

Master Thesis

**Validation of  
Machine-Learning-driven Real-Time  
2D/3D Tracking (Texture Model Registration)  
in Radiotherapy**

Markus Neuner

[neuner.markus@gmx.net](mailto:neuner.markus@gmx.net)

October 2010

Created in the course of the study of medical informatics at the  
University for Health Sciences, Medical Informatics and Technology (UMIT)

and in cooperation with the  
Institute for Research and Development on Advanced Radiation Technologies (radART)  
at the Paracelsus Medical University (PMU)

Major Advisor: Univ.-Prof. Dr. med. Rainer Schubert<sup>1</sup>

Advisor: DDr. Karl D. Fritscher,<sup>2</sup> DI Philipp Steininger<sup>3</sup>

<sup>1</sup>Leader of the Institute for Biomedical Image Analysis (IBIA) at the UMIT

<sup>2</sup>Research associate at the Institute for Biomedical Image Analysis (IBIA) at the UMIT

<sup>3</sup>Research associate at the radART Institute

## Abstract

In almost all image guided medical interventions (IGMI) such as image guided surgery and image guided radiotherapy (IGRT) the spatial alignment of pre- and intra-interventional data plays a crucial role. For example in IGRT the planned patient setup must be verified right before as well as during beam delivery in order to guarantee an efficient treatment and to avoid adverse effects. Most of the IGMI require online (real-time) image information, acquired by projective images (e.g. radiographs) or slice-images (e.g. ultrasound). The current available projection-based 2D/3D registration approaches use optimization strategies that are potentially prone to local minima traps, usually have a data-dependent capture range and hardly meet critical real-time constraints.

In this work a novel framework for 2D/3D image registration (texture model registration, TMR), that utilizes supervised machine learning techniques, was implemented and quantitatively validated to overcome the limitations of current iterative methods. Based on a pre-interventional 3D image and geometry information a prediction rule is derived which is subsequently used for the real-time prediction of the spatial transformation of unseen intra-interventional 2D images. Two simple TMR methods were implemented and validated with a quantitative simulation of 120 experiments, based on realistic lateral and ventral IGRT scenarios on 15 different clinical computed tomography (CT) datasets and synthetic 2D images (DRRs). The implemented TMR pipelines are TMR-PCR, which involves principal component regression (PCR), and TMR-KPCR, which involves kernel PCR.

The results show that TMR is able to predict the translational parameters which are perpendicular to the projection direction ( $\overline{\text{MSE}}$  0.004-0.913 mm<sup>2</sup>) and rotations within this plane ( $\overline{\text{MSE}}$  0.055-0.495 deg<sup>2</sup>) with high accuracy. The prediction of the depth information was less accurate ( $\overline{\text{MSE}}$  2.409-13.211 mm<sup>2</sup>), which was expected, because only a single image was used. The maximum values of the 95th mean target registration error (mTRE) percentile show that TMR produces very robust predictions under ideal conditions (1.156-2.556 mm), even at high initial mTREs. An increased  $\overline{mTRE}$  (0.194-1.59 vs. 0.531-4.184 mm) can be observed at higher CT dataset resolutions. More details in the DRRs and the used non-robust statistical methods (sensitive to inflated variances and noisy pixels) lower the generalization performance. Higher transformation degrees of freedom (DOF) result in a less reliable registration (3.01-16.15 times higher mean  $\overline{mTRE}$ ). This may mainly emerge from the increased dimensionality of the parameter space and can be overcome by more learning samples and better pre-processing operations. The head and neck experiments perform better than the prostate experiments. The lateral and ventral experiments perform similar.

The average intra-interventional registration rates of 43.84 and 64.92 Hz are convincing. TMR-PCR is not able to capture non-linearities in the transformations. TMR-KPCR with a polynomial kernel of degree 3 seems to be the method of choice. The vast majority of 2D/3D registrations in 60 experiments were successful (86.44-99.39%), where an end mTRE smaller 2 mm was defined as successful. The other experiments appeared to clearly suffer from the increased DOF (23.86-70,07%). However, the amount of 2D/3D registrations that have a larger or equal final mTRE than before the registration is very low (at most 0.1-0.31%).

TMR gives access to a wide range of algorithms and methods which are usually applied in a machine learning and computer vision context. In particular non-linear regression methods and manifold embedding methods.

Summing up, the validation results of the very basic setup of TMR are promising to be used in the field of automatic real-time 2D/3D image registration and in other areas of IGMI.

## Zusammenfassung

In nahezu allen bildgestützten, medizinischen Eingriffen (IGMI), wie bildgestützte Chirurgie und bildgestützte Radiotherapie (IGRT), spielt die räumliche Registrierung von prä- und intra-interventionellen Daten eine wichtige Rolle. Beispielsweise muss bei IGRT die geplante Patientenposition kurz vor und während der Bestrahlung verifiziert werden um eine effiziente Behandlung zu garantieren und negative Auswirkungen zu vermeiden. Die meisten IGMI benötigen Bildinformation in Echtzeit, welche mit projektiven Bildern (z.B. Röntgen) oder Schichtbildern (z.B. Ultraschall) gewonnen wird. Die derzeitigen projektionsbasierten 2D/3D Registrierungsverfahren verwenden Optimierungsstrategien die anfällig sind für lokale Minima, eine datenabhängige Fangreichweite aufweisen und keine Echtzeitanforderungen erfüllen.

In dieser Arbeit wurde eine neuartige 2D/3D Registrierungsmethode (texture model registration, TMR), welche auf maschinellen Lernverfahren basiert, implementiert und quantitativ validiert um die Beschränkungen derzeitiger iterativer Verfahren zu bewältigen. Basierend auf prä-interventionellen 3D Bildern und Geometriedaten wurde eine Vorhersageregeln abgeleitet um nachfolgend eine Echtzeitvorhersage der räumlichen Transformation von unbekanntem intra-interventionellen 2D Bildern vorzunehmen. Zwei TMR Methoden wurden implementiert und mit einer quantitativen Simulation von 120 Experimenten validiert. Die Experimente basieren auf realistischen lateralen und ventralen IGRT Szenarien mit 15 unterschiedlichen, klinischen Computertomographie (CT) Datensätzen und synthetischen 2D Röntgenbildern (DRRs). Die implementierten TMR-Methoden sind TMR-PCR, welche Hauptkomponentenregression (PCR) verwendet, und TMR-KPCR, welche Kernel-PCR verwendet.

Die Ergebnisse zeigen dass TMR fähig ist die translatorischen Parameter ( $\overline{\text{MSE}}$  0.004-0.913 mm<sup>2</sup>), welche perpendicular zur Projektionsrichtung stehen, und Rotationen in dieser Ebene ( $\overline{\text{MSE}}$  0.055-0.495 deg<sup>2</sup>) mit hoher Genauigkeit vorherzusagen. Die Vorhersage der Tiefeninformation war erwartungsgemäß weniger genau ( $\overline{\text{MSE}}$  2.409-13.211 mm<sup>2</sup>), da nur ein einziges Bild verwendet wurde. Die Maximalwerte des 95sten Registrierungsfehler (mTRE) Perzentils zeigen dass TMR unter Idealbedingungen eine sehr robuste Vorhersage liefert (1.156-2.556 mm), sogar bei hohen initialen mTREs. Ein erhöhter  $\overline{mTRE}$  (0.194-1.59 vs. 0.531-4.184 mm) wurde bei feineren CT Datensatzauflösungen beobachtet. Mehr Details in den DRRs und die verwendeten nicht-robusten statistischen Methoden (anfällig für überhöhte Varianz und verrauschte Pixel) verringern die Generalisierbarkeit. Mehr Freiheitsgrade (DOF) der Transformation führen zu einer weniger verlässlichen Registrierung (3.01-16.15 mal höherer mittlerer  $\overline{mTRE}$ ). Dies kann hauptsächlich auf die steigende Dimensionalität des Parameterraumes zurückgeführt werden und ist beherrschbar mit mehr Samples der Trainingsmenge und besseren Vorverarbeitungsschritten. Die Experimente vom Kopf/Hals-Bereich haben eine höhere Genauigkeit als die Prostataexperimente. Die lateralen und ventralen Experimente haben eine gleichwertige Performanz.

Die durchschnittlichen intra-interventionellen Registrierungsraten von 43.84 und 64.92 Hz sind beachtlich. TMR-PCR ist nicht in der Lage Nichtlinearitäten in den Transformationen abzubilden. TMR-KPCR mit einem polynomiellen Kernel vom Grad 3 erscheint als die Methode der Wahl. Die Mehrheit der 2D/3D Registrierungen in 60 Experimenten war erfolgreich (86.44-99.39%), wobei ein finaler mTRE kleiner 2 mm als erfolgreich definiert wurde. Die restlichen Experimente leiden deutlich unter den gesteigerten DOF (23.86-70,07%). Allerdings ist die Anzahl an 2D/3D Registrierungen mit einem höheren oder gleichen finalen mTRE als vor der Registrierung sehr gering (höchstens 0.1-0.31%).

TMR ermöglicht den Zugang zu einer großen Auswahl an Methoden und Algorithmen, die üblicherweise im Zusammenhang mit maschinellem Lernen und "Computer Vision" eingesetzt werden. Zusammenfassend sind die Ergebnisse der sehr einfachen TMR Konfiguration aussichtsreich für eine Verwendung im Umfeld der automatischen, echtzeitbasierten, 2D/3D Registrierung und anderen Bereichen der IGMI.

# Contents

<b>List of Abbreviations</b>	<b>3</b>
<b>1. Introduction</b>	<b>4</b>
1.1. Motivation	4
1.2. Radiotherapy	5
Targets and Margins	6
1.2.1. Image-Guided Radiotherapy (IGRT)	7
Pre-interventional Image Data	7
Intra-interventional Image Data	7
Image-Guided Setup	8
1.2.2. LINAC-Based Radiotherapy Systems and Imaging Technologies	9
MV radiographs (portal images, portal filming)	9
kV radiographs (X-ray)	9
kV CT	10
MV CT	10
US	10
1.3. Medical image data	10
1.3.1. Definitions and geometry	10
1.3.2. Sampling Theorem	13
Fourier transform (FT)	13
Discrete Fourier transform (DFT)	14
Aliasing	15
1.3.3. Interpolation	15
Nearest neighbor Interpolation	16
Linear Interpolation	16
B-Spline Interpolation	16
Windowed Sinc Interpolation	17
1.3.4. Medical imaging modalities	17
X-Ray	17
Computed tomography (CT)	19
1.4. Registration	20
1.4.1. Classes of registration	21
1.4.2. Basic components	21
Fixed image	21
Moving image	22
Registration criteria (cost function)	22
Transform	22
Optimization	24
Interpolation	24
1.4.3. Rigid Registration	24
1.4.4. Intensity-based 3D to 2D registration	25
1.4.5. Digitally reconstructed radiograph (DRR)	27
1.5. Volume-rendering	27
1.5.1. Volume-rendering integral	28
1.5.2. Volume-rendering pipeline	29
Sampling	29
1.5.3. Intensity transfer function (ITF)	31
1.6. DRR generation methods	31
Algorithm Complexity	32

1.6.1.	Ray casting . . . . .	32
1.6.2.	Splatting . . . . .	33
	Wobbled splatting . . . . .	34
1.6.3.	Attenuation field (AF) . . . . .	34
	Progressive attenuation field (PAF) . . . . .	35
1.6.4.	Fourier volume-rendering (FVR) . . . . .	36
1.6.5.	Shear-warp . . . . .	36
1.6.6.	Texture mapping . . . . .	37
1.6.7.	Monte Carlo volume-rendering (MCVR) . . . . .	37
<b>2.</b>	<b>Methods</b>	<b>40</b>
2.1.	Validation of IGMI Methods . . . . .	40
2.1.1.	Terms and Definitions . . . . .	40
2.1.2.	Validation of 2D/3D Registration . . . . .	40
	Reference or Gold standard dataset . . . . .	41
	Accuracy Assessment . . . . .	41
	Capture Range . . . . .	42
2.2.	Machine Learning . . . . .	42
2.2.1.	Introduction . . . . .	42
	Data Mining . . . . .	42
	Knowledge Discovery . . . . .	43
	Machine Learning . . . . .	43
2.2.2.	Supervised Learning Definitions . . . . .	44
2.2.3.	Regression . . . . .	44
2.2.4.	Ordinary Least Squares Estimator (OLS) . . . . .	44
2.2.5.	Instability of LS Estimators . . . . .	45
2.2.6.	Correct Regression Models . . . . .	46
2.2.7.	Terms and Definitions . . . . .	46
	Curse of Dimensionality . . . . .	46
	Model Selection and Assessment . . . . .	46
	Bias-Variance Decomposition . . . . .	47
	Over-/Under-fitting . . . . .	48
	Generalization . . . . .	48
	Prediction Accuracy . . . . .	48
	Prediction Error / Generalization Error / Test Error . . . . .	49
2.2.8.	Estimate Prediction Error . . . . .	50
	K-fold Cross Validation (CV/K) . . . . .	50
	Bootstrap . . . . .	50
2.3.	Biased Regression Methods . . . . .	50
2.3.1.	Shrinkage Methods . . . . .	50
	Ridge Regression . . . . .	50
	Regularized Regression . . . . .	51
	Discussion Shrinkage Methods . . . . .	51
2.3.2.	Methods Using Derived Input Directions . . . . .	51
	Principal Components Regression (PCR) . . . . .	51
	Principal / Partial Least Squares Regression (PLSR, PLS) . . . . .	51
	Discussion of Methods Using Derived Input Directions . . . . .	52
2.3.3.	Variable Selection / Subset Selection / Stepwise Methods . . . . .	52
	Discussion Variable Selection . . . . .	52
2.4.	Dimensionality Reduction . . . . .	52
2.4.1.	Principal Component Analysis (PCA) . . . . .	53
2.4.2.	Canonical Variate and Correlation Analysis (CCA, CVA) . . . . .	55

2.4.3.	Projection Pursuit (PP)	55
2.4.4.	Sparse Principal Components	56
2.4.5.	Non-negative Matrix Factorization (NMF)	56
2.4.6.	Archetypal Analysis	56
2.4.7.	Polynomial PCA	56
2.4.8.	Principal Curves and Surfaces	56
2.4.9.	Kernel PCA (KPCA)	57
2.4.10.	Multilayer Auto-associative Neural Networks (ANN)	57
2.4.11.	Multi Dimensional Scaling (MDS)	58
2.4.12.	Assessing the Effective Dimensionality $t$	58
<b>3.</b>	<b>Problem and Objective</b>	<b>60</b>
<b>4.</b>	<b>Materials</b>	<b>62</b>
4.1.	Tools	62
4.1.1.	Hardware and operating system	62
4.1.2.	C++	62
4.1.3.	GNU Compiler Collection (GCC)	63
4.1.4.	CMake	63
4.1.5.	Insight Segmentation and Registration Toolkit (ITK)	63
4.1.6.	Eclipse and CDT	63
4.1.7.	R: A Language and Environment for Statistical Computing	64
4.1.8.	BASH	64
4.1.9.	Subversion (SVN)	64
4.1.10.	Inkscape	64
4.1.11.	T <sub>E</sub> X	65
4.1.12.	Ly <sub>X</sub>	65
4.2.	Used volumetric datasets	65
4.3.	Projection Geometries and Geometric Constraints	66
<b>5.</b>	<b>Results</b>	<b>71</b>
5.1.	Texture Model Registration (TMR)	71
5.1.1.	Definitions	71
5.1.2.	Basic Concept	72
5.1.3.	A Basic Implementation: TMR-PCR	73
	Learning Step	73
	Prediction Step	74
5.1.4.	TMR with kernel PCA and linear regression: TMR-KPCR	74
5.1.5.	Related Methods and Opportunities	74
5.2.	Implemented TMR Pipeline	76
5.2.1.	DRR computation	76
5.2.2.	Pre-processing	77
5.2.3.	Training Task	77
	Model Selection	78
5.2.4.	Prediction Task	78
5.3.	Validation Results	78
5.3.1.	Accuracy of 2D/3D Registration	78
	Experiments L1/V1	78
	Experiments L2/V2	79
	Experiments L3/V3	79
5.3.2.	Execution Time	80
5.3.3.	Chosen Models	80

---

5.3.4. General Behavior . . . . .	81
<b>6. Discussion</b>	<b>87</b>
<b>7. Outlook</b>	<b>89</b>
<b>8. Acknowledgments</b>	<b>90</b>
<b>References</b>	<b>91</b>
<b>Appendices</b>	<b>96</b>
<b>Appendix A. Images</b>	<b>96</b>
<b>Appendix B. Tables</b>	<b>107</b>

## 8. Acknowledgments

It wouldn't be possible to write this thesis without support from others, let it be personal, intellectual or financial. I would like to thank my supervisors Univ.-Prof. Dr. med. RAINER SCHUBERT, DDr. KARL D. FRITSCHER and DI PHILIPP STEININGER. Many ideas in this thesis are based on discussions I had with PHILIPP and KARL, which often were more than just scientific and showed me how much fun science can be and that it is important to take not everything too serious. Special thanks to PHILIPP for the provided DRR generation framework and the dataset preparation.

Moreover, I would like to thank the PMU for supporting my studies by providing all used datasets, treatment data, the infrastructure and I gratefully acknowledge financial support in the course of PMU-FFF grant R-09/03/004-STE. This work benefited from the use of the ITK, R-statistics, their documentation and especially from the books [2, 3, 11, 37, 38].

Last but not least there is a number of people who have nothing to do with my research, but provided an evenly important share in making it possible. I would like to thank my mother INGRID and sister MICHAELA for the support during my studies and in particular my girlfriend MELANIE for her motivation, continuous support and endless patience. Let's rock!

Markus Neuner, October 2010.



## References

- [1] Markelj P, Tomaževič D, Likar B, Pernuš F. A review of 3D/2D registration methods for image-guided interventions. *Medical Image Analysis*. 2010 Apr; In Press, Corrected Proof.
- [2] Peters T, Cleary K, editors. *Image-Guided Interventions: Technology and Applications*. New York, NY, USA: Springer; 2008.
- [3] Preim B, Bartz D. *Visualization in Medicine: Theory, Algorithms, and Applications (The Morgan Kaufmann Series in Computer Graphics)*. San Francisco, CA, USA: Morgan Kaufmann Publishers Inc.; 2007.
- [4] van de Kraats EB, Penney GP, Tomaževič D, van Walsum T, Niessen WJ. Standardized evaluation methodology for 2-D-3-D registration. *IEEE Transactions on Medical Imaging*. 2005;24(9):1177–89.
- [5] Wu J, Kim M, Peters J, Chung H, Samant SS. Evaluation of similarity measures for use in the intensity-based rigid 2D-3D registration for patient positioning in radiotherapy. *Medical Physics*. 2009;36(12):5391–403.
- [6] Jannin P, Grova C, Maurer CR. Model for defining and reporting reference-based validation protocols in medical image processing. *International Journal of Computer Assisted Radiology and Surgery*. 2006;1(2):63–73.
- [7] World Health Organization – WHO. National cancer control programmes: policies and managerial guidelines [document on the Internet]. WHO; 2002. Available from: <http://www.who.int/entity/cancer/media/en/408.pdf> [updated 2009 Feb 23; cited 2010 Sep 6].
- [8] ICRU Report 50: Prescribing, recording and reporting photon beam therapy. Bethesda, Maryland, USA: ICRU; 1993.
- [9] ICRU Report 62: Prescribing, recording and reporting photon beam therapy. Bethesda, Maryland, USA: ICRU; 1999. Supplement to ICRU report 50.
- [10] Yoo TS. *Insight into Images: Principles and Practice for Segmentation, Registration, and Image Analysis*. AK Peters Ltd; 2004.
- [11] Johnson C, Hansen C. *Visualization Handbook*. Orlando, FL, USA: Academic Press, Inc.; 2004.
- [12] Ibanez L, Schroeder W, Ng L, Cates J. *The ITK Software Guide*. <http://www.itk.org/ItkSoftwareGuide.pdf>; 2005.
- [13] Bronstein IN, Semendjajew KA, Musiol G. *Taschenbuch der Mathematik*. vol. 6. Frankfurt am Main: Wissenschaftlicher Verlag Harri Deutsch GmbH; 2005.
- [14] Poularikas AD, editor. *Transforms and Applications Handbook (The Electrical Engineering Handbook Series)*. 3rd ed. CRC Press; 2010.
- [15] *Digital Imaging and Communications in Medicine (DICOM), Part 3: Information Object Definitions*. 1300 N. 17th Street, Rosslyn, Virginia 22209 USA; 2009.
- [16] Lehmann T, Oberschelp W, Pelikan E. *Bildverarbeitung für die Medizin*. vol. 1. Berlin: Springer; 1997.

- [17] Meijering EHW, Niessen WJ, Pluim JPW, Viergever MA. Quantitative Comparison of Sinc-Approximating Kernels for Medical Image Interpolation. In: MICCAI '99: Proceedings of the Second International Conference on Medical Image Computing and Computer-Assisted Intervention. London, UK: Springer-Verlag; 1999. p. 210–7.
- [18] Lamecker H, Wenckeback TH, Hege HC. Atlas-based 3D-Shape Reconstruction from X-Ray Images. In: Proc. 18th International Conference on Pattern Recognition ICPR 2006. vol. 1; 2006. p. 371–4.
- [19] Dong X, Ballester MÁG, Zheng G. Automatic Extraction of Femur Contours from Calibrated X-Ray Images using Statistical Information. *Journal of Multimedia*. 2007;2(5):46–54.
- [20] Goshtasby AA. 2-D and 3-D Image Registration: for Medical, Remote Sensing, and Industrial Applications. 1st ed. Hoboken, New Jersey: John Wiley & Sons, Inc.; 2005.
- [21] Graham J. Image Processing and Analysis: A Practical Approach. 1st ed. New York, NY, USA: Oxford University Press, Inc.; 2000.
- [22] Maintz JBA, Viergever MA. A survey of medical image registration. *Medical Image Analysis*. 1998;2(1):1–36.
- [23] Zitová B, Flusser J. Image registration methods: a survey. *Image and Vision Computing*. 2003;21(11):977–1000.
- [24] Li X, Yang J, Zhu Y. Digitally reconstructed radiograph generation by an adaptive Monte Carlo method. *Physics in Medicine and Biology*. 2006;51(11):2745–52.
- [25] Russakoff DB, Rohlfing T, Rueckert D, Shahidi R, Kim D, Calvin R Maurer J. Fast calculation of digitally reconstructed radiographs using light fields. In: Sonka M, Fitzpatrick JM, editors. *Medical Imaging 2003: Image Processing*. vol. 5032. SPIE; 2003. p. 684–95.
- [26] Buss SR. 3D Computer Graphics: A Mathematical Introduction with OpenGL. 1st ed. New York, NY, USA: Cambridge University Press; 2003.
- [27] Birkfellner W, Seemann R, Figl M, Hummel J, Ede C, Homolka P, et al. Wobbled splatting – a fast perspective volume rendering method for simulation of x-ray images from CT. *Physics in Medicine and Biology*. 2005;50(9):N73–84.
- [28] Mahfouz M, Badawi A, Fatah EEA, Kuhn M, Merkl B. Reconstruction of 3D Patient-Specific Bone Models From Biplanar X-Ray Images Utilizing Morphometric Measurements. In: *IPCV*. vol. 2; 2006. p. 345–9.
- [29] Levoy M. Display of Surfaces from Volume Data. *IEEE Comput Graph Appl*. 1988;8(3):29–37.
- [30] Max N. Optical Models for Direct Volume Rendering. *IEEE Transactions on Visualization and Computer Graphics*. 1995;1(2):99–108.
- [31] Kersken S. *IT-Handbuch für Fachinformatiker*. 3rd ed. Bonn, Germany: Galileo Press GmbH; 2008.
- [32] Csebfalvi B, Szirmay-Kalos SK. Monte Carlo Volume Rendering. In: *VIS '03: Proceedings of the 14th IEEE Visualization 2003 (VIS'03)*. Washington, DC, USA: IEEE Computer Society; 2003. p. 59.
- [33] Csebfalvi B. Interactive Transfer Function Control for Monte Carlo Volume Rendering. In:

- VV '04: Proceedings of the 2004 IEEE Symposium on Volume Visualization and Graphics. Washington, DC, USA: IEEE Computer Society; 2004. p. 33–38.
- [34] Westover L. Footprint evaluation for volume rendering. In: SIGGRAPH '90: Proceedings of the 17th annual conference on Computer graphics and interactive techniques. New York, NY, USA: ACM; 1990. p. 367–76.
- [35] Westover L. Interactive volume rendering. In: VVS '89: Proceedings of the 1989 Chapel Hill workshop on Volume visualization. New York, NY, USA: ACM; 1989. p. 9–16.
- [36] Rohlfing T, Russakoff DB, Denzler J, Mori K, Calvin R, Maurer J. Progressive attenuation fields: Fast 2D-3D image registration without precomputation. *Medical Physics*. 2005;32(9):2870–80.
- [37] Hastie T, Tibshirani R, Friedman J. *The elements of statistical learning: data mining, inference and prediction*. 2nd ed. Springer; 2009.
- [38] Izenman AJ. *Modern Multivariate Statistical Techniques: Regression, Classification, and Manifold Learning*. 1st ed. Springer; 2008.
- [39] van der Maaten L, Postma E, van den Herik J. *Dimensionality Reduction: A Comparative Review*. Tilburg, Netherlands: Tilburg centre for Creative Computing, Tilburg University; 2009. Report No.: TiCC TR 2009-005. Sponsored by NWO/CATCH, project RICH (grant 640.002.401).
- [40] Fodor IK. *A survey of dimension reduction techniques*. Livermore (CA), USA: Center for Applied Scientific Computing, Lawrence Livermore National Laboratory; 2002. Report No.: UCRL-ID-148494. Contract No.: W-7405-Eng-48. Sponsored by the U.S. Department of Energy.
- [41] Schölkopf B, Smola A, Müller KR. Nonlinear component analysis as a kernel eigenvalue problem. *Neural Comput*. 1998;10(5):1299–1319.
- [42] Kubias A, Deinzer F, Feldmann T, Paulus D, Schreiber B, Brunner T. 2D/3D image registration on the GPU. *Pattern Recognition and Image Analysis*. 2008;18(3):381–9.
- [43] The Open Source Definition [homepage on the Internet]. Open Source Initiative (OSI);. Available from: [opensource.org/docs/osd](http://opensource.org/docs/osd) [updated 2010 Jul 20; cited 2010 Aug 14].
- [44] Debian GNU/Linux [homepage on the Internet]. Software in the Public Interest, Inc.;. Available from: [www.debian.org](http://www.debian.org) [updated 2010 Aug 6; cited 2010 Aug 14].
- [45] GNU Project [homepage on the Internet]. Free Software Foundation, Inc.;. Available from: [www.gnu.org](http://www.gnu.org) [updated 2010 Jul 14; cited 2010 Aug 14].
- [46] JTC1/SC22/WG21 - The C++ Standards Committee [homepage on the Internet]. international standardization working group for the programming language C++;. Available from: [www.open-std.org/jtc1/sc22/wg21/](http://www.open-std.org/jtc1/sc22/wg21/) [updated 2010 Jul 7; cited 2010 Aug 14].
- [47] Meyers S. *Effective C++: 55 Specific Ways to Improve Your Programs and Designs (3rd Edition)*. 3rd ed. Addison-Wesley Professional; 2005.
- [48] Stroustrup B. *The C++ Programming Language (Special 3rd Edition)*. 3rd ed. Boston, MA, USA: Addison-Wesley Longman Publishing Co., Inc.; 2000.
- [49] GCC, the GNU Compiler Collection [homepage on the Internet]. Free Software Foundation,

- Inc.; Available from: [gcc.gnu.org](http://gcc.gnu.org) [updated 2010 Aug 7; cited 2010 Aug 14].
- [50] CMake [homepage on the Internet]. Kitware, Inc.; Available from: [www.cmake.org](http://www.cmake.org) [updated 2010 Apr 16; cited 2010 Aug 14].
- [51] The Insight Segmentation and Registration Toolkit [homepage on the Internet]. Insight Software Consortium; Available from: [www.itk.org](http://www.itk.org) [updated 2010 Aug 9; cited 2010 Aug 14].
- [52] Eclipse [homepage on the Internet]. Eclipse Foundation, Inc.; Available from: [www.eclipse.org](http://www.eclipse.org) [updated 2010 Aug 9; cited 2010 Aug 14].
- [53] R Development Core Team. R: A Language and Environment for Statistical Computing. Vienna, Austria; 2010. ISBN 3-900051-07-0. Available from: [www.R-project.org](http://www.R-project.org).
- [54] StatET [homepage on the Internet]. Stephan Wahlbrink & WalWare-Team; Available from: [www.walware.de/goto/statet](http://www.walware.de/goto/statet) [updated 2010 Jun 23; cited 2010 Aug 22].
- [55] CRAN - The Comprehensive R Archive Network [homepage on the Internet]. R Foundation for Statistical Computing; Available from: [cran.r-project.org](http://cran.r-project.org) [updated 2010 May 31; cited 2010 Aug 14].
- [56] BASH [homepage on the Internet]. Free Software Foundation, Inc.; Available from: [www.gnu.org/software/bash/bash.html](http://www.gnu.org/software/bash/bash.html) [updated 2006 Nov 20; cited 2010 Aug 14].
- [57] Subversion (SVN) [homepage on the Internet]. CollabNet, Inc.; Available from: [subversion.apache.org](http://subversion.apache.org) [updated 2010 Jun 21; cited 2010 Aug 14].
- [58] Inkscape [homepage on the Internet]. Free Software Foundation, Inc.; Available from: [www.inkscape.org](http://www.inkscape.org) [updated 2010 Aug 8; cited 2010 Aug 14].
- [59] LaTeX - A document preparation system [homepage on the Internet]. LaTeX project team; Available from: [www.latex-project.org](http://www.latex-project.org) [updated 2010 Jan 10; cited 2010 Aug 14].
- [60] Leisch F. Sweave: Dynamic Generation of Statistical Reports Using Literate Data Analysis. In: Härdle W, Rönz B, editors. *Compstat 2002 — Proceedings in Computational Statistics*. Physica Verlag, Heidelberg; 2002. p. 575–580. ISBN 3-7908-1517-9. Available from: [www.stat.uni-muenchen.de/~leisch/Sweave](http://www.stat.uni-muenchen.de/~leisch/Sweave).
- [61] LyX - The Document Processor [homepage on the Internet]. Free Software Foundation, Inc.; Available from: [www.lyx.org](http://www.lyx.org) [updated 2010 Jul 15; cited 2010 Aug 14].
- [62] Steininger P, Neuner M, Fritscher K, Sedlmayer F, Deutschmann H. A Novel Class of Machine-Learning-driven Real-Time 2D/3D Tracking Methods: Texture Model Registration (TMR). In: *SPIE Medical Imaging*; 2011 Feb 12 - 17; Florida, USA; 2010. [submitted 2010 Aug 02, accepted 2010 Oct 8, Paper Number 7964-15].
- [63] Steininger P, Neuner M, Fritscher K, Sedlmayer F, Deutschmann H. A Novel Class of Machine-Learning-driven Real-Time 2D/3D Tracking Methods: Texture Model Registration (TMR). In: *MICCAI. 2010: Workshop on Medical Computer Vision: Recognition Techniques and Applications in Medical Imaging*; 2010 Sep 20-24; Beijing, China; 2010. [submitted 2010 Jun 15, not accepted 2010 Jul 15].
- [64] Zhang X, Gao Y. Face recognition across pose: A review. *Pattern Recognition*. 2009;42(11):2876–96.

- 
- [65] Murphy-Chutorian E, Trivedi MM. Head Pose Estimation in Computer Vision: A Survey. *IEEE Transactions on Pattern Analysis and Machine Intelligence*. 2009;31(4):607–26.
- [66] Qi W, Gu L, Zhao Q. Effective 2D-3D medical image registration using Support Vector Machine. In: *EMBS 2008: Proceedings of the 30th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*. Vancouver, BC, USA: IEEE Computer Society; 2008. p. 5386–9.