Exploration of time-varying data for medical diagnosis

Sven Kohle[1], Bernhard Preim[1], Jonathan Wiener[2], Heinz-Otto Peitgen[1]

[1]MeVis – Center for Medical Diagnostic Systems and Visualization, Universitätsallee 29, 28359 Bremen, Germany; Email: kohle@mevis.de
[2]Boca Radiology Group, Boca Raton Community Hospital, Boca Raton, FL

Abstract

Dynamic imaging of volume data is used in medicine to detect abnormalities in tissue perfusion, for example in the brain to diagnose an acute stroke or in the female breast for tumor detection and classification. We describe the exploration of such time-varying data for medical diagnosis. As a prerequisite several preprocessing steps are required which have largely been automated to support clinical applicability. Thereafter, the dynamic data are parameterized appropriately and projection methods are applied to convey the spatial relations. We discuss color-mapping schemes to characterize perfusion abnormalities. With these methods, crucial dynamic information can be extracted out of a 4D data volume allowing the simultaneous presentation of dynamic temporal and 3D spatial information.

1 Introduction

Time-varying data are acquired to assess blood flow (perfusion) and tissue kinetics by tracing the distribution of contrast agents. Whether or not a contrast agent is delivered and subsequently absorbed inside a particular region, how long it takes until the maximum amount of contrast agent is delivered or absorbed as well as other parameters are needed for medical diagnosis. Imaging modalities such as CT (computed tomography) and MRI (magnetic resonance imaging) now provide markedly improved spatial and temporal resolution. With modern devices, the effects of blood perfusion can be measured in scales of millimeters and seconds and cover complete organs. Examples include brain MRI perfusion examinations with as many as 20 slices and 40 timepoints and breast MRI with 3D data sets of 80 slices and 6 timepoints.

Currently, time-consuming and non-reproducible techniques are used to analyze the large amount of acquired image data. Subtraction images, which show the difference between two timepoints are analyzed to detect regions of contrast enhancement. However, there is no assistance in choosing the "right" timepoints or the possibility of selecting the correct regions of interest (ROI). Moreover, the 2D data are only used to visually detect abnormalities. Quantitative temporal and spatial information, which could make the diagnostic results more reproducible, is not available. With such tedious analysis methods, the use of 4D data in the clinical routine is rare.

The maximum intensity projection (MIP) based on temporal subtraction data is available in some clinical workstations. With this method, changes in signal intensity are visualized and applied e.g., to depict the spatial distribution of blood vessels.

Recent developments in modeling and quantifying the dynamic information of contrast enhancing agents have been applied to tumor and brain perfusion[1,2]. However, not much effort was spent on visualizing the complex 4D information.

The interpretation of dynamic data often suffers from motion artifacts, e.g., from local patient motion because of breathing, heartbeat and muscle relaxation. This makes an analysis of the dynamical data often difficult or impossible. However, recent developments of image registration algorithms[3] allow correction for motion artifacts.

The work presented here is based on prior work on MT-DYNA™ [4], a commercial software package, which supports the exploration of time-varying image data sets. Based on image data with sufficient spatial and temporal resolution and an algorithm for motion correction, we describe how projection methods are used to explore dynamic information. By contrast to recent work of Tory et al.[5] we do not overlay vectors to avoid selection effects. Instead, the original data is mapped to visualizations directly.

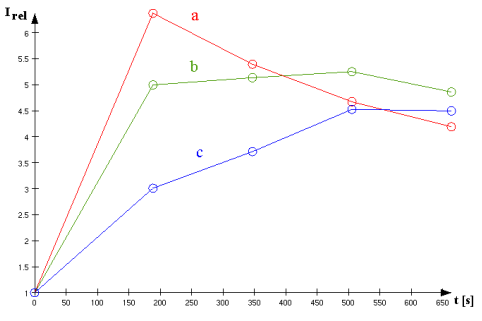

Fig. 1: Contrast agent enhancement curves of different regions in a breast tumor. The enhancement relative to the signal intensity at the first timepoint is shown. The circles indicate the 5 points of time when images were acquired. The time points are connected by straight lines. Curve “a” is especially suspicious because of its strong wash-out, which is typical for malignant tumors.

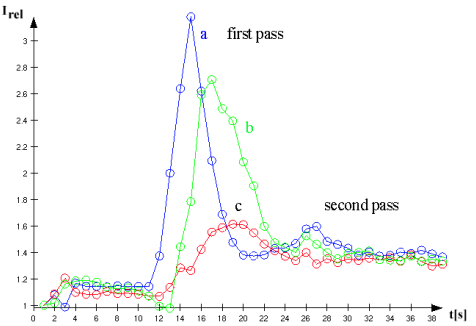

Fig. 2: Contrast agent enhancement curves of gray matter in the brain. By contrast to the data presented in Fig. 1 some 40 measurements have been taken in a shorter period of time. Curve “a” shows normal brain perfusion whereas “b” and “c” show decreased and delayed perfusion around an infarction.

2 Medical Background

The measurement of blood perfusion is essential in a variety of medical disciplines, e.g., perfusion of the brain for stroke diagnosis. Other examples are the assessment of vitality of different types and stages of tumors, the detection and diagnosis of ischemia and infarction of the heart, and perfusion measurement of the extremities.

In these examinations, a bolus of a contrast agent is injected and its distribution is measured by a repeated acquisition of subsequent images covering the volume of interest. The contrast agent provides signal changes either in CT or MRI and works as a tracer of the blood. Depending on the physiological process, either the short-term distribution (< 1 min) of blood flow (perfusion) or the long-term (> 1 min) diffusion process of the tracer particles through the membranes of the micro-vessels (tissue kinetics) are encoded in the varying signal of the image voxels. The extracted time-intensity curves for each voxel are typically converted into relative concentration-time curves. These are called enhancement curves.

The two examples discussed in this paper cover both situations, short-term distribution as well as long term diffusion. Fig. 1 and 2 show typical enhancement curves for the assessment of tumor and brain perfusion.

The physical process of contrast agent enhancement in a tumor can be described by the diffusion of the macromolecular tracer particles from inside the blood vessels into the extracellular space outside and vice versa before it becomes excreted in the kidneys. The permeability of the vessel walls and the extracellular volume fraction determine the amplitude and the shape of the contrast agent enhancement curve.

Enhancement curves, which show a large early enhancement followed by rapid wash-out, i.e. a significant decrease of signal intensity at later timepoints are especially suspicious (see Fig. 1, curve “a”). Less suspicious are those curves showing a plateau at later time, or those which continue to enhance. This is typically observed in benign tumors in the breast.

In contrast to leaky vessels in malignant tumors, micro-vessels in normal brain tissue do not leak as a result of the blood brain barrier. Consequently, there is no enhancement in the extracellular volume over a longer time-period. Instead, we see the “first-pass” of the contrast agent through the vessel bed. About 10 seconds after the first-pass, we see the broadened second-pass after one circulation through the body (see Fig. 2). The volume of blood available in each voxel is diagnostically relevant. It is measured by the integral of the enhancement curve and the mean transit time of the

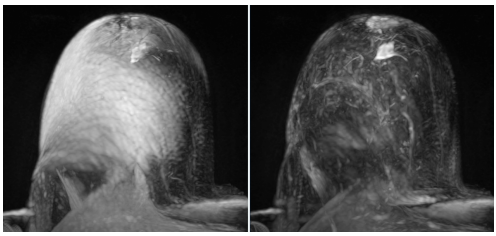

Fig. 3: MIP images of contrast agent enhancement in a female breast. The image intensities at two timepoints of an MRI series were subtracted before the projection images were generated. Because of breast motion the data (left) exhibit bright artifacts in those regions, which are not aligned. After aligning the data (right) the volume becomes more transparent and reveals an enhancing tumor.

blood as measured by the first moment of the curve.
In the next sections, we will discuss the pipeline of data analysis to extract and visualize the diagnostically relevant information.

3 Preprocessing

Typically three image-processing techniques have to be carried out before an appropriate visualization of dynamic information can be achieved.

3.1 Image Registration

Motion correction becomes the more important for visualization when more dynamic information is to be included, particularly when image acquisition takes a longer time (> 1 min). Fig. 3 shows the benefit of image registration for a dynamical breast MRI examination. Without motion correction the data volume is filled with bright artifacts, which contain no diagnostic information but may hide relevant information along the line of sight. We applied a registration algorithm, which is based on the similarity measure of normalized mutual information[6]. We refined the original method with an optimization of local 3D B-spline transformations similar to the work of Rueckert et al[3]. The process is computationally expensive and may take up to several hours on a state-of-the-art PC depending on the size of the 4D dataset. Although faster calculation is desirable, the algorithm is applicable, since no user interaction is required and the quality of the alignment is very good in a large majority of the cases[7].

3.2 Calibration of Signal Intensities

The visualization of dynamic data is often based on the tracking of a contrast agent in tissue to assess perfusion and kinetic properties of the micro-vascular components integrated in a single voxel. While CT imaging provides calibrated signal intensities in “Hounsfield” units, MRI signals are dependent on the scanning sequence used. Therefore, we convert the raw signals into relative concentration of the contrast agent[8,9].

3.3 Segmentation

Projection methods, such as MIP are established methods for visualization of small, enhanced regions embedded in a relatively transparent data volume, e.g., the distribution of filamentary vessels. Regions of interest can be obscured by adjacent tissues. In order to remove occluding structures, it is necessary to segment them. As an example, we apply a brain segmentation procedure for the visualization of brain perfusion datasets (see Sect. 6.2).

4 Mapping Dynamics to Color

For diagnostic purposes, it is essential to extract only those parameters to the physician, which provide essential information. Whereas the relative spatial location to the surrounding organs is relevant in most clinical questions, the parameters describing the dynamics of contrast agent enhancement depend on the underlying physiological process. Thus, different parameters are employed depending on the specific medical question.
Color provides the possibility to independently encode up to three parameters either in the HSV (hue, saturation and value) or RGB color space. The suitability of a representation depends on the interpretation and relative importance of the parameters. When only one parameter should be visualized, e.g., the peak enhancement of a contrast agent, there are several meaningful color representations possible, such as the rainbow scale

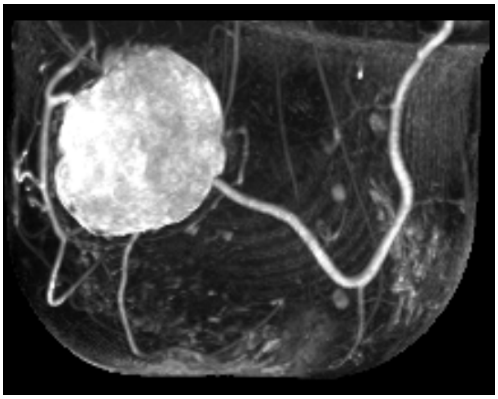

Fig. 4: A malignant breast tumor visualized using a MIP of the subtraction data derived by subtracting the intensities of the first two timepoints of an MRI series.

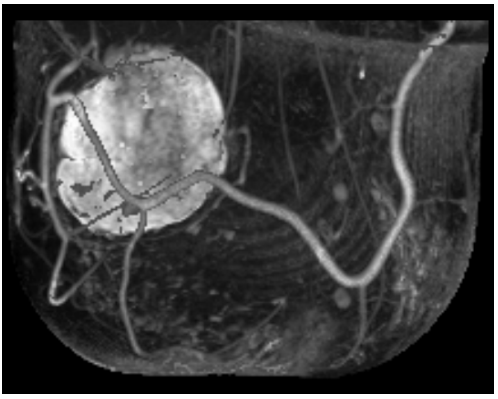

Fig 5: The same data as in Fig. 4, now visualized using a CVP. The spatial course of blood vessels becomes much better conceivable.

or the heated body scale (see [10,11] for a discussion of the perception of color maps).
In order to visualize three independent parameters, we use the HSV color space to map the most suspicious parameter combinations to a red color with high color saturation and high intensity, whereas normal parameter values are mapped to lower saturation and intensity values and a bluish hue component. With this approach, we attempt to direct the viewer's attention to suspicious regions. Other possibilities include viewing the enhancement curve directly or mapping the integral of three different intervals of the enhancement curves into the red, green, and blue color channels.

Integration of Dynamic Information and Morphology

Meaningful dynamic parameters can often be extracted for a restricted region, e.g., where perfusion takes place. However, other constituents such as the bony structures might provide substantial information for displaying the diagnostically relevant regions in their anatomic environment. The method proposed here is to add spatial reference information in the regions not containing dynamic information. While the dynamic information is encoded in a color scale, the reference data is displayed in the background, by using a gray scale.

5 Projection Algorithms

In the previous sections we discussed how the dynamic information embedded in every voxel can be visualized by means of color. However, morphologic information is essential as well for many diagnostic purposes.
A three-dimensional distribution of colors can be visualized using projection techniques. Since every voxel with its corresponding color contains diagnostically relevant information, the usage of volume rendering with alpha blending is not advantageous, since mixed colors are difficult to interpret for diagnosis.
We need to use projection techniques in which every pixel in the projection has a direct link to the corresponding voxels with its enhancement curve. An interactive tool with point and click functionality in the projected image allows assessment of the related original image data.

5.1 Maximum Intensity Projection

The maximum intensity projection (MIP) is conventionally used for grayscale volume data in which the interesting structures have a small volume-filling factor such as vascular structures. For every pixel of the resulting image the voxel with highest intensity along the projection ray is determined. The MIP is also applicable with colored volume data when using the HSV color space. Searching for the maximum based on each voxel's intensity value and representing its color in the projection image can display the same regions as

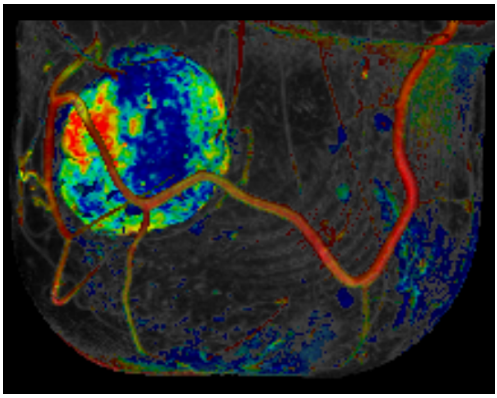

Fig. 6: A grayscale MIP of the subtraction volume of two early timepoints is combined with a CVP with color mapping applied. A color is only assigned to pixels if the projected intensity exceeds a threshold. A CVP is applied there, mapping a color depending on the dynamical behavior of the voxels enhancement curve. Bright voxels show a strong enhancement for an early period, less intense voxels show less enhancement. A blue color indicates a continuous enhancement for a later period in time, a green color indicates a plateau in the enhancement curve. A yellow and in particular a red color indicates a strong "wash-out" behavior. This behavior is often observed in malignant tumors.

in the grayscale MIP but includes the temporal dynamic information its color encoding. The 3D spatial distribution of regions in color MIP images is more difficult to assess than in volume rendered images, because no illumination model is involved. In this case, the animation over different projection angles supports the mental understanding. On the other hand, there is the explicit correspondence to the dynamics of every pixel and there are no more visualization parameters to be adjusted by the physician. The method is therefore easy to use and understand.

5.2 Closest Vessel Projection

The closest vessel projection (CVP) also known as Local MIP was developed to add depth information to MIP images[12,13]. The most intense voxel is no longer selected along the projection ray but rather that voxel which represents the first local maximum above a certain threshold. Thus, a voxel with lower intensity in the foreground can occlude a more intense voxel in the background.

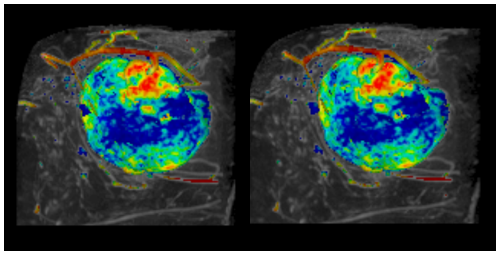

Fig. 7: 3D Stereo image of a malignant breast tumor. The combination of a grayscale maximum intensity projection of early enhancement and a colorized closest vessel projection shows the 3D location of in particularly suspicious red regions with a strong wash-out of contrast agent relative to its surrounding blood vessels.

The threshold has to be adjusted to segment only the interesting structures. As a rule of thumb, a threshold of 20% relative enhancement is an appropriate suggestion for breast tumors. As the name implies this technique is dedicated to the visualization of vascular structures. Again, since there is a direct link to a single corresponding voxel in the dataset, the projected voxel can be displayed in its inherent color. The local maximum is determined based on its intensity value.
When applying the CVP to structures other than vessels (e.g. for tumors), it is helpful to add information for spatial orientation in regions containing no projected voxel. We propose here to add the voxel having the maximum intensity but setting its color saturation to zero (i.e. as gray value) in order to emphasize its different meaning.

6 Clinical Applications

6.1 Tumor Perfusion

There is increasing evidence that both morphological and enhancement characteristics of dynamical breast MR examinations have to be considered in diagnosing suspicious lesions[14-16].
We suggest to encode two parameters describing the diagnostic significant shape and amplitude of each pixel's curve into color: (1) the slope of the early contrast agent enhancement into intensity and (2) the slope of the late wash-out into the color value, encoding suspicious wash-out in red. By using continuous color values there is a smooth transition between slowly enhancing and depleting regions. This is in contrast to the fixed three color scale proposed by Degani et al.[1]. Thus, the 3D-

projection images show less aliasing artifacts. Figs. 4-6 show the conventional grayscale MIP and CVP images as well as the color projection image of a malignant breast tumor. Both the 3D spatial and temporal information in the color pattern are included in Fig. 6. When rotating the dataset or when producing stereoscopic images, the spatial relations are even more evident.

The colorized projection image provides both morphological information aligned with its physiological parameters. This is a new way to analyze 4D information for medical diagnostics.

6.2 Brain Perfusion

Patients with symptoms of acute stroke are often examined with a perfusion study using either CT or MRI. MRI studies suffer from lower spatial resolution compared with CT, but allow scanning of the entire brain, and are thus better suited to detect an infarction, if its location is not a priori known. Beside the location and size of an infarction core (in which the function of the brain is already permanently lost), the identification of "tissue-at-risk" (ischemic penumbra) is crucial before considering any patient treatment. This area is characterized by decreased and delayed perfusion.

Brain perfusion maps can be quantified in terms of absolute blood flow and blood volume[2]. The calibration of these parameters requires the exact measurement of the arterial input function, which is currently not possible in MRI. However, semi-quantitative parameters as well as relative perfusion maps have been obtained with MRI and have been shown to allow prediction of infarct growth [17]. Relative cerebral perfusion maps have also been shown to predict infarct evolution[18].

For the purpose of a fast and automatic visualization of perfusion deficits in the brain, we apply the conversion of signal intensity to relative contrast agent concentration in a preprocessing step. Secondly, we employ a fast and automatic brain segmentation procedure based on the watershed transform[19] to remove non-brain structure. Then, we split the concentration-time curve of the first-pass of contrast agent in each pixel into three equally spaced time intervals. The integrated concentrations in each interval (see Fig. 8) are assigned to the RGB color channels; the blue, green and red channels represent the volumes of the early, intermediate and late arrival of blood, respectively.

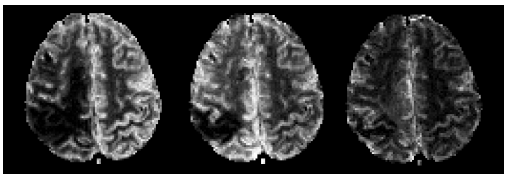

Fig. 8: 2D distribution of delayed and distorted perfusion of a brain experiencing an acute stroke. The integrated concentrations of contrast agent in the early, intermediate and late time interval after injection of the contrast bolus are shown. There is a strong asymmetry of enhancement between both hemispheres in a region around the infarction in the lower left areas.

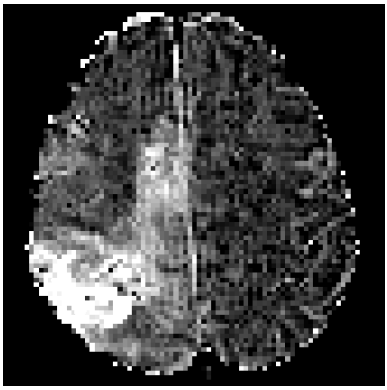

Fig. 9: Derived parameter image of the data shown in Fig. 8. The mean transit time of contrast agent is depicted and reveals a strongly delayed blood supply. Light gray regions around this infarction core represent the "tissue-at-risk".

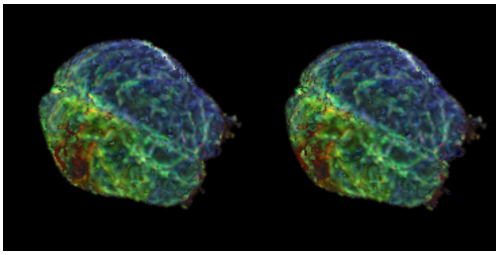

Fig. 10: 3D Stereo image of the brain experiencing an acute stroke. The brightness of each pixel is related to the blood volume of the brain tissue while the color represents the time delay of the perfusion. Note that the perfusion in one hemisphere of the brain is delayed (green, yellow and red color) compared to the normal perfusion in the other hemisphere (blue). Moreover, there is a dark hole, indicating the core of the infarction.

Fig. 10 shows a stereoscopic view of a whole brain suffering an acute stroke. Nearly a complete hemisphere is affected by delayed perfusion as indicated by the green color opposite to the normal perfusion shown in blue on the other hemisphere. The hole inside the dark red region indicates the infarction core surrounded by the tissue-at-risk, which might be rescued by appropriate treatment.

7 Implementation

The algorithms were implemented in the ILAB4 software environment developed at our institute [20]. They include post-processing, analysis, as well as visualization. With appropriate scripting facilities, image analysis networks are "hidden" behind a graphical user interface. Using these facilities, all algorithms presented in this paper are integrated in a research application, called DYNA-MIP. This application provides interactive access to the original 4D data, the projection images as well as derived enhancement curves. The application is currently being used for a clinical evaluation concerning relevance and usability.

8 Concluding Remarks

The main contribution of this paper is the description of a visualization pipeline with an automated preprocessing and projection visualization methods for the exploration of time-varying medical volume data (4D analysis). With the techniques presented, contrast enhancement and thus tissue perfusion and kinetics can be assessed in a reasonable amount of interaction time. The methods presented here are inspired by established clinical processes and attempt to visualize those pixel-based parameters which have a proved and diagnostic relevance.

We are currently exploring methods for feature extraction and classification to direct the physician's attention to suspicious regions (computer aided diagnosis – CAD).

Acknowledgements

We want to thank our colleagues Dr. R. Rascher-Friesenhausen for developing the registration algorithm, B. Kümmerlen, S. Meyer and Dr. H. Jürgens for their work on MT-DYNA™, and our colleagues at MeVis for developing the ILAB4 platform. The research leading to this publication has been supported by the German Federal Ministry of Education and Research under the grant number 01EZ0010 (VICORA).

Reference List

1. Degani,H., Gusis,V., Weinstein,D., Fields,S. & Strano,S. Mapping pathophysiological features of breast tumors by MRI at high spatial resolution. *Nat. Med.* **3**, 780-782 (1997).

2. Barbier,E.L., Lamalle,L. & Decorps,M. Methodology of brain perfusion imaging. *J. Magn Reson. Imaging* **13**, 496-520 (2001).

3. Rueckert,D. *et al.* Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans. Med. Imaging* **18**, 712-721 (1999).

4. Meyer,S., Mueller-Schimpfle,M., Jürgens,H. & Peitgen,H.O. MT-DYNA: Computer Assistance for the Evaluation of Dynamic MR and CT Data in a Clinical Environment. 331-334. 1999. CARS 99.

5. Tory,M., Roeber,N., Moeller,T., Celler,A. & Atkins,M.S. 4D Space-Time Techniques: A medical Imaging Case Study. 473-476. 2002. IEEE Visualization.

6. Wells,W.M., III, Viola,P., Atsumi,H., Nakajima,S. & Kikinis,R. Multi-modal volume registration by maximization of mutual information. *Med. Image Anal.* **1**, 35-51 (1996).

7. Prenzel,H. Algorithmic speed-up techniques for nonrigid registration using B-splines. 2001. Master Thesis, Medical University of Luebeck.

8. Plewes,D.B. The AAPM/RSNA physics tutorial for residents. Contrast mechanisms in spin-echo MR imaging. *Radiographics* **14**, 1389-1404 (1994).

9. Price,R.R. The AAPM/RSNA physics tutorial for residents. Contrast mechanisms in gradient-echo imaging and an introduction to fast imaging. *Radiographics* **15**, 165-178 (1995).

10. Lefkovitz,H. & Herman G. The design and evaluation of color scales for image data. 12(1), 82-89. 1992. IEEE Computer Graphics and Applications.

11. Rogovitz,B. & Kalvin,A.D. The 'WhichBlair Project': A quick visual method for evaluating perceptual color maps. 183-190. 2001. IEEE Visualization.

12. Zuiderveld,K.J., König,A.H. & Viergever M. Techniques for Speeding Up high-quality perspective maximum intensity projection. *Pattern Recognition Letters* **15**, 507-517 (1995).

13. Sato,Y., Shiraga,N., Nakajima,S., Tamura,S. & Kikinis,R. Local maximum intensity projection (LMIP): a new rendering method for vascular visualization. *J. Comput. Assist. Tomogr.* **22**, 912-917 (1998).

14. Kinkel,K. & Hylton,N.M. Challenges to interpretation of breast MRI. *J. Magn Reson. Imaging* **13**, 821-829 (2001).

15. Kuhl,C.K. & Schild,H.H. Dynamic image interpretation of MRI of the breast. *J. Magn Reson. Imaging* **12**, 965-974 (2000).

16. Schnall,M.D., Rosten,S., Englander,S., Orel,S.G. & Nunes,L.W. A combined architectural and kinetic interpretation model for breast MR images. *Acad. Radiol.* **8**, 591-597 (2001).

17. Grandin,C.B. *et al.* Which MR-derived perfusion parameters are the best predictors of infarct growth in hyperacute stroke? Comparative study between relative and quantitative measurements. *Radiology* **223**, 361-370 (2002).

18. Maeda,M. *et al.* Application of contrast agents in the evaluation of stroke: conventional MR and echo-planar MR imaging. *J. Magn Reson. Imaging* **7**, 23-28 (1997).

19. Hahn,H.K. & Peitgen,H.-O. The Skull stripping problem in MRI solved by a single 3D watershed transform. 134-143. 2000. Springer. Proc. of Medical Image Computing and Computer-Assisted Intervention (MICCAI 2000).

20. Schroecker,F. & et al. Highly integrated user-friendly research and development platform for medical image processing and visualization. *Supplement to Radiology* **217**, 699 (2001).