Improving blood vessel tortuosity measurements via highly sampled numerical integration of the Frenet-Serret equations

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Abstract—Measures of vascular tortuosity—how curved and twisted a vessel is—are associated with a variety of vascular diseases. Consequently, measurements of vessel tortuosity that are accurate and comparable across modality, resolution, and size are greatly needed. Yet in practice, precise and consistent measurements are problematic—mismeasurements, inability to calculate, or contradictory and inconsistent measurements occur within and across studies. Here, we present a new method of measuring vessel tortuosity that ensures accuracy. Our method relies on numerical integration of the Frenet-Serret equations. By reconstructing vessel coordinates from tortuosity measurements, we explain how to identify and use a minimally-sufficient sampling rate based on vessel radius. Our work also identifies a key failing in current practices—filtering asymptotic measurements—and highlights inconsistencies and redundancies between existing tortuosity metrics. We demonstrate our method within and across studies. Here, we present a new method of calculating, or contradictory and inconsistent measurements occur.

I. INTRODUCTION

RECENT work in both clinical and mathematical modeling studies has shown that measures of vessel tortuosity—the extent of ‘curliness’, ‘squiggliness’, ‘or wiggliness’—serve as biomarkers of diseases such as atherosclerosis, hypertension, arteriovenous malformations, recovery from stroke or stent implantation, and classification of tumors and their response to intervention [1]–[13]. In the research literature there exists many different definitions of tortuosity, with researchers constructing measures designed specifically to target particular biomarkers and for a given cohort [2]–[16]. Using two components of tortuosity—curvature and torsion—it is possible to completely reconstruct the measured vessel, thereby providing a systematic check for measurement error. Yet, we have not found a single study that exploits this capability. Furthermore, these two mathematical measures of vessels can be linked to local pressures and stresses that act on vessels, connecting physical mechanisms to morphological features [17]–[19].

As part of the measurement process, researchers have used sampling rates that are nearly equal to the voxel dimensions for their images. This practice has proven sufficient for binary differentiation between diseased and healthy vessels as long as there is no significant variation in modality, resolution, and vessel size. However, we show that these voxel-informed choices of sampling rate lead to measurements of curvature and torsion that mischaracterize vessels, thereby muddling efforts of more refined classification (e.g. disease prognosis and progression).

We present a method based on numerical integration that uses curvature and torsion measured at sub-voxel sampling rates. From this we reconstruct vessel centerline coordinates to an accuracy related to the vessel radius, thereby allowing for comparisons across modality, resolution, and size. We use this method to re-examine previously published data of the common, external, and internal carotid arteries [20]; the abdominal aorta, associated right renal artery, and both left and right common iliac arteries [21]; complete coronary arterial trees [22]; and the anterior, posterior, left, and right middle cerebral vascular trees [23]. All data are from healthy human patients.

II. BACKGROUND

A. Curvature, Torsion, and the Frenet-Serret Coordinate Frame

Differential geometry was developed to deal with details of curved surfaces [24], [25]. Here we provide the standard set of techniques borrowed from differential geometry to estimate the tortuosity of vessels.

Spatial curves are described in terms of position vectors, \( \mathbf{r}(s_j) \) that assume Cartesian coordinates—\( \mathbf{r}(s_j) = x(s_j)\hat{x} + y(s_j)\hat{y} + z(s_j)\hat{z} \) with \( (x(s_j), y(s_j), z(s_j)) \) defined relative to the origin of the medical images. The subscript \( j \) represents either the indexed voxel-space of the original images or a subsampled space. We choose \( s_j \) to be the arc length, defined numerically as the sum of the euclidean distances between all neighboring points from the first to the \( j^{th} \) point, so \( s_j = \sum_{i=1}^{j-1} || \mathbf{r}_{i+1} - \mathbf{r}_i || \).

The first and second derivatives of points along a spatial curve define the osculating plane such that changes in the curves shape can be described in two ways—in-plane changes and out-of-plane changes. Curvature, \( \kappa(s_j) \), measures the rate of in-plane changes with respect to the curve’s arc length \( s_j \). Torsion, \( \tau(s_j) \), measures the rate of out-of-plane changes. Together these quantities are fundamental descriptors of any continuously differentiable curve that can be used to reconstruct the spatial \( x_j, y_j, \) and \( z_j \)-coordinates. To calculate

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curvature and torsion, it is essential to introduce the Frenet-Serret coordinate frame.

The Frenet-Serret (FS) frame is a moving coordinate system defined at all points along a curve. This frame exists wherever the second derivative is continuous. The FS-frame can be calculated from the position vector of the curve, \( \mathbf{r}(s) \). The unit-vectors that constitute the FS-frame are the tangent, \( \mathbf{T}(s) \), the normal, \( \mathbf{N}(s) \), and the binormal, \( \mathbf{B}(s) \), vectors (Figure 1). The tangent vector is the normalized, first-derivative of the position vector with respect to arc length, \( \mathbf{T}(s) = \mathbf{r}'(s)/|| \mathbf{r}'(s) || \), and the normal vector is the normalized, second-derivative of the position vector with respect to arc length, \( \mathbf{N}(s) = \mathbf{r}''(s)/|| \mathbf{r}''(s) || \). Assuming smooth laminar flow these two unit-vectors point respectively in the instantaneous directions of velocity and acceleration of transported blood. Finally, the binormal vector is the cross-product of the tangent and normal vectors, \( \mathbf{B}(s) = \mathbf{T}(s) \times \mathbf{N}(s) \) that points in the direction of angular velocity for a rigid body that is rotating in space but not translating through space.

Curvature \( \kappa(s) \) and torsion \( \tau(s) \) are the rates of change of the tangent and binormal vectors that point in the direction of the normal vector. This is expressed formulaically as,

\[
d\mathbf{T}(s) = \nu_j \kappa(s) \mathbf{N}(s) \tag{1}
\]

\[
d\mathbf{B}(s) = -\nu_j \tau(s) \mathbf{N}(s) \tag{2}
\]

where \( \nu_j \) is the “speed” of the curve at \( s_j \), defined as \( \nu_j = ||d\mathbf{r}^j/ds_j|| \). Curvature and torsion can also be interpreted as the rates of rotation about the binormal and tangent unit-vector axes, respectively. Finally, the rate of change of the normal vector in terms of curvature and torsion is,

\[
d\mathbf{N}(s) = -\nu_j \kappa(s) \mathbf{T}(s) + \nu_j \tau(s) \mathbf{B}(s) \tag{3}
\]

Using Eqs. (1–3) and the definitions of the FS-frame, curvature and torsion can be expressed solely in terms of derivatives of the position vector.

\[
\kappa(s) = \frac{|| \mathbf{r}'(s) \times \mathbf{r}''(s) ||}{|| \mathbf{r}'(s) ||^3} \tag{4}
\]

\[
\tau(s) = \frac{\mathbf{r}'(s) \cdot (\mathbf{r}'(s) \times \mathbf{r}''(s))}{|| \mathbf{r}'(s) \times \mathbf{r}''(s) ||^2} \tag{5}
\]

Note that curvature is always a positive quantity, whereas torsion is a signed quantity. Positive and negative values of torsion denote right- and left-handed rotations about the direction of the tangent vector. Furthermore, the definitions of the FS-frame vectors and the forms of Eqs. (1–5) are commonly used when working in a non-arc length parameterization. Analytically speaking, curves expressed in the arc length parameterization have unit-speed, or \( \nu = ||d\mathbf{r}(s)/ds|| = 1 \) (see Bogunovic et al. in [16] or Lorthois et al. in [26]). However, when working with discretized curves originating from data—as we are—this unit-speed condition is not guaranteed.

B. Tortuosity metrics

A multitude of tortuosity metrics are used in the literature [1–16], [20–23], [26–30]. We now briefly review the most commonly used measures.

1) Distance Metric (D): The distance metric is a simple ratio of the total vessel arc length to the distance between endpoints.

\[
D = \frac{\sum_{j=0}^{N-1} || \mathbf{r}_j - \mathbf{r}_{j+1} ||}{|| \mathbf{r}_0 - \mathbf{r}_N ||} \tag{6}
\]

This metric measures any deviation from perfect straightness but fails to differentiate between 2D and 3D curves. This measure is bounded below by a value of 1 corresponding to perfectly straight vessels and approaches infinity when the endpoints are co-located such as in a complete loop or cycle. An alternative definition is \( D_1 \), and defined as \( D_1 = D - 1 \) (see [9], [16], [21], [27] and Supplementary Table S1).

2) Inflection-Count Metric (IC): The inflection-count metric simply counts the number of inflection points along a vessel. This metric is argued to be useful for distinguishing between curves with single arcs versus those with multiple arcs [2]. Two methods of identifying inflection points have been proposed by Bullitt et al. in [2]. One is to identify and count all points where the total curvature is a local minimum. Total curvature, \( \kappa_{\text{tot}} \), is defined by Hart et al. in [14] as \( \kappa_{\text{tot}} = \int \kappa(s)ds \) (also see Falarin et al. in [3]). This is not a well-defined way to detect inflection points however as \( \kappa_{\text{tot}} \) monotonically increases with arc length and can have no local minima. Thus, we instead count the number of local minima in curvature, \( \kappa(s) \). This metric will be denoted as \( \text{IC}_N \).

The other method is to identify and count the local maxima of \( \Delta \mathbf{N} \cdot \Delta \mathbf{N} \) when \( \Delta \mathbf{N} \cdot \Delta \mathbf{N} \) is greater than 1.0 [2], [7]. This latter method will be denoted as \( \text{IC}_N \). For both metrics the value of 1 is added to the count and multiplied by the distance metric. Thus, for scenarios where the curve makes a broad arc, the inflection-count metrics will still return values no less than the distance metric. This practice is standard convention.

3) Sum-of-Angles Metric (SOA): This metric integrates angular changes in orientation between (at least) four neighboring points along a vessel. It is widely used in lieu of curvature and/or torsion [2–7], [10], [11], [26], [28], [29]. It was originally proposed by Bullitt et al. in [2] as a geometric variation on the total curvature, \( \kappa_{\text{tot}} \), that was proposed by Hart et al. in [14] by incorporating torsion into the integration. The motivation for this metric is to identify vessels with
high-frequency, low-amplitude oscillations that are not well quantified by either the distance or inflection-count metrics. The SOA metric is,

\[
SOA(s_j) = \left\{ \cos^{-1} \left( \frac{\Delta \hat{r}(s_j) \cdot \Delta \hat{r}(s_{j+1})}{|\Delta \hat{r}(s_j)| |\Delta \hat{r}(s_{j+1})|} \right) \right\}^2 + \cos^{-1} \left( \frac{\Delta \hat{r}(s_{j-1}) \times \Delta \hat{r}(s_j)}{|\Delta \hat{r}(s_{j-1})| \times |\Delta \hat{r}(s_j)|} \right) \frac{1}{2},
\]

where the \( \Delta \) symbol represents forward differences \(-\Delta \hat{r}(s_j) = \hat{r}(s_{j+1}) - \hat{r}(s_j) \). In Eq. (7), the first term within the square-root captures in-plane changes in orientation, and the second term captures out-of-plane changes. Only three unique indices appear in Eq. (7) \( j - 1 \), \( j \), and \( j + 1 \), yet at least four neighboring points are needed because the simplest discretized derivative requires points \( j \) and \( j + 1 \). Eq. (7) is a local definition of the SOA, and in typical applications the reported value is the summed total divided by the total arc length \(-SOA = \sum_{j=2}^{N-1} SOA(s_j) / \sum_{j=1}^{N-1} s_j \). Importantly, all resulting values from the inverse cosine expressions must be modulated by the value \( \pi / 2 \).

4) Statistical Features of Curvature and Torsion: Some studies treat the metrics of curvature and torsion, Eqs. (4) and (5), as statistical distributions and use various statistical features—such as mean, root-mean-square, or maximum—as singular measures of tortuosity \([21, 24, 27, 29]\), while other studies use integrated measures or weighted-averages \([14, 16, 22, 30]\). Moreover, measures with physical dimensions of inverse length are often defined to be dimensionless, yet at any given point, the resulting value for any feature—such as mean, root-mean-square, or maximum—can be found in the Supplemental Material Section III.

III. METHODS

A. Data Acquisition

Here we reanalyze data from four independent studies. To limit the focus of this paper, we only analyzed data that had already been segmented using \( x, y, z \)-spatial coordinates. We also report the original sampling rates employed for each study. When necessary, all data were smoothed and interpolated as instructed in the respective publications to reproduce the originally published results. Further information on the steps taken to reproduce originally published results, as well as our own measured values, can be found in the Supplemental Material Section III.

1) O’Flynn et al. (2007): The data from O’Flynn et al. consists of four abdominal arteries from one adult male individual \([21]\). Specifically, the abdominal aorta, the right renal artery, and the left and right common iliac artery. The original study employed a sampling rate of 5 points/mm.

2) Bullitt et al. (2010): The data from Bullitt et al. consists of the primary cerebral arteries of 42 adult humans ranging in age from 18 to 49 \([23]\). This is the largest dataset analyzed, with approximately 6,000 individual vessels. The original study had 100 individuals, but segmented data existed for only 42. The sampling rate used in this study was 2 points/mm.

3) Kamenskiy et al. (2012): The data from Kamenskiy et al. consists of the common, external, and internal carotid arteries of 16 individuals \([20]\). Note that the data analyzed was of the averaged coordinates for the 16 patients studied and not for each individual. Furthermore, the common and internal carotid arteries were studied as one continuous vessel. Thus, this is the smallest dataset studied, with only two vessels total. The original sampling rate was 1 point/mm.

4) Vorobstova et al. (2016): The data from Vorobstova et al. consists of coronary trees for three individual adult patients, resulting in 23 vessels \([22]\). The sampling rate used in the original study was not stated, thus we used a sampling rate of 10 points/mm because that allowed us to reproduce the originally published results.

B. Interpolating and Increased Sampling

To increase sampling rates, we interpolate based on fits of a linear combination of polynomials curves (B-splines) that are piecewise-continuous to their fourth derivative. Continuity of higher-order derivatives is essential to ensure that asymptotic features of torsion estimates are not due to discontinuity in any of the required derivatives of the position vector. The particular splining procedure that we used incorporates a penalization to avoid overfitting. Hence, these are called penalized-splines or...
D. Numerical Integration of Frenet-Serret Equations

Reconstructions of vessel centerline coordinates from measures of curvature and torsion can be done by integrating the Frenet-Serret equations. The value of this approach is that it demonstrates the accuracy of the measures of curvature and torsion, particularly in relation to asymptotic regions where curvature approaches zero. The procedure for performing numerical integration of the Frenet-Serret equations begins with re-writing Eqs. (1)-(3) as a linear system of first-order, ordinary differential equations as follows,

\[
\frac{d}{ds} \begin{pmatrix}
\hat{T}(s_j) \\
\hat{N}(s_j) \\
\hat{B}(s_j)
\end{pmatrix} = 
\begin{pmatrix}
0 & \nu_j \kappa_j \mathbf{I} & 0 \\
-\nu_j \kappa_j \mathbf{I} & 0 & \nu_j \tau_j \mathbf{I} \\
0 & -\nu_j \tau_j \mathbf{I} & 0
\end{pmatrix}
\begin{pmatrix}
\hat{T}(s_j) \\
\hat{N}(s_j) \\
\hat{B}(s_j)
\end{pmatrix} + \begin{pmatrix}
0 \\
0 \\
0
\end{pmatrix}
\]

(8)

where \( \mathbf{I} \) is the 3×3 identity matrix, and \( \mathbf{0} \) is the 3×3 matrix of zeros. This equation can be expressed in a compact manner as,

\[
d\Phi(s_j)/ds_j = M(s_j) \Phi(s_j),
\]

where \( \Phi(s_j) \) is the 9×1 vector of FS-frame unit-vector components, and \( M(s_j) \) is the 9×9 matrix of curvature and torsion values as written in Eq. (8).

The conditions for solving Eq. (8) are unique in that the solution is known entirely. This includes the boundary conditions of both Dirichlet (\( \Phi(0), \Phi(N) \)) and Neumann (\( \Phi'(0), \Phi'(N) \)) type. Thus, one can choose whether to use boundary value problem (BVP) or initial value problem (IVP) methods. We have chosen to use IVP methods given that the BVP methods require solving a sparse, \( 9N \times 9N \) non-linear, inverse-matrix problem (where \( N \) represents the number of centerline vessel coordinates) and would require the combination of implicit and iterative methods to yield stable convergence given the eigenvalue structure of \( M(s_j) \). On the other hand, as an IVP we need only solve \( N, 9 \times 9 \) problems (one for each of the \( N \) coordinates along the vessel centerline) using the
Discretization with a forward Euler method, Eq. (9) can be linearized—\( \mathbf{r}'(s_j) = \mathbf{\hat{T}}(s_j) \)—and easily integrated. The methods of integration for Eqs. (8) and (9) are presented in detail in Supplementary Material Section I.

Once Eq. (9) is integrated, a point-wise error, \( \epsilon_j \), can be calculated for comparison against the original (measured, splined, and subsampled) position vector, \( \mathbf{r}'(s_j) \), and also the reconstructed position vector, \( \mathbf{\hat{R}}(s_j) \).

\[
\epsilon_j = ||\mathbf{r}'(s_j) - \mathbf{\hat{R}}(s_j)||
\]

To establish a threshold for satisfactory reconstruction, the maximum of the point-wise error \( \epsilon_j \) was compared against the minimum vessel radius (see Fig. 2). In addition to calculating the point-wise error, it is visually instructive to graph original and reconstructed vessels to identify where breakdowns in reconstruction occur (see Fig. 2).

IV. RESULTS

A. Reconstruction

Qualitative results of the integration reconstruction procedure are presented in Figure 2 for the MARG2 coronary artery from patient B from the Vorobstova et al. dataset. There we can see an example where increasing the sampling rate improves reconstruction accuracy by providing a greater resolution of the middle torsion spike (Fig. 2(a), (b), (e), and (f)). Quantitatively, we find that increasing the sampling frequency universally improves reconstruction accuracy of vessels when compared to the minimum vessel radius (Fig. 4). In other words, sub-millimeter sampling rates (1 – 100 points/mm) for the vessels studied are incapable of providing sufficient curvature and torsion measurements to accurately characterize the vessels. We find that increasing sampling rates to the sub-sub-millimeter level (10 – 1000 points/mm) is sufficient for vessels with an average minimum radius larger than 1 mm, and that 100 – 1000 points/mm is sufficient for vessels with an average minimum radius less than 1 mm.

The effect of filtering is shown to universally result in mischaracterization of the original vessel in terms of erroneous reconstructions, sometimes by as much as 10 times the radius of the vessel itself (see Figs. 3 and 4(b)). This is demonstrated with and without the use of increased sampling. In fact, since the filtering threshold proposed by Bullitt et al. does not account for the step-size between points in calculating the acceleration vector (the factor of \( 1/4\Delta s^2 \)), the effects of filtering are exacerbated by increasing sampling rates because entire vessels are filtered at that threshold.

B. Tortuosity metrics, subsampling, and correlation

The observed changes in tortuosity metrics as sampling rates increase serve to demonstrate the potential for mismeasurement in past studies. Furthermore, we find correlations between the metrics, suggesting redundancy.

The curvature-only metrics saw little change (< 10%) in their measured values with increased resolution, whereas the torsion-only metrics saw large changes (≥ 10%) (see Fig. 5). This difference is expected because calculating torsion requires 2nd- and 3rd-order derivatives of the coordinates, thereby making this metric more sensitive to under-sampling.
In all of the metrics considered, most increases in sampling increased tortuosity estimates (indicated by the percent shifts being positive). However, for each metric at least one of the datasets exhibited negative percent shifts, or smaller tortuosity estimates, at higher sampling rates. For all metrics but the inflection-count metric, insignificant changes (< 5%) occur as the sampling rate is increased from 10X to 100X. This result suggests that—for vessels whose radius is between 0.1-10 mm—sub-sub-millimeter sampling rates (10-100 points/mm) are necessary for the purposes of providing accurate and precise summary statistics of tortuosity measures.

The two different methods of calculating and counting inflection points, $IC_N$ and $IC_{\kappa}$ have contrasting changes as sampling rates are increased (Figs. [5]k and [5]l). For the inflection-count metric based on largest nearest-neighbor changes in the direction of the normal vector, $IC_{\kappa}$, all percent shifts are negative, indicating that the number of inflection points detected is decreasing with increased sampling. This effect is due to the fact that the threshold used to detect a “large enough” change in the direction of the normal vector is not defined in terms of the sampling rate. Thus, increased sampling rates result in naturally limiting the size of $|\Delta \hat{N}_j \cdot \Delta \hat{N}_j|$ until eventually no pair of points will cross the threshold.

For the inflection-count metric based on detecting local minima of the curvature $IC_{\kappa}$, increased sampling leads to gross increases in the measured values. In particular, as high as 439% and 1027% for the Vorobstova et al. and O’Flynn et al. data respectively. This occurs because uniformly distributed, under-sampling heavily influences the number of points that comprise the regions where maxima and minima occur (or where $|\Delta^2 \kappa(s_j)/\Delta s_j^2|$ is greatest).

Fig. 4. Graphs of reconstruction error versus sampling resolution for (a) unfiltered and (b) filtered data. Points are averages of dataset (geometric average for Bullitt et al.) and error bars are standard deviations (back-transformed for Bullitt et al.). Horizontal strips denote one standard deviation in values of vessel minima used to set the threshold for acceptable reconstruction error. In (b), the number of vessels completely filtered at 100X resolution for the datasets are (in order of Kamenskiy, O’Flynn, Vorobstova, then Bullitt) 1/2, 4/4, 16/24, 47/99/58838.

The divergent behavior of these two different ways of detecting and counting inflection points suggests that either the definitions for both of these methods need be refined to account for sampling rates or that alternative approaches be proposed that are not so heavily dependent on sampling rates.

Given the extent to which many tortuosity metrics are defined in terms of curvature and torsion—either directly or indirectly—we examined the correlation coefficients and significance of correlation between all measurements at the 100X sampling rate. These results are presented in Table 1 and are ordered by correlation clustering. We find that all three dimensionful metrics (the un-weighted averaging methods) and the SOA (also a dimensionful metric) are highly correlated with one another. Among these four metrics, the average curvature and average torsion exhibit the weakest correlation (0.48) despite still being significant.

Of particular note in Table I is the complete correlation between the metrics for average combined curvature and torsion, $ACCT$, and the sum-of-angles, $SOA$. To examine further, we graphed the measured values for $SOA$ versus $ACCT$ for each of the sampling rates in Fig. 6. We find that the correlation between $SOA$ and $ACCT$ strengthens as the sampling rate is increased and attains a nearly one-to-one relationship. Specifically, we find that in the limit of high sampling rates, the SOA metric and the average combined curvature and torsion metrics produce the same values.

Using the approximation that $\cos^{-1}(1-\psi^2) \approx 2\psi$ for $|\psi| < 1$, and that

$$SOA = \sum_{j=1}^{N} SOA_j / \sum_{j=1}^{N} \Delta s,$$  

then,

$$SOA = \frac{1}{N} \sum_{j=1}^{N} \sqrt{\kappa_j^2 + \tau_j^2}$$

which is the exact definition of the average combined curvature-torsion metric, $ACCT$. 

In (b), the number of vessels completely filtered at 100X resolution for the datasets are (in order of Kamenskiy, O’Flynn, Vorobstova, then Bullitt) 1/2, 4/4, 16/24, 47/99/58838.
For each tortuosity measure, percent shifts are calculated for each vessel’s corresponding value, then averages were calculated for the distribution of shifts and graphed, with error bars representing one standard deviation in the distribution of shifts. These metrics were calculated as defined in Section II-B. For the Kamenskiy et al., O’Flynn et al., and Vorobstova et al. datasets, distributions were small enough that arithmetic means were sufficient. However, for the Bullitt et al. dataset the distributions were characterized as lognormal, thus the graphed points are geometric means and the standard deviations are back-transformed.

### Table I

| Variables  | 1         | 2         | 3         | 4         | 5         | 6         | 7         | 8         | 9         |
|------------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| 1. AC      |           |           |           |           |           |           |           |           |           |
| 2. AT      | 0.48***   | –         |           |           |           |           |           |           |           |
| 3. ACCT    | 0.73***   | 0.93***   | –         |           |           |           |           |           |           |
| 4. SOA     | 0.73***   | 0.93***   | 1***      | –         |           |           |           |           |           |
| 5. TT      | -0.13***  | 0.42***   | 0.28***   | 0.28***   | –         |           |           |           |           |
| 6. TCCT    | 0.1***    | 0.18***   | 0.22***   | 0.22***   | 0.84***   | –         |           |           |           |
| 7. IC      | 0.29***   | -0.086*** | 0.079***  | 0.076***  | 0.26***   | 0.57***   | –         |           |           |
| 8. TC      | 0.39***   | -0.21***  | 0.017     | 0.014     | 0.25***   | 0.60***   | 0.75***   | –         |           |
| 9. ICN     | 0.44***   | -0.24***  | 0.01      | 0.0085    | -0.075*** | 0.34***   | 0.76***   | 0.78***   | –         |

The SOA metric has been described as an analogue to the total curvature metric, TC, of Hart et al. from [14]. Yet to our knowledge, an exact comparison has never been made until now (see [2], [4], [6], [7], [10]). We find no correlation between these two metrics (see Table I). A key difference between the SOA and TC metrics is that SOA is normalized by arc length, otherwise it would be a dimensionless metric. This motivates further examination of normalizing the dimensionless metrics by total arc length and comparing the results to their average, dimensionful analogues.

In Table S3 we show the results of a correlation analysis comparing all metrics measured at 100X resolution, with the addition of all of the dimensionless metrics being normalized by total arc length L. We find significant correlations of unity between total metrics normalized by arc length and their average analogues. Specifically, these correlations are found between: average curvature, AC, and normalized total curvature TC/L, average torsion AT and normalized total torsion, TT/L, average combined curvature and torsion ACCT, and normalized total combined curvature and torsion TCCT/L.

Not only are these results demonstrated empirically, but they can also be shown analytically. Let $F$ represent a measure
of vessel tortuosity as a generic function of curvature and torsion, such that $F = F(\kappa_j, \tau_j)$. A total (or integrated) measure of $F$, denoted as $\mathcal{T}F$, is typically written as $\mathcal{T}F = \int F(\kappa, \tau)ds$. However, when evaluating such a function on real data using measured values of curvature $\kappa_j$ and torsion $\tau_j$, one must decide upon a numerical method of integration. Choosing a left Riemann sum as an example, we have $\mathcal{T}F = \sum_j F(\kappa_j, \tau_j)(s_{j+1} - s_j)$. Assuming uniform spacing, then $s_{j+1} - s_j = \Delta s$ is a constant for all $j$, and $\Delta s$ can be factored out of the summation, giving $\mathcal{T}F = \Delta s \sum_j F(\kappa_j, \tau_j)$. Expressing total arc length as a summation, $\mathcal{L} = \sum_j \Delta s$, then we again can factor $\Delta s$ from the summation, resulting in $\mathcal{L} = \Delta s N$, for a vessel with $N$ coordinates. Thus, when calculating the normalized total metric we end up calculating the average metric, $\mathcal{T}F/\mathcal{L} = 1/N \sum_j F(\kappa_j, \tau_j)$.

V. DISCUSSION

We present a numerical approach to reconstructing vessel coordinates from measures of curvature and torsion. Using this approach we show the importance that the full spectrum of measured values of curvature and torsion play in accurately characterizing the shape of a vessel. Additionally, we have shed light on the how common tortuosity metrics depend on sampling rates, and based on these findings, we provide a guide for recommended sampling rates (10 – 100 points/mm) in relation to the diameter of the vessels studied (1 – 10 mm). For vessels outside of this range, our numerical approach provides a methodology for determining ideal sampling rate in future studies.

Our analysis raises several questions regarding the motivation and efficacy of established measures of vessel tortuosity, as well as suggesting new avenues of research for the continued improvement of image-based biomarkers. The numerical integration of the Frenet-Serret equations relies solely on finite-difference methods for evaluating derivatives of the vessel position vector, and therefore the vessel curvature and torsion. While we chose to use the combinations of backward Euler, Newton’s method, and forward Euler to perform the numerical integration of Eqs. 8 and 9, future work could focus on examining the performance tradeoffs of alternative numerical methods (e.g. boundary value problem approaches, adaptive time-stepping, or higher-order backward differentiation methods [35]). Similarly, an alternative approach could be working in the parallel-transport frame instead of the Frenet-Serret frame. Although this frame is less physically intuitive, the basis-vectors remain well-defined through straight sections of the vessel and inflection points [16]. Because these two coordinate systems are related by orthogonal transformations, the eigenvalues of the frame matrices are identical, suggesting similar performances during numerical integration. A different coordinate system that is both well-defined and with different eigenvalues is the quaternion frame, more commonly used in computer graphics and aerospace engineering because it requires less computer memory and computation time [36]. Future studies built within the quaternion frame may enable applications to even larger or higher-resolution images, opening up further research questions and directions.

Our investigation into the dependence of established tortuosity metrics on vessel interpolation sampling rates leads to some surprising results. One unexpected finding of our analysis is the redundancy of existing metrics. Specifically, that integrated measures—once normalized by arc length—equate to their average analogues. This result is most notably demonstrated by the sum-of-angles (SOA) becoming equal to the average combined curvature and torsion metrics. This is demonstrated both analytically as well as empirically at high sampling rates in Table 1. Because of the exact equalities and strong correlations among these tortuosity metrics, it is worth considering which sets of metrics give independent and complementary information.

Interestingly, the two operational definitions of the inflection-count metric lead to diverging results as sampling rate is increased. This is despite the intent to capture the same feature of a curve—a point of inflection. Motivation for the $\mathcal{IC}_n$ approach (searching for local minima in curvature) is that, analytically speaking, inflection points for spatial curves are defined as instantaneous locations where there is zero curvature [24], [25]. Yet, in real data, it is very challenging to numerically define what constitutes a true zero—meaning within resolution of the image, numerical precision of the computer and software, error bounds, etc. This is why, in practice, any calculation must rely on local minima and not exact zeroes. Motivation for the $\mathcal{IC}_N$ approach (searching for large rotations of the FS-frame) comes from the fact that as the FS-frame passes through an inflection point in a 2D curve generated from data, it will undergo a sudden rotation of at most $\pi$ depending on the sampling rate being used.

These two definitions based on inflection points are intended to be consistent, as was demonstrated by Bullitt et al. for simulated 2D circular arcs and sinusoidal curves [2]. However, consistency for non-planar (3D) vessels is far from obvious given that the local minima of curvature may correspond to either true inflection points or to regions where the vessel simply changes planar orientation. Indeed our results show these two approaches are inconsistent with one another as sampling rates are increased, suggesting that these two metrics should be revisited and refined.

![Graph of sum-of-angles (SOA) metric versus average combined curvature and torsion for varying sampling rates.](image-url)
We show that the practice of using statistical features—moments of distributions or integrated summed totals and averages—of curvature and torsion is insufficient for accurate vessel reconstruction and to summarize vessel shape with a singular value. In fact, previous studies suggest that these tortuosity metrics are no better than the distance metric $D_{[4], [12]}$, or even the number density of vessels per voxel $[7]$. Furthermore, the motivation for converting a precisely defined quantitative measure into a statistical distribution is unclear. There exists substantial knowledge for how to relate fluid flow through constant curvature and constant torsion shapes—circles and helices—with internal pressures, wall shear stresses, and the subsequent formation of secondary flows $[37]$. Thus, reporting statistical features of curvature and torsion could be viewed as an implicit effort toward approximating all vessels as either circles or helices.

Alternatively, motivation for the integrated curvature and torsion metrics is often presented as part of a need for scale-free (dimensionless) metrics that can be used to compare vessels of different size. Within the analytical literature, there exist the well-defined dimensionless scaling parameters known as the Dean and Germano numbers that relate local radii, curvature, torsion, viscosity, and flow rates for circular (Dean number) and helical (Germano number) pipes. These numbers are analogous to Reynolds numbers for quickly classifying flow behavior. In particular, they are used for classifying secondary flow in the formation and number of vortices $[37]$–$[40]$. Nevertheless, researchers often define their own scale-free parameters, possibly because the Dean and Germano numbers require flow rate and viscosity information that is rarely acquired and cannot be independently measured with only static medical imaging $[14]$–$[16]$, $[22]$, $[30]$.

Despite analyzing vessels with models and assumptions that are rooted in the constancy of curvature and torsion, recent theoretical and computational work has relaxed these constraints to consider scenarios of non-constant curvature and/or torsion. These efforts are expanding the known morphospace of curves and their connection to fluid flow properties as well as bending and twisting moments $[19]$, $[41]$, $[42]$. Insight gained from these studies may point to informative features of curvature and torsion, and more importantly, to their relation to biologic function. For example, the ratio of torsion to curvature—when studied in conjunction with vessel radius, viscosity, and flow rate—can serve as an indicator of changes in the formation of vortices associated with secondary flow patterns and subsequently changes in the local stresses on vessel walls $[19]$.

To summarize, these results raise the question of whether statistical features—whose natural interpretations yield comparisons to circles and helices—are in fact appropriate for describing variation in shape within and across vessels. A promising alternative to singular statistical measures as classifiers are modern machine-learning approaches—such as neural networks—that take advantage of the full feature space of curvature and torsion. In this paper we demonstrate the value of maintaining highly-resolved measures of curvature and torsion as unique descriptors of individual vessels. We have done this by highlighting the utility of these measures in the spatial reconstruction of vessels and by bringing attention to redundancies and inconsistencies between existing metrics.

VI. CONCLUSION

We show that under-sampled measurements of curvature and torsion lead to inaccurate reconstructions of vessels. In particular, we use numerical integration to demonstrate that higher rates of sampling of the Frenet-Serret equations are necessary to accurately reconstruct a curve from its curvature and torsion values. For vessels greater than 1 mm in radius, we find that sampling rates between 10 – 100 points/mm are sufficient. For vessels smaller than 1 mm in radius, we find 100 – 1000 points/mm are sufficient. (Sufficient here means within an error bound equal to the minimum of the vessel radius.)

We show that a consequence of higher sampling is that the majority of common tortuosity measures undergo significant shifts in value, suggesting possible misestimates in previous work. Furthermore, we find that the currently-defined methods for identifying inflection points lead to diverging results as sampling rates are increased. We also show redundancy between the sum-of-angles (SOA) metric and the average combined curvature and torsion metric. Taken together, these results suggest that currently-used methods need revision, and that previous efforts to classify vessel types could benefit from our approach.

Our results should help inform and motivate future work at the interface of theory and measurement to characterize curves, especially for vessels from medical images. Potential applications for increased accuracy in vessel characterization range from tracking patient response after stent implantation to diagnosing vascular diseases afflicting tissues that span multiple scales.

–Supplemental Material–

I. FIVE-POINT STENCILS

Here we list the five-point centered difference methods used for approximating the first three derivatives of the position vector, $\mathbf{P}(s)$. We chose to use five-point centered differences to ensure accuracy in each derivative through the fourth-order. This is of particular importance in approximating the first derivative of the position vector as torsion is a function of its first three derivatives. Here we adopt the following notation: $u_{j,k}$ represents a position vector component ($k = \{x, y, z\}$) evaluated at position $s_j$ along the vessel centerline, $u_{j,k} = u_k(s_j)$; $h$ represents the step size between the uniformly spaced, neighboring points, $h = s_{j+1} - s_j$; and $D_5', D_5''$, and $D_5''$ represent the five-point methods used to approximate the first, second, and third derivatives. These methods are expressed as,
we use the backward Euler method to express
ing the same notation as in Supplemental Material Section I,
dure. For formal sources of information on these methods, the
\begin{equation}
D_3'' u_{j,k} = \frac{1}{h^2} \left[ \frac{1}{2} u_{j+2,k} - u_{j+1,k} + \frac{3}{2} u_{j-1,k} - \frac{1}{2} u_{j-2,k} \right]
\end{equation}
(S3)

II. NUMERICAL INTEGRATION METHODS
Here we present further details on our reconstruction pro-
dure. For formal sources of information on these methods, the
reader is directed toward LeVeque’s Finite difference methods for
ordinary and partial differential equations: steady-state and
time-dependent problems [55]. We assume one has already
\Phi_1 = \Phi_0 + h \Phi_1 + \Phi_2 + \Phi_3 + \Phi_4 + \Phi_5
(\Phi_1 = \Phi_0 + h \Phi_1 + \Phi_2 + \Phi_3 + \Phi_4 + \Phi_5)
(S4)
As Eq. (S4) is nonlinear in \Phi_{j+1}, we employ Newton’s method to
iteratively solve for \Phi_{j+1}. The update step in Newton’s method is written as,
\begin{equation}
\Phi_{j+1} = \Phi_j + hM_{j+1}\Phi_j
\end{equation}
where \Phi_j represents the iteration count, and G(\Phi_j) is a
9 \times 1 column vector defined as,
\begin{equation}
G(\Phi_j) = \Phi_j - hM_{j+1}\Phi_j
\end{equation}
The term within the square brackets in Eq. (S5) is the k, l
entry in the Jacobian matrix of G(\Phi_{j+1}), where the indices
k and l respectively represent the rows and columns of this
matrix and are written explicitly for clarity. The Jacobian of
G(\Phi_{j+1}) is given by,
\begin{equation}
\frac{\partial}{\partial \Phi_j} G(\Phi_j)^T = h \nu_{j+1} \left( \begin{array}{ccc}
\frac{1}{\nu_{j+1}} & -\kappa_{j+1} & 0 \\
\kappa_{j+1} & \frac{1}{\nu_{j+1}} & 0 \\
0 & \tau_{j+1} & \frac{1}{\nu_{j+1}}
\end{array} \right)
\end{equation}
(S7)
where 0 and I are the 3 \times 3 zero and identity matrices. Given
the tridiagonal, skew-symmetric form of Eq. (S7), it is easily
invertible with standard programming packages. Furthermore,
all of the entries in Eq. (S7) depend only on h, \nu_{j+1}, \kappa_{j+1},
and \tau_{j+1}, meaning the Jacobian (and its inverse) need only be
calculated once for each Frenet-Serret frame \Phi_{j+1}. Moreover,
these calculations can also be used for the full iteration over
\{m\} until convergence is reached. Convergence is determined
by setting a threshold on the differences between returned
values in successive iterations: \Phi_j^{[m+1]} - \Phi_j^{[m]} \leq \delta. Tests
for dependence on a suitable threshold were performed by examining the reconstruction error for a range of values spanning 0.1 to 0.0001. We settled on a global value of
\delta = 0.0001 for all vessels.

In order to solve the nonlinear Eq. (S9), we first linearize with
the following argument. We can express the normed derivative
in Eq. (S9) with a forward Euler difference as \|| \tilde{R}_{j+1} - \tilde{R}_j || /
(\nu_{j+1} - \nu_j) = (1/h)(\nu_{j+1} - \nu_j), \nu_j \phi
\text{factored out the scalar, point-to-point distance } h \nu_{j+1} - \nu_j
from the norm. By construction, the vector \tilde{R}_{j+1} - \tilde{R}_j begins
at the point \nu_{j+1} and terminates at the point \nu_j. As the point-
to-point distance h along the arc length is calculated as a
Euclidean length, then the length of the vector \|| \tilde{R}_{j+1} - \tilde{R}_j ||
is exactly equal to the distance from \nu_{j+1} to \nu_j, Therefore
(1/h)(\nu_{j+1} - \nu_j) = 1, a result that is importantly indepen-
dent of step size.

Following the linearization of Eq. (S9), integration is straight-
forward as we are left with a constant equation. Using a
forward-Euler routine to solve for the reconstructed position
vector \tilde{R}, we have,
\begin{equation}
\tilde{R}_{j+1} = \tilde{R}_j + h \tilde{T}_j
\end{equation}
(S8)
A point-wise error in reconstruction is defined as the normed
difference between the original position coordinate vector \tilde{R}(\nu_j)
and the reconstructed coordinate vector \tilde{R}(\nu_j) as,
\begin{equation}
\epsilon_j = || \tilde{R}(\nu_j) - \tilde{R}(\nu_j) ||
\end{equation}
(S9)
By comparing the maximum of the point-wise error, \epsilon_j, against
the minimum vessel radius, we can identify the appropriate
sampling rate, N, for reconstruction.

III. REPRODUCING RESULTS FROM PREVIOUSLY
PUBLISHED DATA
The data used in this study required some standardization to
reproduce originally published results as per each authors’
published instructions. Here we describe how we processed
the different datasets prior to employing our own methods for
analysis.

1) Bullitt et al. (2010): Data received from Bullitt et
al. consisted of the original magnetic resonance imaging (MRI)
files for all 100 patients’ cranial regions, and semi-processed
data for 42 patients. Specifically, for those 42 patients, the MRI
files had been run through the ridge-traversal segmentation
process described in [43], but not through the smoothing and
vessel dendritic connection process described in [44]. Thus,
we employed our own interpolation and smoothing routine using
penalized splines (P-splines) of degree 2 (cubic splines) with
3 knots. The degree was chosen as per instructions in [43]. P-
splines were chosen due to their robustness against over-fitting
[33], and the number of knots was determined iteratively by
comparing measured results against those published in [22].
The sampling rate was chosen to match that from [22], specifically
2 points/mm. Once the measurements for the interpolated
vessels were in sufficient agreement with published values (see
Fig. [S1], the interpolated vessels were then reanalyzed using the methods we describe in the main text.

2) Kamenskiy et al. (2012): The data received from Kamenskiy et al. consisted of the averaged centerline coordinates for the carotid arteries for all 16 patients from their study [20]. This data required zero additional effort on our part in terms of interpolation or smoothing to reproduce their published results of curvature and torsion versus arc length (see Fig. [S2]). Note that we have graphed these curves in a manner that is reflective of the sampling rate used in the original publication. Comparison against the original publication will show that our measurements are in agreement to within the previously published standard errors.

3) O’Flynn et al. (2007): The data received from the authors of O’Flynn et al. [21] were in sets of three, two-dimensional planar-projections of the xyz-coordinates for individual vessels, recovered from scanned images of the author’s dissertation. Thus, for each vessel we had to extract 3 pairs of coordinates from the scanned images and merge into one set of all three coordinates. After this, we followed the instructions for repeated interpolation as per [21] using 9th-degree polynomials with subsampling rates of 5 points/mm. During this procedure one of the five arteries, the left renal artery (LRA), was not usable due to information loss from the projection.

In Figure [S3] we present the curvature and torsion versus arc length graphs for the arteries extracted. Note that we have graphed these curves in a manner that is reflective of the sampling rate used to calculate associated tortuosity values. All results match those originally published except for the sampling rate used to calculate associated tortuosity values. This data required zero additional effort on our part in terms of interpolation or smoothing to reproduce their published results of curvature and torsion versus arc length (see Fig. [S2]). Note that we have graphed these curves in a manner that is reflective of the sampling rate used in the original publication. Comparison against the original publication will show that our measurements are in agreement to within the previously published standard errors.

During this procedure one of the five arteries, the left renal artery (LRA), was not usable due to information loss from the projection.

4) Vorobstova et al. (2016): The data received from Vorobstova et al. consisted of highly sampled and smoothed centerline coordinates for all coronary arteries involved in their original study [22]. This data required zero additional effort on our part in terms of interpolation or smoothing to reproduce their published results (see Table [S2]). However, we did have to determine an appropriate sampling rate as it was not explicitly stated in the original paper. We found the best agreement between the originally published values and our own when using a sampling rate of 10 points/mm.

IV. DEMONSTRATING EQUIVALENCE OF THE SOA AND ACCT METRICS

Here we present an analytical derivation that demonstrates the equivalence between the sum-of-angles (SOA) and average combined curvature and torsion metrics. This derivation was motivated by the strength of the correlation observed between the two metrics in Fig. [6]. To our knowledge, this result does not exist elsewhere in the literature.

Recall the definition of the SOA metric from Eq. (7).

\[
SOA_j = \left\{ [IP_j]^2 + [TP_j]^2 \right\}^{1/2} \tag{S10}
\]

where

\[
IP_j = \cos^{-1}\left( \frac{\Delta \mathbf{r}_j \cdot \Delta \mathbf{r}_{j+1}}{|\Delta \mathbf{r}_j| |\Delta \mathbf{r}_{j+1}|} \right) \tag{S11}
\]

and

\[
TP_j = \cos^{-1}\left( \frac{\Delta \mathbf{r}_j \times \Delta \mathbf{r}_{j+1}}{|\Delta \mathbf{r}_j| |\Delta \mathbf{r}_{j+1}|} \right) \tag{S12}
\]

We focus our attention first on \(IP_j\). Under the assumption of uniform spacing of the vessel coordinates, \(|\Delta \mathbf{r}_j| = \Delta s\) for all \(j\), so \(IP_j\) can be written as

\[
IP_j = \cos^{-1}\left( \mathbf{T}_j \cdot \mathbf{T}_{j+1} \right) \tag{S14}
\]

Using the following dot product identity,

\[
\mathbf{a} \cdot \mathbf{b} = \frac{1}{2} \left( |\mathbf{a}|^2 + |\mathbf{b}|^2 - |\mathbf{a} - \mathbf{b}|^2 \right) \tag{S15}
\]

and multiplying by a factor of \(\Delta s^2/\Delta s^2\), we have

\[
IP_j = \cos^{-1}\left( 1 - \frac{\Delta s^2}{2} \left( \frac{|\Delta \mathbf{T}_j|}{\Delta s} \right)^2 \right) \tag{S16}
\]

Again, in the limit as \(\Delta s \to 0\), \(\Delta \mathbf{T}_j/\Delta s \to d\mathbf{T}_j/ds\). By definition, \(d\mathbf{T}_j/ds = \kappa_j \hat{N}_j\). Thus,

\[
IP_j = \cos^{-1}\left( 1 - \frac{\Delta \kappa_j^2}{2} \right) \tag{S17}
\]

Now turning our attention to \(TP_j\), we focus first on the numerator of the first term, \(\Delta \mathbf{r}_{j-1} \times \Delta \mathbf{r}_j\). The resulting vector can be considered in two parts—the magnitude and direction. We will restrict our attention to the magnitude, as the direction will sort itself out during the process. The magnitude is expressed as \(|\Delta \mathbf{r}_{j-1} \times \Delta \mathbf{r}_j|\). Recall the cross-product relation,

\[
|\Delta \mathbf{r}_{j-1} \times \Delta \mathbf{r}_j| = |\Delta \mathbf{r}_{j-1}| |\Delta \mathbf{r}_j| \sin \theta, \tag{S18}
\]

where \(\theta\) is the angle between the two vectors. Treating \(\Delta \mathbf{r}_{j-1}\) as the hypotenuse of a right-triangle with legs \(\Delta \mathbf{r}_j\) and \(\Delta \mathbf{r}_j - \Delta \mathbf{r}_{j-1}\), we can make the substitution \(\sin \theta = |\Delta \mathbf{r}_j - \Delta \mathbf{r}_{j-1}|/|\Delta \mathbf{r}_{j-1}|\). This gives us
\[
|\Delta \vec{r}_{j-1} \times \Delta \vec{r}_j| = |\Delta \vec{r}_j| |\Delta \vec{r}_j - \Delta \vec{r}_{j-1}| \tag{S18}
\]

Noting that \(\Delta \vec{r}_j - \Delta \vec{r}_{j-1} = \vec{r}_{j+1} - 2\vec{r}_j + \vec{r}_{j-1}\), and multiplying by a factor of \(\Delta s^3/\Delta s^3\) results in

\[
|\Delta \vec{r}_{j-1} \times \Delta \vec{r}_j| = \Delta s^3 \left( \frac{|\Delta \vec{r}_j| |\vec{r}_{j+1} - 2\vec{r}_j + \vec{r}_{j-1}|}{\Delta s^2} \right) \tag{S19}
\]

Recognizing the first fraction as a first-order difference and the second fraction as a second-order difference, in the limit that \(\Delta s \to 0\), \(\Delta \vec{r}_j/\Delta s \to d\vec{r}_j/ds\) and \(\vec{r}_{j+1} - 2\vec{r}_j + \vec{r}_{j-1}/\Delta s^2 \to d^2\vec{r}_j/ds^2\). By definition, \(d\vec{r}_j/ds = \vec{T}_j\), and \(d^2\vec{r}_j/ds^2 = \vec{N}_j[d^2\vec{r}_j/ds^2]\), so

\[
|\Delta \vec{r}_{j-1} \times \Delta \vec{r}_j| = \Delta s^3 \left| \frac{d^2\vec{r}_j}{ds^2} \right| \left( |\vec{T}_j||\vec{N}_j| \right) \tag{S20}
\]

Despite the equation \(|\vec{T}_j| = |\vec{N}_j| = 1\), we will focus on the tangent and normal vectors being perpendicular to each other

\[
\Delta \vec{r}_{j-1} \times \Delta \vec{r}_j = \Delta s^3 \left( \frac{d^2\vec{r}_j}{ds^2} \right) \vec{T}_j \times \vec{N}_j \tag{S21}
\]

Recalling that: this whole term is divided by its own magnitude in \(TP_j\); the same argument can be applied to the second term in \(TP_j\); and the definition \(\hat{\vec{B}}_j = \vec{T}_j \times \vec{N}_j\), so that

\[
TP_j = \cos^{-1} \left( \vec{B}_j \cdot \vec{B}_{j+1} \right) \tag{S22}
\]

Using the same dot-product identity as before gives

\[
TP_j = \cos^{-1} \left( 1 - \frac{\Delta s^2}{2} \left( \frac{\Delta \vec{B}_j}{\Delta s} \right)^2 \right) \tag{S23}
\]

Again, in the limit as \(\Delta s \to 0\), then \(\Delta \vec{B}_j/\Delta s \to d\vec{B}_j/ds\). By definition, \(d\vec{B}_j/ds = -r_j\vec{N}_j\), Thus,

\[
TP_j = \cos^{-1} \left( 1 - \frac{\Delta s^2 r_j^2}{2} \right) \tag{S24}
\]

Returning our attention to the full \(SOA_j\) expression and substituting our approximations based on high sampling rates, we have

\[
SOA_j = \sqrt{\cos^{-1} \left( 1 - \frac{\Delta s^2 \kappa_j^2}{2} \right)^2 + \cos^{-1} \left( 1 - \frac{\Delta s^2 \tau_j^2}{2} \right)^2} \tag{S25}
\]

Using the approximation that \(\cos^{-1} (1 - \psi)^2 \approx 2\psi\) for \(|\psi| < 1\),

\[
SOA_j = \sqrt{\kappa_j^2 + \tau_j^2 \Delta s} \tag{S26}
\]

Finally, as \(SOA = \sum_{j=1}^{N} SOA_j/\sum_{j=1}^{N} \Delta s\), and that \(\Delta s\) is a constant for uniform sampling, we have

\[
SOA = \frac{1}{N} \sum_{j=1}^{N} \sqrt{\kappa_j^2 + \tau_j^2} \tag{S27}
\]

This is exactly the definition of the average combined curvature-torsion metric—\(ACCT\). From this derivation it should be clear how—in the limit of high sampling rates—measurements of the sum-of-angles (SOA) and the average combined curvature-torsion metric are not just strongly correlated but exactly equal. Furthermore, it should be clear that if one is measuring the variation on \(SOA_j\) that neglects the \(TP_j\) term, then the measurements should correlate strongly with the average curvature for low sampling (Lorthois et al. in [26]) and should be exactly equal for high sampling.

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Fig. S1. Graphs of tortuosity metrics for data from Bullitt et al. for cerebral arterial vasculature in the anterior, posterior, left middle, and right middle arterial trees. Metrics measured are average vessel radius, inflection-counts for both methods, $I_{CN}$ and $I_{CN}$, and the sum-of-angles, $SOA$.

| Table S1 | Tortuosity measures of data from O’Flynn et al. (2007) [21]. Metrics here are calculated as per methods used in cited publication. Metrics measured are vessel length, $L$, a variation on the distance metric, $D_1$, a variation on total curvature, $TC^*$, average curvature, $AC$, a variation on total torsion, $TT^*$, average torsion, $AT$, a variation on the total combined curvature-torsion, $TCC^*$', and average combined curvature-torsion, $ACCT$. The arteries studied are the right renal artery (RRA), the abdominal artery (AA), the left common iliac artery (LCA), and the right common iliac artery (RCA). |
|-----------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|           | $L$ (mm) | $D_1$ | $TC^*$ (mm$^{-1}$) | $AC$ (mm$^{-1}$) | $TT^*$ (mm$^{-1}$) | $AT$ (mm$^{-1}$) | $TCC^*$ (mm$^{-1}$) | $ACCT$ (mm$^{-1}$) |
| RRA       | 56.64    | 0.25  | 24.18          | 0.09            | 45.56           | 0.16            | 58.69           | 0.21            |
| AA        | 71.94    | 0.02  | 4.27           | 0.01            | 56.19           | 0.16            | 57.83           | 0.16            |
| LCA       | 56.63    | 0.01  | 3.21           | 0.01            | 33.48           | 0.12            | 34.23           | 0.12            |
| RCA       | 69.91    | 0.03  | 7.28           | 0.02            | 31.81           | 0.09            | 34.50           | 0.10            |
Fig. S2. Graphs of curvature and torsion versus normalized arc length for data from Kamenskiy et al. [20]. (a) is the common carotid artery and internal carotid artery. (b) is the external carotid artery. Note that this data is presented using a sampling rate of 1 point/mm as per the original publication.

Fig. S3. Graphs of (a) curvature and (b) torsion versus arc length for data from O’Flynn et al. [21]. Measurements are graphed with sampling rates of 5 points per millimeter along the arterial arclengths. The arteries studied are the right renal artery (RRA), the abdominal artery (AA), the left common iliac artery (LCA), and the right common iliac artery (RCA).

TABLE S2
TORTUOSITY MEASURES OF DATA FROM VOROBSTOVA ET AL. (2016) [22]. METRICS MEASURED ARE THE DISTANCE METRIC, \(D\), TOTAL TORSION, \(\dot{T}\), AND TOTAL CURVATURE, \(\dot{C}\).

| Patient | Length (mm) | \(D\) (-) | \(\dot{T}\) (-) | \(\dot{C}\) (-) |
|---------|-------------|-----------|----------------|----------------|}
| Patient-A |             |           |                 |                 |
| LMCA    | 7.881       | 1.009     | 7.672           | 0.715           |
| LAD     | 42.764      | 1.051     | 12.959          | 1.708           |
| LAD24   | 41.502      | 1.089     | 16.345          | 4.522           |
| LCX     | 25.683      | 1.050     | 7.166           | 1.511           |
| LCX123  | 84.027      | 1.320     | 27.764          | 5.275           |
| MARG1   | 37.648      | 1.056     | 10.395          | 3.259           |
| SPT2    | 33.394      | 1.035     | 8.663           | 2.250           |
| Patient-B |           |           |                 |                 |
| LAD     | 33.465      | 1.031     | 7.967           | 1.719           |
| LAD2    | 16.402      | 1.200     | 6.026           | 2.474           |
| LCX     | 13.651      | 1.196     | 6.417           | 0.963           |
| LCX1    | 18.994      | 1.133     | 5.672           | 2.277           |
| MARG2   | 18.742      | 1.173     | 8.751           | 5.261           |
| SPT2    | 18.626      | 1.030     | 7.972           | 1.199           |
| SPT3    | 30.647      | 1.123     | 14.477          | 6.425           |
| Patient-C |           |           |                 |                 |
| LAD_1   | 17.574      | 1.015     | 5.853           | 1.359           |
| LAD_2   | 20.874      | 1.015     | 9.546           | 0.879           |
| LAD1    | 26.893      | 1.170     | 7.227           | 3.344           |
| LAD24   | 43.672      | 1.170     | 16.706          | 5.588           |
| LCX     | 18.675      | 1.014     | 9.030           | 0.805           |
| LCX123  | 94.162      | 1.109     | 10.947          | 2.183           |
| MARG1   | 63.429      | 1.180     | 15.370          | 3.465           |
| SPT2    | 34.560      | 1.043     | 10.009          | 1.698           |
**TABLE S3**

**Coefficients of covariance for tortuosity metrics with arc length normalizations included on the dimensionless, integrated measures of total curvature, total torsion, and total combined curvature and torsion.***

\*\*\*p < 0.001. Only measurements made at the resolution of 100X were considered. All correlation coefficients are rounded to two significant digits.

| Variable | 1.   | 2.    | 3. | 4.   | 5.   | 6.   | 7.  | 8.   | 9.    | 10. | 11. | 12. |
|----------|------|-------|----|------|------|------|-----|------|-------|-----|-----|-----|
| 1. AC   | –    |       |    |      |      |      |     |      |       |     |     |     |
| 2. TC/L | 1*** | –     |    |      |      |      |     |      |       |     |     |     |
| 3. AT   | 0.48*** | 0.48*** | – |      |      |      |     |      |       |     |     |     |
| 4. TT/L | 0.48*** | 0.48*** | 1*** | –   |      |      |     |      |       |     |     |     |
| 5. TCC/L | 0.73*** | 0.73*** | 0.93*** | 0.93*** | – |      |     |      |       |     |     |     |
| 6. ACCT | 0.73*** | 0.73*** | 0.93*** | 0.93*** | 1*** | –   |     |      |       |     |     |     |
| 7. SOA  | 0.73*** | 0.73*** | 0.93*** | 0.93*** | 1*** | 1*** | –   |      |       |     |     |     |
| 8. TT   | -0.13*** | -0.13*** | 0.42*** | 0.42*** | 0.28*** | 0.28*** | 0.28*** | – |       |     |     |     |
| 9. TCCCT| 0.1*** | 0.094*** | 0.18*** | 0.18*** | 0.22*** | 0.22*** | 0.22*** | 0.84*** | – |     |     |     |
| 10. ICκ | 0.29*** | 0.29*** | -0.086*** | -0.086*** | 0.077*** | 0.079*** | 0.076*** | 0.26*** | 0.57*** | – |     |     |
| 11. TC  | 0.38*** | 0.37*** | -0.21*** | -0.21*** | 0.015 | 0.017 | 0.014 | 0.25*** | 0.69*** | 0.75*** | – |     |
| 12. ICN | 0.44*** | 0.44*** | -0.24*** | -0.24*** | 0.0087 | 0.01 | 0.0085 | -0.075*** | 0.34*** | 0.76*** | 0.78*** | – |