Effective 2D-3D Medical Image Registration using Support Vector Machine

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ABSTRACT

Registration of pre-operative 3D volume dataset and intra-operative 2D images gradually becomes an important technique to assist radiologists in diagnosing complicated diseases. In this paper, we proposed a novel 2D/3D registration framework based on Support Vector Machine (SVM) to compensate the disadvantages of generating large number of Digitally Rendered Radiographs (DRRs) in the stage of intra-operation. Estimated similarity metric distribution could be built up from the relationship between parameters of transform and prior sparse target metric values by means of SVR method. Based on which, global optimal parameters of transform are finally searched out by an optimizer in order to guide 3D volume dataset to match intra-operative 2D image. Experiments reveal that our proposed registration method improved performance compared to conventional registration method and also provided a precise registration result efficiently.

Keywords: 2D-3D image registration, Support Vector Machine, DRR

1. INTRODUCTION

Registration¹ nowadays gradually becomes a vital technique in daily medical surgery, it is widely used to combine and enhance the information of two or several different modality data sets at different times. Many kinds of modern surgery, including radiation surgery², diagnosis and operation planning employed registration algorithm. Specially, in the field of radiation surgery, most radiologists only diagnose diseases through viewing 2D X-ray film. It is very hard for a radiologist to imagine the complex 3D shapes of tissue or organ various from different patients. To this point, we should induce information of a 3D model reconstructed from pre-operative data obtaining by CT or MRI machine into 2D X-ray image to aid radiologists to diagnose various diseases easily and accurately³.

For this purpose, although we still face with many problems including the low resolution and less information of X-ray image, effective 2D-3D registration algorithm⁴ is required to decide the physical space position of 3D model for matching the intra-operative 2D X-ray image as accurately as possible. Geometry-based registration⁵ matches selected geometric features to minimize the sum of distances between paired features. Gradient-based registration⁶, on the other hand, compares the projections of the volume data gradients with X-ray image gradients to find best similarity. Furthermore, intensity-based algorithms match the intensities between 3D data sets and X-ray images by minimizing a similarity measure to reach the goal of registration^{7,8,9}. Intensity-based registration had been widely used for its simplicity and robustness. As the key technology in this kind of 2D-3D registration, generation of digitally rendered radiographs (DRRs)^{10,11,12}, however, becomes a bottleneck of whole registration routine. During steps of optimization, great number of intra-operative 2D DRRs had to be generated from the 3D data sets for comparison with X-Ray image in order to obtain best similarity metric guiding the parameters of transform to match the 3D data sets with 2D X-ray image. Obviously, it is very time-consuming.

In this paper, to reduce the time of generating intra-operative DRRs, we proposed a novel intensity based 2D-3D registration method using Support Vector Machine (SVM)¹³. It is constructed from the relationship between parameters of transformation for 3D volume data sets and metric distribution, which evaluates the similarity of X-ray image and preoperative DRR image of 3D data sets. Because of the characteristics of SVM, it could avoid generating intra-operative DRRs during optimization steps and naturally compensate the disadvantage of time-consuming calculation of DRR generation to boost up the performance of 2D/3D registration algorithm.

The rest of the paper is organized as follows: in Section 2, the theoretical concept of SVM is briefly reviewed, based on which a novel registration framework is also figured out in this section, while the implementation of the registration algorithm is demonstrated in Section 3. Section 4 presents some experimental results and evaluation. Finally, Section 5 summarizes our current work and leads to outlook on further work.

2. 2D/3D REGISTRATION FRAMEWORK BASED ON SVM

2.1 Support vector machine

Support Vector Machine $(SVM)^{13,14}$ was developed form statistical learning theory¹⁶. It could be applied to solve classification problems¹⁵ and had also been extended to solve lots of regression problems¹⁶, named Support Vector Classification (SVC) and Support Vector Regression (SVR) respectively. SVM is very suitable for estimating values based on non-uniform sampling data sets, which only form a sparse distribution in the input space.

As mentioned above, our target is to estimate the similarity metric without generating intra-operative DRRs to approach real metric distribution depending on sparse pre-operative DRRs as accurately as possible. This problem could be demonstrated as follows:

Given a training data set $\{ (x_i, y_i) \}_{i=1}^l$, minimizes the empirical risk

$$
\arg\min_{f\in H_n} R_{emp}[f] \tag{1}
$$

Where

$$
R_{emp}[f] = \frac{1}{l} \sum_{i=1}^{l} L(y_i, f(x_i))
$$
\n(2)

Hn is hypothesis space, xi is the degrees-of-freedom of transformation in the registration method, yi is the real similarity value between pre-operative DRR image from 3D data and 2D X-Ray image with the current parameter xi of transform and f is a non-linear evaluation function to estimate similarity metric. Furthermore, we choose L as ε -insensitive loss function defined below:

$$
L_{\varepsilon}(y) = \begin{cases} 0 & \text{for} \quad |f(x) - y| < \varepsilon \\ |f(x) - y| - \varepsilon & \text{otherwise} \end{cases}
$$
 (3)

This problem is equivalent to the regression problem using SVR method¹⁶:

$$
\min_{w,b,\xi_i,\xi_i^*} \frac{1}{2} \mathbf{w}^T \mathbf{w} + C \sum_{i=1}^l \xi_i + C \sum_{i=1}^l \xi_i^* \tag{4}
$$

subject to

$$
f(x_i) - y_i \le \varepsilon + \xi_i,
$$

\n
$$
y_i - f(x_i) \le \varepsilon + \xi_i^*,
$$

\n
$$
\xi_i, \xi_i^* \ge 0, i = 1, ..., l.
$$

\n(5)

Where ε , *C* are both customized, ξ , ξ ^{*} are slack variables, we assumed that f(x) is composed of several non-linear basic functions $\{\varphi_i(x)\}\$ as follows:

$$
f(\mathbf{x}) = \mathbf{w}^T \varphi(\mathbf{x})
$$
 (6)

After inducing Lagrange function, the above optimization problem could be converted into its dual problem, which is easy to be realized by means of computer programming.

$$
\min_{\alpha,\alpha^*} \quad \frac{1}{2} (\boldsymbol{\alpha} - \boldsymbol{\alpha}^*)^T Q (\boldsymbol{\alpha} - \boldsymbol{\alpha}^*) + \varepsilon \sum_{i=1}^l (\alpha_i + \alpha_i^*) + \sum_{i=1}^l y_i (\alpha_i - \alpha_i^*)
$$
\n⁽⁷⁾

Subject to

$$
\sum_{i=1}^{l} (\alpha_i - \alpha_i^*) = 0, \ \ 0 \le \alpha_i, \alpha_i^* \le C, \ \ i = 1, ..., l. \tag{8}
$$

 α_i , α_i^* are Lagrange multipliers. ${\bf \alpha} = {\alpha_i}$, ${\bf \alpha}^* = {\alpha_i^*}$, ${\bf w} = \sum_{i} (\alpha_i - \alpha_i^*)$ $\sum_{i=1}^{n} (\alpha_i - \alpha_i^*) \varphi(x)$ *l* μ_i α_i , μ_i *i* $(\alpha_i - \alpha^*)\varphi(x_i)$ $\mathbf{w} = \sum_{i=1}^{\infty} (\alpha_i -$

$$
Q_{ij} = K(x_i, x_j) \equiv \varphi(x_i)^T \varphi(x_j)
$$
\n(9)

 $K(x_i,x_j)$ is the Kernel function. In our paper, we choose exponential radial basis function to satisfy the special characteristic of similarity metric in 2D/3D registration. Finally, we find appropriate Lagrange multipliers to construct the approximate function, which could estimate the metric value without generating intra-operative DRR image in a reasonable time. The approximate function is like:

$$
\sum_{i=1}^{l} (\alpha_i^* - \alpha_i) K(x_i, x) \tag{10}
$$

2.2 Novel 2D/3D registration framework

In our paper, we apply SVR method to estimate similarity metric between 3D data sets and 2D X-Ray image without the help of generating intra-operative DRR images in every optimization step. In other words, we could utilize the promising empirical performance of SVR to predict the similarity metric value by means of sparse training data sets. Through which we could build up an evaluation metric function of similarity for optimizer in registration method to find the optimal parameters of transformation to match 3D data sets with 2D X-Ray perfectly. Then complicated and indispensable information of pre-operation 3D data could be fused into intra-operative 2D X-Ray image to assist radiologists in making surgery plan and diagnosing disease.

In detail, in the pre-operative stage, a 3D model reconstructed from CT or MRI machine when doing the routine check of patient. The next step is to generate the DRR images from 3D volume data set according to the real coordinates and focal position of X-Ray machine, which would be used for the radiation surgery at the subsequent stage. Note that we just generate a little number of DRR images on the key position of each degree of freedom separately as training data. The operations of this stage are all offline and we could also save these intermediate results into database classified by each different patient for future use. These information presented the current status of patients are very important not only for the radiologists or other doctors, but for the intra-operative registration method as well.

In the intra-operative stage, we divided it into two sub-stages. The first sub-stage called pre-registration is responsible for generating the training data constructed by the information of DRR images and the intra-operative X-Ray images. SVR method, which is defined in section 2, plays the main role of this sub stage. Particularly, features of training data for SVR method are composed of each degree of freedom which had already been determined at the pre-operation stage. The outputs of training data for SVR method are the real sparse similarity metric values between the pre-operative DRR images and the intra-operative X-Ray images. After training, SVR could build up an estimated hypothesis searching space mapping the parameters of transformation to metric criterion of 3D volume data and 2D fluoroscopic X-Ray image. Through which, it could avoid the problem of local minima and also keep the similarity measure distribution against the multi-parameters of transformation. In this stage, SVR training time has significant effects on performance of registration method, a suitable SVR method has to be determined carefully by various experiments to maintain the performance.

The second sub-stage called intra-registration is responsible for searching the optimal parameters in the estimated space built up in the previous stage. To some extent, it is very similar to the conventional 2D/3D registration method^{3,4}. The

most obvious difference is that in each step of optimization in our proposed method, there is no need to generate the DRR image comparing with the intra-operative fluoroscopic X-Ray image. The reason is that estimated metric function is already obtained in the previous stage against the multi-parameters, thus we could directly predict the similarity metric value with the help of promising empirical performance of proposed SVR method. Then optimization method is adopted onto the estimated metric searching space to find the optimal parameters as usual. Finally optimal multi-parameters could be obtained until the convergence of optimizer. With the help of these optimal parameters, 3D data set could be transformed to match 2D X-Ray image perfectly for fusing information with each other.

The framework of our effective 2D/3D registration method is depicted as the following figure:

Fig.1. Novel 2D/3D Registration Framework using SVR.

3. ALGORITHM

The process of our hybrid registration method is substantially to solve a multi-parameters optimization problem according to similarity metric criterion. We utilize SVR to build up the multi-parameters searching space ready to be optimized, through which the bottle neck of generating DRR images could be eliminated in the process of registration.

According to the above framework we proposed, each function encapsulated as components, which could be implemented respectively sharing with distinct programming interface. Four main components would be demonstrated in our paper. First component realizes the DRR generation, which still plays an important role of bridge between 3D volume data set and 2D X-Ray image. Due to the generation ability of SVR method, only a little number of DRR images should be generated as source images of training data sets. Second component focuses on similarity metric, which could

be predicted by SVR quickly and accurately. Third component applies six degree-of-random rigid transformation to 3D volume data during the process of registration. Fourth component involves the optimization, which is used to adjust the parameters of transformation described in third component for searching the optimal similarity metric described in second component. Finally, optimal parameters of transformation are determined to control the moving 3D data matching the referenced 2D X-ray image.

3.1 Digitally reconstructed radiographs

Many accelerated DRR generation algorithm, including shear-warp rendering¹⁰, lightfield¹¹ and GPU based generation¹² are proposed in the past in order to overwhelm the obstacles of conventional method. However, considerable number of intra-operative DRRs still had to be computed out during steps of optimization.

In our proposed method, we had built up a bridge between parameters of transform and similarity of 3D volume data and 2D X-Ray image by means of SVR. Just like the framework demonstrated above, we do not have to generate the DRR image except at the key node of parameters. That is to say, only a small number of computational DRR image should be generated in advance for SVR training, then we could predict the similarity metric during the online operations through SVR trainer instead of computational DRR images. Since the generation of DRR is no longer the bottle neck of intraoperation registration and we could adopt the high-accurate ray casting method to generate DRR before surgery. For each pixel of the imaging plane, a ray is back-projected into the 3D volume. Then a sum of all voxels in the volume that the ray intersects with is computed. Finally, we generate DRR image onto the imaging plane by rays through the focal point to the imaging plane. Fig.2. explains this approach briefly.

Fig.2. Ray Cast DRR generation

3.2 Similarity metric

In our paper, two kinds of similarity metric should be considered. Firstly, at the pre-registration stage, real similarity metric between DRR images and intra-operative 2D X-Ray image should be computed by Mutual Information^{17,18} according to key positions of each degree of freedom which are recorded at the pre-operation stage. These similarity metric values have significant effects on the final accuracy of registration, so we apply the normalized mutual information (NMI)¹⁹ based on entropy theory, which is less sensitive to changes in overlap parts of two images. It satisfies the following equation:

$$
NMI(M,R) = \frac{H(M) + H(R)}{H(M,R)}
$$
\n⁽¹¹⁾

Here M represents the pre-operative DRR images, while R is the 2D X-Ray reference image. And H is the Shannon entropy defined as:

$$
H = -\sum p_i \log p_i \tag{12}
$$

pi is probability of intensity distribution. In the case of H(M,R), pi means the joint intensity distribution of moving (DRR) and reference image (X-Ray). Fig.3. illustrates the similarity value distribution by NMI metric against x-axis rotation of 3D volume.

Fig.3. Value of metrics to describe similarity against x-axis rotation. Each point is used as training data for SVR.

Just like the above 1D distribution of similarity metric, it could be extended to the case of multi-parameters. As described in Section 2.1, each degree of freedom would be treated as a feature and the corresponding NMI similarity metric distribution would be treated as outputs of training model in the SVR method. Subsequently, the training model is trained in the pre-registration stage to help predicting the similarity metric by means of equation (10).

Refer to our proposed method and registration framework, another kind of similarity metric (Estimated Metric) is computed by SVR in the stage of intra-registration during surgery. Because of the prediction feature of SVR, the similarity metric values could be estimated without generating corresponding DRR image. Fig.4 illustrates the comparison between real sparse training data and continuous estimated similarity distribution by SVR method against Yaxis transformation. Consequently, SVR method has not only built up an estimated searching space successfully and it is still able to keep the characteristic of the target metric function as well.

Fig.4. Thin dot line describes the training similarity data, and thick solid line shows the regression result by SVR to estimate the distribution of similarity metric.

3.3 Transformation

Because the parameters of transformation are chosen as the features in the SVR method, its degree of freedom represents the complexity of regression problem. In this paper, rigid-body transformation is well satisfied the experimental brain data. Thus the dimension of searching space is six, which is a typical case of SVR method. We represent the parameter of transform as a six-component vector including three rotation degree of freedom ($\phi x, \phi y, \phi z$) and three translation degree of freedom (tx, ty, tz).

3.4 Optimization

In our 2D/3D registration, patient alignment is achieved by iteratively solving an optimization problem in six degrees of freedom. Firstly, parameters are initialized as the current position related to the standard position of 3D volume. Subsequently, during the process of optimization, the 3D volume undergoes rigid-body transformations where each degree of freedom is varied until an optimum estimated similarity value is achieved.

For many conventional optimization problems, preventing from getting trapped into local optima of the similarity function is always the popular topic. One possible solution is to repeatedly start the optimization from different starting points in the searching space, eventually choosing the best result as optimum. However, it is highly time-consuming and the performance of registration procedure would also be deteriorated. Another widely used technique to overcome local optima is simulated annealing method, which follows local gradients, but occasionally will move against the gradient in order to escape a local extremum. This method would be induced in our future application of registration in the case of the existence of local optima in similarity metric function.

Fortunately, in this paper, it turned out that the estimated similarity function distribution generated by SVR method is smooth enough to be optimized (refer to Fig.5.). The global optimum also implies the best pose of transform to be used to register between DRR and X-Ray image. By tuning the learning step of gradient ascent optimal strategy on the estimated searching spaces given by SVR method like Fig.4, optimal parameters of transformation are finally determined to guide the original 3D volume matching the 2D X-Ray image.

4. EXPERIMENTAL RESULTS

We evaluated our 2D/3D registration methods with preoperative MRI data sets and simulated intra-operative fluoroscopic X-Ray image. The format of 3D T1-MRI data is $181 \times 217 \times 181$, slice thickness is 1mm. 2D X-Ray image is simulated by 3D MRI using DRR method, its size is 220×250 . The experiments are performed on a PC with Core-T2400 1.83GHz, 1GB RAM.

4.1 Kernels of SVR

In the pre-registration stage of our experiments, there is a trade-off between accuracy of similarity metric prediction and time consuming on training by SVR. On the other words, the performance of SVR has significant effects on the registration results. To this point, various kinds of kernel function of SVR method described in (9) are experimented with different capacity control C to build up the estimated distribution of similarity metric function. Fig.5 illustrates the comparison NMI metric estimation function against z-axis rotation of 3D volume with different SVR parameters. Other parameters of transformation would lead to similar results. Table.1 illustrates the time consuming against different capacity control C corresponding to Fig.5.

Three types of Kernel in SVR method are demonstrated as follows:

RBF Kernel:

$$
K(\mathbf{x}_i, \mathbf{x}_j) = \exp(-\gamma \left\| \mathbf{x}_i - \mathbf{x}_j \right\|^2), \gamma > 0
$$
\n(13)

Linear Spline Kernel:

$$
K(\mathbf{x}_i, \mathbf{x}_j) = \prod_{d=1}^n K_d(\mathbf{x}_i^d, \mathbf{x}_j^d)
$$
 (14)

$$
K_d(u, v) = 1 + uv + \frac{1}{2}uv \min(u, v) - \frac{1}{6} \min(u, v)^3
$$
 (15)

 is the d-th dimension of vector x. *d* **x**

Exponential RBF Kernel:

$$
K(\mathbf{x}_i, \mathbf{x}_j) = \exp(-\gamma \|\mathbf{x}_i - \mathbf{x}_j\|), \gamma > 0
$$
\n(16)

Fig. 5. Comparison of various SVR method. Thin dot lines describe the training similarity metric, and thick lines (solid and dashed) show the regression result by SVR to estimate the distribution of similarity metric. a) $K1 = Radial Basic$ Function (RBF), C = ∞(thick dashed line), C = 200(thick solid line); b) K2 = Linear Spline Kernel, C = ∞(thick dashed line), $C = 200$ (thick solid line); c) K3 = exponential RBF, $C = \infty$ (thick dashed line), $C = 200$ (thick solid line).

Table.1 Training Time against different capacity control C.

Training Time (s)	$C = 200$	$C = \infty$
Radial Basic Fucntion (RBF)	106.4	481.2
Linear Spline Kernel	114.7	2429.2
Exponential RBF	96.8	473.2

Experimental results reveal that exponential RBF with infinite C ought to be the best one suitable for estimation of similarity metric in our 2D/3D registration method. Undoubtedly, the smoother and the more accurate estimated similarity metric distribution is, the faster optimizer could find the optimum out. However, when capacity control is assigned as infinite, the training time is much long than the case of smaller C. Consequently, it had unexpectedly increased computing time of pre-registration and delayed the inter-operative process of registration as well. On the other hand, we could also notice that when capacity control C is finite, e.g. $C = 200$, the solution is only incapable of accurately modeling the peak in the data, but it could still keep the characteristic of the target metric function. That is to say, the peak of the estimated function located at the same position as the one of target function, which does not hinder the performance of our optimizer to find the optimum in the estimated searching space if we tune the searching step carefully. In brief, SVR with exponential RBF kernel by additional capacity control ($C = 200$) would be ultimately chosen for the subsequent steps of 2D/3D registration to reach the target of robustness and efficiency.

4.2 MRI X-Ray experiment

Once most suitable SVR is decided and the estimated searching space is acquired, we could adopt our optimizer, which is described in section 3, to search the space finding the optimal parameters. An experimental result of registration for 3D MRI Brain data set and 2D X-Ray image is illustrated in Fig. 6.

Fig.6 Registration between 3D MRI data and simulated X-Ray image. a) shows the 2D X-Ray image with contours (white lines) of DRR image at an initial position. b) shows the 2D X-Ray image with contours of DRR image at an final position by our proposed registration method.

In order to evaluate the results of our proposed registration method, Table.2 summarized some attributes in order to compare our proposed registration method with the conventional one, which uses Mutual Information as similarity metric and calculates large number of intra-operative DRRs at each optimization step for searching the optimal six rigid parameters of transformation.

Table.2 Evaluation of our proposed method compared with conventional method.

By means of our registration method, we could find that result is as accuracy as the conventional method. SVM model generate a very smooth and accurate searching space. And because of its sparse, no intra-operative DRR images should be generated, which compensate the disadvantages of generating large number of DRR images at each step of optimization in the conventional method. To this point, we successfully saved the computing time to boost up the performance of intra-operative stage in our novel 2D/3D registration framework.

5. CONCLUSION

This paper proposed a novel 2D/3D registration framework using Support Vector Machine. With the help of SVR method, we estimated the similarity metric efficiently and avoid generating time-consumed intra-operative DRR images successfully. The experiments also reveal that our method has a satisfying performance comparing with the conventional registration method.

Our future work will be focus on eliminating the current limitation of rigid registration. It would be promoted to apply for the non-rigid registration by changing the parameters of rigid transform into free-from deformation. In SVR method, the input of training data becomes to be the parameters of free-from deformation instead of rigid ones. The main challenges are efficiency, robustness and accuracy.

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REFERENCES

¹ J. B. Antoine Maintz and Max A. Viergever, "A Survey of Image Registration", Medical Image Analysis **2(1)**, 1–37, 1998.

² Adler J. Jr., Murphy, M., Chang, S. and Hancock, S., "Image-guided robotic radiosurgery", Neurosurgery **44(6)**, 1999.

³ Wolfgang Wein, "Intensity Based Rigid 2D-3D Registration Algorithms for Radiation Therapy", Ph.D. thesis, Dec. 2003.

⁴ Roland Gocke, Jurgen Weese, and Heidrun Schumann, "Fast Volume Rendering Methods for Voxel-based 2D/3D Registration – A Comparative Study", International Workshop on Biomedical Image Registration, Bled, Slovenia, 1999.

⁵ Besl, P. and McKay, N., "A method for registration of 3D shapes", IEEE Trans. On Pattern Analysis and Machine Intelligence **14(2)**, 1992.

⁶ H. Livyatan, Z. Yaniv, L. Joskowicz., "Gradient-Based 2D/3D Rigid Registration of Fluoroscopic X-ray to CT". IEEE Trans. on Medical Imaging, 22(11): 1395-1406, 2003.

⁷ Lilla Zollei, "2D-3D RigidBody Registration of X-Ray Fluoroscopy and CT Images". Ph.D. thesis, 2001.

⁸ J. Weese, Graeme P.Penney, Paul Desmedt, Thorsten M.Bu

2-D/3-D Registration of Fluoroscopy Images and CT Scans for Image-Guided Surgery". IEEE transactions on information technology in biomedicine **1(4)**,1997.
⁹ LaRose, D.A, Bayouth, J., and Kanade, T., Transgraph, "Interactive intensity-based 2D/3D registration of X-ray and

CT data", SPIE Image Processing, 2000.

Philippe Lacroute and Marc Levoy, "Fast Volume Rendering Using a Shear-Warp Factorization of the Viewing Transform", Computer Graphics Proceedings, Annual Conference Series, 1994.
¹¹ Daniel B. Russakoff, Torsten Rohlfing, Daniel Rueckert, Ramin Shahidi, Daniel Kim, Calvin R. Maurer, "Fast

calcluation of Digitally Reconstructed Radiographs using light fields". SPIE, Medical Imaging, **5032**, 2003. 12 Tobias Gross, "2D/3D Registration of X-Ray and CT Data Using Accelerated Volume Rendering and Gradient

Calculation", 11th Central European Seminar on Computer Graphics, April 2007.

¹³ Christopher J.C. Burges, "A Tutorial on Support Vector Machines for Pattern Recognition", Kluwer Academic Publishers, 1-43, Boston, 1998.

¹⁴ C. Cortes and V. Vapnik, "Support-vector network", Machine Learning, **20**, 273-297,1995.
¹⁵ C.-W. Hsu and C.-J. Lin, "A comparison of methods for multi-class support vector machines", IEEE Transactions on Neural Networks, 13(2), 415-425, 2002.
¹⁶ V. Vapnik, *Statistical Learning Theory*, Wiley, New York, NY, 1998.
¹⁷ Viola, P., Wells III, W., "Alignment by Maximization of Mutual Information", International Journal of Co

Vision, 24(2), 137-154, 1997.
¹⁸ Frederik Maes, Andre Collignon, Dirk Vandermeulen, Guy Marchal, and Paul Suetens., "Multimodality Image

Registration by Maximization of Mutual Information", IEEE Transactions on Medical Imaging, **16(2)**, 187-198, 1997.

¹⁹ Josien P.W.Pluim, J.B. Antoine Maintz, and Max A. Viergever, "Mutual-Information-Based Registration of Medical Images: A Survey", IEEE Transactions on Medical Imaging, **22(9)**, 986-1004, 2003.