ANTONIA Perfusion and Stroke

A Software Tool for the Multi-purpose Analysis of MR Perfusion-weighted Datasets and Quantitative Ischemic Stroke Assessment

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Summary
Objectives: The objective of this work is to present the software tool ANTONIA, which has been developed to facilitate a quantitative analysis of perfusion-weighted MRI (PWI) datasets in general as well as the subsequent multi-parametric analysis of additional datasets for the specific purpose of acute ischemic stroke patient dataset evaluation.

Methods: Three different methods for the analysis of DSC or DCE PWI datasets are currently implemented in ANTONIA, which can be case-specifically selected based on the study protocol. These methods comprise a curve fitting method as well as a deconvolution-based and deconvolution-free method integrating a previously defined arterial input function. The perfusion analysis is extended for the purpose of acute ischemic stroke analysis by additional methods that enable an automatic atlas-based selection of the arterial input function, an analysis of the perfusion-diffusion and DWI-FLAIR mismatch as well as segmentation-based volumetric analyses.

Results: For reliability evaluation, the described software tool was used by two observers for quantitative analysis of 15 datasets from acute ischemic stroke patients to extract the acute lesion core volume, FLAIR ratio, perfusion-diffusion mismatch volume with manually as well as automatically selected arterial input functions, and follow-up lesion volume. The results of this evaluation revealed that the described software tool leads to highly reproducible results for all parameters if the automatic arterial input function selection method is used.

Conclusion: Due to the broad selection of processing methods that are available in the software tool, ANTONIA is especially helpful to support image-based perfusion and acute ischemic stroke research projects. Correspondence to:

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1. Introduction

The quantitative analysis of perfusion-weighted MRI (PWI) datasets is an integral part in today’s clinical routine as well as for image-based research projects that aim at improving the basic understanding of several cerebral diseases such as stroke, tumors, and multiple sclerosis [1–3]. An improved understanding of the perfusion may ultimately lead to improved clinical decision making and subsequent therapies for the patient. Apart from this, perfusion analyses have also been proven useful for several other organs such as the heart, liver, and placenta [4–6].

Although the sole analysis of PWI datasets is often a crucial part of image-based research projects and clinical decision making, advanced image processing methods and quantitative analyses of additional datasets may be required depending on the organ or disease of interest. This is especially the case in patients with an acute ischemic stroke. Here, it is most important to enable a combined analysis of diffusion-weighted MRI (DWI) together with PWI datasets to determine the so-called perfusion-diffusion mismatch [7] or predict the tissue outcome prediction on a voxel-by-voxel level using high-level multi-parametric classification techniques [8]. Beyond that, the additional analysis of FLAIR (fluid-attenuated inversion recovery) MR datasets may help to identify patients with unknown stroke onset who are eligible for thrombolysis therapy by analyzing the DWI-FLAIR mismatch [9].

The different image processing methods that are required for the quantitative analysis of PWI datasets and subsequent combined evaluation of multi-parametric datasets can be performed using a variety of software tools that are freely available, subject to charge, or only available with vendor-related hardware such as MR scanners. Commonly, several tools have to be used to implement an image processing chain for a specific analysis, which can make such an analysis complicated and often requires profound knowledge about the tools, programming languages, or image format.
conversion and, therefore, representing an important error source.

The aim of this work is to present the perfusion and stroke (PS) version of the software tool ANTONIA (Analysis Tool for Neuro Imaging Data), which has been developed to enable a quantitative analysis of perfusion-weighted MRI datasets in general as well as the subsequent combined analysis of additional datasets for the specific purpose of acute ischemic stroke patient dataset evaluation.

2. Methods

2.1 Multi-Purpose Perfusion Analysis Methods

At this point, the ANTONIA software tool is capable of handling standard single-gradient-echo DSC (dynamic susceptibility contrast) and DCE (dynamic contrast-enhanced) PWI datasets. Overall, three different methods for the quantitative analysis of perfusion-weighted MRI datasets are currently implemented in ANTONIA, which can be case-specifically selected. The three methods comprise an input-free fitting-based method, the deconvolution-based perfusion analysis, and the deconvolution-free blood flow quantification method. The latter two methods differ from the fitting-based method in a way that a previous definition of an arterial input function is required for the quantitative perfusion analysis. These three methods will be described in the following subsections after an overview of the implemented methods for pre-processing of PWI datasets, which differ with respect to the PWI acquisition technique used, is given.

2.1.1 Pre-processing of Dynamic Susceptibility Contrast PWI Datasets

The complete flowchart for processing of DSC PWI datasets is illustrated in Figure 1. One problem that is often encountered with PWI datasets is patient movement.
during image acquisition, which may make the quantitative perfusion analysis error-prone or even impossible. For DSC PWI datasets, a partial correction of patient movement is optionally performed in ANTONIA PS by applying slice-wise 2D rigid registrations. Therefore, each slice of the raw PWI dataset is registered to the corresponding slice of the previous time point by minimizing the mean squared difference between the images. Although a 3D registration may seem more accurate for correcting patient movements, the rather large slice thickness commonly used for DSC PWI acquisition may introduce even more errors in case of a 3D registration and would also require longer computation times. Moreover, a 3D registration would lead to problems regarding the subsequent slice-time correction of DSC PWI datasets described below.

Briefly described, DSC PWI techniques make use of susceptibility effects arising from application of paramagnetic contrast agents. These susceptibility effects result in a $T_2^*$ shortening of the proton spin relaxation times as the contrast agent bolus travels through the vessels and brain tissue leading to decreasing signal intensities. Assuming that the relationship between the change of the transverse relaxation rate and the concentration of the parametric contrast agent $[10]$ is linear, the signal intensity curve $S(t)$ for each voxel can be converted to a curve representing the relative transverse relaxivity changes $\Delta R'_2(t)$ employing the following formula:

$$\Delta R'_2(t) = \frac{k}{TE} \ln \left( \frac{S(t)}{S_0} \right),$$  \hspace{1cm} (1)$$

where $S_0$ denotes the baseline MR signal intensity, which is estimated based on the first three time points, $TE$ the echo time, and $k$ a proportionality constant, which is typically set to 1.0.

After conversion, all commonly used perfusion analysis methods that require positive instead of negative contrast agent peaks can be applied to each curve. However, $\Delta R'_2(t)$ is only relative to the real tracer concentration. To overcome this problem, the correction formulas and values described in $[11]$ were used in this work to convert each $\Delta R'_2(t)$ to the corresponding concentration time curve, which represents an estimation of the time-dependent contrast agent concentrations in mM.

DSC PWI datasets are typically acquired using an interleaved 2D slice acquisition. This leads to the problem that two neighboring slices in a 3D dataset exhibit a temporal difference regarding the acquisition time of up to $TR/2$ ($TR =$ repetition time), which may have a crucial influence on the subsequent analysis steps, especially in case of simple time-to-peak estimation. Therefore, a slice-time correction is used in ANTONIA PS to correct for this problem.

This is implemented by using a $b$-spline interpolation or b-spline approximation of the concentration time curves. In general, the $b$-spline interpolation performs about four times faster compared to the approximation. However, the benefit of the $b$-spline approximation is that it enables an improved noise reduction of the concentration time curves while at the same time preserving the rather skew shape of the curves, which is not the case if using typical linear smoothing filters. The interpolation method can be interactively selected by the user, whereas the $b$-spline approximation is the preselected choice.

The $b$-spline interpolation or approximation does not only allow to perform a slice-time correction in terms of temporal normalization to a reference frame, which is commonly the first or second slice, but also to resample the concentration time curves with a standardized temporal resolution regardless of the original temporal resolution used for the image acquisition. This is especially helpful to reduce a potential bias that may arise when using multiple DSC PWI datasets acquired with different temporal resolutions in a study. The standard output temporal resolution is currently set to 1.0 second per 3D dataset.

### 2.1.2 Pre-processing of Dynamic Contrast-enhanced PWI Datasets

In contrast to DSC PWI imaging, DCE PWI imaging techniques rely on the change of $T_1$ relaxation time by contrast agent extravasation. Thus, a conversion from signal intensity to concentration time curves is not necessary for these datasets. Likewise, a slice-time correction is also not required since DCE PWI datasets are usually acquired using a 3D imaging technique, which simplifies the required pre-processing considerably.

More precisely, only three pre-processing steps are required for DCE PWI data- sets, whereas two of these steps are only optional. First, the motion correction can be applied optionally if required using the same technique as described above (only in 3D). The second pre-processing method, which is always applied to DCE PWI datasets is the baseline correction. Here, the mean intensity is calculated for the first three time points of a given concentration time curve. The mean baseline value is then subtracted from each value of the corresponding concentration time curve.

The interpolation or approximation of the concentration time curves is the third optional processing step. Since DCE PWI datasets are often acquired using low temporal resolutions, resampling to a fixed temporal resolution may lead to high memory requirements as well as long processing times in the subsequent processing steps.

### 2.1.3 Fitting-based Perfusion Analysis

The fitting-based perfusion analysis has been used for data acquired from various indicator dilution techniques in the past. Here, the main idea is to fit a continuously defined model function to the discrete time points of each concentration time curve, which is supposed to reduce the problem of noise artifacts and exclude potentially present bolus recirculation contributions from the concentration time curves such that only the first bolus passage is used for the quantitative perfusion analysis. After fitting of the model function to the discrete sample points of a given concentration time curve, the typically used perfusion parameters can be estimated based on the fitted curve.

Several hemodynamic model curves have been presented in the past such as the gamma variate model $[12]$, the modified log-normal model $[13]$, the reference-based linear curve fitting model $[14]$, and the local density random walk (LDRW) model $[15]$. Although the gamma variate
model has been mostly used for this purpose, the LDRW model is implemented and used in ANTONIA as it has been suggested that this model leads to better fitting results, especially in case of low signal drops between the first and second bolus passage [16]. Furthermore, it has been found that fitting of the Gamma Variate function is problematic due to the non-linearity of the optimization parameters [17]. The LDRW model is defined by Equation 2 (Figure 2), which is valid for \( t > AT \), where \( \alpha \) denotes the area under the curve, \( \mu \) the transit time of the median particle, \( \lambda \) the parameter describing the skewness of the curve, and \( AT \) the appearance time of the distribution. The second benefit of the LDRW model is that relative estimates of the mean transit time (MTT) and the cerebral blood volume (CBV), which are two important perfusion parameters, are directly determined during the optimization process \( (\mu = \text{MTT} \text{ and } \alpha = \text{CBV}) \) and, thus, do not have to be calculated separately. After fitting of the model curve, the time-to-peak (TTP) parameter can be estimated by determining the time until the fitted model curve achieves its maximum and the cerebral blood flow (CBF) parameter can be estimated using the central volume theorem [18]:

\[
\text{CBF} = \frac{\text{CBV}}{\text{MTT}}
\]

2.1.4 Deconvolution-based Perfusion Analysis

The benefit of the fitting-based perfusion analysis is that it can be applied directly to the concentration time curves without any additional input, which may exclude a potential source of variability associated with selection of these input parameters. This is, for example, beneficial if single subject longitudinal perfusion changes are of interest. However, it has to be pointed out that the fitting-based perfusion analysis is quite time consuming and, even more important, the corresponding results are not corrected for the arterial input such that the contrast agent injection protocol needs to be kept equal for obtaining comparable results.

In case of multi-subject analyses using DSC PWI datasets, the deconvolution-based perfusion analysis represents today’s gold standard for the quantitative perfusion analysis. In theory, the deconvolution-based perfusion analysis is corrected for the arterial input function, which depends on the injection protocol and cardiac output function. However, the deconvolution-based perfusion analysis requires a previous definition of an arterial input function \( C_a(t) \), which may also introduce an additional source of variability to the quantitative analysis. It should be highlighted that a different correction is required to convert an arterial input function to the corresponding concentration time curve \( \Delta R^a(t) \), which was implemented using the quadratic formula and corresponding values also described in [11].

The main idea of the deconvolution-based perfusion analysis is to determine the residue function \( R(t) \), which represents the amount of contrast agent in the vascular bed at a given time point [19], of a voxel using the following relation:

\[
C(t) = CBF \cdot R(t) \otimes C_a(t)
\]

where \( CBF \) denotes the cerebral blood flow and \( \otimes \) the convolution parameter. Obviously, the CBF parameter results directly from the deconvolution in terms of the maximum of the residue function and does not need to be calculated separately. In accordance to [20], the following definitions have been used in ANTONIA for determining the remaining important perfusion parameters:

\[
\text{CBV} = \int_0^\infty R(t) \, dt
\]

\[
T_{\text{max}} = \arg \max_t R(t)
\]

\[
\text{MTT} = \frac{\text{CBV}}{\text{CBF}}
\]

The numerical integration required for CBF calculation was implemented using Simpson’s rule. The CBF and CBV values are further corrected for the mean density of brain volume, which was assumed to be \( \rho = 1.04 \, \text{g/mL} \), and for the different hematocrit levels in capillaries and large vessels using the dimensionless coefficient \( \alpha = 0.73 \).

Compared to the fitting-based perfusion analysis, the deconvolution-based perfusion analysis counterpart to the TTP parameter is the Tmax parameter. The main benefit of the Tmax parameter is the automatic correction for the systemic bolus delay, which depends on the time between contrast agent application and image acquisition starting time. Thus, theoretically the Tmax parameter does not need to be normalized, for example, using a volume of interest in the contralateral hemisphere to compare different subjects.

The deconvolution is an ill-posed problem and several methods have been proposed to solve this equation, whereas the block-circulant singular value decomposition together with a truncation threshold of 15% is used in ANTONIA for this purpose as it has been shown to lead to good results [21].

2.1.5 Deconvolution-free Perfusion Analysis

The fitting-based as well as the deconvolution-based perfusion analysis methods have in common that the PWI datasets to be analyzed have to be acquired at a rather high temporal resolution, which is often not the case for DCE PWI datasets such that these models cannot be applied directly to this image sequence. Apart from these drawbacks, the deconvolution itself may also represent a source of error due to the ill-posed nature of this problem but also in case of inappropriate truncation threshold selection, which may lead to strong oscillations in the residue functions and subsequent errors regarding the perfusion parameter value calculation.

The third perfusion analysis method, the deconvolution-free approach, has been integrated in ANTONIA PS especially for...
the blood flow analysis in DCE PWI datasets using the basic methodology of the steepest slope model [22] but it can also be used for perfusion parameter determination in DSC PWI datasets. In contrast to the two perfusion analysis methods described above, the original formulation of the steepest slope model enables only the calculation of the blood flow parameter. Despite this drawback, this perfusion model is known to be numerically robust and fast. The steepest slope model can be used to determine the blood flow using the following relation [22, 23]:

\[
\text{CBF} = \frac{\max (C'(t))}{\max (C_a(t))}
\]  
where \(C'(t)\) denotes the first derivative of the concentration time curve \(C(t)\) and \(C_a(t)\) the arterial input function. For reduction of the influence of noise and prevent a smoothing related underestimation of the perfusion values, the first derivative is calculated in ANTONIA using an iterative three-point linear regression analysis.

Apart from the usage of the steepest slope model for blood flow quantification, ANTONIA PS has also been extended in a way that the other three perfusion parameters of interest (CBV, MTT, Tmax/TTP) can also be computed deconvolution-free using the following definitions:

\[
\text{CBV} = \frac{\int_0^t C(t) \, dt}{\int_0^t C_a(t) \, dt}
\]

\[
\text{Tmax} = \arg \max \left\{C(t) - \arg \max C_a(t) \right\}
\]

\[
\text{MTT} = \frac{\text{CBV}}{\text{CBF}}
\]

2.1.6 Local Perfusion Analysis

Figure 3 exemplarily shows the four perfusion parameter maps obtained from one DSC PWI dataset using the three different perfusion analysis methods. Although the resulting maps from the three different perfusion analysis methods correlate well on a visual basis, quantitative differences have to be expected. Thus, the results of the three different methods should not be mixed when analyzing one study population.

After quantitative perfusion analysis using one or more of the aforementioned perfusion analysis models, a local perfusion quantification can be performed in ANTONIA by manually defining volume-of-interests (VOIs) in the DSC or DCE PWI dataset. Therefore, a single time point can be manually selected from the PWI dataset, which serves as the basis for the VOI definition. A VOI can be defined by interactively placing points at the border of the region of interest in each slice of the dataset. These points are automatically connected using a cubic spline interpolation. Finally, a 3D VOI is generated based on the 2D spline contours. This procedure can be performed multiple times such that several VOIs can be defined and analyzed in a quantitative manner, whereas the mean value and corresponding standard deviation is calculated for each available perfusion parameter and VOI. Noteworthy, such a VOI can also be used for normalization of the extracted perfusion parameter maps.
2.2 Multi-Parametric Ischemic Stroke Analysis

The quantitative perfusion analysis using one of the models described above and the subsequent local perfusion analysis can be used to analyze the perfusion situation of an organ of interest at a given time point as well as for evaluation of longitudinal single subject perfusion changes. However, a combined analysis of a PWI dataset together with other image sequences may be of high interest depending on the disease or organ of interest.

Within this context, especially the multi-parametric stroke analysis is of high importance in today’s clinical routine and research. Therefore, the ANTONIA PS tool has been extended to enable such a quantitative multi-parametric analysis of acute ischemic stroke datasets. The following subsections describe the implemented methods for the multi-parametric stroke analysis that focus especially on DWI and FLAIR image sequences.

2.2.1 Combined PWI-DWI Analysis and Mismatch Quantification

The pipeline for the PWI-DWI mismatch quantification, which is described in the following, is illustrated in Figure 4. For calculation of the PWI-DWI mismatch, ANTONIA PS requires at least two DWI datasets acquired with different diffusion weightings as well as the corresponding DSC PWI dataset. More precisely, a DWI dataset acquired without diffusion weighting \((b=0 \text{s/mm}^2)\), which is basically a T2-weighted dataset, and at least one other DWI dataset acquired with a higher \(b\)-value, which is preferably \(\geq 1000 \text{s/mm}^2\), are required. After registration of the DWI dataset with the higher \(b\)-value to the DWI dataset acquired without diffusion weighting using a rigid transformation, linear interpolation, and maximization of the mutual information [24], the two DWI datasets are used to calculate the corresponding quantitative apparent diffusion coefficient (ADC) dataset using the following formula [25]:

\[
S = S_0 \exp(-b \cdot \text{ADC}). \tag{12}
\]

Here, \(S_0\) describes the baseline value while \(b\) denotes the corresponding \(b\)-values.

After calculation of the ADC parameter dataset, an automatic skull stripping is performed to exclude non-cerebral tissues. This is implemented using intensity thresholding, followed by a morphological opening operation and a largest connected component analysis. After skull stripping, the cerebrospinal fluid (CSF) is automatically excluded from the segmented brain tissue using an upper threshold of \(1200 \times 10^{-6} \text{mm}^2/\text{s}\).

In a next step, the stroke lesion can be semi-automatically segmented in the ADC dataset by interactively placing seed points in the stroke region. After this, a 3D volume growing approach is performed to define the acute stroke lesion. Practically, the upper threshold for this can be manually selected. However, an ADC threshold of \(550 \times 10^{-6} \text{mm}^2/\text{s}\) is used in ANTONIA PS as the standard value for this purpose, which is in accordance to previous stroke studies such as [26]. Depending on the threshold used, several seed points may be necessary to include all regions of reduced diffusion in the volume growing segmentation.

The identification of the PWI-DWI mismatch volume usually requires a registration of the two image sequences due to different field-of-views used for the image acquisition or even due to patient movement between the two acquisitions. Therefore, a registration of the PWI to the DWI image sequence is automatically performed in ANTONIA PS using a rigid transformation, linear interpolation and maximization the mutual information [24] between the DWI \(b = 0 \text{s/mm}\) and baseline PWI dataset calculated by averaging the first three time points. The resulting transformation is then used to transform the perfusion parameter maps to the ADC image sequence using a linear interpolation.

After registration, a volumetric definition of the PWI-DWI mismatch becomes possible. In theory, all perfusion parameters described above can be used for this. However, the Tmax parameter dataset resulting from the deconvolution-based perfusion analysis is most often used for this purpose and is also defined in ANTONIA PS as the standard choice.

More precisely, all voxels of the acute stroke infarct core (ADC lesion) are used as seed points for an automatic volume growing method in the registered perfusion parameter image to define the hypoperfused tissue. The parameter threshold used for this can be modified interactively. However, a delay threshold of Tmax > 6 s represents the preselected standard threshold in ANTONIA PS if the Tmax parameter dataset is used for definition of the hypoperfusion, which is in line with current large stroke studies such as EXTEND [27]. Moreover, only voxels part of the brain segmentation and not part of the CSF segmentation are used for this purpose.

For quantitative PWI-DWI mismatch definition, the acute stroke lesion as segmented in the ADC dataset is subtracted.
2.2.2 Automatic Arterial Input Function Definition

Although all three perfusion analysis methods described above can be used for perfusion parameter map calculation and subsequent PWI-DWI mismatch identification, the deconvolution-based approach has been used in most recent stroke studies. Like the deconvolution-free perfusion-free perfusion analysis, this method requires the definition of an arterial input function (AIF), which may be a potential source of variability.

Besides the interactive AIF definition by selection of a single voxel, an automatic AIF definition method has been developed and also implemented in ANTONIA. In contrast to the manual AIF definition, which can be used for any organ, the automatic AIF definition method can be only employed for cerebral PWI datasets since it uses the probabilistic cerebrovascular atlas described in [28].

More precisely, the probabilistic arterial cerebrovascular atlas, which was generated by segmenting the arterial cerebrovascular system in 700 time-of-flight MRA datasets of healthy volunteers and subsequent registration into the MNI (Montreal Neurological Institute) atlas space [29], was first segmented using a lower threshold of 15%. This threshold was selected since the corresponding segmentation contains only major cerebral arteries like the internal carotid artery or middle cerebral artery (MCA). After this, all segmented structures not part of the M1 or M2 segment of the MCA (middle cerebral artery) were manually removed from this segmentation.

In order to employ this segmentation for automatic AIF definition, the MNI brain atlas [29] is registered to the baseline PWI dataset, which is generated by averaging the first three time points of the raw PWI dataset, using an affine transformation, linear interpolation, and maximization of the mutual information metric. After affine transformation of the corresponding binarized probabilistic MCA information to the PWI dataset using a nearest-neighbour interpolation, the concentration time curves of all segmented voxels are extracted. The segmented probabilistic atlas MCA structures are considerably larger than the real patient-individual MCA vessels. Thus, the tissue concentration time curves need to be excluded from the extracted concentration time curves prior to the AIF calculation. This was performed by calculating the maximum intensity and time to maximum contrast agent enhancement of each extracted curve. These two values are then used for a k-means clustering (k = 2) of the concentration time curves. Here, it is assumed that the cluster with the higher maximum intensities and earlier times to maximum contrast agent enhancement corresponds to arterial structures. Finally, the concentration time curves corresponding to this cluster are averaged using an adapted version of the reference curve generation method described in [14], whereas the result of this is used as the AIF.

2.2.3 Combined DWI-FLAIR Analysis and Mismatch Quantification

The PWI-DWI mismatch is clinically relevant as it has been shown that patients with a large mismatch volume are more likely to benefit from thrombolysis therapy. Compared to the PWI-DWI mismatch, the concept of the DWI-FLAIR mismatch is rather new. The basic idea of this concept is that acute ischemic strokes lead to a diffusion restriction within minutes after onset but not to an immediate water uptake, which can only be measured using T2-weighted MRI sequences after a few hours. Therefore, the DWI-FLAIR mismatch concept assumes that patients with a visible DWI lesion but no corresponding FLAIR hyperintensities are likely to be eligible for a thrombolysis therapy, which is only approved for a time window of 4.5 hours after symptom onset [9]. Thus, patients with an unknown time point of symptom onset are currently excluded from thrombolysis therapy, which is especially relevant in case of the so-called wake-up strokes that occur during sleep. Although the DWI-FLAIR mismatch can be rated visually, this procedure is associated with a rather high inter-observer variability [9] and a quantitative evaluation of this mismatch concept may be more favorable. FLAIR intensities can vary considerably based on the imaging parameters such that only a semi-quantitative analysis of the DWI-FLAIR mismatch is possible.

The pipeline for the semi-quantitative DWI-FLAIR mismatch analysis implemented in ANTONIA, which is described in the following, is illustrated in Figure 5. For this purpose, the DWI datasets are processed in the same manner as described in the PWI-DWI mismatch section. In addition to the processing steps described above, the hemispheric fissure needs to be defined in the ADC parameter maps. Therefore, the fissure is manually defined in two axial slices as distant as possible using a straight line that can be interactively placed and moved in the dataset. The endpoints of these two lines are then employed to construct a 2D plane, which is used to mirror the infarct core segmentation to the contralateral hemisphere.

After this, the FLAIR dataset is registered to the ADC dataset using a linear interpolation, rigid transformation and maximization of the mutual information between the FLAIR image sequence and
the DWI dataset acquired without diffusion weighting \((b = 0 \text{ s/mm})\). After registration, the average FLAIR intensity signals in the infarct core segmentation and its mirrored counterpart are determined and used to calculate the corresponding FLAIR signal intensity ratio.

### 2.2.4 Volumetric and Distance Measurements

One benefit of the image processing pipeline is that it is not only valuable for the volumetric PWI-DWI mismatch calculation but also renders the possibility to calculate volumetric analyses of the brain. Within this context, it is possible to extract the whole brain volume as well as the volume of the CSF as estimated from the ADC segmentation methods. If the hemispheric fissure was defined by the user, these values can be also calculated separately for each hemisphere, which may be valuable as a surrogate for brain atrophy. However, due to the fact that the separation of the hemisphere is performed by a 2D plane, which may not represent an optimal choice for all patients, subtle atrophic changes may be too small to lead to a significant change in full brain volumetric analyses. To overcome this drawback, ANTONIA also renders the possibility to perform 2D measurements that can, for example, be used to determine the inter-caudate distance, which has been shown to be a good marker for atrophic changes [30].

At long last, ANTONIA PS also enables a semi-automatic definition of the follow-up lesion in FLAIR image sequences (Figure 6), which, among others, can be used as a surrogate endpoint in clinical trials. Therefore, the final infarct lesion can be manually surrounded in each slice using the same technique as described in the *Local Perfusion Analysis* section by placing points in the image that are connected using a cubic spline. In a subsequent step, an intensity threshold, which can be interactively varied, can be used to refine the final lesion segmentation. If required, a slice-wise drawing tool is also implemented in ANTONIA, which allows the manual removal of segmented voxels as well as the additional segmentation of non-segmented voxels.

### 2.3 Implementation Details

The ANTONIA PS tool has been developed in close collaboration of the local departments of neuroradiology and neurology. It is implemented in C++ using the freely available libraries ITK (Insight Toolkit) for image processing, VTK (Visualization Toolkit) and QT for visualization and graphical user interface (GUI) design, as well as AlgLib for the basic methods required for the hemodynamic analysis.

ANTONIA offers an intuitive graphical user interface (Figure 7), which was developed with direct feedback from the medical experts using this tool. Within this context, great care was taken to minimize the required user interaction, e.g. by automatically suggesting standard thresholds and input parameters as well as automatic serialization of consecutive processing steps that do not require any user interaction. Furthermore, the menu bar was designed in a way that the different functions are separated into different menus representing the main processing steps and image sequences (e.g. DWI Analysis, FLAIR analysis, DSC PWI analysis, etc.) and the corresponding functions listed in the order in which they should be used.

 Moreover, direct feedback and reasoning is given to the user if a selected function cannot be executed due to missing data or lack of previous calculations.

Currently, ANTONIA can be executed on a standard computer with Windows or Linux OS and the sole requirement of at least 2 GB of RAM.

### 2.4 Evaluation

Within the scope of this work, ANTONIA was evaluated regarding the inter-rater reliability of the multi-parametric stroke analysis. Therefore, two experienced observers with several years of dedicated experience in image-based stroke research processed DSC PWI, DWI and acute as well as follow-up FLAIR datasets of 15 stroke patients admitted to our hospital. More precisely, both observers determined the following five values for each patient using ANTONIA: 1) acute ADC lesion volume, 2) acute FLAIR signal intensity ratio, 3) acute tissue-at-risk volume determined with manually defined AIF, 4) acute tissue-at-risk volume determined with automatically defined AIF, and 5) follow-up lesion volume using FLAIR datasets acquired seven days after stroke onset.

All MR measurements were performed on a 1.5T Sonata Scanner (Siemens, Erlangen, Germany). DSC PWI were acquired after application of contrast agent (approx. 15 ml of Bayer Magnevist) using a TR = 1500 ms, TE = 37 ms, flip angle = 90°, and spatial resolution of \(0.94 \times 0.94 \times 5 \text{ mm}^3\). The DWI datasets were acquired without diffusion weighting \((b\text{-value} = 0 \text{ s/mm}^2)\) and with application of diffusion gradients in three directions with strong diffusion weighting \((b\text{-value} = 1000 \text{ s/mm}^2)\) using a TR = 3500 ms, TE = 89 ms, flip angle = 90°, and spatial resolution of \(0.94 \times 0.94 \times 5 \text{ mm}^3\). Acute and follow-up FLAIR imaging was performed using a TE = 108 ms, TR = 7900 ms, TI = 2500 ms, flip angle = 150°, and spatial resolution of \(0.45 \times 0.45 \times 5 \text{ mm}^3\).

After extraction of all values for each patient, Pearson’s cross correlation was calculated for each parameter, while the Dice overlap metric \(D\) was additionally calculated for the extracted lesion segmentations (acute ADC lesion, tissue-at-risk volumes, acute FLAIR signal intensity ratio, acute tissue-at-risk volume determined with manually defined AIF).

### Figure 6
Illustration of the follow-up lesion definition. Selected slice from a follow-up FLAIR dataset of a patient with an ischemic stroke (left), interactively encircled lesion including a safety margin (center) and corresponding lesion after interactive threshold-based refinement (right).


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The Dice metric is defined by:

\[ D(O_1, O_2) = \frac{2 \cdot |O_1 \cap O_2|}{|O_1| + |O_2|} \]  

(13)

Whereas \( O_1 \) and \( O_2 \) denote the two corresponding manual segmentations. Dice values close to 1 indicate a good consensus.

Furthermore, the required processing time was determined for each processing step using a standard computer with a dual core 2.4 GHz processor, 8 GB RAM and a 64 Bit Linux operating system.

3. Results

The quantitative results of the reliability evaluation are given in Table 1. Overall, very high correlation and Dice overlap values were found for all parameters except for the tissue-at-risk volumes that were determined using manual AIF definition.

Regarding the definition of the acute ADC lesion, inter-observer differences may arise due to the threshold and placement of the seed points used for 3D region growing. Since the standard ADC threshold of \( 550 \times 10^{-6} \, \text{mm}^2/\text{s} \) was not changed by the observers, the seed point placement was the only source of variability in this experiment, which explains the very high correlation of \( r = 0.999 \) and Dice values between 0.96 and 1.0 except for one dataset with a Dice overlap value of \( D = 0.84 \). This patient (#8) exhibits a very small ADC lesion such that only a few voxel difference leads to a considerable downgrade of the Dice value. Likewise, all segmentation differences could be ascribed to small lesion components consisting of only a few voxels, which were segmented by only one of the observers. However, the main ADC lesion components were equal for all datasets.

The FLAIR ratios measurements depend on the ADC lesion segmentation as well as the interactive definition of the hemispheric fissure using two straight lines. Again, very high correlation values were found for this parameter with an average difference between the two observers of less than 1%. Only in two patients (#1 and #4), the difference was greater than 2%. However, these patients exhibit a strong FLAIR mismatch, such that this difference would not be clinical relevant.

Apart from the AIF dependency, the tissue-at-risk volumes are also influenced by the ADC lesion segmentation as well as the perfusion parameter and threshold used for definition of the hypoperfused tissue. Due to the fact that the \( T_{\text{max}} \) perfusion parameter (deconvolution-based perfusion analysis) together with a temporal delay threshold of \( >6 \) was used by both observers in all cases for definition of the tissue-at-risk, the AIF definition and ADC lesion were the only sources of variability in this experiment. The most considerable differences between the two observers were found for the tissue-at-risk volumes determined using manually selected AIFs. In five of the 15 cases used in this evaluation, the volumetric difference between the two observers was even higher than 20 ml. This difference led to a correlation value of only \( r = 0.826 \) and an average Dice overlap value of \( D = 0.823 \). These inter-observer differences can be considerably decreased by using the automatic AIF definition method, which reduced the volumetric difference between the two observers to only 0.271 mL in the worst case (#4). The automatic AIF definition improves the correlation value to \( r = 1.0 \) and the mean Dice overlap to \( D = 0.997 \). In case of strong differences between the tissue-at-risk volumes determined by the manually defined AIFs, the tissue-at-risk volumes determined by the automatically defined AIFs were always considerably closer to the volumetric tissue-at-risk results of one of the two observers obtained by using the manually defined AIF.

Regarding the segmentation of the follow-up lesion in the FLAIR datasets ac-
required 7 days after stroke symptom onset, the definition of the initial lesion region using spline contours as well as the threshold used for refinement are the two potential sources of variability. On average, the follow-up lesion segmentation by the two observers differed by 1.827 mL leading to a correlation value of $r = 0.991$ and a mean Dice overlap value of $D = 0.93$. Most differences could be attributed to the usage of different thresholds for refinement such that one of the two segmentations was larger at the edge of the lesion. However, the general shape of the follow-up lesion was very similar in all cases.

The required times for automatic computation as well as manual interaction of the single processing steps are given in Table 2. Here, it can be seen that the manual interaction time for a typical data-computation as well as manual interaction of the general shape of the follow-up lesion is the fitting-based manual interaction time for a typical data-computation as well as manual interaction of the general shape of the follow-up lesion is the fitting-based manual interaction time for a typical data-set is between 1 and 3 minutes depending on the processing steps used. Regarded the automatic computation time, the most time-consuming step is the fitting-based perfusion analysis with ~ 8 minutes, which is considerably longer compared to the deconvolution-based and deconvolution-free perfusion analysis (10 and 25 seconds). Apart from this, the registration methods are also time-consuming with the PWI motion correction requiring the longest time (~ 4 min) followed by the automatic AIF definition method and other coregistration methods (60–80 s). Apart from this, the slice-time correction using the b-spline approximation requires about 4 times longer than the corresponding method using the b-spline interpolation (~ 25 s). A complete analysis of an acute stroke patient including DWI, DSC PWI and FLAIR datasets requires approximately 5–6 minutes if no motion correction is required, the b-spline interpolation is used and the AIF is manually selected. However, the complete time for analysis of a dataset can be 3–4 times higher depending on the methods used. It should be noted that a rather basic computer with only a dual core 2.4 GHz CPU was used for computation time assessment, which is a setup that is broadly available everywhere. Nevertheless, using faster multi-core processors would lead to a significant improvement of the computation time.

**4. Discussion**

The reported version of ANTONIA PS has already been used for various research studies. For example, it was used to compare the PWI-DWI mismatch volumes resulting from the application of different hemodynamic models [7]. Here, it was found that the choice of the hemodynamic model for curve fitting with and without subsequent deconvolution with an arterial input function has a clinically relevant influence on the PWI-DWI mismatch volumes.

The FLAIR-DWI mismatch is a rather new concept, which is currently evaluated in large prospective multi-center studies, such as the EU funded Wake-Up project [31]. Within this context it was shown in a previous work, describing the results of a large multi-center retrospective analysis, that it is possible to identify patients with an unknown time point of symptom onset,

**Table 1**

Quantitative results of the inter-rater reliability evaluation of the multi-parametric stroke analysis with correlation values $r$ and average Dice values (bold)

<table>
<thead>
<tr>
<th></th>
<th>ADC Lesion Volumes</th>
<th>FLAIR Ratio</th>
<th>Tissue-at-Risk Volumes with manual AIF definition</th>
<th>Tissue-at-Risk Volumes with automatic AIF definition</th>
<th>Follow-Up Lesion Volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obs1</td>
<td>Obs2</td>
<td>Dice</td>
<td>Obs1</td>
<td>Obs2</td>
</tr>
<tr>
<td>1</td>
<td>0.90</td>
<td>0.88</td>
<td>0.99</td>
<td>1.136</td>
<td>1.107</td>
</tr>
<tr>
<td>2</td>
<td>7.57</td>
<td>7.50</td>
<td>1.00</td>
<td>1.118</td>
<td>1.119</td>
</tr>
<tr>
<td>3</td>
<td>7.08</td>
<td>7.04</td>
<td>1.00</td>
<td>1.077</td>
<td>1.082</td>
</tr>
<tr>
<td>4</td>
<td>17.84</td>
<td>18.51</td>
<td>0.98</td>
<td>1.336</td>
<td>1.312</td>
</tr>
<tr>
<td>5</td>
<td>4.63</td>
<td>4.70</td>
<td>0.99</td>
<td>1.103</td>
<td>1.109</td>
</tr>
<tr>
<td>6</td>
<td>1.98</td>
<td>1.83</td>
<td>0.96</td>
<td>1.071</td>
<td>1.067</td>
</tr>
<tr>
<td>7</td>
<td>0.60</td>
<td>0.60</td>
<td>1.00</td>
<td>1.153</td>
<td>1.160</td>
</tr>
<tr>
<td>8</td>
<td>0.29</td>
<td>0.28</td>
<td>0.84</td>
<td>0.992</td>
<td>1.000</td>
</tr>
<tr>
<td>9</td>
<td>0.30</td>
<td>0.30</td>
<td>1.00</td>
<td>0.966</td>
<td>0.969</td>
</tr>
<tr>
<td>10</td>
<td>7.17</td>
<td>7.52</td>
<td>0.96</td>
<td>1.091</td>
<td>1.087</td>
</tr>
<tr>
<td>11</td>
<td>9.59</td>
<td>9.59</td>
<td>1.00</td>
<td>1.023</td>
<td>1.022</td>
</tr>
<tr>
<td>12</td>
<td>7.86</td>
<td>7.82</td>
<td>1.00</td>
<td>1.021</td>
<td>1.023</td>
</tr>
<tr>
<td>13</td>
<td>6.28</td>
<td>6.16</td>
<td>0.99</td>
<td>1.104</td>
<td>1.116</td>
</tr>
<tr>
<td>14</td>
<td>4.50</td>
<td>4.48</td>
<td>1.00</td>
<td>1.088</td>
<td>1.073</td>
</tr>
<tr>
<td>15</td>
<td>2.71</td>
<td>2.85</td>
<td>0.97</td>
<td>1.099</td>
<td>1.100</td>
</tr>
</tbody>
</table>

$r = 0.999$ 0.978  $r = 0.993$ 0.826  $r = 0.826$ 0.823  $r = 1.000$ 0.997  $r = 0.991$ 0.930
who would be eligible for thrombolysis therapy with a sensitivity of 62%, specificity of 83%, and positive predictive value of 83% by analyzing the FLAIR-DWI mismatch [9]. Moreover, it was demonstrated that a longer time to MRI, lower age, and larger DWI lesion volume are important independent predictors for lesion visibility in FLAIR image sequences. However, the rather low sensitivity and inter-observer agreement (Kappa $\kappa = 0.569$) raised the question if a semi-quantitative analysis of this mismatch may lead to improved results. This question was also analyzed using ANTONIA and the described methods in a secondary analysis of the same dataset [32]. Here, it was found, that the semi-quantitative analysis of this mismatch does not lead to improved classification results but at least solves the problem of the high inter-observer variability. Furthermore, using ANTONIA it was analyzed in another secondary work if the DWI-FLAIR mismatch depends on the perfusion situation [33]. Here, no relation between FLAIR lesion visibility and the extent of the perfusion deficit or the TTP distribution within the stroke were found. However, it may be interesting to validate this finding also for the other commonly used perfusion parameters.

Apart from these selected stroke studies, ANTONIA has also been successfully applied for an analysis of the placenta perfusion in a mouse model [6] using the described steepest slope analysis of DCE PWI datasets. It was found in this study that the placenta consist of a low and a high flow perfusion compartment, which need to be analyzed separately to prevent an erroneous averaging across the two functional zones.

Several tools that cover at least some of the methods implemented in ANTONIA are currently available. The two most similar software tools that are described in literature are RAPID [34] and PerfTool [35].

RAPID was developed for a fully automatic PWI-DWI mismatch quantification. Similar to the software tool described in this work, RAPID contains also methods for the PWI motion correction, slice-time correction using a b-spline interpolation, signal to concentration time curve conversion, automatic AIF detection, deconvolution in the frequency domain, perfusion parameter map calculation, DWI-PWI co-registration, automatic lesion and tissue-at-risk identification, and direct PACS connection. Due to the fully-automatic processing pipeline, RAPID enables a convenient image-based patient selection for stroke studies.

In contrast to this, the main focus of PerfTool is the comparison of different bolus tracking methods employing different deconvolution methods, regularization parameters and AIF selection strategies. Thus, it enables the problem-specific perfusion parameter map calculation with a high degree of freedom but does not allow performing any multi-parametric analyses such as the PWI-DWI or DWI-FLAIR mismatch analysis.

The main benefit of ANTONIA PS as compared to RAPID and PerfTool is the possibility to semi-quantitative analyze the DWI-FLAIR mismatch, to semi-automatically segment stroke lesions in follow-up FLAIR datasets, and to case-specifically select one of the three perfusion analysis methods, whereas each of them has its own benefits and drawbacks. Although the availability of multiple perfusion analysis methods may also introduce an additional source of user-based errors due to false model selection, it also enables a more problem-specific perfusion analysis.

Within this context, it should be emphasized that the acute stroke imaging research roadmap [36] discusses the need of a formal comparison between deconvolution-based perfusion analysis methods and other hemodynamic models and ap-

### Table 2: Time required for automatic processing and manual interaction for the different image processing steps of typical datasets

<table>
<thead>
<tr>
<th>Processing step</th>
<th>Automatic computation time without user interaction (in s)</th>
<th>Manual interaction time (in s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dicom import and data selection</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>DWI registration and ADC calculation</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>ADC lesion, Brain and CSF segmentation</td>
<td>1</td>
<td>30–60</td>
</tr>
<tr>
<td>Hemisphere definition</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>ADC lesion mirroring &amp; hemisphere separation</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>DWI – FLAIR registration</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>PWI motion correction</td>
<td>230</td>
<td>0</td>
</tr>
<tr>
<td>DCE PWI baseline correction</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>DSC PWI signal to concentration conversion</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Slice-time correction using b-spline interpolation</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>Slice-time correction using b-spline approximation</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Manual arterial input function definition</td>
<td>0</td>
<td>30</td>
</tr>
<tr>
<td>Automatic arterial input function definition</td>
<td>80</td>
<td>0</td>
</tr>
<tr>
<td>Fitting-based perfusion analysis</td>
<td>480</td>
<td>0</td>
</tr>
<tr>
<td>Deconvolution-based perfusion analysis</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Deconvolution-free perfusion analysis</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>DWI – Perfusion parameter map registration</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Tissue-at-risk Identification</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Follow-Up lesion segmentation</td>
<td>0</td>
<td>30–60</td>
</tr>
<tr>
<td>DWI – Follow-Up FLAIR registration</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Statistical analysis</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Saving results in NIfTI format</td>
<td>30</td>
<td>10</td>
</tr>
</tbody>
</table>
proaches to proof the superiority of this method. The steepest slope model is explicitly named as a potential alternative to the deconvolution-based analysis. Thus, ANTONIA would render the possibility to perform such an analysis.

Theoretically, the methods implemented in ANTONIA allow analyzing stroke patients and subsequent treatment decision making using the state-of-the-art knowledge. For example, the semi-quantitative analysis of the DWI-FLAIR mismatch can be used to decide if a patient with unknown stroke symptom onset is eligible for a thrombolysis therapy. After this, or in case the symptom onset is known, the PWI-DWI mismatch quantification can be used to decide if the potential benefits of this therapy outperform the potential treatment risks. Finally, the volumetric brain measurements or 2D distance measurements may help to identify patients that are likely to develop a malignant infarction.

Although the presented software tool could be used for image-based patient selection in stroke studies, the support of sophisticated image-based research projects remains the intended main scope of application. Fully-automatic software tools like RAPID that do not require any user interaction or model selection are far better suited for automatic patient selection in stroke studies. Within this context, it needs to be emphasized that the analysis of the PWI-DWI or FLAIR-DWI mismatch requires user interaction and cannot be performed fully automatically in ANTONIA. For example, the user has to place seed points in the ADC parameter map to segment the lesion, define the hemispheric fissure, or select the perfusion analysis method, perfusion parameter map and threshold.

The optimal location for AIF definition in perfusion studies in general and in cerebral perfusion analysis studies in particular is still a matter of debate. Therefore, a manual AIF selection is still available in ANTONIA although the results of the reliability evaluation show that the manual AIF selection leads to considerable source of variability for the AIF-based perfusion analysis methods. Furthermore, this option is still required for perfusion analyses of different organs.

Future developments will aim at integrating automatic methods for the identification of the acute diffusion restriction and definition of the hemispheric fissure in the ADC dataset. Even with these add-ons, it is planned that the user retains the possibility to intervene at each processing step to offer the whole degree of freedom for the analysis for experienced researchers and also provide an intuitive and standardized processing chain for less experienced users.

It has been shown that multi-parametric tissue outcome predictions lead to improved results compared to the simple PWI-DWI mismatch identification using only a single perfusion parameter [8, 40–43]. Therefore, we are currently working on extending ANTONIA with a multi-parametric tissue outcome prediction using high-level machine learning techniques. This may not only be beneficial in terms of better tissue outcome predictions in case of a conservative treatment approach but may also enable the development of therapy-specific prediction models that can be used for treatment decision such as thrombolysis vs. thrombectomy.

The perfusion analysis of DCE PWI datasets is currently limited to the steepest-slope analysis although these datasets allow to determine several other parameters by pharmacokinetic analysis, for example, using the Tofts models [44]. Thus, it is planned to extend ANTONIA with such a model to enable an extended DCE PWI analysis.

Finally, it needs to be highlighted that a quantitative analysis of CT perfusion (CTP) datasets is currently not supported by ANTONIA as these datasets require a different pre-processing chain due to the worse signal-to-noise ratio. Nevertheless, CTP is becoming more and more important in today’s clinical routine due to the wide-spread availability of CT scanners, development of improved imaging techniques that enable an enlarged field-of-view and faster imaging times. Thus, it is also planned to extent ANTONIA with suitable methods for a quantitative analysis of CTP datasets.

5. Conclusion

The presented ANTONIA tool is a powerful tool for various perfusion analyses in general and multi-parametric stroke studies in particular. Due to the degree of freedom and associated required user interaction, the main aim of this software tool is to support the image-based perfusion and acute ischemic stroke research.

Acknowledgment

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   vascular tracer bolus passages. Part II: Experimen-
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   inger M, Kohrmann M, et al. Quantitative measurements of relative fluid-attenuated inver-
   76–84.
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   fusion deficit does not relate to the visibility of acute ischemic lesions on fluid-attenuated inver-
   sion recovery imaging. J Neuroimaging 2013; 23
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   sion-perfusion mismatch analysis in acute stroke. J
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   fusion MRI parameters in 97 sub-6-hour stroke patients using voxel-based receiver operating characteristics analysis. Stroke 2009; 40 (6):
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   Bagher-Ebadian H, Zhao Q, et al. Predicting final infarct size using acute and subacute multipara-
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