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Gap-Free Segmentation of Vascular Networks with Automatic Image Processing Pipeline

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Abstract (251)

Current image processing techniques capture large vessels reliably but often fail to preserve connectivity in bifurcations and small vessels. Imaging artifacts and noise can create gaps and discontinuity of intensity that hinders segmentation of vascular trees. However, topological analysis of vascular trees require proper connectivity without gaps, loops or dangling segments. Proper tree connectivity is also important for high quality rendering of surface meshes for scientific visualization or 3D printing. We present a fully automated vessel enhancement pipeline with automated parameter settings for vessel enhancement of tree-like structures from customary imaging sources, including 3D rotational angiography, magnetic resonance angiography, magnetic resonance venography, and computed tomography angiography. The output of the filter pipeline is a vessel-enhanced image which is ideal for generating anatomical consistent network representations of the cerebral angioarchitecture for further topological or statistical analysis. The filter pipeline combined with computational modeling can potentially improve computer-aided diagnosis of cerebrovascular diseases by delivering biometrics and anatomy of the vasculature. It may serve as the first step in fully automatic epidemiological analysis of large clinical datasets. The automatic analysis would enable rigorous statistical comparison of biometrics in subject-specific vascular trees. The robust and accurate image segmentation using a validated filter pipeline would also eliminate operator dependency that has been observed in manual segmentation. Moreover, manual segmentation is time prohibitive given that vascular trees have

more than thousands of segments and bifurcations so that interactive segmentation consumes excessive human resources. Subject-specific trees are a first step toward patient-specific hemodynamic simulations for assessing treatment outcomes.

Introduction (878)

Medical imaging data acquired from Magnetic Resonance Imaging (MRI), Computed Tomography Angiography (CTA), and Interventional Digital Subtraction Angiography (DSA) provide valuable information regarding patient vascular health for clinical diagnosis of cerebral vascular diseases (CVD)¹. Currently, biometrics of the vasculature cannot be readily accessed from the medical images, because manual segmentation of the entire arterial tree would require weeks of labor which is impractical. What is needed is an automatic image processing pipeline for the robust and reliable extraction of patient-specific vascular biometrics to characterize the patient's cerebral angioarchitecture. A critical property for automatic image segmentation is preservation of tree connectivity needed to perform topological and statistical analysis of cerebrovascular trees. The connectivity is often lost due to four reasons: (i) large variations in image intensity along centerlines, (ii) sign changes in the eigenvalues close to bifurcations, (iii) artificial gaps introduced into vessel segments due to finite image slice spacing, and (iv) artifacts due to overlapping structures, such as cortical surfaces or cerebrospinal fluid spaces. In addition, 3D visualization of vascular trees may be helpful for treatment planning², education of medical students or patients before intervention to lower anxiety, and for 3D printing of vascular networks. There is also a pressing need for subject-specific vasculature segmentation for computational fluid dynamics (CFD) studies. Researchers and physicians utilize cerebral hemodynamic simulations to acquire more insight in the cause of CVDs. Patient-specific CFD also enables planning of

endovascular interventions such as bypass surgery^{3,4}, aneurysm clipping⁵ and arteriovenous malformation rupture risk⁶. Prior CFD studies were often limited to small sections such as the carotid bifurcation⁷⁻¹⁰ or the Circle of Willis (CoW)¹¹⁻¹³. However, since CFD affect the entire circulation, it is important to reconstruct larger portions of the cerebrovascular angioarchitecture

Despite the contrast enhancement with iodine or gadolinium or specialized imaging protocols (Time-of-Flight, TOF, and Phase Contrast, PC)⁶⁻⁹, signals belonging to the cerebral vasculature often coincide with information from other anatomical structures including skull, gray or white matter, this overlap deteriorates the specificity of blood vessel detection. Especially, small vessels like communicating arteries in the CoW are easily obfuscated in medical images due to image scattering artifact or relatively weak contrast compared to surrounding tissues. Furthermore, imaging artifacts and unavoidable noise often introduce discontinuity or gaps that hinder automatic segmentation of vascular structures as shown in Fig 1. The gap between image slices also tend to severs blood vessels unless the spacing is much smaller than the thinnest blood vessel. Since, the smallest capillaries measure only 4 micrometers in diameter, severed vessel between slice are inevitable in most modalities. In practice, several dedicated software use probability and logic to reconnect severed vessels to maintain connectivity¹⁸. Here we propose an alternative without the need to reconnect severed vessels or fill erroneous gaps. We show that intensity equalization drastically reduces the probability of artificial gaps, suppresses information that does not belong to tree-like structures. Moreover, the use of

Gaussian smoothing to propagate intensity information across gaps between image slices to avoid broken vessel segments.

Numerous prior studies presented excellent *vesselness* filters^{19–25}, using the eigenvalues of the Hessian matrices of the image intensity to identify blood vessels. Vesselness filters enhance intensity of voxels whose eigenvalues correspond to elongated structures while suppressing signals from other anatomical features and noise. However, the eigenvalues of the Hessian matrix changes sign and magnitude at bifurcations. This phenomenon causes vesselness filters to erroneously weaken the contrast in bifurcations which results in disconnected segments in the network. To address this issue, a filter was designed to enhance the contrast in bifurcations^{23,24}. However, this improvement for bifurcations has the side effect of suppressing neighboring segments in the vicinity, which introduces artificial gaps²⁵. This side effect is undesirable because bifurcations near other branches frequently occur in the convoluted pial network. Moreover, all prior filters were designed for a specific image modality which limits their general applicability. It would be ideal to have a filter which highlights vessels, preserves bifurcations, maintains connectivity in highly-branched networks, and is applicable to any imaging modality. We recently introduced the mathematical operation for a multi-scale vessel contrast enhancement filter for magnetic resonance angiography images. However, our previous work was not automated, required manual tuning and was used for research only. Here we present the fully automated processing pipeline with customized settings and a software implementation ready for general use by the scientific community.

In our experience based on reconstructing hundreds of vascular datasets, we found it easier to eliminate false connections than guessing correct connections where gaps are present. Therefore, it is paramount to avoid introducing gaps. The critical need for circumventing the artificial introduction of gaps is achieved by several procedures: Gaussian smoothing at multiple length scales, intensity equalization, and contrast enhancement in bifurcations. To offer optimal filter performance for each dataset, the filter pipeline has three adjustable parameters that control shape detection and background level. The automated filter pipeline performs intensity histogram equalization throughout the image to preserve connectivity of tree-like structures. It segments the subject-specific cerebral angioarchitecture without gaps, broken bifurcations, dangling segments and loops.

This paper is organized as follows. First, image acquisition protocols for four different imaging modalities are introduced. Then, the mathematical background of the automatic image processing pipeline and its implementation is provided. Next, we compare filter performance in different case studies from multiple imaging modalities. Finally, we discuss potential applications and indicate future research directions.

Methods (1047)

First, we outline the methods for acquiring medical image of vascular structures. Specifically, we introduce methods for acquiring high resolution images of the cerebral vasculature using clinical 3D rotational angiography (3DRA). Moreover, computed tomography angiography (CTA), magnetic

resonance angiography (MRA) and venography (MRV) procedures will be described briefly. In addition, a tubular phantom was created to demonstrate introduction of artificial gaps. Finally, we provide an overview of the automatic image processing pipeline and a brief description for filtering the information from 3DRA, CTA, MRA, and MRV.

Clinical Digital Subtraction Angiography

We acquire high resolution images of the entire cerebral arterial tree using 3D rotational angiography. Nineteen 3DRA datasets were selected from a retrospective database at the Department of Neurosurgery, University of Illinois at Chicago. Standard diagnostic DSA data had been acquired for all patients from the practice of the Endovascular Section-Department of Neurosurgery at our institution in accordance with Institutional Review Board approved protocols. The vasculature of the main arterial network had been acquired after a 5 second contrast infusion with a Siemens Artis Zee C-arm system with typically 130 rotational slices and reconstructed into DICOM image sets with 509 axial slices. The conversion of the rotational slices into 3D voxel matrix with 512x512x509 voxels was performed with software provided by the Siemens system.

Human Magnetic Resonance Angiography and Venography

To demonstrate acquisition of arterial and venous tree data with magnetic resonance imaging, six healthy human subjects with no known cerebral vascular disease were recruited and underwent MR imaging on a GE 3T MR750 scanner using a 32 channel phased array coil. MRA was acquired under Institutional

Review Board approval at our institution. Before the scan, stability pads were provided to reduce motion artifacts. No motion artifacts affecting the scan was observed in all six cases. For MRA, a 3D TOF pulse sequence was used with the following parameters: TR=26ms, TE=3.4ms, NEX=1, Flip Angle=18°, acceleration factor=2, number of slab=4, magnetization transfer=on, matrix size=512x512x408, voxel size=0.39x0.39x0.3mm³, scan time=30min.

For the venous system, MRV was performed using a 2D INHANCE pulse sequence with the following imaging parameters: TR=18.5ms, TE=5.65ms, NEX=1, Flip Angle=8°, matrix size=512x248x512, voxel size=0.47x0.8x0.47mm³, scan time=15min. The MRA and MRV captured major branches of the cerebral arterial and venous systems, respectively.

Clinical Computed Tomography Angiography

CTA images were also collected for comparison. Two series were available, CT scans with and without contrast injection. For the series without contrast injection, image resolution was 0.488x0.488x2.5 mm³ with 512x512x72 voxels. The series with contrast injection has image resolution of 0.494x0.494x1.25 mm³ with 512x512x159 voxels. The images were acquired with a Generic Electric Medical Systems CT with iodine contrast agents.

Automatic Contrast Enhancement with Automatic Segmentation Pipeline

All DICOM image sets acquired with 3DRA, CTA, MRA or MRV are input into an executable procedure that can be downloaded from the author's website (<http://lppd.bioe.uic.edu/VesselFilter.zip>). First, we read 3D voxel matrices that encode digitized image intensity, $I(x, y, z)$. The MCF algorithm performs three

major operations: multi-scale contrast enhancement, normalization, output final filter response.

Fig 2 provides an overview of the automated image filtering pipeline. First, the original images are read by selecting all images in a pop-up window. The intensity information in the images are stored in a 3D matrix for further computation. Dimensions and number of 2D image slices containing the intensity information are automatically retrieved from the header information. In addition, the image pipeline retrieves parameter settings from an input file which specifies required filter parameters (sphericity a , tubeness b , background suppression c , scale parameter σ). For ease of use, four custom setting files (`dsa.txt`, `cta.txt`, `mra.txt`, `mrvt.txt`) are provided: the file `dsa.txt` is used for 3DRA images and contains default settings for detecting human arterial trees. Equally, the settings file, `cta.txt` and `mra.txt` serves as a default for CTA and MRA images respectively, and `mrvt.txt` for MRV images. In addition, users are encouraged to fine-tune their filtered images using customized settings file to optimize results in their applications. This can be simply implemented by creating a new settings file to replace the default settings. Guideline for tuning optimal image processing parameter will be discussed in the Results section.

Multi-scale Contrast Enhancement. In the next step, the raw intensity voxel matrix $I(x, y, z)$ is convolved with a Gaussian filter using the scale parameter σ in eq. 1. To enjoy the benefit of multi-scale contrast enhancement, the automatic pipeline performs several convolutions with different scale parameters σ within the range of σ_{min} and σ_{max} . For each length scale σ , the Hessian matrix,

$\tilde{H}_\sigma(x, y, z)$, is computed from the smoothed intensity in eq. 2, and the eigenvalues are calculated using a direct cubic polynomial root finding procedure using the Cardano formula.

$$I_\sigma(x, y, z) = G_\sigma(x, y, z) \otimes I(x, y, z)$$

eq. 1

$$\text{with } G_\sigma(x, y, z) = \frac{1}{(\sigma\sqrt{2\pi})^3} e^{-\frac{(x^2+y^2+z^2)}{2\sigma^2}}$$

$$H_\sigma(x, y, z) = \begin{bmatrix} \frac{\partial^2 I_\sigma}{\partial x^2} & \frac{\partial^2 I_\sigma}{\partial x \partial y} & \frac{\partial^2 I_\sigma}{\partial x \partial z} \\ \frac{\partial^2 I_\sigma}{\partial y \partial x} & \frac{\partial^2 I_\sigma}{\partial y^2} & \frac{\partial^2 I_\sigma}{\partial y \partial z} \\ \frac{\partial^2 I_\sigma}{\partial z \partial x} & \frac{\partial^2 I_\sigma}{\partial z \partial y} & \frac{\partial^2 I_\sigma}{\partial z^2} \end{bmatrix}$$

eq. 2

$$\lambda_1, \lambda_2, \lambda_3 \leftarrow eig\{H_\sigma(x, y, z)\}$$

Normalization. Two auxiliary scalar fields, $C_\sigma(x, y, z)$ and $D_\sigma(x, y, z)$ needed to obtain two stages of sequential filter operations, are computed next. The field, $C_\sigma(x, y, z)$, gives for each voxel, (x, y, z) , and for each eigenvalue set ($\lambda = \lambda_1, \lambda_2, \lambda_3$ with $\lambda_1 \leq \lambda_2 \leq \lambda_3$) a scalar value that can be interpreted as the probability of this voxel to belong to a blood vessel. The enumerator of eq. 3 accounts for a measure of the *sphericity* (r_A), the *tubeness* (r_B), and the *background suppression* (r_S). In eq. 3, parameters r_A , r_B , and r_S are computed for each voxel using the eigenvalues $\lambda_1, \lambda_2, \lambda_3$. The filter function $C_\sigma(x, y, z)$ is determined with the computed parameters and the input parameters, a , b , and c . The input parameters specify the detection threshold and sensitivity of the filter function. Optimal values of each input parameter can be retrieved from the settings files, the criteria for each parameter choice are commented in the

Discussion section. Appendix A encloses a MATLAB function for computing eq. 3. Finally, to obtain a comparable measure over the entire image domain, the value for each voxel is scaled with highest scoring voxel, $C_{\max}$, in the denominator of eq. 3. Thus the $C_{\sigma}(x, y, z)$ field has values between $[0,1]$, as expected for a probability. For each voxel, the filtered intensity, $I_C(x, y, z)$, is equal to the highest probability obtained by different length scales, σ , as in eq. 4.

The next step convolves $I_C(x, y, z)$ again with Gaussian filters at all length scales to obtain a scalar intensity field $D_{\sigma}(x, y, z)$ as in eq. 5. After computing the Hessian matrix and its eigenvalues, $\tilde{\lambda} = \tilde{\lambda}_1, \tilde{\lambda}_2, \tilde{\lambda}_3$, the probability for a voxel to belong to a blood vessel is $E_{\sigma}(x, y, z)$ in eq. 6. The computed filter function $E_{\sigma}(x, y, z)$ is necessary to avoid the introduction of gap in bifurcations as shown in Fig. 1B. Moreover, it is assigned zero in case its value is negative. This occurs when middle eigenvalue, $\tilde{\lambda}_2$, is positive, which corresponds to a dark tubular structure and is usually noise that is thus suppressed. Appendix A encloses a MATLAB function for computing eq. 6. Finally, the multi-scale contrast enhanced vessel image, $I_{MCF}(x, y, z)$, corresponds to the length scale with the highest probability of being a vessel segment with values between 0 and 1 as given in eq. 7.

$$C_{\sigma}(x, y, z) = \frac{\left(1 - e^{\frac{r_A^2}{2a^2}}\right) \cdot e^{\frac{r_B^2}{2b^2}} \cdot \left(1 - e^{\frac{r_S^2}{2c^2}}\right)}{C_{\max}} \quad \text{eq. 3}$$

$$r_A = \frac{|\lambda_2|}{|\lambda_3|}; r_B = \frac{|\lambda_1|}{\sqrt{|\lambda_2 \lambda_3|}}; r_S = \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2};$$

$$C_{max} = \left\| \left(1 - e^{\frac{r_A^2}{2a^2}} \right) \cdot e^{\frac{r_B^2}{2b^2}} \cdot \left(1 - e^{\frac{r_S^2}{2c^2}} \right) \right\|_{\infty}$$

$$I_C(x, y, z) = \max_{\sigma} C_{\sigma}(x, y, z) \quad \text{eq. 4}$$

$$D_{\sigma}(x, y, z) = G_{\sigma}(x, y, z) \otimes I_C(x, y, z) \quad \text{eq. 5}$$

$$\tilde{\lambda}_1, \tilde{\lambda}_2, \tilde{\lambda}_3 \leftarrow \text{eig}\{\tilde{H}_{D_{\sigma}}(x, y, z)\}$$

$$E_{\sigma}(x, y, z) = \max \left(\frac{-\sigma^2 \tilde{\lambda}_2}{\|-\sigma^2 \tilde{\lambda}_2\|_{\infty}}, 0 \right) \quad \text{eq. 6}$$

$$I_{MCF}(x, y, z) = \max_{\sigma} E_{\sigma}(x, y, z) \quad \text{eq. 7}$$

Output Final Response. The final $I_{MCF}(x, y, z)$ is output as a filtered DICOM image with identical header information and dimensions as in the original image, but with enhanced vessel contrast and the background noise removed.

The image pipeline depicted in Fig 2 was applied to nineteen 3DRA, one CTA, and six MRA and MRV image sets shown in the Results section. More on the mathematical background and performance evaluation using various phantoms, detail statistical analyses using surface distance error, positional offset errors of the multi scale filtering procedure is described elsewhere²⁶.

Results (715)

Bifurcation Preservation in a Phantom

Intensity gaps can be caused by imaging noise and artifacts as shown in Fig 1A. Weak or interruptions in intensity prohibits automatic recognition of blood vessels. Image processing with filters can compensate for image noise and artifacts as depicted by the red dotted line in Fig 1A. Moreover, gaps can also be introduced artificially by inappropriate image filtering as shown in Fig 1B. A digital

tube bifurcation phantom was processed with a previously published filter which created an Y-shaped gap in the bifurcation, severing the three tubular segments. It is critical to avoid this problem in cerebral vascular networks with hundreds of bifurcations. In contrast, the proposed automatic image filter pipeline preserves the bifurcation, while enhancing all tubular structure in the digital phantom as shown in Fig 1B.

Image enhancement in DSA

We collected 3DRA images from nineteen patients as shown in Fig 3. The top row of Fig 3 shows an axial, sagittal, and coronal view of the original 3DRA image. Each view is a maximum intensity projection displayed with its maximum and minimum intensity as the contrast window. In DSA image acquisition, two image sessions are performed to produce 3DRA, rotational angiography with and without contrast agent injection. The image without contrast is subtracted from the image with contrast to remove high density structures such as the cranium. The mask subtraction and contrast injection shown in Fig 3 produces high intensity values for vessels throughout the cerebral vasculature. However, turbulence of the blood flow causes uneven distribution of the contrast agent which causes wide intensity variations in the same vessel as depicted in the zoomed image in the first row of Fig 3. Furthermore, the inverse Radon transform used to reconstruct the 3DRA often introduces artifacts as depicted as arrows shown in the detailed view of second row in Fig 3. The pipeline response shown in Fig 3 not only suppresses the reconstruction artifacts, but also equalizes the intensity in all vessels in the entire network. Bottom row in Fig 3 shows the

specific σ length scales that generated the final filter response. This result shows that different portions of the arterial tree are optimally enhanced by different length scale settings.

Image enhancement in MRA

We performed the MRA image acquisition and filtering in six volunteers. One case showing typical results are presented with more detail in Fig 4. The top row of Fig 4 shows an axial, sagittal, and coronal view of the original MRA image. Each view is a maximum intensity projection displayed with its maximum and minimum intensity as the contrast window. The middle cerebral arteries (MCA) and external cerebral arteries appear the brightest. The sagittal view also depicts the major branches of the anterior (ACA) and posterior cerebral artery (PCA) territories. The Circle of Willis can only be seen partially in the coronal view. The thin anterior communicating (ACOM) and posterior communicating arteries (PCOMs) are barely visible in the original MRA as highlighted in the magnified view in the last column of Fig 4 with arrows indicating their usual anatomical position. In general, smaller arteries, particularly in the ACA and PCA territory, are hard to discern in the raw image.

Results for the automatic image filter pipeline are shown in Fig 4 bottom row. All blood vessels are enhanced in the image including large carotid arteries and small communicating arteries. Specifically the PCOMs which are entirely missed in the raw images, are now discernible in the vessel enhanced images. This result demonstrates that the pipeline not only sharpens vessel contrast, but more importantly crisply delineates small vessels whose signals are too faint to be

seen in raw images. The pipeline also preserves the contrast around bifurcations, which is an essential feature for maintaining network connectivity without introducing dangling segments.

Image enhancement in CTA

Very coarse CTA images were collected to test MCF filtering in this modality. for comparison. The original CTA data are very widely spaced with a gap of 1.5 mm between slices. Despite the use of iodine contrast agents, blood vessels appear faint with intensity level ranging from 1200 to 1500 compared to the high intensity of dense structures such as the skull with intensity level greater than 2000. Blood vessels in the CoW can barely be distinguished as shown in Fig 5 even after contrast injection. Soft tissues surrounding the blood vessels exhibits intensity levels from 1000 to 1400, further obfuscate blood vessels. With MCF filtering, the major branches of the arteries in the CoW as well as the communicating arteries become clearly visible.

Validation

The Dice coefficient is commonly used to determine performance of filtering and segmentation algorithms. For validation, we compute the Dice similarity coefficient given in eq. 8 between the filter response and manual vessel detection in the original images. The ground truth is established by manual vessel detection by an operator to identify voxels belonging vessels. The manual detection is compared to the automatic filter pipeline for true positives (TP), false positive (FP), and false negative (FN). Selected regions of interest were analyzed

since the small vessels cannot be reliably detected in original images. High dice coefficients demonstrate the reliability of the filter response.

$$Dice\ coefficient = \frac{2 \cdot TP}{(2 \cdot TP + FP + FN)} \quad eq. 8$$

The Dice coefficients are computed for all imaging modalities in Table 3 with 0.92, 0.89, 0.89, and 0.85 for 3DRA, CTA, MRA, and MRV respectively. All Dice coefficients were above 0.8, which underscores the high specificity of the automated image filtering pipeline in all modalities.

Discussion (1066)

Statistical Analysis

We rigorously quantified filter performance in terms of number of identified segments as well as range of reconstructed vessel diameters with results summarized in Table 1. As expected, the arterial trees detected from the 3DRA data had the most detail, with about N=7841 segments in the 19 subjects. The smallest diameter that could be detected was $d_{min} = 0.361\text{mm}$. In some cases with finer resolutions ($0.251 \times 0.251 \times 0.251\text{mm}^3$), vessel segments down to diameter of $d_{min} = 0.252\text{mm}$ could be successfully reconstructed. Hence, DSA images provided the best data for vascular tree reconstructions. For MRA, the average number of segments extracted from six subjects were N=5827. The smallest diameter that could be detected was 0.5% higher than the image resolution ($0.39 \times 0.39 \times 0.3\text{ mm}^3$) with $d_{min} = 0.392\text{mm}$. For MRV, the average number of segments identified in six subjects were N=1422. The venous reconstruction is poorer than MRA, because the MRV imaging protocol leads to lower resolution and can merely be acquired sequentially using a 2D imaging

sequence. The lower quality protocol also causes coarser diameter reconstruction with smallest featured diameter of $d_{\min} = 0.821\text{mm}$.

CTA data set were acquired with the most coarse slice spacing. Here we chose only to analyze the CoW. MCF image processing succeeded in enhancing the arteries in the CoW. The partial arterial tree had, $N=1315$, segments. A full reconstruction of CTA requires acquisition with narrower slice spacing, and skull stripping to remove the skull signal before vessel filtering. The statistics also show for all cases in our database (MRA $N=6$, MRV $N=6$, DSA $N=19$) that the automated pipeline to segment the vascular trees was successful in all imaging modalities.

Parameter Settings

This section discusses tuning and proper selection of adjustable filter parameters. For DSA, we chose parameter settings, $\sigma = \{1, 2, 3, 4, 5, 6, 7\text{mm}\}$. This recommendation is slightly wider than the range we proposed for human MRA in normal subjects, since DSA were performed in patients with CVD who often have larger vessel diameter. It is worth noting that the minimal value of σ should be chosen 3-5 times larger than the image resolution to achieve optimal filter response. When the threshold is set equal to the image resolution, the Gaussian filter basis is equal to one voxel, this case noise is also indiscriminately enhanced, which is undesirable. The recommended wider range gives optimal results in all patient DSA we performed. For the remaining parameter, it is recommended to choose $a=0.5$, $b=0.5$ and $c=1500$ for optimal filter response in DSA. Background suppression $c=1500$ was chosen since intensity levels range

from 0 to approximately 15000 in DSA. In general the background suppression threshold should be set to approximately 10% of the maximum intensity in the image. The filter parameters and recommendations used in the settings files are summarized in Table 2.

For CTA and MRA, we chose parameter settings, $\sigma = \{1, 2, 3, 4, 5\text{mm}\}$. This range spans the relevant length scales in the human arterial tree. The recommended range gives optimal results in all MRA we performed. Furthermore, it is recommended to choose sphericity $a=0.5$, tubeness $b=0.5$, and background suppression $c=150,1000$ for optimal filter response in MRA and CTA. For MRV, a slightly larger range for scale, $\sigma=\{1, 2, 3, 4, 5, 6, 7, 8\text{mm}\}$ is chosen since the veins typically have thicker radius. The sphericity $a=0.25$ and tubeness $b=0.25$ is also set wider to adapt to more oval shape of the veins. The default value of background suppression was set to be $c=200$, because intensity levels range from 0 to approximately 2500 in the MRV dataset.

To make the vessel segmentation more sensitive, users can choose to either expand the scale range or tune the quality by inserting intermediate ranges in addition to the original setting. Users can customize their own settings file and apply. For example, we have also performed reconstruction of microcirculation structures²⁷ (data not shown), where we used $\sigma_{min} = 2 \mu\text{m}$ and $\sigma_{max} = 20 \mu\text{m}$ in order to detect the features of the capillary bed in the mouse cortex with average capillary diameter of $d \sim 5 \mu\text{m}$.

Subject-Specific Modeling for Computational Fluid Dynamic Studies

After filtering, a threshold can be set to distinguish between voxels that delineates vessels or background. The thresholding creates binary maps that can be feed into *fast marching algorithms* for finding the centerline, vessel connectivity, and compute diameter information²⁹⁻³³. By gradually propagating an evolving front from the centerline to the boundaries of the binary mask. The radius is precisely determined using a level set calculation, which calculates the time needed to reach the boundary. Due to the level set calculations, it provides sub-voxel precision estimation of vessel radii. Combined with the multi-scale sensitivity of the pipeline, vessel radii across all ranges can be reliably reconstructed for the subject-specific vascular network. These image-derived biometrics can be used for computational modeling of subject-specific cerebral vasculature to provide information in computer-aided diagnosis.

For example, Fig 6A displays vectorized subject-specific arterial and venous trees as well as the cortical surface. Vessel enhanced images are ideal for creating computational meshes for visualization and simulation. Volumetric meshes are created using marching cubes algorithm³³ after image segmentation. Fig 6B depicts a schematic derived from the tree representation of the Circle of Willis. Missing communicating arteries demonstrate the subject specific variability in angioarchitecture and may indicate the availability of collateral blood supply. Using the image-derived centerline and diameter information, the vessel territories of subject-specific virtual vascular network can be detected. The results of manual territory labeling are shown in Fig 6C. This procedure could further be automated using Machine Learning algorithms³⁴. Identification of the

ICA, ACA, PCA, MCA territories is a necessary step to analyze territory-specific blood flow volume and distribution.

The image derived tree reconstructions can also be used to generate parametric meshes for detailed blood flow simulations with CFD³⁵. By using flow measurements from quantitative MRA as summarized in Table 4, CFD simulations derived from subject-specific trees can be used to generate estimates of hemodynamic metrics that cannot be measured directly. For example, Fig 7 shows blood pressure and wall shear stress inferred from subject-specific trees with the *in vivo* flow measurements in Table 4 for six subjects. These hemodynamic metrics are implicated with risk factors of CVD. For example, wall shear stress has been associated with potential rupture sites of aneurysms^{7,36,37}. The CFD studies also allow researchers to understand the cerebral circulation in its entirety. We expect that the proposed filter pipeline will be a critical enabling technology for vascular reconstruction

Epidemiological studies of large data set

The intensity equalization effect of the filter pipeline facilitates automation of centerline and diameter extraction in medical images without user intervention. The elimination for the need of user input and its replacement with crisp mathematical expressions removes operator bias. Unbiased extraction of biometrics from reconstructed trees would enable computerized analysis of large databases of image data to identify statistics and topological features associated with cerebral vascular diseases. Tree length, diameter, orientation of major branch, number of links to other subtrees, total tree volume, total tree resistance,

and Strahler order can be automatic computed for large data sets³⁸. The fully automated workflow is expected to enable epidemiological studies of vascular trees across institutions.

Conclusion (142)

An automatic image filtering pipeline utilizing the eigenvalues of the Hessian matrix to achieve blood vessel enhancement over all relevant length scales. Our case studies confirm the feasibility of applying our automatic vesselness filter to various imaging methods for contrast enhancement. Enhanced images provide more complete information about the blood supply for physicians to assess the status of the patient's cerebrovascular angioarchitecture. Moreover, our filtering process enhances both large and small vessels without compromising network connectivity. The pipeline allows the fully automatic reconstruction of cerebrovascular networks for the generation of high quality subject-specific computational meshes. The novel filter will enable future studies on hemodynamic simulations of blood flow through the subject-specific angioarchitecture. It also enable automatic analysis of large datasets for epidemiological studies of cerebral angioarchitectre. The information gathered from large patient population may be useful for better predicting the likely outcome of planned intervention such as bypass surgery, stenting, or coiling of aneurysms.

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Fig 1. Imaging artifacts, noise and image processing techniques introduce gaps and result in incomplete segmentation of blood vessels. A. Imaging artifacts such as motion and scattering suppresses image intensities leading to premature termination of vessel segmentation. After filtering with MCF, the intensities are more equalized in vascular segments indicated by the red dotted lines. B₁ shows a digital bifurcation phantom exhibiting high intensity inside the tubular segments. After application of a conventional vesselness filter, artificial gaps around the bifurcation are introduced in B₂, causing incomplete segmentation of vascular structures. The MCF preserves connectivity in bifurcations without creating gaps in B₃.

Fig 2. Information flow for the automated image filtering pipeline. In Step 1, the image is read from the DICOM datasets. Filtering parameters (a, b, c, σ) are read from the settings file. In Step 2, the filter response for each provided scale is computed. Each filter response is normalized and the maximum response among all scales are chosen. In Step 3, the final filter response is determined and outputted.

Fig 3. Maximum intensity projection (MIP) of the original 3DRA and filtered 3DRA in two patient cases. The maximum intensity projection in the axial, sagittal, and coronal is displayed to demonstrate the cerebral vasculature in the original and filtered 3DRA. In the original 3DRA with contrast enhancement, the cerebral vasculature exhibits high intensity compared to the background. However, in a closer look, it is shown that the intensity is not evenly distributed even in larger vessels. After filtering, a more uniform intensity distribution in the vessels is observed. Moreover, in a single slice view, the original image exhibits significant scattering artifact as indicated by the arrows which may lead to erroneous segmentation. After filtering, the scattering artifact is suppressed allowing for more accurate segmentation. The last row demonstrates the σ -values that lead to the optimal final filter image. This shows that different sections of the arterial tree are enhanced optimally at distinct length scales.

Fig 4. Maximum intensity projection (MIP) of the original MRA and filtered MRA. The first, second, and third column are the MIP of axial, sagittal, and coronal respectively. The filtered image crisply delineates the cerebral vasculature while suppressing the signals from surrounding tissues. The fourth column depicts a zoomed view of the Circle of Willis. The posterior communicating arteries are not visible in the original image but easily detected in the vessel enhanced image.

Fig 5. Analysis of the Circle of Willis with CTA. The intensity projection in the original CoW shows only faint contrast of the blood vessels despite contrast injection. The lack of contrast makes identification of the arteries in the CoW difficult. The MCF contrast enhancement accentuated the major vessel of the CoW, and produces a clearer picture highlighting prominently the MCAs, the PCAs and the PCOM arteries.

Fig 6. Application of subject-specific cerebral vascular modeling. A. Vectorized display of Grey Matter (Grey), Cerebral Arteries (Red), and Cerebral Veins (Blue). B. Circle of Willis anatomy for each subject. The closure of communicating arteries highlights the large subject variability of collateral blood supply. C. Vessel territory categorization, including, ACA (red), ICA (blue), RMCA (yellow), LMCA (purple), and PCA (green).

Fig 7. A. Pressure simulations in subject-specific cerebral vasculature. B. Wall shear stress simulations in the entire arterial tree. These measurements facilitates the studies of cause in CVDs.

Table 1. Statistical analysis of vascular networks after automatic filter pipeline

	Number of Subjects	Average Number of Segments	Image Resolution (mm)	Smallest Diameter (mm)
3DRA	19	7841	0.36x0.36x0.36	0.361
MRA	6	5827	0.39x0.39x0.29	0.392
MRV	6	1422	0.47x0.81x0.47	0.821
CTA	1	1315	0.49x0.49x1.25	0.527

Table 2. Filter parameters for different image modalities.

	a	b	c	σ	Filename
3DRA	0.5	0.5	1500	1,2,3,4,5,6,7	dsa.txt
MRA	0.5	0.5	150	1,2,3,4,5	mra.txt
MRV	0.25	0.25	200	1,2,3,4,5,6,7,8	mrvtxt
CTA	0.5	0.5	1000	1,2,3,4,5	cta.txt

Table 3. Dice similarity coefficient analysis of the automatic image filter pipeline in different imaging methods.

	3DRA	MRA	MRV	CTA
Dice Coefficient	0.92	0.89	0.85	0.89

Table 4. Volumetric blood flow rate acquired by quantitative MRA in major cerebral arteries (mL/min).

	Subject 1	Subject 2	Subject 3	Subject 4	Subject 5	Subject 6	Average
RICA	277	295	168	406	241	242	271.5
RACA	112	120	-	179	95	96	120.4
RMCA	102	190	166	213	145	116	155.3
RPCA	63	92	70	96	60	59	73.3
LICA	190	265	312	318	247	226	259.7
LACA	68	96	159	131	66	70	98.3
LMCA	102	171	172	202	184	131	160.3
LPCA	61	97	89	113	62	62	80.7
BA	106	122	181	232	135	126	150.3