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Karol KUCZYŃSKI[1], Maciej SICZEK[2], Rafał STĘGIERSKI[1]

APPLICATION OF IMAGE REGISTRATION TECHNIQUES IN DYNAMIC MAGNETIC RESONANCE IMAGING OF BREAST

Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is a relatively new, promising technique for breast cancer diagnostics. A few series of images of the same body region are rapidly acquired before, during and after injection of paramagnetic contrast agent. Propagation of the contrast agent causes modification of MR signal over time. Its analysis provides information on tissue properties, including tumour status, that is not available with the regular MRI. Unintentional patient's movements during the examination result with incorrect alignment of the consecutive image series. Their analysis is then difficult, inaccurate or even impossible. The purpose of this work is to design a registration scheme that could be applied to solve the problem in a routine manner, in standard hospital conditions. The proposed registration framework, composed of B-spline transformation, mean squares metric and LBFGSB optimizer, is able to produce satisfactory results within reasonable time.

1. INTRODUCTION

Breast cancer is a vital social problem in most countries of the world. World Health Organization reports that *breast cancer is the leading cancer killer among women aged 20-59 years in high-income countries* [1]. Thanks to development of mammography and ultrasonography (USG), breast cancer mortality has been greatly reduced. It has been proved in recent years that breast dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) offers superior sensitivity [2,3], though is not free from some limitations (including high cost). During a DCE-MRI session, a few series of images of the same body region are rapidly acquired before, during and after injection of paramagnetic contrast agent (usually Gd-DTPA). Propagation of the contrast agent causes modification of MR (Magnetic Resonance) signal over time. Its analysis provides information on tissue properties, including tumour status, unavailable with the regular MRI.

A patient is expected to remain motionlessly inside a scanner during the whole session. For some of them can it be hard due to uncomfortable position, claustrophobia or other factors. Unintentional movements result with breast deformation and misalignments between consecutive sequences of images. Cancer diagnostics either looses accuracy or becomes waste. Repetition of the whole imaging session is time-consuming, expensive, not always possible and does not guarantee a success. The most rational solution is thus to perform image registration procedure. It is intended to find a geometrical transformation that relates corresponding points in both images.

The purpose of the presented work is to design, tune and test a registration scheme that could be successfully used in a routine manner, with not always perfect data acquired in a hospital. It has to be fully automatic, reliable and accurate enough. It is also desirable to run fast enough not only on a very high performance machine, but also a typical desktop PC.

[1] Maria Curie-Skłodowska University, pl. M. Curie-Skłodowskiej 1, 20-031 Lublin, Poland.
[2] Ministry of Interior and Administration Hospital, ul. Grenadierów 3, 20-331 Lublin, Poland.

2. MATERIALS AND METHODS

2.1. IMAGE DATA

The data collection currently available for the authors consists of more than 100 DCE-MRI breast examinations. The main (dynamic) part of every imaging session consists of six consecutive image sequences showing the same body fragment. Each sequence consists of about sixty T1 FATSAT axial slices. Their size is 512 by 512 pixels. Every slice is timestamped. An example fragment of a dataset is shown in Fig. 1. A vast majority of the images is perfectly aligned (thanks to patient's positioning system inside the scanner) and does not need any registration, but a few percent of the datasets may be problematic.

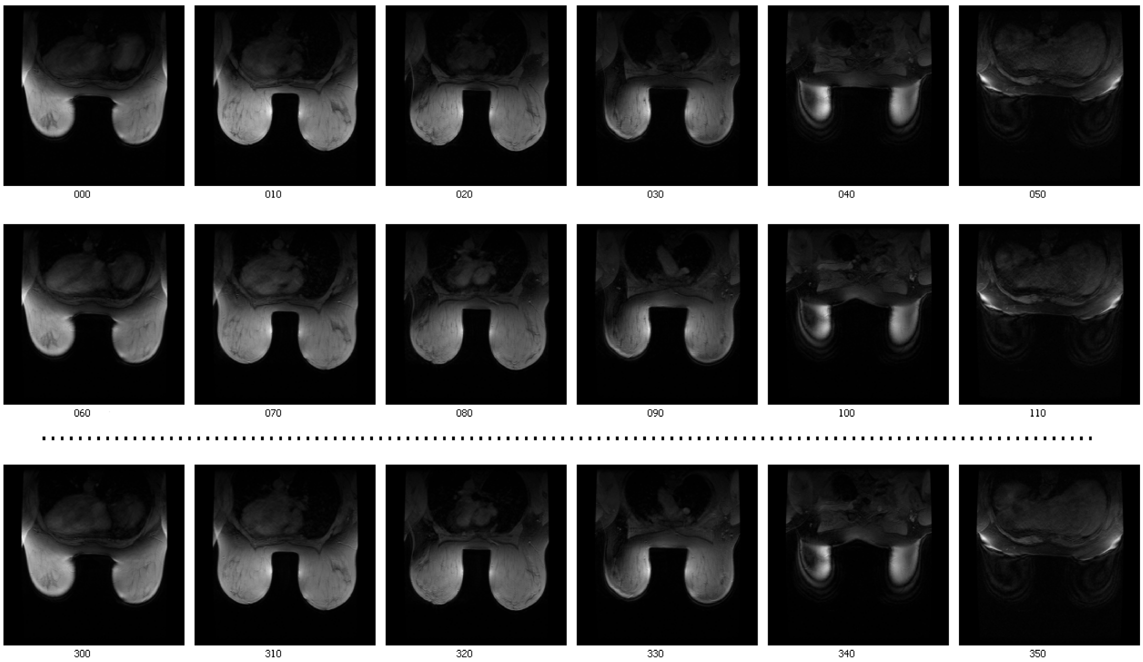


Fig. 1. Selected slices from three (1^{st}, 2^{nd} and 6^{th}) image sequences from a single imaging session.

The whole registration task can be decomposed into five subtasks. The first sequence is usually treated as a fixed image. Sequences 2nd to 6th are treated as moving images and are registered to the first one. All the final images are then composed into a new DICOM dataset. The timing information and other study details need to be preserved in order to analyse the DCE-MRI data.

2.2. REGISTRATION ALGORITHMS

A rich variety of image registration techniques is currently known [4-8]. Most of them are general-purpose algorithms, used not only in medical imaging. Any registration procedure can be decomposed into the following building blocks:

- geometrical transformation,
- similarity measure (optimisation criterion),
- optimisation routine,
- interpolator.

They need to be properly elected, according to the given registration problem.

In the presented task, subtle local deformations are expected, rather than large rotations, translations, scaling or shearing distortions. It has been shown that deformable transform using a B-spline

[9] representation is appropriate for breast image registration [10,11]. B-spline is a parametric curve of degree n, composed of basis B-splines of degree n:

$$S(t) = \sum_{i=0}^{m-n-2} \mathbf{P}_i b_{i,n}(t), t \in \langle t_n, t_{m-n-1} \rangle \tag{1}$$

t_i values are knots:

$$t_0 \leq t_1 \leq \ldots \leq t_{m-1} \tag{2}$$

and $\mathbf{P}_i$ are control points.

A coarse grid of nodes is associated with an image. Knowing deformations of the node points, a deformation vector for any image point can be then calculated, using B-spline interpolation. Actually, additional 3 nodes are required as a finite support region for the B-spline computation. For example, in order to create a 3D 5×5×5 grid of nodes within an image, 8×8×8 grid needs to be created. The transformation is then described by 1536 parameters (3 parameters per node in a 3D grid) that are to be found.

Image registration is an optimization problem, so it is necessary to implement a metric, to measure how well images are matched, according to current transformation parameters. If it is possible to locate some corresponding points in the two images, then sum of distances between them is to be minimized. Either artificial markers or natural structures can be used. In the presented application, this approach is useless due to nature of tissue and its deformation. It is necessary to use a similarity measure that operates directly on image data. In case of multi-modality registration (where correspondence between greylevels in both images is not evident), mutual information may be employed:

$$I(X,Y) = H(X) - H(X \mid Y) \tag{3}$$

H denotes entropy and X, Y are images that are treated as random variables. Various methods of images' mutual information evaluation [4] are commonly applied. This option has to be considered, because pixel intensities change during the session, according to concentration of the contrast agent. In the presented solution, implementation proposed by Mates [11] has been tested.

On the other hand, if intensity changes are negligible, then simple mean squares metric may be adequate [12]:

$$MS(X,Y) = \frac{1}{N} \sum_{i=1}^{N} (X_i - Y_i)^2 , \tag{4}$$

where X_i and Y_i are pixel intensities on i-th position in images, composed of N pixels.

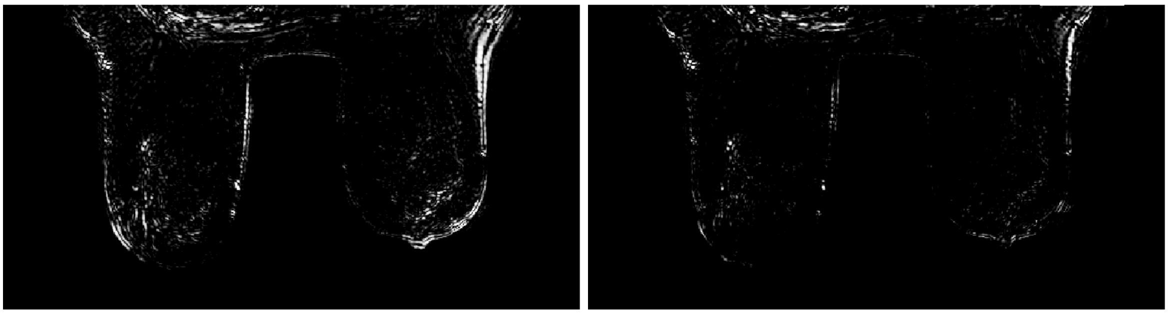
The interpolator evaluates intensity values at non-grid positions of the moving image. Linear interpolation has been implemented.

The optimization process is done with LBFGSB [13] algorithm in the presented system. It is a general-purpose optimizer, commonly used for bound constrained problems with a large or a very large number of parameters.

The final, usually performed step, is a transformation of the moving image, using the final parameters. The moving image is resampled using linear interpolation and saved in the fixed image space.

The software has been implemented in C++ language (GCC compiler), using ITK library [12] for image processing. Multithreading features, described later, are based on Boost library (http://www.boost.org/).

3. RESULTS



a) b)

Fig. 2. Difference images (pixel-wise squared difference between corresponding slices); number of bright pixels corresponds to misregistration level; a) before the registration, b) after the registration.

Fig. 2a presents pixel-wise squared difference between corresponding images from two sequences in one of the problematic sessions. The patient's shift is well visible (bright pixels). Fig. 2b presents the same slices after the registration process. Difference between the images is greatly reduced. The achieved accuracy was good enough to perform further analyses.

Splines of order 3 have been used in all the experiments. Mean squares metric was used as the similarity measure. The grid size was between 4 and 10 nodes in one dimension within the image. Using more grid nodes results with better registration accuracy, for the price of considerably longer computing time. This relation is illustrated by Fig. 3. Accuracy is measured by number of dark pixels in the difference image. Using a 5-node B-spline grid, the registration time was between 1 and 3 hours per one image pair, depending on misregistration extent and image properties (Intel™ Core® i5 M520, 2.4 GHz computer; registration performed in a single thread). The five registration subtasks can be performed either sequentially or in parallel threads (implemented with Boost.Thread library). The real computation time in these two schemes is presented in Fig. 4.

The registration has been performed also using mutual information. The achieved accuracy was not superior to the one using mean square metric. The computing time for a single image pair was about 5 hours for the grid size of 5, and 7.5 hours for the grid size of 7. In this case it is problematic to register all the five images in parallel threads on a single PC, due to high memory requirements (about 4GB of RAM per single image pair registration).

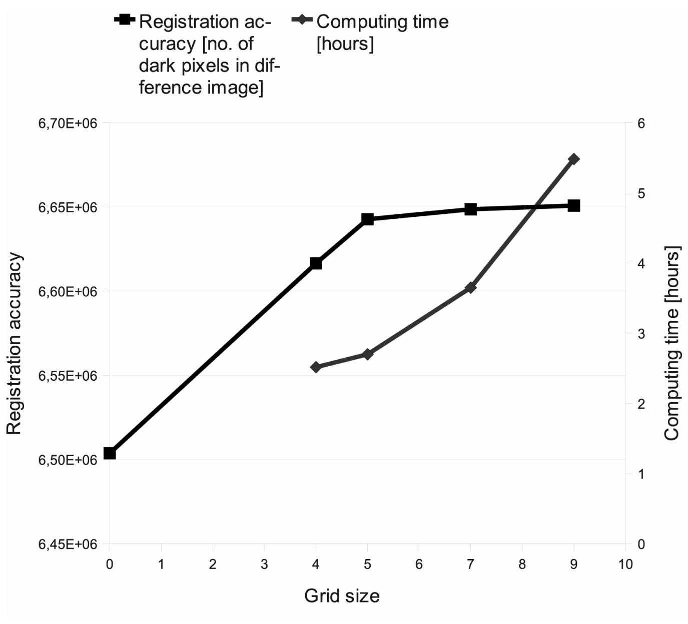


Fig. 3. Registration accuracy and computing time versus grid size.

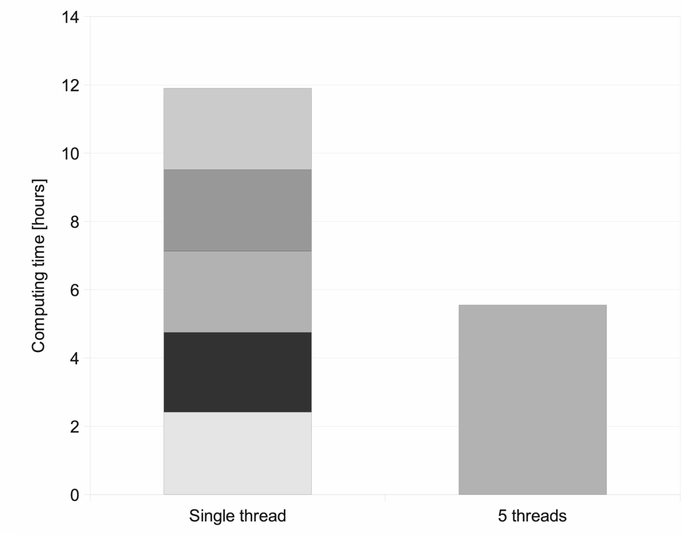


Fig. 4. Computation time of five registration subtasks performed sequentially in a single thread or in parallel, using multiple threads on a quad-core processor (Intel™ Core® i5 M520, 2.4 GHz) computer.

4. DISCUSSION

The registration process was successful using both mutual information and mean squares metric, despite the fact that some pixel intensities vary during the session. Mutual information estimation is much more computationally and memory intensive, but did not provide superior results in the examined datasets.

According to the presence of bright pixels in Fig. 2b, the registration is not perfect. However, the resulting misregistration regards mainly the large scale movements related to heartbeat and breathing that do not need to be corrected in this application. Pixel intensity change due to contrast agent action is also reflected.

The next problem is to set the optimal grid size for B-spline transformations. Adding more nodes results with better accuracy but costs more processing time. It is necessary to find a trade-off between required accuracy and acceptable computing time. According to Fig. 3, increasing the grid size over 5 nodes is in most cases unprofitable. Increasing it up to about 10 nodes may be necessary only for especially complicated cases, with misregistration resulting from multiple movements. Processing time can be greatly reduced by limiting registration process to the region of interest only, but it has to be manually selected by a doctor. Among other aspects, the optimizer's stop criterion (gradient tolerance) should be considered. Registration accuracy is also limited by the fact that usually voxel size along *z* axis is considerably larger than in *xy* plane and intensity approximation is needed. To sum up, the accuracy in the region of interest of most of the tested images was satisfactory and made performing of the desired DCE-MRI analyses possible.

The major part of ITK [12] image registration procedures is executed in a single thread. Most of modern PCs have at least two CPU cores. Whilst a single task consists of five independent image pairs registrations, it is reasonable to run them in parallel, in five threads. The time gain is presented in Fig. 4. Multithreading usage on a quad-core processor has reduced the computing time by more than 50%. It makes both the accuracy and the computing time acceptable for the hospital the example data comes from, considering that not more than a few breast DCE-MRI examination are performed per week.

Selection of datasets that do need to be registered is also a problematic task. Except for evident cases, it is not trivial to distinguish between misalignments that are acceptable or should be corrected. In authors' opinion, it is reasonable to perform a registration process on all datasets. If images are initially properly registered, then the optimisation procedure relatively quickly converges to the identity transform.

5. CONCLUSION

DCE-MRI examination procedure is quite complicated, time consuming and expensive (compared for example to USG). Its result is very valuable diagnostically. However, the final result can be easily destroyed by patient's movements during a session. Application of a registration procedure gives a chance to restore proper image alignment. Because of these facts, registration of breast DCE-MRI images is a problem that needs to be addressed.

It has been shown that it is possible to successfully register DCE-MRI breast images using a typical, modern PC (preferably with a multi-core processor), assuming that the algorithms have been properly chosen, adjusted and implemented according to particular needs. The proposed registration framework, composed of B-spline transformation, mean squares metric and LBFGSB optimizer, is able to produce satisfactory results within reasonable time.

6. ACKNOWLEDGEMENT

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BIBLIOGRAPHY

[1] World Health Organization, Women's health, Fact sheet No. 334, November 2009, http://www.who.int/mediacentre/factsheets/fs334/en/.

[2] OJEDA-FOURNIER H., COMSTOCK C.E., MRI for breast cancer: Current indications, Indian J. Radiol. Imaging 2009, Vol. 19, pp. 161-9.

[3] LI X., DAWANT B.M., WELCH E.B., CHAKRAVARTHY A.B., FREEHARDT D., MAYER I., KELLEY M., MESZOELY I., GORE J.C., YANKEELOV T.E., A Nonrigid Registration Algorithm for Longitudinal Breast MR Images and the Analysis of Breast Tumor Response, Magn. Reson. Imaging, Vol. 27, No. 9, November 2009, pp. 1258-1270.

[4] VIOLA P., WELLS W.M., Alignment by Maximization of Mutual Information, International Journal of Computer Vision, Vol. 24, No. 2, 1997, pp. 137-154.

[5] ZITOVA B., FLUSSER J., Image registration methods: a survey, Image and Vision Computing 21, 2003, pp. 977-1000.

[6] MAINTZ J.B.A., VIERGEVER M.A., A Survey of Medical Image Registration, Medical Image Analysis, Vol. 2, No. 1, 1998, pp. 1-37.

[7] GOSHTASBY A., 2-D and 3-D Image Registration for Medical, Remote Sensing and Industrial Applications, Wiley Press, 2005.

[8] KUCZYŃSKI K., MIKOŁAJCZAK P., Information theory based medical image processing, Opto-Electronics Review, Vol. 11, No. 3, Warsaw 2003, pp. 253-259.

[9] UNSER M., Splines: A Perfect Fit for Signal and Image Processing, IEEE Signal Processing Magazine, Vol. 16, No. 6, November 1999, pp. 22-38.

[10] RUECKERT D., SONODA L.I., HAYES C., HILL D.L.G., LEACH M.O., HAWKES D.J., Nonrigid registration using free-form deformations: Application to breast mr images, IEEE Transaction on Medical Imaging, Vol. 18, No. 8, 1999, pp. 712-721.

[11] MATTES D., HAYNOR D.R., VESSELLE H., LEWELLEN T.K., EUBANK W., PET-CT image registration in the chest using free-form deformations, IEEE Trans. on Medical Imaging, 22(1), January 2003, pp. 120-128.

[12] IBANEZ L., SCHROEDER W., NG L., CATES J., The ITK Software Guide, Second Edition, Updated for ITK ver. 2.4, 2005, http://www.itk.org.

[13] BYRD R.H., ZHU C., NOCEDAL J., L-bfgs-b: Algorithm778: L-bfgs-b, fortran routines for large scale bound constrained optimization, ACM Transactions on Mathematical Software, Vol. 23, No. 4, November 1997, pp. 550–560.