A cerebrovascular tortuosity quantification toolbox with additional simulation-based metric validation tool

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Abstract
Determining cerebrovascular structural abnormalities has many important clinical implications. Vessel tortuosity has been suggested as a possible relevant parameter in many cerebrovascular disorders. This article outlines a Matlab based toolbox – Toolbox for Quantifying the Tortuosity of blood Vessels (TQTV) – which provides a method of tubular analysis upon magnetic resonance angiograms (MRA). The toolbox contains vessel selection tools to isolate a specific vessel in 3D and incorporates three tortuosity measures: distance metric, sum of angles metric, inflection count metric. Although these metrics were chosen, others could be incorporated relatively easily given proficiency in Matlab script writing. The tool was validated through computer simulated vessel centrelines, modulating the centreline's contributing parameters across ranges to investigate their applicability to real vessels and determining associated errors in the toolbox's incorporated methods.

Keywords: cerebrovascular tortuosity, vessel quantification, vessel length, vessel centreline, Matlab toolbox

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1.1 Introduction

Cerebral angiograms have many valuable clinical applications and with ever advancing computing capacity, knowledge about specific variables amongst cerebrovascular architecture is giving us new insights into vascular disease. Here in particular, vascular tortuosity has been identified as a measurable abnormality parameter (Desai and Toole, n.d.; Turior, 2012), especially in age related disease(Popa-Wagner et al., 2012). However, clinician's tortuosity labelling is often time consuming and subjective. Considering the multitudinous nature of a human population study, an efficient & accurate tortuosity quantification tool is desirable to understand the relationships between tortuosity and cerebrovascular disease. However, abnormality definitions are conditional and limited, and as a result various tortuosity metrics have been proposed (Bullitt et al., 2003), of which none have been outlined as definitive. Although previous tortuosity quantification software exists, often they only use the simplest tortuosity metrics("Geometric Analysis | VMTK – the Vascular Modelling Tool-kit," n.d.) , are not open-source (Marchenko et al., 2010), only compute 2D tortuosity measurements (Seaman et al., 2011) or are based in a coding language uncommon to medical applications ("TubeTK," n.d.). Although some have very good quantification methods, there isn't a united Matlab platform encompassing a validation method for each metric. Furthermore, they don't fit the specific motivational research application in mind.

This paper outlines the development of the TQTV, based in Matlab, mentioning which methods were implemented and why. The tool was developed in conjunction with a specific research intention, namely age-related tortuosity changes with respect to an increased risk of stroke. With this in mind, MRA were the base

1 TQTV – Toolbox for Quantifying the Tortuosity of blood Vessels, MRA – Magnetic Resonance Angiograms
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data source, however the tool could be applied to any tube related quantification problem given a few adjustments to the code.

This paper also outlines the validation process, namely the development of an additional tool which applies the same vessel centreline calculations as TQTV to simulated centrelines.

The toolbox was applied to a population of men, with and without hypertension, to investigate it's ability to distinguish between them.

We will mention limitations and additional comments not present in the code, to allow for an educated use of the tool as well as facilitating any future development of the software.

2.1. Materials and Methods – Outline of Toolbox Methods

A Matlab toolbox was developed using the GUIDE tool in Matlab version R2013a on Windows 7 platform. The input data was individual DICOM image slices of MRAs. The DICOM data format stores the MRA variables, such as voxel size and slice number, which were automatically extracted by the code and included in the calculations. Although the methods of data selection and processing are intrinsic to the toolbox, the various calculations applied to the extracted vessel centreline by these methods are stored in an external function, allowing easy editing and testing.

The following section outlines the process of centreline extraction and tortuosity calculation from the image slices.

2.1.1 Individual vessel isolation

After importing the image slices into the tool, they are converted into a viewable format and displayed for the user to begin vessel isolation. From here, the maximum and minimum signal intensity thresholds of the voxels can be altered to optimize the visibility of vasculature, and also to reduce noise from the signal extremities.

Figure 1- Stacked x-y plane images as loaded into the tool

To isolate specific vessels, the graphical user interface (GUI) contains a region-of-interest (ROI.) selection, which is initiated by the “Select ROI.” button, and is used to trace around a vessel by selecting a polygon of edge voxels. The ROI. selection method is applied onto a 2D x-y plane slice over a full-brain vessel-projection (fig.1 bottom image) to maximise the proportion of vessel body included. The toolbox then applies this 2D ROI template upon all other slices, compiles them and plots the data points inside that ROI in a separate 3D figure. The user can then minimize the ROI z-axis boundaries (middle-right panel fig.2) to speed up the centreline extraction algorithm.

Figure 2- Flowchart of Quantification Toolbox

2.1.2. Centreline extraction and cleaning

There are a multitude of centreline extraction algorithms amongst the medical imaging literature (Gávez et al., 2007; Jiang and Gu, 2005; Lee et al., 1994; Maddah et al., 2005).The fastest and most accurate centreline extraction method for this application was found to be parallel medial axis thinning as implemented in the “Skeleton3D” tool (Kerschnitzki et al., 2013). This method iteratively removes outer layers of the input 3D object until it’s left with the centreline, in a process commonly referred to as thinning.

The “Plot Centreline” button initiates centreline extraction and then plots the outcome on a figure (fig.2 bottom panel), after which there are three cleaning tools. Firstly, defining minimum branch length limits excessive spurious branches to produce a single centreline(Lee et al., 1994). The user can also introduce a “cluster-limitation” if there are excessive clumps of noise data points outside of the vessel or away from the

centreline. For each data point, this algorithm calculates the distance between all other data points. These distances are then ranked in size order and then the user can define a minimum distance requirement for a number of nearest-neighbours, and so removing small clumps of spurious data points. Finally, the crudest cleaning tool simply allows the user to selects portions of the centreline which they deem unnecessary deviations from the "true" centreline, when compared to the original vessel, and delete them. These are predominantly obvious outliers.

The resultant centreline is then smoothed through a Savitzky-Golay, S-G, filter (Savitzky and Golay, 1964; "Savitzky-Golay filtering - MATLAB sgolayfilt - MathWorks United Kingdom," n.d.) (fig.3) and then interpolated to give even spacing between centreline points ("interparc - File Exchange - MATLAB Central," n.d.), as is a requirement for the SOAM calculation. This processed version of the centreline is then used to calculate the values of the various tortuosity metrics (see theory section).

Figure 3 – Centreline spline before filter (blue), S-G filtered centreline spline (red)

The length of this centreline is taken as the length of the segmented portion of the vessel.

2.1.3. Error Calculations

The introduction of S-G smoothing on the centreline introduces an associated error, or deviation of the data points away from the coordinate axes. The associated errors in centreline length are therefore calculated from the average error in the filtered line as compared to the original extracted centreline. This can be visualised in figure 3 as the difference in path length between the red and blue lines. This was the error used to calculate the respective error for the length, DM and ICM. Calculated error values are therefore highly dependent on the centreline extraction methods used, including the segmentation of the vessel from the rest of the vasculature. The SOAM smoothing associated error was not calculated as it proved rather convoluted to calculate and wasn't of significant value.

2.2. Validation method – Phantom centreline toolbox

The tool, as described thus far, estimates the tortuosity and length of a selected vessel centreline however, the applicability and reliability of these measurements is thus far unknown. An additional toolbox was created which simulates phantom centrelines of vessels to test the tortuosity metrics. The toolbox facilitates dynamic testing of each tortuosity metric by allowing the user to define the characteristics of the phantom centreline.

Figure 4 – Screen shot of Validation Toolbox

The validation tool has four basic input centreline types: straight, sinusoidal, coil and highly coiled. This encompasses the current literature based definitions of tortuous vessel types (Bullitt et al., 2003). The centrelines were generated with 3D sine and cosine formulas, where frequency and amplitude have their standard meanings, refer to 'centreline_tort' function for full details.

After the initial generation of a type of vessel centreline, by selecting from the drop down menu (fig. 4 bottom "Centreline Attributes" panel), the user can modulate a selected parameter over a defined range to test the metrics applicability within this range (fig. 4 "Range testing" panel). For example, in figure 4, the amplitude of a sinusoidal centreline is varied from 0 to 20 and the outputs of the tortuosity metrics are calculated and plotted (y-axis-magnitude of tortuosity metric, x-axis–range of modulated parameter). The errors associated with the tortuosity metrics here are the *rmse* (standard error) of a smoothing spline fit upon the modulated data sets, to replicate the smoothing process upon the real vessel centrelines.

3. Experimental -Data Collection

MRA images were taken on a Signa HDx GE Medical Systems 3T MRI scanner using a 3D time-of-flight

protocol with repetition time 24ms, echo time 2.7ms, inversion time 0ms, flip angle 15deg and number of averages 1.

The full code used to do the analysis of the data can be found is the supplementary documents.

4.1. Theory

The reliability of tortuosity metrics to accurately quantify vessel abnormalities has been explored extensively measure(Bullitt et al., 2003; Hart et al., 1999). Often with an application in retinal vessels, the focus has been largely on 2D images (Hart et al., 1999; Turior, 2012; Turior et al., 2013). However, there is a demand for automatic 3D tortuosity quantification of intra-cerebral vessels to increase the processing speed and reliability of tortuosity measurements, rather than relying on clinician definitions which follow relatively subjective ruling. Tortuosity quantification can focus on either a group of vasculature, global tortuosity or, as in this paper, individual vessel measurements, namely that of the vertebral and basilar arteries, particularly related to an increased risk of age-related stroke.

4.2. Tortuosity metrics

There is currently no universally agreed upon measure for tortuosity amongst the literature. Bullitt has tested a variety of tortuosity metrics in phantom and real data sets of vessels(Bullitt et al., 2003) , concluding that the metrics have different applicability and although there is no universal tortuosity metric, some prove better at describing the type of abnormality. We extended their metric analysis to further validate their findings and to see where these metrics can apply to individual vessels. In all the cases explored here, the tortuosity is derived from the vessel centreline.

Below we summarise three common tortuosity metrics. The specifics of the tortuosity metrics implementation can be found in the “centreline_tort” function provided in the supplementary documents.

4.2.1. Distance Metric (DM)

The distance metric can be defined as a dimensionless ratio between the centreline length and the distance between start and end points of the centreline. As a result is doesn’t have the ability to distinguish, for example, between the curvature of “C” and “S” shape vessels of equivalent centreline length. However, this is the simplest metric, and as a result most commonly used metric in the literature (Bullitt et al., 2003; Helmberger et al., 2014; Seaman et al., 2011; Turior, 2012)

4.2.2. Inflection count metric (ICM)

An extension of the DM is the inflection count metric, which is defined as the product of the DM and the number of inflection points along the vessel. An inflection point is defined as a change in orientation of close to 180 degrees of the normal and binomial axes of the Frenet frame(Bullitt et al., 2003). It has been shown to have strong tortuosity classification accuracy (Rashmi Turior Pornthep Chutinantvarodom, 2012).

4.2.3. Sum of angles metric (SOAM)

Generally used for the quantification of tightly coiled vasculature, the sum of angles metric is produced by calculating the angle between a vector pair defined by each successive trio of centreline points. The angles are summed and normalised by path length (Bullitt et al., 2003, 2007). The outcome measurement has units of radians/mm. It is a requirement for this metric that points along a centreline are evenly spaced.

It has been proposed that the effectiveness of a tortuosity quantification method is in its ability to discriminate normal from abnormal vessels (Bullitt et al., 2003), furthered by its ability to be scalable, shape sensitive, modulation sensitive and additive (Turior et al., 2013). This knowledge facilitated the development of the additional validation tool, to test the metrics ability to meet these criteria.

4.3. - Calculation

In contrast, a Calculation section represents a practical development from a theoretical basis.

Here, I could go into the use of additional metrics. What it is about tortuosity that makes it difficult to measure. Expand on the metrics? Possible?

5.1 Results

Here we will discuss the findings from the phantom vessel tortuosity calculations as well as comparing TQTV to previous studies of real vessel tortuosity quantification. The toolbox is then applied to real human data.

5.2. Phantom Vessel Results

The relationship between the various tortuosity metrics and the contributing variables of the phantom centrelines were explored. We wanted to quantify the ability of the various tortuosity metrics in describing simulated centrelines given a various range of centreline parameters.

5.2.1. Sinusoidal phantom centrelines

Figure 5.1	Figure 5.2
Figure 5.3	Figure 5.4

Figure 5 – Sinusoidal phantom centreline tortuosity metric modulation graphs

These graphs reveal the relationships between phantom sinusoidal centrelines and the tortuosity metrics. The DM is observed to have a linear relationship with frequency and amplitude. The ICM, based on DM, shows an exponential relationship with frequency and linear for amplitude >2. The SOAM has a frequency-magnitude dependency for changes >1 but levels off beyond this and for amplitudes greater than 10 its magnitude begins to decline. The number of points in the centreline was shown to have a minimum requirement of 200 points, under this the metrics and length calculations can vary greatly, especially the ICM. The length dependency of metrics also shows us the DM and ICM are only truly valid for long vessels, greater than 50 units apart, i.e. 50 voxels.

5.2.2. Coiled phantom centrelines

The simulated coil centrelines relationship with frequency and shape is more complex but still should relate closely to its tortuosity, so again the relationship was explored. This has previously been explored with the distance metric for the length of the coil (Diedrich et al., 2011), we made one for comparison but were ultimately more interested in frequency dependence of the metrics.

Figure 6.1	Figure 6.2
Figure 6.3	Figure 6.4

Figure 6 – Coiled phantom centreline tortuosity metric modulation graphs

The DM and ICM are matched in all plots, showing that no inflection points are measured on the coil phantom. They are both however amplitude and frequency dependent. The SOAM again only has a magnitude-frequency dependency at small frequency values <1. The SOAM magnitude-amplitude dependency shows a negative correlation for amplitude >2. The number of points for magnitude-number of point interdependency is >100 points. The magnitude-length plot shows that the DM has a negative exponential relationship with length.

5.3. Comparison to previous simulated vessel study

Although the input lengths of phantom centrelines are different the measurements of types of centrelines match closely to that of a previous study by Bullitt (Bullitt et al., 2003).

	Frequency	Amplitude	Length	DM	ICM	SOAM
Sine Bullitt	3	10	13.9	1.6	9.7	0.9
Sine TQTV	3	10	100	1.6163	9.698	0.8725
Sine Bullitt	10	3	13.9	1.6	32.3	3.1
Sine TQTV	10	3	100	1.5937	31.8733	2.8199
Sine Bullitt	20	1.5	13.9	1.6	64.7	6.2
Sine TQTV	20	1.5	100	1.5225	60.8988	5.7556
Coil Bullitt	3	6.3	13.9	1.5	1.5	1.3
Coil TQTV	3	6.3	100	1.5503	1.5503	1.5833
Coil Bullitt	10	1.9	13.9	1.5	1.5	4.5
Coil TQTV	10	1.9	100	1.5335	1.5335	4.9727
Coil Bullitt	20	0.94	13.9	1.5	1.5	9.2
Coil TQTV	20	0.94	100	1.4577	113.6992	8.7008
Sine Bullitt	3	10	13.9	1.6	9.7	0.9
Sine TQTV	3	10	100	1.6163	9.698	0.8725
Sine Bullitt	3	20	22.9	2.7	16	0.7
Sine TQTV	3	20	100	2.6646	15.9875	0.5305
Sine Bullitt	3	40	42.6	5	29.7	0.4
Sine TQTV	3	40	100	4.9536	29.7215	0.291

Table 1 – Comparison to tortuosity of phantom centrelines in previous study

5.4. Comparison to previous real vessel study

The toolbox was then applied to real cerebral vessels of interest, and compared to a previous tortuosity quantification study. The values did not match neither in magnitude or correlate. Bullitt's data was however in mice not humans with vascular disorders, as our data was.

5.5 Real Human data – Hypertensive vs normaltensive

The toolbox was then applied to a real population, the results are summarised in the table below.

INSERT DATA AFTER ANALYSIS

6. Discussion

In this study a toolbox is developed, quantifying the tortuosity of cerebral vessels of interest. In conjunction with this, a validation toolbox tested the tortuosity measures against phantom vessel centrelines. Combined, they provide a rigorous platform for the experimental investigation of vessel tortuosity.

FINDINGS AND COMPARISON - significance

The phantom values of tortuosity closely matched that of a previous study, however there was a deviation as seen in table 1 of the require centreline input length to obtain comparable results. This was interpreted as the difference in the definition of the phantoms – check this.

The aim of the phantom validation tool was to reveal how well the tortuosity metrics conveyed changes in a phantom centreline as a change in its magnitude. Ideally, indicating a relation to a basic definition of tortuosity as frequency and/or amplitude modulation. For sinusoidal phantom centrelines, the DM and ICM were found to both be frequency and amplitude dependent. It also further validated the ability for the ICM to combine DM values with additional number of inflection points in the curves. The SOAM was only frequency and amplitude dependent for small values. Contrary to Bullitt concluding the SOAM is most effective at quantifying tightly coiled vessels, this indicates the SOAM would only be suitable for low frequency and amplitude centrelines, namely vessels with small radii centreline. Furthermore, Turior found the ICM to decrease with frequency and amplitude modulation in simulations (Turior et al., 2013), whereas

here the ICM was found to increase for both. This could be due to different definitions of inflection point, Turior counts them as the number of twists, whereas here we follow the original method stated by Bullitt (Bullitt et al., 2003).

Considering the tool was developed for use of researchers; speed, accuracy and reliability were paramount in the choice of methods. Having said this, the methods can be optimised further to increase the speed at which reliable values can be extracted from vessels. For example, the extraction of individual vessels could be optimized by selecting points of constant values within a volume (isosurfaces), which would reduce noise and unwanted vasculature from the centreline extraction. This however increases code run time dramatically. Another potentially more accurate method of segmentation is snake filling, which require user definition of a seed start point from which a surface is "filled" by a snake like algorithm to isolate specific vasculature.

It has been noted that the most complete validation method would include a "ground truthing" method. Namely, hand labelling of vessel centrelines and comparisons to neurologists labels of tortuosity. This would be completed with a Jaccard or Sorensen-Dice index calculation between sets to quantify the overlap between computers extracted values and clinician labelled values of centreline and tortuosity. Another possible route of investigation would be to take MRA of artificial vessels with known projection angles, then running the images through the toolbox to test methods further. In this way comparisons could be made between phantom, artificial and real vessels, testing the reliability of the skeletisation method also.

One clinical application of tortuosity is to hypertension. Something to consider is that the MRA images don't replicate vessels exactly, they only image moving blood. The vessel walls therefore are ignored in these calculations. However, blood pressure is the pressure of blood against the vessel walls and therefore when trying to relate tortuosity to blood pressure ignoring the variability vessel wall thickness may be unwise. But as with most medical diagnosis multiple factors have to be considered.. Also, the accuracy of parameter calculations rely heavily on the accuracy of MRA images themselves, so we require knowledge of noise in the signal and discuss how this would affect the desired parameters – sources?.

Another point to consider is the variability of clinician's definitions of start-end points of vasculature – thoughts?. When isolating specific vessels there may be some ambiguity.

The obvious next line of investigation would be to include other measures of tortuosity quantification based on centreline analysis methods, such as curvature and total squared curvature (Hart et al., 1999). Including other metrics, such as the discrete-derivative measure, a method based on the second differences of the positions of the vessel centreline. It quantifies tortuosity as the sum of these values divided by the sampling interval (Diedrich et al., 2011). Also the total square curvature, which has been shown to match clinical definitions of tortuosity(Hart et al., 1999)**,** a measure defined as the integral of the square curvature of the vessel centreline.

Beyond these measures of centreline curvature it has been investigated that the thickness of the vessel at various points along its curve may contribute to tortuosity(Marchenko et al., 2010). As such the phantom toolbox could be expanded to generate 3D vessels, with defined wall thickness', to test this against previous measures and compare.

7. 1. Conclusions

TQTV in conjunction with the simulated vessel centreline tool provide a rigorous platform for tortuosity experimentation. As there are few human cerebral tortuosity studies to compare to, further work is required to validate findings. Expand

8.1 Acknowledgements

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10.1 Vitae

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To do on the Paper

- Error in sum of angles calculation (Ignore torsional angle)
- Error calculations (SOAM and ICM)
- Explore scalability of metrics (simulated)
- Laplace metric?

Extra Resources

http://chenlab.ece.cornell.edu/Publication/Cha/icip01_Cha.pdf
http://www.sciencedirect.com/science/article/pii/S0895611110001096
Triangulation based volume calculation - Andrew Y.T. Kudowor

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