AnToNIa: A Software Tool for the Hemodynamic Analysis of Cerebral Vascular Malformations Using 3D and 4D MRA Image Sequences

Nils Daniel Forkert[1], Dennis Säring[1], Jens Fiehler[2], Till Illies[2] and Heinz Handels[1]

[1]Department of Medical Informatics,
[2]Department of Diagnostic and Interventional Neuroradiology
University Medical Center Hamburg-Eppendorf
Martinistraße 52, D-20246 Hamburg
n.forkert@uke.uni-hamburg.de

Abstract: Stroke is the second most common cause of death and major cause of disability worldwide. Approx. 20% of cerebral strokes are caused by hemorrhages due to rupture of cerebral vascular diseases like aneurysms or arteriovenous malformations. In case of an early diagnosed cerebral vascular disease an exact knowledge of the individual anatomy and hemodynamic situation is needed for an improved rating of the disease and therapy planning. New 3D and 4D MRA imaging techniques can improve the diagnostic possibilities while reducing the risk for the patient at the same time. The combined analysis and visualization of these image sequences for the diagnosis of vascular malformations pose new complex and special requirements, which are not met by established neuro imaging software tools so far. In this paper a new software tool named AnToNIa (Analysis Tool for Neuro Imaging Data) for the analysis of cerebral hemodynamics based on 3D and 4D MRA image sequences is presented. Within this scope methods for the segmentation and combined analysis and visualization of 3D and 4D MRA datasets are described. In a first in-house trial by clinicians AnToNIa was rated to provide the opportunity for improved clinical diagnostics of cerebral malformations.

1 Introduction

Cerebrovacular diseases are a major reason for strokes. In case of an early diagnosed cerebral vascular disease an exact knowledge of the individual anatomy and hemodynamic situation is needed for an improved rating of the disease and therapy planning.
In the majority of cases high resolution CT or MR angiography is used to obtain anatomical information about the intracranial vessel system while the intravenous digital subtraction angiography (DSA) with high temporal resolution remains the gold standard for the analysis of the patient individual hemodynamics. The DSA offers several drawbacks like the ionizing radiation and complications due to the invasive procedure. Furthermore DSA supplies only 2D projections of the vessel system.
Recent development in the field of MR image acquisition techniques, like echo sharing and parallel imaging techniques, enables 4D imaging of the blood flow with a high temporal

resolution. 4D MRA techniques can overcome the typical drawbacks of the DSA and offer advanced information about the cerebral hemodynamics for diagnosis, therapy planning.
On the other hand 4D MRA imaging comes along with an information overflow due to the high number of images acquired. In order to also provide a benefit for the diagnosis of these diseases for clinicians an easy to use softwaretool for the combined analysis and visualization of high resolution 3D and 4D MRA image sequences is needed to meet the complex requirements.
Several commercial and free software tools for the analysis of neuro image data are available. All tools are unique in their own way relating to their primary applications and target user group. Most software tools for the analysis of neuro imaging data focus either on fMRI analysis or on surgery planning and navigation. A tool especially for the analysis of cerebral malformations based on 3D and 4D MRA image sequences has not been established yet.

2 AnToNIA - Analysis Tool for Neuro Imaging Data

The software system AnToNIa (Analysis Tool for Neuro Imaging Data) was developed to enable the combined visualization and analysis of cerebral veascular malformations in spatial and spatiotemporal MRA datasets. For this purpose several features like image preprocessing, vascular segmentation, hemodynamic analysis and combined analysis and visualization have been developed and modularly implemented, such that the results from any given phase can be used and saved independently.

2.1 Supported MRA images sequences

The methods described in the following were developed and tested based on common MRA datasets like high resolution 3D Time-of-Flight (TOF), 3D contrast enhanced, 4D Time-resolved echo shared angiographic technique (TREAT) and 4D Time-resolved Angiography With Interleaved Stochastic Trajectories (TWIST) MRA sequences. The tested image sequences were acquired by different MR scanners with different field strengths (1.5 - 7 T). The MRA datasets can be loaded using the original dicom sequences.

2.2 Preprocessing

High resolution MR sequences suffer from several artifacts caused by acquisition. Three methods for reduction of typical artifacts have been implemented in AnToNIa.
A common problem especially for TOF image sequences is the slab boundary artifact [KAP02] caused by multi-slab acquisition technology which results in slice-to-slice amplitude variations associated with imperfect slab definitions. In a device related preprocessing step the measurements are carried out with a slab overlap of 20 to 30 % which are

combined to a single dataset usually using a maximum operation of corresponding voxels. Despite this preprocessing a reduction of the amplitude can still be observed in the overlapping region. In order to prevent consequential suboptimal results during further processing steps these intensity inhomogeneties can be reduced using a histogram matching technique proposed by Kholmovski et al. [KAP02].
Magnetic field inhomogeneities might lead to signal variations, the bias field. In order to compensate these variations the method proposed by Styner et al [SBSG00] was implemented. Finally the anisotropic diffusion smoothing approach as presented by Whitaker and Xue [WX01] is available in AnToNIa.

2.3 Vessel Segmentation

The extraction of the vascular structures from high resolution 3D MRA datasets is the basis for an improved visualization and the hemodynamic analysis of cerebrovascular malformations. Several methods for the segmentation of the vascular system have been proposed. Due to the complex structure of malformations a method incorporating the intensities as well as information about typical vessel structures as proposed by Forkert et al. [FSW$^+$09] has been implemented.
Based on the high resolution 3D image a vesselness [SNS$^+$98] and a maximum parameter image are computed first. These parameter images are then combined with the 3D MRA sequence using a fuzzy inference system. The resulting fuzzy image offers an improved enhancement of small as well as malformed vessels against the remaining brain. Finally, the fuzzy-connectedness approach is used to extract the vascular system.
Based on this segmentation a 3D surface model can be computed using the Marching Cubes algorithm [LC87]. Furthermore this segmentation allows automatic regional quantifications like vessel diameters.

2.4 Hemodynamic Analysis

The 4D MRA image sequences serve as the basis for the hemodynamic analysis. The estimation of bolus arrival times (BATs) based on time density curves is one of the most important hemodynamic parameters needed for the diagnosis and research of cerebral vascular malformations. For example differences between the BATs of corresponding vessel locations between the left and right hemisphere might provide information about the extent of the malformation [IFS$^+$08].
The number of publications dealing with this problem is high. In general these methods can be distinguished in model independent and model depended approaches. An extensive overview of current approaches is given by Shpilfoygel et al. [SCVD00].
Three methods (model independent, gamma variate fit and linear curve fit) have been incorporated into AnToNIA and will be described in more detail in the following.

2.4.1 Model Independent Bolus Arrival Time Estimation

Model independent (MI) approaches estimate the BAT parameter directly based on the concentration time curve. Several criteria have been proposed in the literature whereas the following seven have been implemented in AnToNIa:

- time to peak (TP)
- time to trailing half peak (TTHP)
- time to leading half peak (TLHP)
- time to maximum slope (TMaxS)
- time to minimum slope (TMinS)
- mean concentracion time (MCT)
- mean bolus arrival time (MBAT)

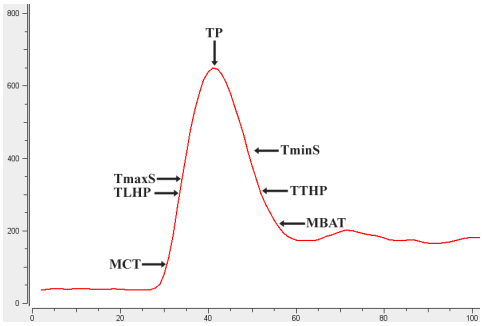

Figure 1: Criteria for model independent BAT estimation based on a concentration time curve (red)

2.4.2 Gamma Variate Fit Bolus Arrival Time Estimation

The main drawback using model independent criterias is the fixed discrete BAT estimation which depends on the temporal resolution of the data. This drawback can be overcome by fitting a gamma variate function to a concentration time curve (see Fig. 1) as first introduced by Thompson et al. [TSWM64] It was demonstrated that a concentration time curve can be represented by the gamma variate function:

$$C(t) = K(t - AT)^{\alpha} e^{-(t-AT)/\beta} \tag{1}$$

which is valid for $t > AT$ where t is the independent variable, AT the appearance time, K the constant scale factor and α and β are arbitrary parameters.
As reported by Madsen a change of the α and β parameters does not only affect the rise and fall times of the function but also lead to a change of the location and magnitude of the function maximum. Since this might lead to problems during the fitting progress Madsen [Mad92] presented a simplified but entirely equivalent form of the gamma variate function:

$$C(t) = y_{\max} t'^{\alpha} e^{\alpha(1-t')} \tag{2}$$

with $t' = \frac{t-AT}{t_{\max}-AT}$ which was implemented in AnToNIa using Powell's algorithm for optimization of the parameterset α, AT, $t_{\max}$ and $y_{\max}$.
For definition of a BAT the same parameters as listed above can be calculated for every fitted gamma variate function. Furthermore the gamma-variate function allows the computation of further hemodynamic parameters such as cerebral blood volume (CBV), cerebral blood flow (CBF) and mean transit time (MTT).

2.4.3 Linear Curve Fit Bolus Arrival Time Estimation

As a third approach for estimation of the BAT the reference based curve fitting method as proposed by Forkert et al. [FSF+09] was implemented. First of all in this approach a patient individual hemodynamic reference curve is computed by calculating the normalized mean curve of the concentration time curves, whereas curves which do not exhibit a typical form are excluded from this calculation. In order to enable the evaluation of the reference curve between the sample points a B-Spline interpolation is performed on the extracted discrete reference curve. Due to the averaging, the extracted reference curve generally exhibits clear characteristics. For this reason in a next step the same characteristics as mentioned in section 2.4.1. can be extracted as the reference BAT.
In order to estimate the BAT for a given, also normalized, concentration time curve $s(t)$ the reference curve $r(t)$ is fitted to $s(t)$, such that the sum of squared differences (SSD)

$$\text{SSD}(s, r(f)) = \sum_{i=1}^{m} (s(t) - r(f(t)))^2 \tag{3}$$

with $f(t) = at + b$ is minimized (see Fig. 1), whereas a is the scaling factor, b the shift factor and m the number of sample points of the concentration time curve. Powell's optimization algorithm is used to reduce the computation time. In order to define the BAT of the concentration time curve the computed parameters a and b are used to transform the reference BAT to the concentration time curve.

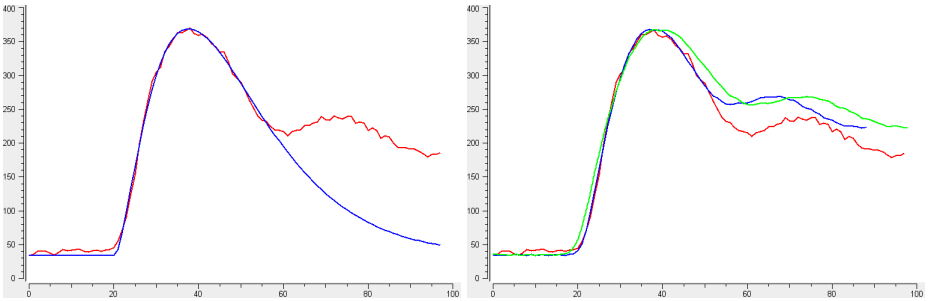

Figure 2: Gamma variate fit (left): concentration time curve (red) and fitted gamma variate function (blue) and reference curve fit (right): concentration time curve (red), reference curve (green) and transformed reference curve (blue)

2.5 Visualization

AnToNIa offers serveral visualization options. Besides the slicewise display of the datasets in all anatomical directions with window-level functions 3D and 4D visualizations have been implemented. Besides the direct volume rendering of the anatomical data an improved visualization based on surface models of the segmented vascular structures is possible. The 3D display of the vascular system allows rotating, panning and zooming.

The methods described above for the hemodynamic analysis can not only be used to calculate the BATs voxelwise but also for a whole 4D dataset. The estimated BATs can then be transferred to the surface model using the registration method described in Säring et al. [SFF+07]. After transfer of the BATs to the surface model they can be visualized dynamically. In doing so points of the 3D model which have an earlier BAT than a user supplied threshold are colored red while the other points are colored white.

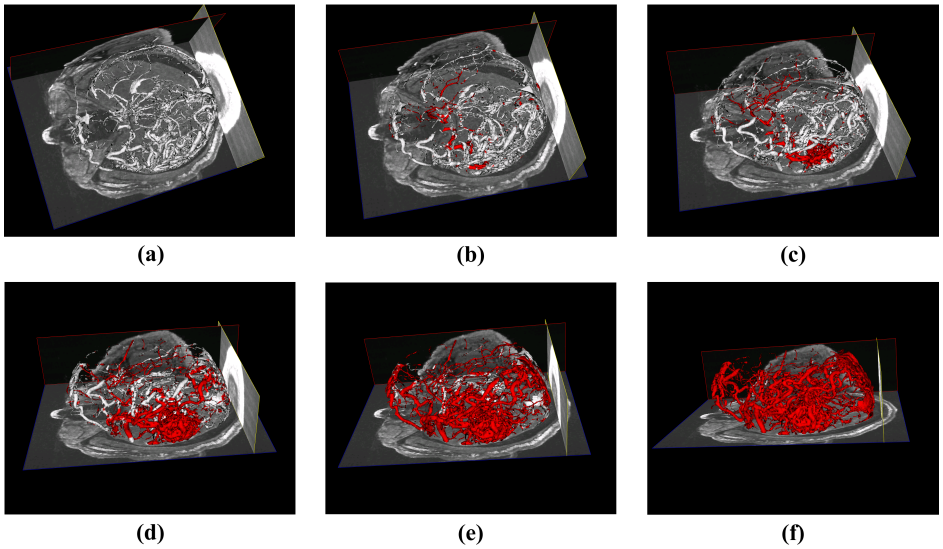

Figure 3: Selected Frames from a dynamic 3D visualization of the cerebral blood flow

3 Results

AnToNIa was implemented in C++ based on the open insight segmentation and registration toolkit (ITK), the open visualization toolkit (VTK) and QT. Classes were problem-oriented customized and new classes were developed.
At the moment the software prototype AnToNIa is in the beta-phase and tested by neuroradiology experts. In a first qualitative evaluation of the software tool, AnToNIa was judged to offer diagnostic benefit compared to the diagnostic state of the art. The dynamic visualization of the blood flow based on the combination of 3D and 4D MRA image sequences was rated to be of high clinical relevance especially regarding risk prediction, therapy planning and clinical monitoring after therapy. All aforementioned methods have been encapsulated in a graphical user interface (GUI) (see Fig. 4). The GUI was rated to be intuitive and easy to use.
The possibility of estimating the BAT for any given point in three dimensions has already been incorporated in medical studies [FIP+, IFS+08].

4 Discussion

The patient individual dynamic blood flow is of great importance for diagnosis of cerebral vascular diseases. AnToNIa can fill the existing gap of missing tools for the analysis and visualization of the cerebral hemodynamics based on 3D and 4D image sequences. So far AnToNIa has only been used for research purposes and not for clinical tasks. AnToNIa has to be provided under the common approvals and certificates in order to allow the following planned multi-centered test phase and establish AnToNIa for clinical purposes like therapy planning.
It is planned to extent AnToNIa by computational fluid dynamics (CFD) methods in the future to allow the computation of parameters like pressure and wall shear stress. A long term goal is the simulation of the blood flow based on a planned therapy using CFD. In summary AnToNIa can support the clinicians for diagnosis and rating of cerebral vascular diseases in the future.

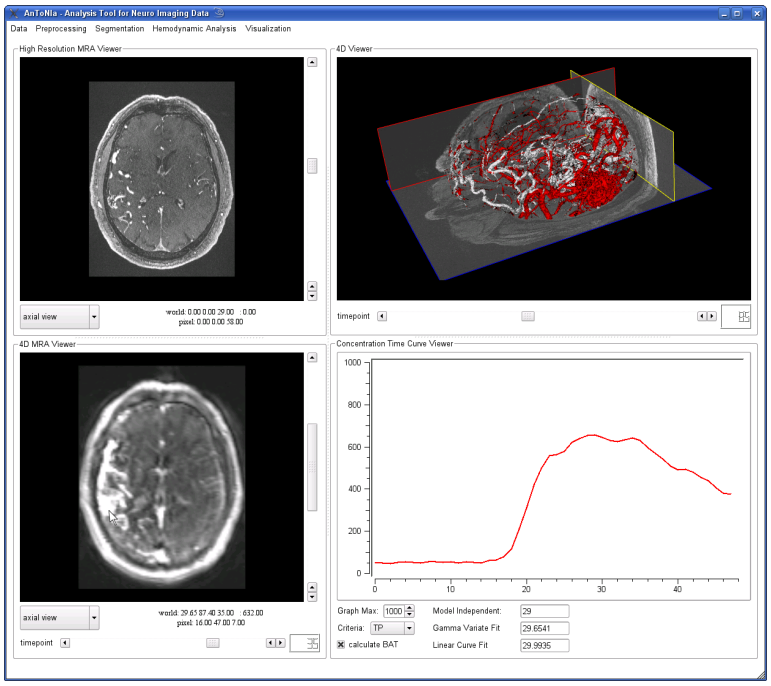

Figure 4: The Graphical User Interface of AnToNIa

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