A visualization platform for high-throughput, follow-up, co-registered multi-contrast MRI rat brain data

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ABSTRACT

Multi-contrast MRI is a frequently used imaging technique in preclinical brain imaging. In longitudinal cross-sectional studies exploring and browsing through this high-throughput, heterogeneous data can become a very demanding task. The goal of this work was to build an intuitive and easy to use, dedicated visualization and side-by-side exploration tool for heterogeneous, co-registered multi-contrast, follow-up cross-sectional MRI data. The deformation field, which results from the registration step, was used to automatically link the same voxel in the displayed datasets of interest. Its determinant of the Jacobian (detJac) was used for a faster and more accurate visual assessment and comparison of brain deformation between the follow-up scans. This was combined with an efficient data management scheme. We investigated the functionality and the utility of our tool in the neuroimaging research field by means of a case study evaluation with three experienced domain scientists, using longitudinal, cross-sectional multi-contrast MRI rat brain data. Based on the performed case study evaluation we can conclude that the proposed tool improves the visual assessment of high-throughput cross-sectional, multi-contrast, follow-up data and can further assist in guiding quantitative studies.

Keywords: Visualization, Exploration, Side-by-side, Multi-contrast MRI, Follow-up, Cross-sectional, High throughput, Rat, Brain, Image Processing, Image Registration

1. INTRODUCTION

Preclinical neuroimaging uses the combination of various imaging techniques to help understand the brain and treat brain disorders. One of the imaging techniques most frequently used to characterize the brain is multi-contrast MRI. Combined, this heterogeneous data allows overcoming the limitations of the individual imaging techniques by providing the researcher with complementary information. However, in studies with several subjects and multiple time-points, exploring and browsing through the multi-contrast, cross-sectional, longitudinal heterogeneous data becomes a very demanding task.

One way to combine heterogeneous data is to use image registration, which allows t o find the spatial relation between the cross-sectional, longitudinal or multi-modal images, thus combining them into a common reference frame [1-7]. In this work we focus on lifespan multi-contrast neuroimaging, where detection of local deformations over the lifespan is essential. Though several registration and brain analysis toolkits are publicly available [8-10], there are currently no simple, dedicated and easy to use applications that allow quick inspection of such life-span MR data in an integrated and intuitive way.

The main contributions of this work are:

i. We provide an intuitive platform to integrate and visualize high-throughput co-registered multi-modal, cross-sectional follow-up data
ii. Our approach allows for an efficient data management and improves side-by-side exploration of high-throughput data by automatically linking the same region of interest(ROI)/voxel in the datasets using the deformation field obtained during the registration. Combining the latter with a determinant of the Jacobian visualization [7, 11-18] allows for a more accurate and faster visual assessment of brain change/deformation with time
iii. The presented tool was evaluated by means of an end-user case study evaluation [19] with three experienced domain scientists and made publicly available. Life span, cross-sectional, multi-contrast MRI rat brain data was used

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2. METHODS

2.1 A visualization platform for high-throughput, follow-up, co-registered multi-contrast MRI brain data

To model local deformation in different regions of the brain over an individual's life-cycle, non-rigid B-spline registration is used [1-7, 11-18]. After a registration is performed, the deformation field and its determinant of Jacobian (detJac) are calculated. The deformation field is a vector image, where each voxel contains the information about its displacement (in physical coordinates) during the registration. The detJac extracts local expansion/compression information from the deformation field. In the construction of the data visualization application proposed in this work we explore the combination of displaying the images of interest (as originally acquired) with the information provided by the deformation field and its detJac.

When comparing 2 different datasets (e.g.: same subject, 2 time-points) the information provided by the deformation field is used to link the same ROI in the displayed datasets of interest: without distorting the original data one can automatically pin-point the exact same region/voxel in both datasets and understand what deformation the brain underwent from one time-point to another in all directions.

The detJac is used to inspect that deformation field: values between 0 and 1 indicate local compression, values above 1 indicate local expansion, and 1 indicates volume preservation [7, 11-18]. Identifying areas of local compression or expansion can facilitate the detection of areas of interest (brain change/deformation) in longitudinal studies and allows for a faster screening of the brain data before further proceeding to quantitative studies.

To handle high throughput co-registered data and to allow quick selection and switching between the hundreds of datasets a logical data management approach was devised. The final application consists of a two-step wizard: after the user defined the main data directory, a list of all the available co-registered data is presented, which can be sorted by subject name, age, modality or type of experiment; in the second step, the user performs the data analysis/exploration, selecting and switching between any dataset of interest. Figure 1 shows and describes in more detail the main components of the application.

2.2 Experimental set-up

To demonstrate and evaluate the application potential of the proposed visualization and exploration tool from an end-user point of view, a case-study with three experienced domain scientists was performed. Multi-contrast longitudinal MRI rat brain data from an existing life span study, exploring juvenile development and ageing processes of the brain was chosen to test the application.

2.3 Rat brain data

From postnatal day 21, two groups of four male Wistar rats (Harlan-Winkelmann GmbH, Borchen, Germany) were housed pairwise under standardized environmental conditions. Food restriction (80% of *ad libitum* consumption) started at an age of about 3 months in order to minimize obesity, a risk factor for age-related diseases [20]. The different groups were introduced into the study with different ages: Group 1 was followed from the age of three weeks with data available up to 14 months at the time of co-registration; Group 2 from ten until 24 months.

Animals were employed in MRI experiments on a bimonthly basis, with supplementary scans in the first 3 months to account for the fast cerebral growth. MRI experiments were conducted on an 11.7 T Bruker BioSpec^{TM} horizontal bore scanner (Bruker Biospin, Ettlingen, Germany). Animals were anaesthetized using 2% Isoflurane (Forane, Baxter, Deerfield, IL, USA) in 70:30 N_2O:O_2, and vital functions were monitored continuously.

This study design shows traits of both a longitudinal and a cross-sectional approach. This beneficial combination allows monitoring the development of the same individuals over time, and at the same time excluding, or identifying possible long-term effects created by repeated measurement and anaesthesia.

T2 weighted images were chosen for their anatomical detail, diffusion tensor imaging (DTI) for the information on tissue anisotropy and myelination. T2 maps were calculated from an MSME (multi slice multi echo) sequence (10 echoes) with TE = 10 ms, TR = 5000 ms (IDL version 6.4, Boulder, CO, USA). The DTI datasets were used to calculate fractional anisotropy (FA), mean diffusivity (MD) and eigenvalue maps (DTI studio version 3.0.3, Baltimore, MD, USA). Both datasets were acquired with identical geometry, slice positioning and spatial resolution (FOV = 28 x 28 mm, resolution 0.146 x 0.146 mm inplane and 0.5 mm slice thickness; without gaps). Multiplying the number of subjects by the number of time-points and by the numbers of different MRI maps the total number of datasets exceeds 500.

2.4 Image registration

Image registration was performed between every two consecutive time-points and between each time-point and the baseline. In Group 1, the 3m old brain served as the baseline, for Group 2, the 10m old brain served as baseline. All registrations were performed using the first echo of the MSME data, chosen for its high anatomical detail and high SNR. The resultant transforms were propagated to the T2 maps and the DTI data. To compensate for any rotation, translation and scaling that exists between different datasets, rigid and affine transformations were applied. These are linear global transformations. To model local differences that allow detecting changes in different regions of the brain over the life-cycle (deformation, volume change, eventual tumor development, etc.), non-rigid B-spline registration was performed after the global initialization. For this data the following parameters were chosen: normalized correlation coefficient as a similarity measure, a four-level Gaussian image pyramid with downsampling and the B-spline with an eight point spacing transformation model. For all images a binary mask was available, made by an expert using the BET tool of the FSL package [9]. The image registration was performed using the publicly available `elastix` toolbox [7, 21].

With the registration results for any possible combination of data at hand, one can easily choose what to visualize and compare side-by-side: same subject-same modality-different time-points, different subjects-same modality-same time-points, same subject-different modalities-different time-points, different subjects-different modalities-same time-point, etc. The presented tool was developed in MeVisLab™ [22], is cross-platform and does not require any other software to be installed.

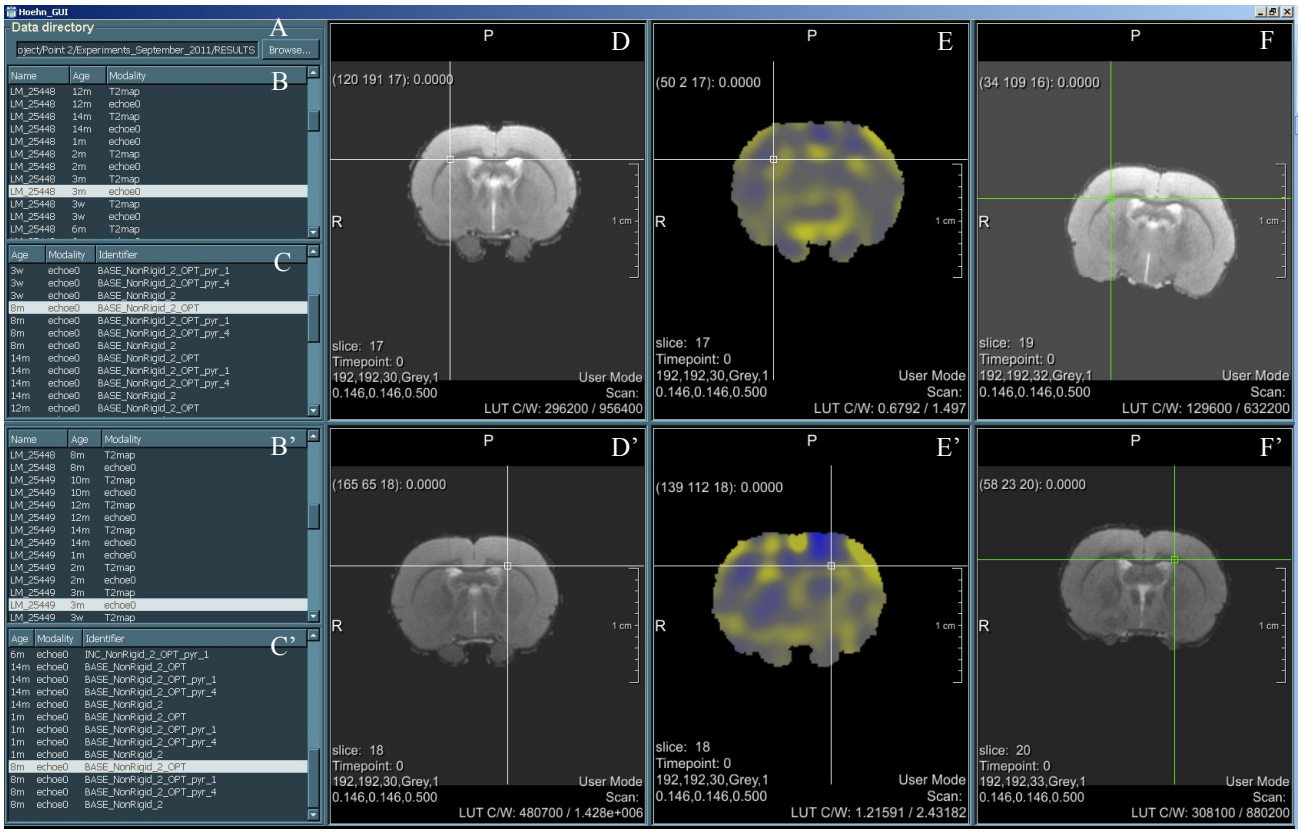

Figure 1. A screenshot of the proposed visualization platform for co-registered high-throughput multi-contrast, follow-up, cross-sectional MRI brain data exploration. Once the main directory is defined in (A), (B) presents a list with all the available data: different subjects acquired using different modalities in different time-points. This list can be sorted according to subject name, age or modality. After a baseline dataset of interest is selected in (B) a list of all the datasets co-registered to it (other subjects, time-points, modalities, types of experiment) is presented in (C). This way a quick overview of the co-registered data is available. The view panel (D) shows the selected baseline from (B), and panel (F) shows the dataset of interest that was previously co-registered to the selected baseline. These 2 datasets of interest are now

automatically linked using the deformation field obtained in the registration. This way, the anatomical location of a voxel in the baseline dataset on the left (white cursor), is pinpointed on the right (green cursor) allowing for an intuitive side-by-side exploration of the original, non-distorted data. The view panel in the middle (E) shows the detJac, allowing for a quick visual assessment of brain change/deformation that occurred between the time-point in (D) and the time-point in (F). Values above 1 (bright yellow) indicate local expansion, values between 0 and 1 (bright blue) indicate local compression and values equal or very close to 1 (grey) indicate volume preservation. The bottom row – (B'), (C'), (D'), (E') and (F') duplicates the functionality of the top row – (B), (C), (D), (E) and (F). This allows making different types of comparisons as described in the paragraph above. The images displayed are an example of the co-registered rat brain data: on the top row two time-points for subject S1 are shown and compared to the bottom row where the same time-points for subject S2 are presented

2.5 End-user evaluation and results

The proposed visualization and exploration tool was evaluated based on the principles and terminology set out by Yin for case study research [19]. The main study question was formulated as: *"How can the visualization platform assist neuroimaging researchers in studying changes over time in multi-modal rat brain data?"* and the case was defined as *"use of the tool by three domain and widely published scientists, referred to as DW, a clinical and experimental MRI expert, CB, a medical and pre-clinical visualization expert and LvdW, a neuroimaging, pre-clinical MRI expert"*. None of the users was involved in any stage of the development of the application before taking part in the evaluation presented here. Together with each of the domain scientists, in three separate, independent sessions, we used the application to analyze the multi-contrast, follow-up cross-sectional rat brain MRI data. That data was acquired to study juvenile development and ageing processes of the brain. During the evaluation sessions, feedback on the application was gathered and structured according to the following study propositions. Following, each proposition is stated, together with its related feedback, after which general comments and preliminary conclusions are presented.

Easy to use, does not have a steep learning curve

All three users confirmed this statement. CB added that all basic functions were straight-forward and indeed after a few minutes of explanation one could start using the application and that one of the positive aspects of the application was that since all files in the user-defined directory followed a naming convention all the data could be easily read by application. He also pointed out that it was positive that selecting a baseline automatically showed all registered datasets to ease selection of the follow-up datasets. LvdW also confirmed that the application was straightforward and intuitive to use. Both CB and LvdW suggested that auto-adjust the window-level for each selected dataset would be an improvement and that it should also be linked between the datasets being compared side-by-side.

The proposed platform allows for a fast selection and switching between the datasets of interest, efficiently handling the high-throughput data (more than 500 datasets).

DW confirmed this statement. CB commented that the tool indeed allows for fast selection from large sets, without having to waste time with orthodox file opening dialogs. However, there is room for improvement in terms of assisting the user in their progress, for example keeping track of comparisons they've made, perhaps even suggesting interesting comparisons based on image metrics. CB found the proposition a bit too broadly defined: he fully agreed that it facilitates selection and comparison, but there is more to be done in terms of integrated efficient handling of high-throughput data. LvdW noticed that the application is indeed convenient to load registered/linked data and suggested an improvement: make it possible to sort the data based on modality, subject, age, etc.

Automatically linking the same ROI/voxel in the displayed datasets, by using the deformation field of the previously performed registration improves side-by-side exploration of follow-up data.

DW confirmed that the linked cursor improved side-by-side exploration. CB noted that indeed this is an effective way that helps one to relate the registered parts of the two datasets being compared, adding that an interesting possibility would be extending the cursor's region of influence, so that local deformation could be better investigated. LvdW commented that automatic linking contributed to a considerable time saving.

The proposed platform allows for an intuitive exploration of cross-sectional and multi-modal data.

DW and LvdW agreed with the statement, the latter one adding that one really gets to know their data well with this application. CB stated that he was not sure what intuitive meant in this context. He added that slice-views were important in any application based on tomographic data and this tool enables basic comparison with slice-views, and so can form a basic part of any comparison toolbox. He expects that it will be useful for the visual inspection of cross-sectional and multi-modal data.

Combining the display of the two time-points of interest together with a detJac visualization allows for a more accurate and faster visual assessment of brain change/deformation.

DW agreed with this statement. CB stated that the detJac visualization is definitely useful for the quick location of areas of significant shrinkage and expansion, which is important in many small animal follow-up studies. He added that side-by-side visualization of time-points is a basic but reliable way to compare data and in the case of this tool, one could also consider putting the baseline and follow-up views directly adjacent to ease comparison. LvdW said that the assessment of brain change/deformation was definitely faster also because of the linked cursor.

The above also holds true in the detection of asymmetries in brain deformation.

All three users agreed with this statement. CB added, that indeed it seemed easy to spot (as)symmetries in the colour coded detJac and that it would help to have a detJac threshold operator to filter out small changes.

All three also suggested that a colorbar showing color scale of the detJac would be helpful.

The tool can be also used for a fast, qualitative assessment of the registration accuracy, since one can quickly check if the clicked points in image-time-point 1 have the correct correspondence in the image-time-point 2.

All three users agreed that the tool could be in principle used to qualitatively assess the registration accuracy. DW commented that one could recognize misregistration, but for a routine quality check he prefers an overlay image. CB stated that he was not convinced, because one has to probe the positions. He agreed that one can spot-check easily for registration accuracy, but this is not the best way to check for whole slices or even the whole volume. In the case of slices, he would prefer also having alpha-blended slices or even red-green blended slices. LvdW stated that it required some expertise for someone to notice that something is wrong with the registration accuracy and that this was not the most obvious tool for that; if we want to make it visual, she'd rather look at a difference image.

The tool can help guide the quantitative study of age-related brain deformation, in that, areas of interest can be localized and qualitatively assessed before further studied

DW agreed with the statement and added that it had indeed potential. CB also confirmed this statement, adding that this kind of explorative tool should be part of any quantitative analysis pipeline, both for quality checking the data and for finding areas of interest that deserve further quantification. LvdW stated what this tool is something that she'd certainly use for getting a feel for the data, since often, one starts by looking through the data to see what quantification use in the experiment. She concluded by adding that a possibility to draw a region of interest and propagate through all the time-points would also be advantageous.

Regarding the execution times of the implemented tool, once the user defined the main data directory, the elaboration of the list of all co-registered datasets organized by subject name, age and modality (more than 500) takes no more than10 seconds on a 2.40GHz Intel Quad Core™ with 4GB of RAM, normal Windows™ desktop PC. Once the list is ready, the selection and switching between different datasets of interest takes around one tenth of a second.

3. DISCUSSION, CONCLUSION AND FUTURE WORK

In this paper we presented a tool that allows to visualize and explore high-throughput multi-contrast, cross-sectional follow-up co-registered MRI data of rat brain. It is independent of the used registration toolkit and does not distort the original data. Using the proposed tool, one can automatically link the same ROI in the displayed datasets by using the deformation field of the previously performed registration, thus improving side-by-side exploration of follow-up data and quickly visually assess brain change/deformation by combining the display of the two time-points of interest together with a detJac visualization.

The proposed visualization and exploration platform was evaluated by three domain experts based on the methods set out by Yin [19] for case study research. All three were enthusiastic with the application. CB commented that he expects it to be useful for the visual inspection of cross-sectional, follow-up and multi-contrast data and form the basis of any comparison toolbox. LvdW commented on the possibility of using the tool in future studies in her research group once the tool becomes publicly available. All three domain experts commented that to assess the registration accuracy they would prefer either a difference or an overlay or and alpha-blended image. The authors agree with this comment, but since the evaluation of the registration accuracy was not the main concern while implementing this tool, it is definitely a

feature that one can add in the future versions together with the option to draw ROIs and propagate their deformation through all the time-points.

Since the performing of the case study evaluation with the domain experts, we implemented several essential suggestions made by the users: auto-adjustment of the window-level and its linkage between the datasets that are being compared; make it possible to sort the listed data (based on modality, subject, age, etc.); add a threshold operator to filter out changes and a colorbar showing the color scale of the detJac. Based on the analysis of the performed case study we can conclude that the proposed application can improve the visual assessment of high-throughput multi-contrast follow-up data and further assist in guiding the quantitative studies. The proposed tool was tested and evaluated using longitudinal MR rat brain data. However, it can be applied to any type of co-registered pre-clinical or clinical follow-up, cross-sectional multi-modal data.

Besides the input from the interviewed domain experts, we must add that from our own experience, the side-by-side visualization tool combined with the detJac map was successfully used to identify and follow in time a spontaneous brain tumor growth, later confirmed *ex vivo* and identified as melingeoma [23]; and to detect changes in cortical thickness during juvenile development allowing the creation of physiologically meaningful ROIs for quantitative analysis of imaging parameters [24].

To add new options and features, the presented tool, together with the correspondent source code and a user-manual will be made publicly available for download via www.lkeb.nl

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REFERENCES

[1] Maintz, J.B.A. and Viergever, M.A., ,"A survey of medical image registration," Med Image Anal, 2, 1-36 (1998)
[2] Zitova, B. and Flusser, J., "Image registration methods: a survey," Image Vision Comput 21, 977-1000 (2003)
[3] Lester, H. and Arridge, S.R., "A survey of hierarchical non-linear medical image registration," Pattern Recognit 32(1), 129–149
[4] Hill, D.L.G., Batchelor, P.G., Holden, M. and Hawkes, D.J., "Medical image registration," Phys Med Biol 46(3), R1–R45 (2001)
[5] Hajnal, J.V., Hill, D.L.G. and Hawkes, D.J. editors [Medical image registration], CRC Press, (2001)
[6] Modersitzki, J., [Numerical methods for image registration], Oxford University Press, (2004)
[7] Klein, S., Staring, M., Murphy, K., Viergever, M.A. and Pluim J.P.W., "elastix: a toolbox for intensity based medical image registration," IEEE T Med Imaging, 29(1), 196-205 (2010)
[8] Gouws, A., Woods, W., Millman, R., Morland, A. and Green, G., "DataViewer3D: An Open-Source, Cross-Platform Multi-Modal Neuroimaging Data Visualization Tool," Front Neuroinformatics, 3: 9 (2009)
[9] http://www.fmrib.ox.ac.uk/fsl/index.html (Version 4.1.7, 15 October 2012)
[10] http://www.freesurfer.net/ (15 October 2012)
[11] Rohlfing, T., Maurer, Jr.C.R., Bluemke, D.A. and Jacobs, M.A., "Volume-preserving nonrigid registration of MR breast images using free-form deformation with an incompressibility constraint," IEEE T Med Imaging, 22(6), 730-741, (2003)
[12] Lorenzi, M., Ayache, N. and Pennec, X., "Alzheimer's Disease Neuroimaging Initiative, Schild's Ladder for the Parallel Transport of Deformations in Time Series of Images," Inf Process Med Imaging, 22, 463-74, (2011)
[13] Maheswaran, S., Barjat, H., Rueckert, D., Batec, S.T., Howlett, D.R., Tilling, L., *et al.,* "Longitudinal regional brain volume changes quantified in normal aging and Alzheimer's APP×PS1 mice using MRI," Brain Res, 1270, 19-32 (2009)
[14] Lau, J.C., Lerch, J.P., Sled, J.G., Henkelman, R.M., Evans, A.C., and Bedell. B.J., "Longitudinal neuroanatomical changes determined by deformation-based morphometry in a mouse model of Alzheimer's disease," Neuroimage, 42(1), 19-27 (2008)
[15] Zamyadi, M., Baghdadi, L., Lerch, J.P., Bhattacharya, S., Schneider, J.E., Henkelman, R.M., *et al.,* "Mouse embryonic phenotyping by morphometric analysis of MR images," Physiol Genomics, 42A(2), 89-95 (2010)

[16] Spring, S., Lerch, J.P. and Henkelman, R.M., "Sexual dimorphism revealed in the structure of the mouse brain using three-dimensional magnetic resonance imaging," Neuroimage, 35(4), 1424-33 (2007)
[17] Falangola, M.F., Ardekani, B.A., Lee, S.P., Babb, J.S., Bogart, A., Dyakin, V.V., *et al.,* "Application of a non-linear image registration algorithm to quantitative analysis of T2 relaxation time in transgenic mouse models of AD pathology," J Neurosci Methods, 144(1), 91-7 (2005)
[18] Lerch, J.P., Carroll, J.B., Spring, S., Bertram, L.N., Schwab, C., Hayden, M.R., *et al.,* "Automated deformation analysis in the YAC128 Huntington disease mouse model," Neuroimage, 39(1): 32–9 (2008)
[19] Yin, R. K., [Case study research: design and methods], 4th edn. Sage (2009)
[20] Mattson, M. P., and Wan, R. Q., "Beneficial effect of intermittent fasting and caloric restriction on the cardiovascular and cerebrovascular systems," J Nutr Biochem 16, 129-137 (2005)
[21] http://elastix.isi.uu.nl (15 October 2012)
[22] http://www.mevislab.de/ (Version 2.1(VC8), 15 October 2012)
[23] Khmelinskii, A., Mengler, L., Kitslaar, P., Staring, M., Po, C., Reiber, J.H.C., Hoehn, M. and Lelieveldt, B.P.F., "Interactive system for exploration of multi-modal rat brain data," Proc EMIM (2011)
[24] Mengler, L., Khmelinskii, A., Po, C., Staring, M., Reiber, J.H.C., Lelieveldt, B.P.F., and Hoehn, M., "Juvenile development and ageing mediated changes in cortical structure and volume in the rat brain," Proc EMIM (2011)