors which might contribute to variations in image content, namely, i) differences in body positioning, ii) breathing motion and iii) the local movement of lymph node inside body iv) pathological change due to disease progression. The first difficulty, which might involve translation, rotation and scaling, can be corrected by an affine registration. A more flexible deformation method, such as B-spline and Demons, would be suitable to minimize the differences caused by the second and third factors, whose deformation field is more locally defined.

More remarkably, disease progression puts a big challenge for the use of registration method to establish structural correspondence for small structures such as lymph node over time. This is because disease progression usually brings in additional tumor mass or change in lymph node size between two images, which makes the two images to be registered differ in their image content. Consequently, medical image registration becomes an ill-posed problem [5], and it can be extremely difficult to establish structural correspondence between two images. The inherent difference in image content is an unwanted effect for registration and might cause misleading/unrealistic deformation field in a 'forced' manner.

For lung cancer patient undergoing treatment, depending on the extent to which disease progression has caused a major difference in the image content over time, it could play a significant role in deciding the degree of lymph node alignment using deformable registration. Thus the images to be studied were classified into three different groups according to status of disease progression. The first group is lymph nodes which itself and its surrounding do not have significant change, which happens to be cases when treatment was fairly neutral and the disease has somehow stabilized. The second group is those lymph nodes which themselves have undergone significant changes in size over time but the surrounding tissues have remained similar. Here lymph nodes are classified as having significant changes if their absolute area difference over time is more than 25%.

These typically reflect patients' individual response to their respective treatment, where shrinkage in size indicates positive response to the therapy. For the last group of lymph nodes, there is additional growth of tumor mass in the region nearby the lymph node of interest, which has dramatically changed the surrounding environment of targeted lymph node. This occurrence often signifies negative disease progression which requires further medical intervention. Typical examples of the three cases are illustrated in Fig. 1.

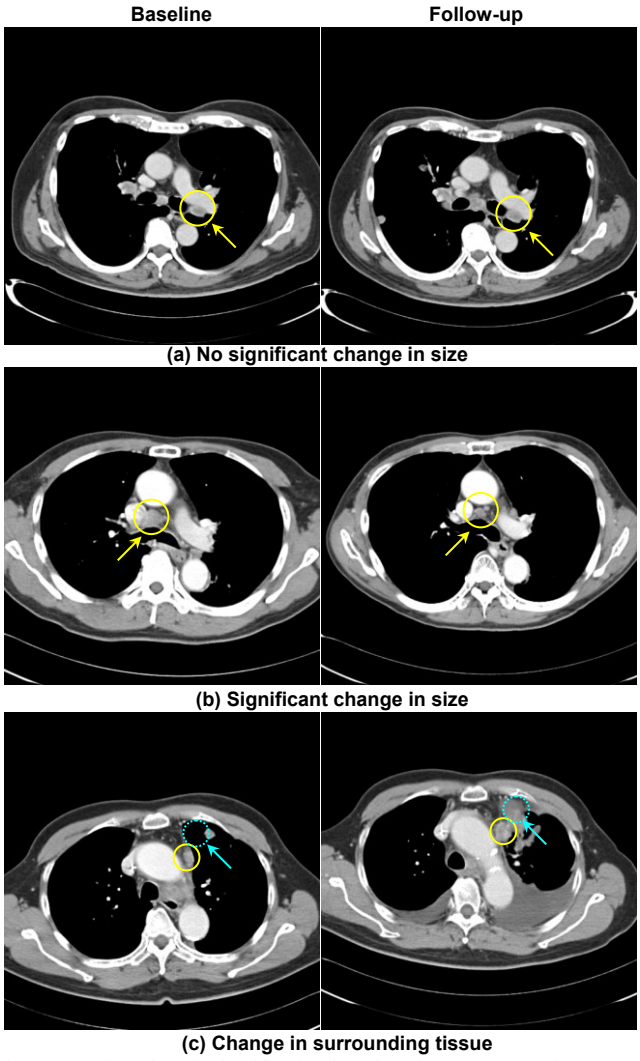


Fig. 1. Lymph node pair classification based on disease progression. (a) No significant change in size, (b) significant change in size, (c) change in surrounding tissues over time. Corresponding lymph nodes of interest are circled in yellow. Dotted blue circles indicate changes over time due to additional tumor growth.

To examine the effectiveness of registration in lymph node tracking in the context of disease progression, the coordinate of lymph node centroid in the baseline image is mapped onto the follow-up image using the deformation found in the registration to estimate the location of corresponding lymph node. Affine registration is applied first to align the two images globally prior to deformable registration. This is used as a mean to prevent local minima in optimization if deformable registration is applied directly to two globally misaligned images. It also alleviates computational burden to optimize over deformable registration for any large deformation to happen. Due to the involvement of regional difference in two medical images over time, deformable registration is required after affine registration as a refinement to handle local deformation. Both B-spline [6] and Demons [7] registrations were investigated respectively. Both were carried out in a multiresolution scheme. For B-spline registration, the number of control points was up to 131×131 in the finest level, with a thin-plate bending energy incorporated to smooth the transformation field. Regularization on demons was achieved through Gaussian filtering. They were implemented by Kroon [8, 9] and made available in Matlab central. The final deformation is the combination of affine and respective deformable registration. The distance from the estimated location to the actual centroid of lymph node in the follow-up image is calculated to assess the accuracy of tracking using respective registration method, as shown in Fig. 2. A closer distance would indicate a better performance of registration to align the lymph node between images over time. The results from B-spline and Demons registration as a refinement are compared to evaluate their respective ability to deal with lymph node tracking in medical images over time, particularly in response to disease progression.

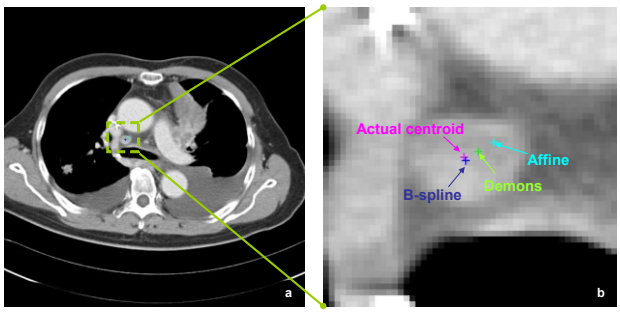


Fig. 2. Example of estimated locations in follow-up image.

## III. Results and Discussion

Retrospective thoracic CT images from 8 patients suffering from lung cancer that were collected over an interval between 3-6 months for longitudinal study were analyzed in this study. The cross-sectional images are of size 512×512 pixels, with a resolution 0.64mm×0.64mm×5mm. Out of the 1440 images examined for lymph node involvement 17 lymph nodes with a major axis longer than 1 cm at baseline were identified by an experienced radiologist for monitoring. In total, 17 pairs of images containing the lymph node of interest were used to investigate the use of deformable registration method for lymph node tracking over time. All lymph nodes in the study are of aortic, mediastinal, interlobar and hilar in their respective anatomic locations.

The follow-up image containing the same lymph node was registered with the corresponding baseline image using affine registration and followed by refinement using Demons and B-spline respectively for the purpose of lymph node tracking. As demonstrated in previous work [3], deformable registration provides a local refinement to affine registration in lymph node tracking. The results showed that all program-estimated points using B-spline refinement were located within the boundary of lymph node of interest at the

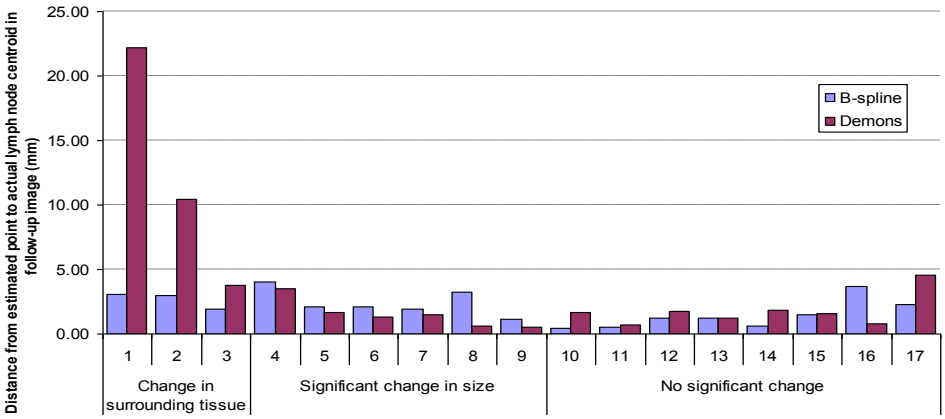


Fig. 3. Comparison between B-spline and Demons registration in lymph node tracking.

corresponding image. On the other hand, 2 out of 17 pairs, the estimated points by Demons fell outside the lymph node boundary. The average distance from estimated point to actual centroid using B-spline registration is 2.01 mm while Demons has an average distance of 3.51 mm. The comparison between two deformable registration methods for individual lymph node pairs is plotted in Fig. 3. As disease progression poses a big challenge for registration to establish structural correspondence, the analysis of results is based on the extent of disease progression.

### *A. No significant change in size*

We can see from Fig. 3 that for lymph node with no significant change over time, deformable registration is quite competent. The performance of B-spline and Demons are similar, and their respective average distance is less than 2 mm. This is because the method only needs to provide minimal local deformation to adjust the alignment of small structures after affine registration has brought large structures into alignment in general.

### *B. Significant change in size*

More interestingly, when there is significant change in size involved over time, the performance of Demons is better than B-spline. This trend is observed consistently among the group. These types of lymph nodes display certain levels of difficulty in deformable registration for lymph node tracking. Because after affine registration has found an overall alignment for general structures, the role of deformable registration is to recognize the minor misalignment of small structures, such as lymph node, and to offer the desirable local deformation to refine the overall image alignment. As Demons registration generally has higher flexibility than B-spline transformation with limited number of control points, this added degree of freedom is useful to improve on the alignment of small structures such as lymph node in the whole image. This is true when temporal change is limited to lymph node alone, so that structural correspondence is relatively easy to establish.

### *C. Change in surrounding tissue*

However, the added degree of freedom by Demons proves to be a disadvantage when it comes to cases where there are changes in surrounding tissues. As shown in Fig. 4, for the case with tumor growth in the surrounding region, Demons registration exerted too much a force on the baseline image, such that the lymph node in baseline almost had been 'torn apart' to resemble the intensity patterns in the follow-up image. However, this forced alignment does not make physical sense and is undesirable. Consequently, the mapped centroid in follow-up image lies far away from the actual lymph node location and results a poor estimation. On the other hand, B-spline registration gives a closer estimation on the location of lymph node in follow-up image by achieving a visually more realistic deformed baseline image. Therefore, when change in surrounding tissue has caused severe mismatch in image content, for example structures present in one but missing in another, it is difficult for deformable registration to recognize the real structural correspondence. More restricted B-spline transformation naturally imposes a good constraint on deformation field to prevent it from going

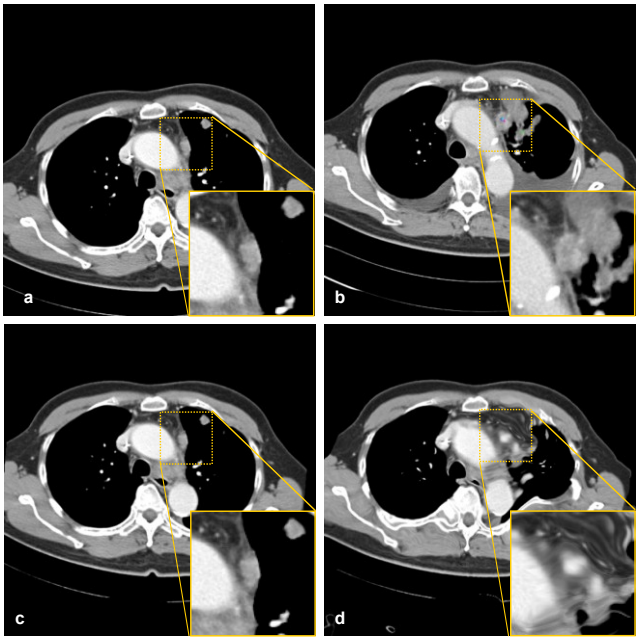


Fig. 4. Registration results for a case with tumor growth nearby. (a) Original baseline, (b) original follow-up, (c) registered baseline image using B-spline, (d) registered baseline image using Demons. Note the unrealistic deformation of the lymph node as a result of Demons registration in (d).

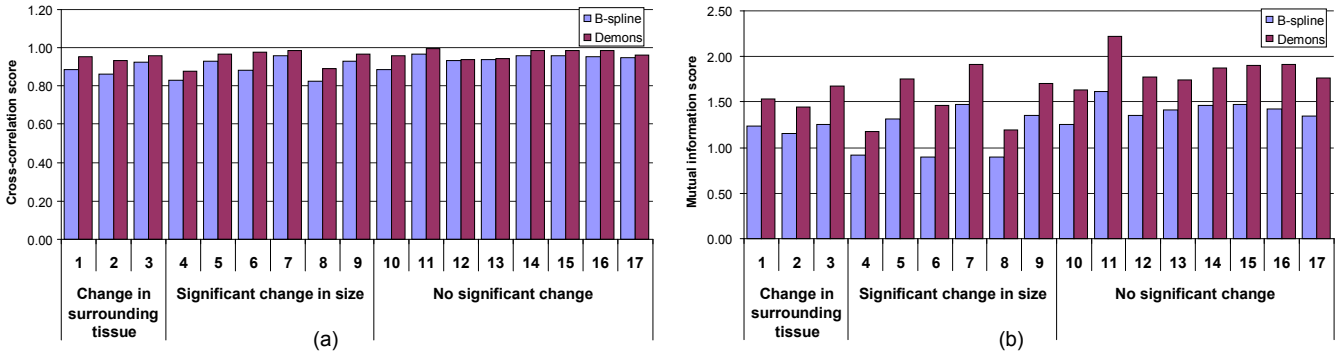


Fig. 5. Similarity scores between target image and registered image using B-spline and Demons. (a) cross-correlation, (b) mutual information.

in an uncontrolled manner. It is important to note that even though some of the deformation fields found in this study were unrealistic, they are acceptable for tracking the location of lymph nodes. If registered image shall be used for measurement purpose, more regularization on deformation field is needed to make physical sense. Overall, B-spline has a small average distance from the actual centroid and suffices to estimate a point inside lymph nodes in follow-up study. It would be interesting to compare the performance of other deformable registration methods in future work as well.

Furthermore, for all pairs of corresponding images, the registered images using Demons had a consistently higher similarity score with the target image in term of cross correlation than those using B-spline, as presented in Fig. 5. The same trend is also observed for mutual information. These suggest a greater flexibility Demons has over B-spline. However, higher degrees of flexibility do not always translate into greater effectiveness in lymph node tracking in terms of closer estimation to the actual centroid location.

Even though tracking of lymph node is done and validated in 2D, we believe the same results can be extended to 3D. The present work conforms to current clinical practice, where quantitative measure of lymph node is carried out manually in 2D slices as the availability of both thin-slice 3D data and means for 3D measurement are limited in clinical settings. Because of its small size, only thin-slice 3D images would allow a reasonable reconstruction of lymph node in 3D so that the work can be validated in 3D. Future work will focus on reconstructing and extracting 3D information for lymph node tracking and measurement. Due to the high variability and complication of medical images over time, a good tracking method should be made to suit different scenarios.

## IV. Conclusion

The characteristics of small structures need to be monitored and analyzed over time in clinical practice to assess disease progression in cancer patients. Other than study at one point in time, it may be possible to integrate multiple studies and automatically derive temporal analysis in structures of interest.

The paper studied the use of deformable registration in lymph node tracking, particularly in the context of disease progression. We found that the extent of disease progression plays an important role in determining the performance of deformable registration in aligning up small anatomic structure, such as lymph node. In overall, both Demons and B-spline registration did well in estimating a close point to the actual centroid when there is no significant structural change over time. But Demons is better when change is limited to lymph node alone. In cases where severe change in surrounding tissues have occurred, more restricted B-spline or even non-deformable registration (such as affine) is a better choice to lymph node tracking.

## Acknowledgment

P. C. Yu would like to thank the university for supporting her Ph.D. study through NTU Research Scholarship.

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