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Measuring Shape Relations Using $r$-Parallel Sets

Hans J. T. Stephensen$^1$ · Anne Marie Svane$^2$ · Carlos B. Villanueva$^3$ · Steven A. Goldman$^3$ · Jon Sporring$^4$

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Abstract
Geometrical measurements of biological objects form the basis of many quantitative analyses. Hausdorff measures such as the volume and the area of objects are simple and popular descriptors of individual objects; however, for most biological processes, the interaction between objects cannot be ignored, and the shape and function of neighboring objects are mutually influential. In this paper, we present a theory on the geometrical interaction between objects inspired by $K$-functions for spatial point-processes. Our theory describes the relation between two objects: a reference and an observed object. We generate the $r$-parallel sets of the reference object, calculate the intersection between the $r$-parallel sets and the observed object, and define measures on these intersections. The measures are simple, like the volume or surface area, but describe further details about the shape of individual objects and their pairwise geometrical relation. Finally, we propose a summary-statistics. To evaluate these measures, we present a new segmentation of cell membrane, mitochondria, synapses, vesicles, and endoplasmic reticulum in a publicly available FIB-SEM 3D brain tissue data set and use our proposed method to analyze key biological structures herein.

Keywords Multidimensional shape analysis · Hausdorff measure · $r$-parallel sets · Cross-$K$ function · Germ-grain process

1 Introduction

Measuring the geometry and statistics of objects is a fundamental tool used in all areas of the natural sciences. Geometric object-descriptors vary in complexity from simple measures such as point count, area, and volume to parameterized domain-specific shape models. See [26] for a review of shape representations.

In many cases, we are further interested in the relation between objects to answer questions like: How do synaptic vesicles distribute in the neighborhood of a synapse during stress [8]? How are astrocytes distributed w.r.t. the position and shapes of their nearby neuronal cells in amyotrophic lateral sclerosis [12]? What is the relation between the position and shape of the cartilage of the tibia and femur and osteoarthritis [11]? A simple approach is to summarize each object as a point and consider the set of points as a point-process, which has a well-developed theory and readily available software, e.g. [1]. However, this approach is limited since it does not take the geometry of individual objects into account, thereby ignoring important physical correspondence.

In this article, we propose a set of measures that consider the relation between different types of sets. For example, Fig. 1 shows the segmentation of an electron microscopy image where different object types have been identified. Our method measures the relation between reference and observed objects by first calculating one-parameter curves for each pair and then summarizes these as summary-statistics curves, as illustrated in Fig. 2. This figure shows the two summary-statistics curves for the relation between the synaptic regions and the mitochondria and vesicles, respectively. From these, we conclude that the mitochondria are rarely
Fig. 1 An example of the FIB-SEM data set and our segmentation. Red objects are synaptic regions, blue are vesicles, and green are mitochondria.

(a) An image slice.

(b) The slice’s segments.

(c) A 3D neighbourhood of segments.

Fig. 2 Normalized area comparison of vesicles and mitochondria as a distance to the synapse for a total of 365 synapses and their neighborhood vesicles and mitochondria

We observe very close to the synaptic regions, and that there is a high density of vesicles near the synaptic regions. We discuss these figures in more detail in Sect. 7.

We base our method on the cross $K$-function from the statistics of point-processes, which describes the relation between paired point-processes [2]. A classic example often used to present the cross $K$-function is to model the occurrence of crimes and the locations of police stations by point-processes $X$ and $Y$, respectively. The cross $K$-function measures the expected number of crime occurrences $x \in X$ within distance $r$ of a police station $y \in Y$ as

$$K(r) = \mathbb{E}_{y \in Y}|\{x \in X|d(x, y) \leq r\}|.$$  

(1)

Here, $X, Y \subset \mathbb{R}^2$ are discrete point sets, $d$ is a distance measure, often the Euclidean distance, $| \cdot |$ is the set-size operator, and $\mathbb{E}_{y \in Y}$ is the conditional expectation given $y \in Y$.

We extend the cross $K$-function to general geometric objects. We will consider objects $X, Y \subseteq \mathbb{R}^d$, which we will call the observed and the reference object, respectively.
These objects may be points but could also be surfaces or solids. We extend the notion of distance to be the shortest distance between two objects. As an example, in Fig. 3 we show equidistant curves from the reference objects in red and how these distance curves interact with the observed objects in blue. To quantify the observed objects w.r.t. the reference objects, we calculate a family of sets \( Y^r \) consisting of all points within a distance \( r \) from \( Y \), which we call the \( r \)-parallel sets. For each \( r \)-parallel set, we intersect it with the observed object and measure the number of points in the intersection of boundaries, the length of the inner and outer contours, and the area. These are also known as Hausdorff measures related to the intersection between \( Y^r \) and \( X \).

Aspects of this method have been seen use in the literature. In [21], we propose 3 statistical summary measures for population of curves, one of which is the overlap between a curve with the mathematical dilation of another. In [12], they measure the density of astrocyte glial cells by a weighted distance with the mathematical dilation of another. In [12], they measure the distance at which the astrocyte volume-fraction peaks in relation to dendritic spines and axonal boutons. In [4], a dissimilarity criterion is formed by intersections of distance parameterized sets of a segmentation mask compared to a manual reference mask. However, the theoretical foundation has been absent so far. Our contribution is to remedy this shortcoming and broaden the scope to include the full family of \( a \)-dimensional Hausdorff measures. To demonstrate the usefulness of our method, we present a segmentation of a publicly available FIB-SEM 3D data set of an adult rodent [10] in greater detail than previously available and use it as a subject for analysis using our proposed measures.

\[ Y^r = \{ \alpha \in \mathbb{R}^d \mid \inf_{y \in Y} d(\alpha, y) \leq r \}. \]  

Here, \( d(\alpha, y) \) denotes the distance between \( \alpha \) and \( y \), typically the Euclidean distance.

We measure \( X \cap Y^r \) by a measure \( \mu(X, Y^r) \). In all our applications, \( \mu \) has the form

\[ \mu_{\varepsilon, \varepsilon'}(X, Y^r) = \mathcal{H}^{d-\varepsilon-\varepsilon'}(\partial^\varepsilon X \cap \partial^{\varepsilon'} Y^r), \]

where \( \mathcal{H}^k \) denotes the \( k \)-dimensional Hausdorff measure, \( \varepsilon, \varepsilon' \in [0, 1] \), and for a closed set \( C \subseteq \mathbb{R}^d \), \( \partial^\varepsilon C = C \) is just \( C \) itself, while \( \partial^{\varepsilon'} C = \partial C \) is the boundary of \( C \). The interpretation of \( \mathcal{H}^k \) and \( \mu_{\varepsilon, \varepsilon'}(X, Y^r) \) in 2D and 3D is shown in Table 1. Since the boundary of the boundary is the boundary, i.e., \( \partial \partial C = \partial C \), this is the complete list of measures in 2 and 3 dimensions, in the sense that setting \( \varepsilon > 1 \) or \( \varepsilon' > 1 \) does not give rise to new measures. Further, these lists of measures generalize naturally to any dimension.

In applications, we typically observe a collection of objects spread out in space. To model a collection of objects, we equip each object with a reference point. The reference point can for instance be chosen geometrically as the center of mass or the center of the smallest ball containing the object. At other times, the application provides a natural center point such as the nucleus of a cell. Thus, we obtain a marked point-process \( \mathcal{X} = (x_i, X_i)_{i \geq 0} \) on \( \mathbb{R}^d \times \mathcal{C} \), where the mark space \( \mathcal{C} \) is the space of all compact sets in \( \mathbb{R}^d \) with reference point at the origin. The point \( x_i \) is the reference point, and the associated mark \( X_i \) can be thought of as the shape. Such a marked point-process is also known as a germ-grain process [17]. The collection of objects, sometimes called a germ-grain model, is then

\[ \bigcup_{i \geq 0} (x_i + X_i), \]

where \( v + X = \{ v + x \mid x \in X \} \).

Let \( \mathcal{X}, \mathcal{Y} \) be germ-grain processes modeling the observed and reference objects, respectively. Writing \( v + \mathcal{X} = v + \{ x_i, X_i \}_{i \geq 0} = \{ v + x_i, X_i \}_{i \geq 0} \), we say that the processes are jointly stationary if \( (v + \mathcal{X}, v + \mathcal{Y}) \) has the same distribution as \( (\mathcal{X}, \mathcal{Y}) \) for any translation vector \( v \in \mathbb{R}^d \). In the following, we let \( \mathcal{X} \) and \( \mathcal{Y} \) denote the point-processes of reference points.
underlying $\mathcal{X}$ and $\mathcal{Y}$, respectively, and let $\rho_\mathcal{X}$ and $\rho_\mathcal{Y}$ denote the spatial intensities of $\mathcal{X}$ and $\mathcal{Y}$.

A global functional summary statistic is given by

$$K_{\varepsilon,\varepsilon'}(r) = \frac{1}{\rho_\mathcal{X}} \mathbb{E}_{\mathcal{Y}} \left( \sum_{(x,X) \in \mathcal{X}} \mu_{\varepsilon,\varepsilon'}(x + X, y + Y') \right). \tag{5}$$

where $Y$ is the particle with reference point at the origin. The interpretation of $K_{\varepsilon,\varepsilon'}(r)$ is that, conditioned on $Y$ having a reference point at the origin, it is the expected value of $\mu_{\varepsilon,\varepsilon'}(x + X, y + Y')$ summed over all particles $x + X$ within distance $r$ from the object $Y$ averaged by the expected number of particles from $\mathcal{X}$ per unit volume. An estimator is:

$$\hat{K}_{\varepsilon,\varepsilon'}(r) = \frac{1}{\mathcal{H}^d(W) \rho_\mathcal{X} \rho_\mathcal{Y}} \mathbb{E}_{\mathcal{Y}} \sum_{(y,Y) \in \mathcal{Y}} \sum_{(x,X) \in \mathcal{X}} I_{\{y \in W\}} \mu_{\varepsilon,\varepsilon'}(x + X, y + Y'). \tag{6}$$

Here, $\mathcal{H}^d(W)$ is the volume of the sampling window. Note that we only sample reference objects with reference point $y \in W$, but in order to compute $\hat{K}_{\varepsilon,\varepsilon'}(r)$, we must be able to observe all of the associated $Y'$ even if it intersects the boundary of $W$, which may not be possible in practice. In Sect. 2.1, we present edge-correction strategies for handling cases where the $r$-parallel exceeds the observation window $W$.

**Theorem 1** If $(\mathcal{X}, \mathcal{Y})$ are jointly stationary, then $\hat{K}_{\varepsilon,\varepsilon'}$ is an unbiased estimator for $K_{\varepsilon,\varepsilon'}$.

**Proof** The expected value of $\hat{K}_{\varepsilon,\varepsilon'}$ is

$$\mathbb{E}_{\mathcal{X}} \left( \sum_{(x,X) \in \mathcal{X}} \mu_{\varepsilon,\varepsilon'}(x + X, y + Y') \right) = \frac{1}{\mathcal{H}^d(W) \rho_\mathcal{X} \rho_\mathcal{Y}} \int_W \rho_\mathcal{Y} \mathbb{E}_{\mathcal{Y}} \mu_{\varepsilon,\varepsilon'}(x + X, y + Y') \, dy$$

which is $\mathbb{E}_{\mathcal{X}} \left( \sum_{(x,X) \in \mathcal{X}} \mu_{\varepsilon,\varepsilon'}(x + X, y + Y') \right)$. In (8), we used the translation invariance of $\mu_{\varepsilon,\varepsilon'}$, and in (9), we used the joint stationarity of the point processes.

The normalization only by the intensity $\rho_\mathcal{X}$ may seem unnatural since the resulting $K$-function will depend on the Hausdorff measure of the objects in $(\mathcal{X}, \mathcal{Y})$. As in [14], we, therefore, also consider the normalized measures,
In practice, we observe objects inside a finite window $W$. We suggest the following three edge corrections, based on the most common edge corrections for point-process $K$-functions [15].

1. Sampling in a smaller window: Here, we sample only objects inside a smaller window $W$, so instead of the measures $\mu_{e,e'}(X, Y')$, we are only able to measure

$$\mu_{e,e'}^W(X, Y') = H^{d-e'}(\partial^e Y').$$

If these $\mu_{e,e'}^W$ are used instead of $\mu_{e,e'}$ in (6), then $\hat{K}_{e,e'}$ is no longer an unbiased estimator for $K_{e,e'}$.

We solve this problem by introducing edge corrections in (6). That is, in the definition of $\hat{K}_{e,e'}$, we replace the measures $\mu_{e,e'}(X, Y')$ by edge corrected measures $e_{e,e'}(y, X, Y')$ and obtain

$$\hat{K}_{e,e'}(r) = \frac{1}{H^d(W)} \sum_{(y, y') \in \mathcal{Y}} \mathbb{1}_{\{y \in W\}} \times \sum_{(x, x') \in \mathcal{X}} e_{e,e'}(y, x + X, y + Y').$$

We suggest the following three edge corrections, based on the most common edge corrections for point-process $K$-functions [15].

1. Sampling in a smaller window: Here, we sample only objects from $\mathcal{Y}$ with a reference point inside a smaller window $W$, so we have full information about the objects and correct for the reduced window size.

As a sampling window, we may take

$$W \ominus B_M(0) = \{z \in \mathbb{R}^d \mid z + B_M(0) \subseteq W\}.$$  

Here, $B_s(c)$ denotes the Euclidean ball of radius $s$ centered at $c$, and $M = m_y + r$, where $m_y$ is an upper bound on the diameter of objects from $\mathcal{Y}$. In practice, $m_y$ will have to be chosen based on prior knowledge about the size of objects.

The resulting estimator corresponds to (15) with edge corrections

$$e_{e,e'}(y, X, Y') =$$

$$\frac{1}{\rho_X} \int_{W} \mathbb{E}_{0 \in \mathcal{Y}} \sum_{(x, x') \in \mathcal{X}} \int_{\partial^e Y' \cap (W-y)} \mathbb{1}_{\{y \in W\}}.$$
Letting $\nu$ As before, we compute the mean of

$$e_{\mu_e, \epsilon'}(y, X, Y') = \int_{\rho_X \cap \rho_{Y'}} \frac{\mathcal{H}^{d-1}(\partial B_{|w-y|}(y))}{\mathcal{H}^{d-1}(\partial B_{|w-y|}(y) \cap W)} \mathcal{H}^{d-e}dw.$$  \hspace{1cm} (22)

We say that two germ-grain processes $(X', Y')$ are jointly isotropic if $\{RX_i, RX_i\}_{i \geq 0}, \{RY_i, RY_i\}_{i \geq 0}$ has the same distribution as $\{X_i, X_i\}_{i \geq 0}, \{Y_i, Y_i\}_{i \geq 0}$ for any rotation $R \in SO(d)$.

**Theorem 3** When $(X', Y')$ are both jointly stationary and isotropic, the edge corrections in (22) yield an unbiased estimator of (10).

**Proof** As before, we compute the mean of $\hat{K}_{e, \epsilon'}(r)$:

$$\mathbb{E}\left(\frac{1}{\rho_X \rho_Y} \mathcal{H}^{d}(W) \sum_{(y, X) \in Y} \sum_{(x, X) \in X} \int_{\Omega} \frac{\mathcal{H}^{d-1}(\partial B_{|w-y|}(y))}{\mathcal{H}^{d-1}(\partial B_{|w-y|}(y) \cap W)} \mathcal{H}^{d-e}dw\right)$$

$$= \frac{1}{\rho_X \rho_Y} \mathcal{H}^{d}(W) \int_{W} \mathbb{E}_{0 \in \hat{Y}}$$

$$\left(\sum_{(x, X) \in X} \int_{\partial(\{X+y\} \cap \partial\epsilon'-Y \cap (W-y))} \frac{\mathcal{H}^{d-1}(\partial B_{|w|}(y))}{\mathcal{H}^{d-1}(\partial B_{|w|}(y) \cap W)} \mathcal{H}^{d-e}dw\right)dy. $$  \hspace{1cm} (23)

Letting $\nu$ denote the normalized Haar measure on $SO(d)$, the isotropy assumption yields

$$\frac{1}{\rho_X \rho_Y} \mathcal{H}^{d}(W) \int_{SO(d)} \int_{W} \mathbb{E}_{0 \in \hat{Y}}$$

$$\left(\sum_{(x, X) \in X} \int_{\partial(\{X+y\} \cap \partial\epsilon'-Y \cap (W-y))} \mathcal{H}^{d-1}(\partial B_{|w|}(y)) \mathcal{H}^{d-e}dw\right)dy \nu(dR)$$

$$= \frac{1}{\rho_X \rho_Y} \mathcal{H}^{d}(W) \int_{W} \mathbb{E}_{0 \in \hat{Y}}$$

$$\left(\sum_{(x, X) \in X} \int_{\partial(\{X+y\} \cap \partial\epsilon'-Y \cap (W-y))} \mathcal{H}^{d-1}(\partial B_{|w|}(y)) \mathcal{H}^{d-e}dw\right)dy \nu(dR)$$

$$=\frac{\mathcal{H}^{d-1}(\partial B_{|w|}(y))}{\mathcal{H}^{d-1}(\partial B_{|w|}(y) \cap W)} \mathcal{H}^{d-e}dw$$

$$\frac{1}{\rho_X} \mathbb{E}_{0 \in \hat{Y}} \left(\sum_{(x, X) \in X} \int_{\partial(\{X+y\} \cap \partial\epsilon'-Y \cap (W-y))} \mathcal{H}^{d-1}(\partial B_{|w|}(y)) \mathcal{H}^{d-e}dw\right)dy \nu(dR)$$

which is $K_{e, \epsilon'}(r)$.

This estimator again has the disadvantage that the Hausdorff measures are replaced by integrals. However, when $y$ is further away from the boundary than $|y-w|$, so (22) reduces to $\mu_{e, \epsilon'}(X, Y')$ whenever $y \in W \ominus B_{m_{Y'}, r}(0)$. We therefore only need to calculate the edge corrections of the $y$ that are close to the boundary.

### 2.2 Examples of Simple Object Relations

For simple objects, we can evaluate $\mu_{e, \epsilon'}$ analytically. As an example, consider an infinite line/plane in 2D/3D as a reference object and a circle/sphere inside $W$ of radius $R$ as an observed object. Assume that the center of the circle/sphere is at distance $R$ from the line/plane. Then, for $r \geq 0$, we get the closed-form expressions given in Table 2 by using the formulas for a circular segment and spherical cap, respectively. In this example, $N_{e'} = \infty$, hence the normalized functions $\nu_{e, \epsilon'}$ are all 0. We use the expressions in Table 2 for verification in Sect. 5.

### 3 Shape Equivalence Under the Measures

Representing objects by the measure $\mu_{e, \epsilon'}(X, Y')$ encodes selected characteristics of the shape of $X$. In this section, we investigate to which extent the measures $\mu_{e, \epsilon'}(X, Y')$ with a fixed reference object $Y$ determines the observed object $X$ uniquely. Let $S \subseteq \mathcal{C}$ denote the class of possible shapes. For a fixed $Y$, this leads to an equivalence class $[X_i]$ for each $X_i \in S$ where

$$[X_i] = \{X_j \in S \mid \forall (r, e, e') : \mu_{e, \epsilon'}(X_i, Y') = \mu_{e, \epsilon'}(X_j, Y')\}. $$  \hspace{1cm} (36)

We examine the special case $d = 2$ where the reference object $Y$ is the line $x = 0$ meaning that the $r$-parallels are the sets given by $-r \leq x \leq r$. We consider the class of equivalent shapes $S$ emerging from an object $X$ that can be described solely by two functions $f(x)$ and $g(x)$ on the interval $[a, b]$.  

\[ \boxed{\mathbb{E}} \] Springer
Here, we let $f, g$ represent the upper and lower contour of $X$, respectively, with $f(x) > g(x)$ for all $x$ in $[a, b]$. Further, we require $f(a) = g(a)$ and $f(b) = g(b)$ such that the object is closed. Thus, the measures $\mu_{\epsilon, \delta}(x)$ are

$$
\mu_{00}(x) = \int_a^x (f(x') - g(x'))dx' 
$$

(37)

$$
\mu_{01}(x) = f(x) - g(x) 
$$

(38)

$$
\mu_{10}(x) = \int_a^x (\sqrt{1 + f'(x)^2} + \sqrt{1 + g'(x)^2})dx 
$$

(39)

$$
\mu_{11}(x) = 2 
$$

(40)

Roughly speaking, $\mu_{01}$ describes the instantaneous change of $\mu_{00}$. Hence, they constrain the equivalence class of $X$ through $f$ and $g$ equally, with both measures requiring $f(x) - g(x)$ to be fixed for each $x$. The derivatives $f'(x)$ and $g'(x)$ are constrained by the arc-length of $f(x)$ and $g(x)$ through $\mu_{10}$. Since $\mu_{10}$ is the sum of two arc-lengths, ignoring everything else, we could shorten the length of $f$ by lengthening $g$ or vice versa. Similarly, since the sign of the derivative of $f$ and $g$ does not change the arc-length, this measure allows for all combinations of the sign of the derivative. However, in combination with the other measures, we can narrow the set of equivalent shapes down to two possible continuations of the object in every point $x$. We illustrate this first by assuming $f$ and $g$ are piecewise linear functions (see Fig. 4). Consider a linear segment of the object on a subinterval from $x_0$ to $x_1$ with $\Delta x = x_1 - x_0$. Let $L = \mu_{10}(x_1) - \mu_{10}(x_0)$ denote the total length of the two linear functions on this subinterval and introduce a length splitting parameter $t$, such that the length of $f$ and $g$ on the subinterval is $t$ and $L - t$, respectively. (see Fig. 5). Fixing $\mu_{01}(x_0)$ and letting $t$ and $\mu_{01}(x_1)$ vary we get a shape space parameterized by $t$ and $\mu_{01}(x_1)$ in which the equivalent shapes are given as the solutions to the equation

$$
\mu_{01}(x_1) = \mu_{01}(x_0) \pm \sqrt{t^2 - \Delta x^2} \pm \sqrt{(L - t)^2 - \Delta x^2}.
$$

(41)
increasing ratio of \( L \) to \( \Delta x \). We see that two possible solutions for each \( \mu(x_0) \) exist converging at unique solutions at the top and the bottom. Scaling of \( \Delta x \) and \( L \) equally corresponds to a scaling of the curve. Starting from a different value of \( \mu(x_0) \) corresponds to a vertical translation of the entire solution curve in the shape space.

We have now handled the possible equivalent shapes of a single linear segment of an object. Consider again a single linear segment on the interval \([x_0; x_1]\). We can equally define this linear segment as two linear segments on \([x_0'; x']\) and \([x'; x_1]\) where \( x_0 < x' < x_1 \). Since these two linear segments represent \( f \) and \( g \) exactly as before the measures \( \mu(x_0) \) are unchanged under this substitution. With one linear segment, we had up to two possible equivalent solutions given the measures. With two linear segments, we have all combinations given a total of up to 4 possible solutions. But since we can now recursively split linear segments into two segments, we enter the domain of infinitely jagged fractal functions such as the Weierstrass function without changing the measures of the object. However, in most real-world scenarios, objects often consist of approximately smooth parts that do not present this jaggedness.

Assume now that \( f, g \) are \( C^1 \) smooth functions (see Fig. 7). In this case, \( f \) and \( g \) can no longer recursively be broken into smaller segments and reflected since that would break the smoothness constraint in most cases. The exceptions are at points \( x \) where \( f'(x) = -g'(x) \). Consider a shape with a finite set of such points, and consider the intervals between neighboring points.

**Lemma 1** The measures (37)–(40) are invariant under vertical translation of both \( f \) and \( g \).

**Proof** Let \( d \) denote the vertical translation distance of \( f \) and \( g \) such that the translated functions are \( \hat{f}(x) = f(x) + d \) and \( \hat{g}(x) = g(x) + d \). Since \( f(x) - \hat{g}(x) = f(x) + d - g(x) - d = f(x) - g(x) \), the claim follows for both (37) and (38). Since the derivative is unaffected by constant terms, \( \hat{f}'(x) = f'(x) \), so it also holds for (39). For (40), it is trivially true.

Note that objects mirrored about \( x = 0 \) are equivalent. That is, if \( f(x) \), \( g(x) \) denote functions on \([a; b]\) defining an object, then the functions \( \hat{f}(x) = f(-x) \) and \( \hat{g}(x) = g(-x) \) on \([-b; -a]\) define an object with equivalent measures. Further, if there exists a point \( x' \) such that \( f'(x') = -g'(x') \), then the curves may be inflected at this point, i.e., we may generate new functions

\[
\hat{f}(x) = \begin{cases} f(x), & \text{if } x < x' \\ f(x') + g(x') - g(x), & \text{else} \end{cases} \quad (42)
\]

\[
\hat{g}(x) = \begin{cases} g(x), & \text{if } x < x' \\ g(x') + f(x') - f(x), & \text{else} \end{cases} \quad (43)
\]

These function will still be in \( C^1 \). This gives rise to the notion of inflection intervals:

**Definition 1** We define an inflection interval to be an interval \([x_0; x_1]\) such that for \( x \in [x_0; x_1] \), \( f'(x) = -g'(x) \) or \( f(x) = g(x) \) if and only if \( x = x_0 \) or \( x = x_1 \).

**Definition 2** We define a symmetric interval to be an interval \([x_0; x_1]\) such that for all \( x \in [x_0; x_1] \), \( f'(x) = -g'(x) \).

Note that every object in our constrained example can be separated into intervals overlapping only at the boundary, which are either inflection intervals or symmetric intervals.
Given a inflection interval \([x_0, x_1]\), an inflected shape is:

\[
\hat{f}(x) = \begin{cases} 
  f(x), & \text{if } x < x_0 \\
  f(x_0) + g(x_0) - g(x), & \text{if } x_0 \leq x < x_1 \\
  f(x_0) + g(x_0) - (g(x_1) + f(x_1)) + f(x), & \text{else}
\end{cases}
\]  

(44)

\[
\hat{g}(x) = \begin{cases} 
  g(x), & \text{if } x < x' \\
  g(x_0) + f(x_0) - f(x), & \text{if } x_0 \leq x < x_1 \\
  g(x_0) + f(x_0) - (f(x_1) + g(x_1)) + g(x), & \text{else}
\end{cases}
\]  

(45)

These functions are in \(C^1\).

Now, we can state the following theorem.

**Theorem 4** The measures (37)-(40) are invariant under inflections of inflection intervals \([x_0, x_1]\).

**Proof** For \(x < x_0\), the functions are unchanged. For the inflection interval, consider the horizontal line \(y = (f(x_0) + g(x_0))/2\), and let \(\tilde{f}(x) = 2y - g(x)\) and \(\tilde{g}(x) = 2y - f(x)\) denote the functions after reflection across \(y\). Since \(\tilde{f}(x) = \tilde{g}(x) = 2y - g(x) = (f(x) + g(x))\), the theorem holds for (37) and (38). We also have \(\tilde{f}'(x)^2 = (-g'(x))^2 = g'(x)^2\) and likewise \(\tilde{g}'(x)^2 = (-f'(x))^2 = f'(x)^2\) and thus the theorem holds for (39). For (40), the theorem is trivially true. For \(x \geq x_1\), the functions are unchanged expect for an added constant and by Lemma 1 we conclude that the measures are invariant under inflections. \(\square\)

**Theorem 5** Let \(n\) denote the number of inflection intervals of an object. Ignoring vertical translations and reflections across \(Y\), the equivalence class of the object has size \(2^n\) and all equivalent objects can be generated by reflecting a subset of the inflection intervals.

**Proof** We know we can generate new objects by reflecting each inflection interval. This gives at least \(2^n\) objects by all combinations of reflections of the \(n\) inflection intervals. Assume now there is another object in the equivalence class which is not among the \(2^n\) objects. Let \(\hat{f}, \hat{g}\) denote the upper and lower function of this object, respectively. Since all measures must be the same for this object, by (38) this means \(\hat{f}(x) - \hat{g}(x) = f(x) - g(x)\). As all functions are assumed to be \(C^1\), we get

\[
\hat{f}'(x) - \hat{g}'(x) = f'(x) - g'(x).
\]  

(46)

We then look at the derivative of (39). Using the fundamental theorem of calculus, we have

\[
\sqrt{1 + \hat{f}'(x)^2} + \sqrt{1 + \hat{g}'(x)^2} = \sqrt{1 + f'(x)^2} + \sqrt{1 + g'(x)^2}
\]  

Together, (46) and (47) imply either

\[
\hat{f}'(x) = f'(x)
\]  

(48)

\[
\hat{g}'(x) = g'(x)
\]  

(49)

The complete equivalence class for object consisting of \(C^1\) functions \(f\) and \(g\) are therefore all vertical translations of \(2^n\) objects symmetrically on both sides of \(Y\). If we ignore translations and reflections in the horizontal and vertical axis, we have \(2^{n-1}\) unique objects equivalent under the measures because half of them are the reflections of another shape across the horizontal. We show an example of the \(2^n\) equivalent shapes in Fig. 8.

Extending the results on the equivalence class to the general case requires us to consider: (1) general shapes of \(X\), (2) variations in the \(r\)-parallel which is determined by the shape of \(Y\), and (3) the extension to higher dimensions. The main obstacle here is finding a suitable framework for such an analysis. This is outside the scope of this work.

### 4 Implementation

For implementation, we have experimented with the following 3 approaches.

1. Grid-based: The simplest approach is to work exclusively on a regular grid. We represent \(Y'\) only through a distance map \(D\) on the window \(W\) with \(D(w) = \min_{v \in Y} \{|w - v|\}\) for \(w \in W\). Our sample points are given on a regular grid. The distance map \(D\) can be approximated by methods such as the Fast Marching Method. We then represent \(X\) as a \([0, 1]\) mask on the regular grid. Counting the overlapping voxels of the mask consisting of the voxels \(w\) for which \(D(w) < r\) and the mask of \(X\) gives an estimate of \(\mu_{00}\). Using morphological operations, subtracting \(X\) from the dilation of \(X\) approximates the boundary of \(X\). This can similarly be done for \(Y'\). Note here that we are limited in accuracy by the pixel representation, and that the error increases significantly when working with the boundary measures \(\mu_{01}, \mu_{10}\) and \(\mu_{11}\), as voxel masks...
do not, in general, represent boundaries accurately. For a review, see [24].

2. Parameterized surfaces: When \( Y' \) can be parameterized easily, we can represent \( X \) and \( Y \) as contours and meshes for \( d = 2 \) and \( d = 3 \), respectively. Libraries such as the python library Shapely can calculate set intersections, set unions, and set differences on contours as well as area and curve length. Similarly, libraries such as PyMesh support the same operations but for meshes.

3. Mesh-based: Our favorite algorithm is based on triangulated surface-meshes of the objects \( X \) and \( Y' \) which we have implemented for \( d = 3 \):

(a) Given surface meshes of \( X \) and \( Y \), we produce a tessellation of the interior of \( X, Y \), and \( Y' \), whose vertices we will denote \( V_X \), etc. Moreover, \( V_{\partial X} \subset V_X \) denotes the surface vertices.

(b) For each \( r \)-parallel set \( Y' \), we identify interior, intersecting, and exterior simplices in \( V_X \). For the intersecting simplices, we estimate the intersecting surface by linear interpolation.

(c) For \( \mu_{10} \) and \( \mu_{01} \), we sum the surface of intersections, for \( \mu_{00} \), we sum the volume of the interior simplices and the relevant part of the intersecting simplices. For \( \mu_{11} \), we calculate the length of the intersecting line.

For shortest vertex to mesh distance, we used PyMesh, and we used the Fast Marching method implementation in the scikit-fmm python package with linear interpolation implemented in Scipy. The integration of the measures over the meshes was implemented in C++ compiled with SWIG for use in Python.

For a run-time analysis of triangulation and tetrahedralization of label images, we refer the reader to the corresponding articles on TetGen [20] or TetWild [7]. Calculating the distance function as basis for the \( r \)-parallels can be accomplished by solving the Eikonal equation using a method such as the Fast Marching method. The Fast Marching method has time complexity \( O(n \log n) \) [19], where \( n \) is the number of grid points in the rectilinear grid used to discretize the domain. For a faster result on a rectilinear grid, the level-set re-initialization method is often faster trading accuracy for speed. Alternatively, the distances can be calculated directly on the meshes by mesh to point algorithms, which have time complexity \( O(V \log(F)) \) where \( V \) is the number of vertices in the observed object mesh and \( F \) is the number of faces in the reference object mesh.

The integration of the meshes is done by iterating over \( r \). For each value of \( r \), we consider the intersection between the boundary of \( Y' \) and the \( X \)-simplex mesh. Each simplex of \( X \) can either be completely inside, partially inside or completely outside of \( Y' \). Simplicies that are partially inside \( Y' \) are subdivided into smaller simplicies that are completely inside or outside \( Y' \). Determining the overlap and performing subdvision can be done in constant time. Thus, for \( N \) different values of \( r \) and \( M \) simplicies, the total time complexity is \( O(NM) \).

We then experiment on randomly generated vertices and faces, running on Lenovo ThinkPad T470, Intel Core i7-7500U 2.70GHz CPU. Shown in Table 3, we see an acceptable run-time for most applications. In this implementation, there is still room for optimizations since most of the current brute force loops are both trivially parallelizable and have a significant overlap in calculations.

5 Experiments on Synthetic Objects

In the following, we will give examples of experiments conducted on synthetic data.

As a first experiment and in the spirit of the analytical examples in Sect. 2.2, consider \( \mathbb{R}^3 \) with an infinite plane as the reference object, 2 spheres and a cube as observed objects near the plane and with a cubic observation window aligned with the reference object. Figure 9 shows the experimental evaluation of \( \mu_{E,E'} \) on these objects. The experiments show that \( \mu_{00} \) is a monotonically increasing function of the integral of the volume of the observed object from 0 to \( r \) with \( \mu_{10} \) as its derivative. The surface measure \( \mu_{10} \) for the spheres is a linearly increasing function, while the cube has two dis-
Table 3 Run-time results for the mesh integrator at $d = 3$

| Mesh tetrahedra | Discretization steps | Mean ($n = 200$) | Variance ($n = 200$) |
|-----------------|----------------------|------------------|----------------------|
| $\mu_{00}, \mu_{01}$ | 1k 1k | 54.27 ms | 1.86 $\mu$s |
| | 10k 1k | 426.05 ms | 571.68 $\mu$s |
| | 100k 1k | 3.12 s | 2.47 ms |
| | 1M 1k | 28.76 s | 163.89 ms |
| | 1k 10k | 386.73 ms | 111.04 $\mu$s |
| | 10k 10k | 4.31 s | 1.06 ms |
| | 100k 10k | 18.10 s | 60.41 ms |
| | 1M 10k | 358.50 s | 175.11 s |
| $\mu_{10}, \mu_{11}$ | 1k 1k | 6.85 ms | 0.34 $\mu$s |
| | 10k 1k | 73.56 ms | 4.02 $\mu$s |
| | 100k 1k | 711.67 ms | 1.08 ms |
| | 1M 1k | 7.97 s | 17.03 ms |
| | 1k 10k | 9.85 ms | 0.69 $\mu$s |
| | 10k 10k | 338.33 ms | 12.39 $\mu$s |
| | 100k 10k | 5.07 s | 21.17 ms |
| | 1M 10k | 57.80 s | 1.30 s |

![Fig. 9](image-url) Example of measures and relative error. The observed objects $X$ are either of 2 spheres of different sizes and a cube, as shown in (c) with colors corresponding to the curves. The reference object $Y$ is an infinite plane at a minimum distance of 100 units from the relevant object. The observation window is a cube of side-length 500 with a side coinciding with $Y$ and otherwise centered around the observed object. The bottom row shows the relative error $(\mu_{x,\varepsilon}(r) - \hat{\mu}_{x,\varepsilon}(r))/\mu_{x,\varepsilon}(r)$, where $\mu_{x,\varepsilon}$ is the measure from the theoretic reference and $\hat{\mu}_{x,\varepsilon}$ is the measure estimated from mesh representations.

Continuous steps caused by the alignment of the cube with the observation plane. The curve measure $\mu_{11}$ is quadratic for the spheres and constant for the cube. In the bottom row of Fig. 9, we show the relative error of each of the measures $(\mu_{x,\varepsilon}(r) - \hat{\mu}_{x,\varepsilon}(r))/\mu_{x,\varepsilon}(r)$, where $\mu_{x,\varepsilon}$ is the measure from the theoretic reference and $\hat{\mu}_{x,\varepsilon}$ is the measure estimated from mesh representations. Two sources of error can here be observed. A baseline error across the entire measure, which is dependant on the mesh refinement and how curved the object is as highly curved objects, such as balls, will be approximated less accurately. These meshes are rather rough with an approximate edge length of about 18 units giving...
Fig. 10 Example of the volume measures on uniformly distributed and clustered spheres. A slight difference can be seen directly in the $\mu_{00}(X, Y^r)$ graph, but the clustering is clearly visible in $\nu_{00}(X, Y^r)$ a baseline error of about 1%. The second type of error is observed at the edges of the object in the $r$-parallel direction. These show significantly higher error. However, this is due to limitations in the mesh representation for curved objects. For the cube, this error is not present because it has no curvature. The limited increase in error seen in the $\mu_{00}$ is most likely due to some slight interpolation error in the integration across tetrahedra.

As a second synthetic experiment, we consider two realizations of sets of spheres $X$ and $Y$ randomly distributed in a window of size $256^3$ pixels, as shown in Fig. 10. Here, $X$ is shown as blue and orange spheres for the two realizations with the black spheres representing $Y$. In both cases, the center point of each sphere in $Y$ is generated uniformly at random, and this is likewise the case for the blue spheres. The orange spheres are generated by a Gaussian distribution around each sphere in $Y$. The processes are constructed to be hard-core by discarding and replacing any sphere overlapping with a previously placed sphere. Each sphere has radius 6. Looking at Fig. 10a, we see two $\mu_{00}(X, Y^r)$ volume graphs showing a slight difference between the two groups. For the normalized measure $v_{00}(X, Y^r)$, shown in Fig. 10b, the effect of the normalization factor is striking. Now, we clearly see a distinction between the two groups: For both curves, $v_{00}(X, Y^r)$ is close to zero for small values of $r$. For the blue spheres, $v_{00}(X, Y^r)$ (in blue) converges quickly to a horizontal line, while for the red spheres, $v_{00}(X, Y^r)$ (in red) peaks at $r \sim 175$ and converges to the blue horizontal line for $r \gtrsim 500$. From these curves, we thus conclude that for both experiments the spheres do not overlap with the $Y$ shapes, that the blue sphere are randomly distributed, while the red spheres cluster near the $Y$ shapes with a characteristic distance of about $r \sim 175$, but appear randomly distributed for distances $r \gtrsim 500$.

6 Experiments with Edge Correction

To assess the effectiveness of the edge corrections (17), (18) and (22), we generate synthetic germ-grain realizations by placing a number of non-overlapping observed objects of 3 variants and a reference object in form of a triangle. We consider two windows $W$ and $W_{\text{large}}$. We calculate the edge corrected $K_{e,e'}^{\varepsilon_{\varepsilon'}}$-estimator on $W$ and compare with the ground truth on non-edge corrected $K_{e,e'}^{\varepsilon_{\varepsilon'}}$-estimator on $W_{\text{large}}$. An example region can be seen in Fig. 11.

For the edge correction of (17), we disregard all measurements where $y$ did not fall into the smaller window $W \ominus B_M(0)$. For the translatative edge correction, each pixel area element is weighted by the area ratio (18) before sum-

Fig. 11 Example of the synthetic germ-grain realizations used for testing edge correction. We show the observed objects $X$ as gray and teal sets with Poisson placed germs $x$ and three different grain types $X$. Each object in $X$ has a random shape selected uniformly at random and is rotated uniformly on $[0, 2\pi)$ around the germ point $x$. Overlapping objects are replaced. We show $Y$ and $Y^r$ in green and $W$ and $W_{\text{large}}$ as black contours.
Fig. 12 The two-dimensional area measure using different edge correction strategies. We show $\mu_{00}$ without correction alongside translative correction, isotropic correction, and correction by shrinking the set of $\gamma$ used in the measured. For comparison, we also display the measure using a sufficiently large window to remove edge effects. The result is an average of 1000 simulations.

We average the measures over 1000 simulated realisations of $X, Y$. Shown in Fig. 12, we see the uncorrected reading underestimates the measure as expected while the corrected version gives estimates better consistent with the expected measure.

7 Experiments on Cellular Ultrastructures

Communication by neurons in humans is mainly achieved by a combination of electric potential changes and chemical signaling. The vesicles serve as transient containers of the chemicals released towards another neuron at a connection point, the synapse, upon voltage potential changes in the neuron. Synaptic vesicles are therefore almost exclusively observed directly next to synapses. The mechanisms of replenishment of the vesicles are thought in part to be done by two main routes. The first is by only partly release of the neurotransmitters, the vesicle membrane is thus preserved [3,9]. The second is by a slow endosomatic route, where an endosome is formed from the membrane, pinched off into vesicles and filled with neurotransmitters. An open question is if the cells keep a reservoir of vesicles at some distance to the synapse with some evidence [13]. To assess the above, we examine a publicly available FIB-SEM dataset of the CA1 hippocampus region of a healthy adult rodent. Original dimensions before registration were $2048 \times 1536 \times 1065$ with a voxel size of $5 \times 5 \times 5$ nm. We have segmented the complete volumetric image into cell wall, synapses, mitochondria, vesicles, endoplasmatic reticulum, and the segmentation is available at [23].

The FIB-SEM were segmented by a neural network U-Net model [16] and cleaned up using an Avizo Amira pipeline [18]. The volume was registered to correct for drift using a model-based approach described in [22]. From the masks, we generate mesh reconstructions using a Marching Cubes Lewiner implementation in the SciPy Python package [25]. The meshing is further refined with the PyMesh Python package, and the TetWild C++ library to do mesh simplification and tetrahedralization [7]. Examples of the resulting segmentation are shown in Fig. 1.

In Fig. 2, we show $L_{01}$ for mitochondria and vesicles when using the synapse as the reference object. No correction for cell walls has been performed. From Fig. 2a, we see that the mitochondria is absent close to the synapse, with a gradually increasing presence until around 800 nm, where the expected presence of mitochondria goes towards the global area fraction of mitochondria in the whole sample. From Fig. 2b, we see a presence of vesicle at the very close range $\approx 25$ nm followed by a proportionally greater measure of peaking around 25–100 nm. Before the measure tends to the global area fraction, we see a slight increase in vesicles near the 500 nm range which could indicate a presence of a vesicle reservoir at that range for these neuronal processes.

8 Conclusion

We have presented a novel method that extends the theoretical foundations of $K$-function summary-statistics in the field of spatial point statistics to geometric objects, adds elegant reasoning about the shape of one object with respect to a reference object and includes some existing shape-relation measures. We show that the method can be used to display spatial relations such as spreading or clustering compared to uniformly random distribution, and that the method is sensitive to properties such as cross-sectional area and thickness. A core strength is that the method is built on the $n$-dimensional Hausdorff measure enabling us to intuitively understand the shape relations. Statistical tests have been developed for the comparison of $K$-functions in the context of spatial point-processes [6] and are readily available for the comparison between groups.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.
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Hans J. T. Stephensen received the Ph.D. degree in Computer Science in 2021 from the University of Copenhagen. His main focus is on method development, algorithm design and software development to solve geometrical, spatial and stochastic problems in bioimaging.

Anne Marie Svane is currently assistant professor in spatial statistics at Aalborg University. She received the Ph.D. degree in mathematics in 2011 from Aarhus University within the field of algebraic topology. Her research interests include stochastic geometry and spatial statistics, convex geometry, image analysis, topological data analysis, and biostatistics.
Carlos B. Villanueva Area of focus: investigating nanometer scale changes observed in striatal MSNs as a consequence Huntington’s disease injury and the rescue of this damage by the introduction of human stem cells as treatment vectors.

Steven A. Goldman is the URMC Distinguished Professor of Neuroscience and Neurology, and co-Director of Rochester’s Center for Translational Neuromedicine. He has a concurrent appointment as Professor of Neuroscience at the University of Copenhagen in Denmark, where he serves as co-director of its sister Center for Translational Neuromedicine, and as Professor of Neurology at its affiliated Copenhagen University Hospital. Goldman moved to Rochester in 2003 from the Weill Medical College of Cornell University, where he was the Nathan Cummings Professor of Neurology, and Attending Neurologist at New York Presbyterian Hospital. A summa cum laude graduate of the University of Pennsylvania, he obtained his Ph.D. with Fernando Nottebohm at the Rockefeller University in 1983, and his MD from Cornell in 1984. Dr. Goldman interned in Medicine and did his residency in Neurology under Fred Plum at New York Hospital-Cornell, and Jerome Posner at the Memorial Sloan-Kettering Cancer Center, before joining the Cornell faculty. Goldman moved to Rochester as the Dean Zutes Chair in Biology of the Aging Brain, and as Chief of the Neurology department’s Division of Cell and Gene Therapy; he subsequently served as the founding program director for Rochester’s neuro-oncology training program and served as Chairman of the Department (2008–12). Dr. Goldman remains active clinically, with subspecialty interests in stroke, myelin disease and neuro-oncology.

Jon Sporring My primary research field is Computer Science and particularly mathematical and medical image processing, computer graphics, information theory, and pattern recognition. My present research involves: (1) Medical image registration: We work on fast algorithms for aligning medical images such as CT and MR images. (2) Statistics of subcellular geometric structures: We reconstruct and study the three-dimensional structure of the synaptic area as seen through electron microscopes. (3) Differential geometry of the muscle cells in the heart in 3D. We model the cells as measured by diffusion tensor imaging.