

Analysis of the spatial organization of molecules with robust statistics: Supplementary Material

Thibault Lagache^{1,2,*}, Gabriel Lang³, Nathalie Sauvonnet^{4,2}, Jean-Christophe Olivo-Marin^{1,2,*}

1 Unité d'Analyse d'Images Quantitative, Institut Pasteur. Paris, France

2 Unité de Recherche Associée 2582, Centre National de la Recherche Scientifique. Paris, France

3 Unité Mixte de Recherche 518 Mathématiques et Informatique Appliquées, AgroParisTech and INRA. Paris, France

4 Unité de Biologie des Interactions Cellulaires, Institut Pasteur. Paris, France

*** E-mail: thibault.lagache@pasteur.fr, jcolivo@pasteur.fr**

In this supplementary material, our goal is to compute the four first moment of the Ripley's K-function $K(r, n)$. Computation of $\mathbb{E}\{K(r, n)\}$ and $\text{var}\{K(r, n)\}$ can be found in [1], however we refine here the computation of $\text{var}\{K(r, n)\}$ for a small number of points in section 2 and we reproduce the computation of $\mathbb{E}\{K(r, n)\}$ for sake of clarity in section 1. Finally, the third and the fourth moments of $K(r, n)$, $\mathbb{E}\{(K(r, n) - \mathbb{E}\{K(r, n)\})^3\}$ and $\mathbb{E}\{(K(r, n) - \mathbb{E}\{K(r, n)\})^4\}$, are computed in sections 3 and 4.

1 computation of $\mathbb{E}\{K(r, n)\}$

Denoting $\psi(\mathbf{x}, \mathbf{y}) = \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| \leq r\}} k(\mathbf{x}, \mathbf{y})$, we decompose the symmetric function $\phi(\mathbf{x}, \mathbf{y})$ as

$$\phi(\mathbf{x}, \mathbf{y}) = \frac{1}{2} (\psi(\mathbf{x}, \mathbf{y}) + \psi(\mathbf{y}, \mathbf{x})), \quad (1)$$

and we re-write $K(r, n)$ as

$$K(r, n) = \frac{a}{n(n-1)} \sum_{\mathbf{x} \neq \mathbf{y}} \phi(\mathbf{x}, \mathbf{y}) = \frac{a}{n(n-1)} \sum_{\mathbf{x} \neq \mathbf{y}} \frac{1}{2} (\psi(\mathbf{x}, \mathbf{y}) + \psi(\mathbf{y}, \mathbf{x})). \quad (2)$$

Then, assuming a uniform distribution of points in Ω and denoting

$$\alpha_r = n(n-1) \dots (n-r+1) a^{-r} \mu_{2r}, \quad (3)$$

where μ_{2r} is the Lebesgue measure on $\mathbb{R}^{2r}$, we have [1]

$$\mathbb{E}\{K(r, n)\} = \frac{a}{n(n-1)} \int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}). \quad (4)$$

that is

$$\mathbb{E}\{K(r, n)\} = \frac{a}{n(n-1)} \int_{\Omega^2} \psi(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}). \quad (5)$$

Denoting

$$I_0 = \int_{\Omega^2} \psi(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = \int_{\Omega^2} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| \leq r\}} k(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}), \quad (6)$$

we re-write

$$\mathbb{E}\{K(r, n)\} = \frac{I_0}{a}, \quad (7)$$

and we further compute I_0 by considering local polar coordinates $\mathbf{y}(r_{\mathbf{y}}, \theta_{\mathbf{y}})$ around $\mathbf{x}(0, 0)$ in Ω , with $0 \leq r_{\mathbf{y}} \leq r$ and $-\frac{\Theta(r_{\mathbf{y}})}{2} \leq \theta_{\mathbf{y}} \leq \frac{\Theta(r_{\mathbf{y}})}{2}$ where $\Theta(r_{\mathbf{y}})$ is the part of the perimeter $b(\mathbf{x}, r_{\mathbf{y}})$ that is in Ω :

$$(2\pi - \Theta(r_{\mathbf{y}})) r_{\mathbf{y}} = |\partial b(\mathbf{x}, r_{\mathbf{y}}) \cap \Omega|, \quad (8)$$

that is

$$2\pi - \Theta(r_{\mathbf{y}}) = \frac{|\partial b(\mathbf{x}, r_{\mathbf{y}}) \cap \Omega|}{r_{\mathbf{y}}} = \frac{2\pi}{k(\mathbf{x}, \mathbf{y})}. \quad (9)$$

We then have

$$I_0 = \int_{\Omega} \int_0^r 2\pi r_{\mathbf{y}} dr_{\mathbf{y}} d\mathbf{x} = a\pi r^2. \quad (10)$$

Finally, reinjecting I_0 (Eq. (10)) in Eq. (7) we have

$$\mathbb{E} \{K(r, n)\} = \frac{I_0}{a} = \pi r^2. \quad (11)$$

Integrals $(I_j)_{j \geq 0}$ that are introduced all along this supplementary material are summarized with their numerical value in Supplementary Table **S1**.

2 computation of $\text{var} \{K(r, n)\} = \mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^2 \right\}$

We first introduce the centered ($\mathbb{E} = 0$) estimator $K_0(r, n)$:

$$K_0(r, n) = K(r, n) - \mathbb{E} \{K(r, n)\} = \frac{a}{n(n-1)} \sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y}), \quad (12)$$

where

$$\phi_0(\mathbf{x}, \mathbf{y}) = \phi(\mathbf{x}, \mathbf{y}) - \frac{\pi r^2}{a}. \quad (13)$$

We then have

$$\text{var} \{K(r, n)\} = \mathbb{E} \{K_0^2(r, n)\} = \frac{a^2}{(n(n-1))^2} \mathbb{E} \left\{ \left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y}) \right)^2 \right\}, \quad (14)$$

that we expand as

$$\begin{aligned} \left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y}) \right)^2 &= a_2 \sum_{\mathbf{x} \neq \mathbf{y}} \phi_0^2(\mathbf{x}, \mathbf{y}) + a_3 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \\ &\quad + a_4 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}). \end{aligned} \quad (15)$$

Computing the number of terms in each sum of the equation above, we obtain that

$$(n(n-1))^2 = a_2 n(n-1) + a_3 n(n-1)(n-2) + a_4 n(n-1)(n-2)(n-3), \quad (16)$$

that is

$$n^4 - 2n^3 + n^2 = a_4 n^4 + (a_3 - 6a_4) n^3 + (a_2 - 3a_3 + 11a_4) n^2 + (-a_2 + 2a_3 - 6a_4). \quad (17)$$

Identifying polynomial coefficients, we obtain that

$$a_2 = 2, a_3 = 4, \text{ and } a_4 = 1, \quad (18)$$

leading to

$$\begin{aligned} \text{var} \{K(r, n)\} &= \frac{a^2}{(n(n-1))^2} \left(2\mathbb{E} \left\{ \sum_{\mathbf{x} \neq \mathbf{y}} \phi_0^2(\mathbf{x}, \mathbf{y}) \right\} \right. \\ &\quad \left. + 4\mathbb{E} \left\{ \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \right\} + \mathbb{E} \left\{ \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \right\} \right). \end{aligned} \quad (19)$$

Considering that $\mathbf{x}$ and $\mathbf{y}$ are uniformly distributed in Ω , Eq. (19) becomes

$$\begin{aligned} \text{var} \{K(r, n)\} &= \frac{a^2}{(n(n-1))^2} \left(2 \int_{\Omega^2} \phi_0^2(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}) \right. \\ &\quad \left. + 4 \int_{\Omega^3} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{w}) d\alpha_3(\mathbf{x}, \mathbf{y}, \mathbf{w}) + \int_{\Omega^4} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{w}, \mathbf{z}) d\alpha_4(\mathbf{x}, \mathbf{y}, \mathbf{w}, \mathbf{z}) \right) \end{aligned} \quad (20)$$

where α_r is given by Eq. (3). Because

$$\int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}) = \int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}) - a\pi r^2 = 0, \quad (21)$$

we have

$$\int_{\Omega^4} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{w}, \mathbf{z}) d\alpha_4(\mathbf{x}, \mathbf{y}, \mathbf{w}, \mathbf{z}) = \alpha_4 \int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) \int_{\Omega^2} \phi_0(\mathbf{w}, \mathbf{z}) d(\mathbf{w}, \mathbf{z}) = 0. \quad (22)$$

Then, denoting $\beta = \frac{\pi r^2}{a}$, we expand the two remaining integrals of Eq. (46)

$$\phi_0(\mathbf{x}, \mathbf{y})^2 = \phi(\mathbf{x}, \mathbf{y})^2 - 2\beta\phi(\mathbf{x}, \mathbf{y}) + \beta^2, \quad (23)$$

and

$$\phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) = \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) - \beta(\phi(\mathbf{x}, \mathbf{y}) + \phi(\mathbf{x}, \mathbf{z})) + \beta^2, \quad (24)$$

Because $\int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y}) = a\pi r^2 = a^2\beta$, we have

$$\int_{\Omega^2} \phi_0^2(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = \int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y})^2 - 2\beta\phi(\mathbf{x}, \mathbf{y}) + \beta^2 d(\mathbf{x}, \mathbf{y}) = \int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y})^2 - a^2\beta^2, \quad (25)$$

and

$$\int_{\Omega^3} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}) = \int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}) - a^3\beta^2. \quad (26)$$

Consequently, we are now left with the computations of the integrals

$$I_1 = \int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y})^2 d(\mathbf{x}, \mathbf{y}) \quad (27)$$

and

$$I_2 = \int_{\Omega^3} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}). \quad (28)$$

We first observe that for points $\mathbf{x}$ that are at a distance $|\mathbf{x} - \partial\Omega| > 2r$ from the domain boundary, there is no edge correction for any points $\mathbf{y}, \mathbf{z}$ inside the domain Ω : $k(\mathbf{x}, \mathbf{y}) = k(\mathbf{y}, \mathbf{x}) = \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| < r\}}$. Consequently, integrals I_1 and I_2 can be decomposed as follows

$$\begin{aligned} I_1 &= \int_{\Omega^2} \mathbf{1}_{\{|\mathbf{x}-\partial\Omega| > 2r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| < r\}} d(\mathbf{x}, \mathbf{y}) \\ &\quad + \frac{1}{4} \int_{\Omega^2} \mathbf{1}_{\{|\mathbf{x}-\partial\Omega| < 2r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| < r\}} (k(\mathbf{x}, \mathbf{y}) + k(\mathbf{y}, \mathbf{x}))^2 d(\mathbf{x}, \mathbf{y}) \end{aligned} \quad (29)$$

and,

$$\begin{aligned} I_2 &= \int_{\Omega^3} \mathbf{1}_{\{|\mathbf{x}-\partial\Omega| > 2r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| < r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{z}| < r\}} d(\mathbf{x}, \mathbf{y}, \mathbf{z}) \\ &\quad + \frac{1}{4} \int_{\Omega^3} \mathbf{1}_{\{|\mathbf{x}-\partial\Omega| < 2r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}| < r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{z}| < r\}} (k(\mathbf{x}, \mathbf{y}) + k(\mathbf{y}, \mathbf{x})) (k(\mathbf{x}, \mathbf{z}) + k(\mathbf{z}, \mathbf{x})) d(\mathbf{x}, \mathbf{y}, \mathbf{z}). \end{aligned} \quad (30)$$

Because $\int_{\Omega} \mathbf{1}_{\{\mathbf{x}-\partial\Omega>2r\}} d\mathbf{x} = |\Omega| - 2r|\partial\Omega| = a - 2ur$, where $u = |\partial\Omega|$ is the perimeter of the domain Ω , and that for all $\mathbf{x}$, such that $|\mathbf{x} - \partial\Omega| > 2r$, $\int_{\Omega} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}|<r\}} d\mathbf{y} = \pi r^2$, we have

$$\int_{\Omega^2} \mathbf{1}_{\{|\mathbf{x}-\partial\Omega|>2r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}|<r\}} d(\mathbf{x}, \mathbf{y}) = (a - 2ur)\pi r^2, \quad (31)$$

and

$$\int_{\Omega^3} \mathbf{1}_{\{|\mathbf{x}-\partial\Omega|>2r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{y}|<r\}} \mathbf{1}_{\{|\mathbf{x}-\mathbf{z}|<r\}} d(\mathbf{x}, \mathbf{y}, \mathbf{z}) = (a - 2ur) (\pi r^2)^2. \quad (32)$$

Consequently, denoting $A_h = \{\mathbf{y} \in \Omega \text{ such that } |\mathbf{x} - \mathbf{y}| < r \text{ given that } |\mathbf{x} - \partial\Omega| = h\}$, I_1 and I_2 reduce to

$$I_1 = (a - 2ur)\pi r^2 + \frac{u}{4} \int_0^{2r} \int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h))^2 d\mathbf{y} dh \quad (33)$$

and,

$$I_2 = (a - 2ur) (\pi r^2)^2 + \frac{u}{4} \int_0^{2r} \left(\int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h)) d\mathbf{y} \right)^2 dh. \quad (34)$$

Assuming that the edge of the domain boundary $\partial\Omega$ is straight where it intersects $b(\mathbf{x}, |\mathbf{x} - \mathbf{y}|)$, $k(h, \mathbf{y})$ and $k(\mathbf{y}, h)$ can be determined analytically [2], and are given by:

$$\begin{aligned} k(h, \mathbf{y}) &\approx \left(1 - \frac{1}{\pi} \arccos \left(\frac{\min(|\mathbf{x} - \mathbf{y}|, h)}{|\mathbf{x} - \mathbf{y}|} \right) \right)^{-1}, \text{ and,} \\ k(\mathbf{y}, h) &\approx \left(1 - \frac{1}{\pi} \arccos \left(\frac{\min(|\mathbf{x} - \mathbf{y}|, |\mathbf{y} - \partial\Omega|)}{|\mathbf{x} - \mathbf{y}|} \right) \right)^{-1}. \end{aligned} \quad (35)$$

However, using analytical expressions (35) in Eq. (33)-(34) does not lead to closed form expressions for I_1 and I_2 . We thus use a finite difference algorithm with respect to the variable h ($n_h = \frac{2r}{dh}$ steps of size $dh = 0.001$) coupled with a Monte-Carlo sampling of $\mathbf{y}$ in each $A_{h_j=j \cdot dh}$, $1 \leq j \leq n_h$ ($n_{\mathbf{y}} = 1000$ random draws $\mathbf{y}_i$, $1 \leq i \leq n$), and approximate

$$\int_0^{2r} \int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h))^2 d\mathbf{y} dh \approx \sum_{j=1}^{n_h} |A_{h_j}| \frac{1}{n_{\mathbf{y}}} \sum_i^{n_{\mathbf{y}}} (k(h_j, \mathbf{y}_i) + k(\mathbf{y}_i, h_j))^2 dh \quad (36)$$

and

$$\int_0^{2r} \left(\int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h)) d\mathbf{y} \right)^2 dh \approx \sum_{j=1}^{n_h} \left(|A_{h_j}| \frac{1}{n_{\mathbf{y}}} \sum_i^{n_{\mathbf{y}}} (k(h_j, \mathbf{y}_i) + k(\mathbf{y}_i, h_j)) \right)^2 dh \quad (37)$$

with [3]

$$|A_{h_j}| = \pi r^2 \left(1 - \frac{1}{\pi} \left(\arccos \left(\frac{h_j}{r} \right) + \frac{h_j}{r} \sqrt{1 - \left(\frac{h_j}{r} \right)^2} \right) \right). \quad (38)$$

Finally, we obtain following numerical approximations

$$\frac{u}{2} \int_0^{2r} \int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h))^2 d\mathbf{y} dh \approx ru(\pi r^2) 2.305, \quad (39)$$

and

$$\frac{u}{4} \int_0^{2r} \left(\int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h)) d\mathbf{y} \right)^2 dh \approx ru(\pi r^2)^2 2.0066. \quad (40)$$

Reinjecting approximations (39) and (40) in (33) and (34), we have

$$I_1 = a^2 \beta \left(1 + 0.305 \frac{ur}{a}\right) \text{ and } I_2 = a^3 \beta^2 \left(1 + 0.0066 \frac{ur}{a}\right), \quad (41)$$

leading to

$$\int_{\Omega^2} \phi_0^2(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = I_1 - a^2 \beta^2 = a^2 \left(\beta \left(1 + 0.305 \frac{ur}{a}\right) - \beta^2 \right), \quad (42)$$

and

$$\int_{\Omega^3} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}) = I_2 - a^3 \beta^2 = a^3 \beta^2 \left(0.0066 \frac{ur}{a}\right). \quad (43)$$

Finally, we obtain

$$\begin{aligned} \text{var} \{K(r, n)\} &= \frac{a^2}{(n(n-1))^2} \left\{ 2 \int_{\Omega^2} \phi_0^2(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}) + 4 \int_{\Omega^3} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{w}) d\alpha_3(\mathbf{x}, \mathbf{y}, \mathbf{w}) \right\} \\ &= \frac{2a^2}{n(n-1)} \left(\beta \left(1 + 0.305 \frac{ur}{a}\right) - \beta^2 + 2(n-2)\beta^2 \left(0.0066 \frac{ur}{a}\right) \right) \end{aligned} \quad (44)$$

that is

$$\text{var} \{K(r, n)\} = \frac{2a^2}{n(n-1)} \left(\beta \left(1 + 0.305 \frac{ur}{a}\right) + \beta^2 \left(-1 + 2(n-2)0.0066 \frac{ur}{a}\right) \right). \quad (45)$$

which reduces for $n \gg 1$ to

$$\text{var} \{K(r, n)\} \approx \frac{2}{\lambda^2} \left(\beta \left(1 + 0.305 \frac{ur}{a}\right) + \beta^2 (-1 + 0.0132) \frac{ur}{a} \right). \quad (46)$$

where $\lambda = \frac{n}{a}$ is the empirical density of points. Formula (46) is in agreement with [1], page 40.

3 computation of $\mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^3 \right\}$

Using $\phi_0(\mathbf{x}, \mathbf{y}) = \phi(\mathbf{x}, \mathbf{y}) - \beta$, we have

$$\mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^3 \right\} = \frac{a^3}{(n(n-1))^3} \mathbb{E} \left\{ \left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y}) \right)^3 \right\}. \quad (47)$$

We expand $\left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y}) \right)^3$ as

$$\left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y}) \right)^3 = \sum_{j=2}^6 S_j \quad (48)$$

where S_j is the sum of the terms containing j different points:

$$\begin{aligned} S_2 &= a_2 \sum_{\mathbf{x} \neq \mathbf{y}} \phi_0^3(\mathbf{x}, \mathbf{y}) \\ S_3 &= a_3^1 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) + a_3^2 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{z}), \\ S_4 &= a_4^1 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) + a_4^2 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \\ &\quad + a_4^3 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}), \\ S_5 &= a_5 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{r}), \\ \text{and } S_6 &= a_6 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}), \end{aligned} \quad (49)$$

and we then have

$$\mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^3 \right\} = \frac{a^3}{(n(n-1))^3} \sum_{j=2}^6 \mathbb{E} \{S_j\}. \quad (50)$$

We are thus left with the computations of each mean $\mathbb{E}(S_j)$, for $2 \leq j \leq 6$. We begin with the computation of multiplicative coefficients $a_2, a_3^1, a_3^2 \dots a_5$ and a_6 in following sub-section 3.1, and will perform the computations of each term $\mathbb{E}(S_j)$ in sub-section 3.2.

3.1 computation of coefficients $a_2, a_3^1, \dots a_6$

Computing the number of terms appearing in each sum of Eq. (48), we obtain

$$(n(n-1))^3 = a_2 \tilde{\alpha}_2 + \sum_{j=1}^2 a_3^j \tilde{\alpha}_3 + \sum_{j=1}^3 a_4^j \tilde{\alpha}_4 + a_5 \tilde{\alpha}_5 + a_6 \tilde{\alpha}_6, \quad (51)$$

where $\tilde{\alpha}_i = n(n-1) \dots (n-i+1)$ is the number of ways to choose an ordered subset of i points among n . Expanding Eq. (51), we obtain

$$\begin{aligned} n^6 - 3n^5 + 3n^4 - n^3 &= a_6 n^6 + (-16a_6 + a_5) n^5 + (85a_6 - 10a_5 + \sum_{j=1}^3 a_4^j) n^4 \\ &+ (-225a_6 + 35a_5 - 6 \sum_{j=1}^3 a_4^j + \sum_{j=1}^2 a_3^j) n^3 \\ &+ (274a_6 - 50a_5 + 11 \sum_{j=1}^3 a_4^j - 3 \sum_{j=1}^2 a_3^j + a_2) n^2 \\ &+ (-120 + 24a_5 - 6 \sum_{j=1}^3 a_4^j + 2 \sum_{j=1}^2 a_3^j - a_2) n, \end{aligned} \quad (52)$$

Identifying polynomial coefficients in Eq. (52), we have

$$a_2 = 4, \sum_{j=1}^2 a_3^j = 32, \sum_{j=1}^3 a_4^j = 38, a_5 = 12 \text{ and } a_6 = 1. \quad (53)$$

Then, because $\phi_0(\mathbf{x}, \mathbf{y})$ is a symmetric function there is $3 \times 2^3 = 24$ ways of writing $\phi_0^2(\mathbf{x}, \mathbf{y})\phi_0(\mathbf{x}, \mathbf{z})$. Indeed, there is 3 possible positions for $\phi_0(\mathbf{x}, \mathbf{z})$ and 2 ways to write each symmetric term. Consequently, $a_3^1 = 24$, and $a_3^2 = \sum_{j=1}^2 a_3^j - a_3^1 = 8$. Similarly, there is $3 \times 2^3 = 24$ ways of writing $\phi_0^2(\mathbf{x}, \mathbf{y})\phi_0(\mathbf{z}, \mathbf{w})$, but in that case, the expression is symmetric in $\mathbf{x}$ and $\mathbf{y}$ as well as in $\mathbf{z}$ and $\mathbf{w}$. Consequently, $\phi_0^2(\mathbf{x}, \mathbf{y})\phi_0(\mathbf{z}, \mathbf{w})$ is counted 4 times in $\sum_{\mathbf{x} \neq \mathbf{y}} \sum_{\mathbf{z} \neq \mathbf{w}} \phi_0^2(\mathbf{x}, \mathbf{y})\phi_0(\mathbf{z}, \mathbf{w})$ and $a_4^1 = 24/4 = 6$. Concerning a_4^2 , there is $6 \times 2^3 = 48$ ways of writing $\phi_0(\mathbf{x}, \mathbf{y})\phi_0(\mathbf{x}, \mathbf{z})\phi_0(\mathbf{x}, \mathbf{w})$ and the expression is symmetric in $\mathbf{y}, \mathbf{w}$ and $\mathbf{z}$ leading to $a_4^2 = 48/6 = 8$. Finally, there is 48 ways of writing $\phi_0(\mathbf{x}, \mathbf{y})\phi_0(\mathbf{y}, \mathbf{z})\phi_0(\mathbf{z}, \mathbf{w})$ and the symmetric role of the couple of points $(\mathbf{x}, \mathbf{y})$ and $(\mathbf{z}, \mathbf{w})$ leads to $a_4^3 = 24$. We can check here that $a_4^1 + a_4^2 + a_4^3 = 38$.

3.2 computation of $\mathbb{E} \{S_j\}$ for $2 \leq j \leq 6$

3.2.1 computation of $\mathbb{E} \{S_2\}$

First, assuming a uniform distribution of the points inside Ω and using $\alpha_r = n(n-1) \dots (n-r+1) a^{-r} \mu_{2r}$, we have

$$\mathbb{E} \{S_2\} = 4 \int_{\Omega^2} \phi_0^3(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}), \quad (54)$$

that we expand as

$$\begin{aligned}\mathbb{E}\{S_2\} &= 4\alpha_2 \int_{\Omega^2} (\phi^3(\mathbf{x}, \mathbf{y}) - 3\beta\phi^2(\mathbf{x}, \mathbf{y}) + 3\beta^2\phi(\mathbf{x}, \mathbf{y}) - \beta^3) d(\mathbf{x}, \mathbf{y}) \\ &= 4\alpha_2 \left(\int_{\Omega^2} \phi^3(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) - 3\beta I_1 + 3\beta^2 I_0 - a^2\beta^3 \right).\end{aligned}\quad (55)$$

We are thus left with the computation of $I_3 = \int_{\Omega^2} \phi^3(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y})$ that we decompose as in section 2 (see Eq. (33) and (34)):

$$I_3 = \int_{\Omega^2} \phi^3(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = (a - 2ur)\pi r^2 + \frac{u}{8} \int_0^2 \int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h))^3 dy dh, \quad (56)$$

where $k(h, \mathbf{y})$ and $k(\mathbf{y}, h)$ are given by Eq. (35). A finite difference scheme with respect to variable h coupled with a Monte-Carlo sampling of $\mathbf{y}$ in A_h leads to the approximation

$$I_3 \approx a^2\beta \left(1 + 0.76 \frac{ur}{a} \right). \quad (57)$$

Finally, using Supplementary Table **S1** in Eq. (55), we obtain

$$\mathbb{E}\{S_2\} \approx 4\tilde{\alpha}_2 \left(\beta \left(1 + 0.76 \frac{ur}{a} \right) - 3\beta^2 \left(1 + 0.305 \frac{ur}{a} \right) \right) \quad (58)$$

3.2.2 computation of $\mathbb{E}\{S_3\}$

Denoting

$$\mathbb{E}\{S_3^1\} = \alpha_3 \int_{\Omega^3} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}) \quad (59)$$

and

$$\mathbb{E}\{S_3^2\} = \alpha_3 \int_{\Omega^3} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}), \quad (60)$$

we have

$$\mathbb{E}\{S_3\} = 24\mathbb{E}\{S_3^1\} + 8\mathbb{E}\{S_3^2\}, \quad (61)$$

Expanding $\mathbb{E}\{S_3^1\}$ and using Monte-Carlo numerical integration to account for Ω boundaries we find that $\mathbb{E}\{S_3^1\} \approx 0$. We then expand $\mathbb{E}\{S_3^2\}$, as

$$\mathbb{E}\{S_3^2\} = \alpha_3 \left(\int_{\Omega^3} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{y}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}) - 3\beta I_2 + 3a\beta^2 I_0 - a^3\beta^3 \right). \quad (62)$$

and are left with the computation of

$$I_4 = \int_{\Omega^3} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{y}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}). \quad (63)$$

First, for $\mathbf{x}$ such that $|\mathbf{x} - \partial\Omega| > 2r$, there is no boundary correction and we decompose $I_4 = I_4^{in} + I_4^{border}$ where

$$\begin{aligned}I_4^{in} &= \int_{\Omega^3} \mathbf{1}_{\{|\mathbf{x} - \partial\Omega| > 2r\}} \mathbf{1}_{\{|\mathbf{x} - \mathbf{y}| < r\}} \mathbf{1}_{\{|\mathbf{x} - \mathbf{z}| < r\}} \mathbf{1}_{\{|\mathbf{y} - \mathbf{z}| < r\}} d(\mathbf{x}, \mathbf{y}, \mathbf{z}) \\ &= (a - 2ur) \int_{\Omega^2} \mathbf{1}_{\{|\mathbf{x} - \mathbf{y}| < r\}} \mathbf{1}_{\{|\mathbf{x} - \mathbf{z}| < r\}} \mathbf{1}_{\{|\mathbf{y} - \mathbf{z}| < r\}} d(\mathbf{y}, \mathbf{z}),\end{aligned}\quad (64)$$

and

$$\begin{aligned}I_4^{border} &= \frac{u}{8} \int_0^{2r} \int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h)) \\ &\quad \int_{A_h} (k(h, \mathbf{z}) + k(\mathbf{z}, h)) \mathbf{1}_{\{|\mathbf{y} - \mathbf{z}| < r\}} (k(\mathbf{y}, \mathbf{z}) + k(\mathbf{z}, \mathbf{y})) d\mathbf{z} dy dh.\end{aligned}\quad (65)$$

We then rewrite I_4^{in} as

$$I_4^{in} = (a - 2ur) (\pi r^2)^2 \Pr \{ |\mathbf{y} - \mathbf{z}| < r \text{ given that } (\mathbf{y}, \mathbf{z}) \in b(\mathbf{x}, r) \}. \quad (66)$$

Because $\mathbf{y}$ and $\mathbf{z}$ are uniformly distributed in $b(\mathbf{x}, r)$, we have

$$\Pr \{ |\mathbf{y} - \mathbf{z}| < r \text{ given that } (\mathbf{y}, \mathbf{z}) \in b(\mathbf{x}, r) \} = \frac{1}{(\pi r^2)^2} \int_{b(\mathbf{x}, r)} |b(\mathbf{y}, r) \cap b(\mathbf{x}, r)| d\mathbf{y} \quad (67)$$

where $b(\mathbf{x}, r)$ and $b(\mathbf{y}, r)$ are the ball centered at $\mathbf{x}$ and $\mathbf{y}$ with radius r . Considering local polar coordinates: $\mathbf{y}(0 \leq r_y \leq r, 0 \leq \theta_y \leq 2\pi)$ around $\mathbf{x}(0, 0)$, we have

$$I_4^{in} = (a - 2ur) \int_{r_y=0}^r \int_{\theta_y=0}^{2\pi} A(r_y, \theta_y, r) r_y d(r_y, \theta_y) \quad (68)$$

where $A(r_y, \theta_y, r) = |b(\mathbf{x}(0, 0), r) \cap b(\mathbf{y}(r_y, \theta_y), r)|$ is equal to [3]

$$A(r_y, \theta_y, r) = A(r_y, r) = 2r^2 \cos^{-1} \left(\frac{r_y}{2r} \right) - \frac{r_y}{2} \sqrt{4r^2 - r_y^2}. \quad (69)$$

Finally, a direct integration I_4^{in} using Eq. (69) yields

$$I_4^{in} = (a - 2ur) 2\pi r^4 \left(\frac{\pi}{2} - \frac{3\sqrt{3}}{8} \right), \quad (70)$$

that is

$$I_4^{in} = (a - 2ur) a^2 \beta^2 \left(1 - \frac{3\sqrt{3}}{4\pi} \right) \approx (a - 2ur) a^2 \beta^2 0.587, \quad (71)$$

On the other hand, a numerical integration of I_4^{border} gives

$$I_4^{border} \approx a^3 \beta^2 1.38 \frac{ur}{a}, \quad (72)$$

leading to

$$I_4 = I_4^{in} + I_4^{border} \approx a^3 \beta^2 \left(0.587 + 0.207 \frac{ur}{a} \right). \quad (73)$$

Finally, reinjecting Eq. (73) in Eq. (62), and given that $\mathbb{E} \{ S_3^1 \} \approx 0$, we obtain

$$\mathbb{E} \{ S_3 \} \approx 8 \mathbb{E} \{ S_3^2 \} = 8 \tilde{\alpha}_3 \left(\beta^2 \left(0.587 + 0.207 \frac{ur}{a} \right) - \beta^3 \right). \quad (74)$$

3.2.3 computation of $\mathbb{E} \{ S_4 \}$

We decompose the computation of $\mathbb{E} \{ S_4 \}$ as follows

$$\mathbb{E} \{ S_4 \} = a_4^1 \mathbb{E} \{ S_4^1 \} + a_4^2 \mathbb{E} \{ S_4^2 \} + a_4^3 \mathbb{E} \{ S_4^3 \} = 6 \mathbb{E} \{ S_4^1 \} + 8 \mathbb{E} \{ S_4^2 \} + 24 \mathbb{E} \{ S_4^3 \} \quad (75)$$

with

$$\mathbb{E} \{ S_4^1 \} = \alpha_4 \int_{\Omega^4} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (76)$$

$$\mathbb{E} \{ S_4^2 \} = \alpha_4 \int_{\Omega^4} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (77)$$

and,

$$\mathbb{E} \{ S_4^3 \} = \alpha_4 \int_{\Omega^4} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}). \quad (78)$$

First $\int_{\Omega^2} \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{z}, \mathbf{w}) = 0$ leads to $\mathbb{E}\{S_4^1\} = 0$. We then expand $\mathbb{E}\{S_4^2\}$ as

$$\mathbb{E}\{S_4^2\} = \alpha_4 \left(\int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}) - 3\beta a I_2 + 3\beta^2 a^2 I_0 - a^4 \beta^3 \right), \quad (79)$$

and decompose $\int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w})$ as

$$\begin{aligned} \int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}) &= (a - 2ur) a^3 \beta^3 \\ &+ \frac{u}{8} \int_0^{2r} \left(\int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h)) d\mathbf{y} \right)^3 dh. \end{aligned} \quad (80)$$

Numerical integration of Eq. (80) gives

$$\int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}) \approx a^4 \beta^3 \left(1 + 0.02 \frac{ur}{a} \right). \quad (81)$$

and using Supplementary Table **S1** in Eq. (79), we compute that

$$\mathbb{E}\{S_4^2\} \approx 0. \quad (82)$$

Similarly, we expand $\mathbb{E}\{S_4^3\}$ as

$$\mathbb{E}\{S_4^3\} = \alpha_4 \left(\int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{y}, \mathbf{z}) \phi(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}) - \beta (2a I_2 + I_0^2) + 2a^4 \beta^3 \right) \quad (83)$$

and we are left with the numerical integration of $I_5 = \int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{y}, \mathbf{z}) \phi(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w})$. For $\mathbf{y}$ such that $|\mathbf{y} - \partial\Omega| > 3r$, points $\mathbf{x}$ and $\mathbf{z}$ such that $|\mathbf{x} - \mathbf{y}| < r$ and $|\mathbf{z} - \mathbf{y}| < r$ are at a minimal distance of $2r$ from the domain boundary $\partial\Omega$ and there is no boundary correction in I_5 . We thus decompose I_5 as

$$\begin{aligned} I_5 &= (a - 3ur) (\pi r^2)^3 + \frac{u}{8} \int_0^{3r} \int_{A_h} (k(\mathbf{x}, h) + k(h, \mathbf{x})) d\mathbf{x} \\ &\quad \int_{A_h} (k(\mathbf{z}, h) + k(h, \mathbf{z})) \int_{A_z} (k(\mathbf{z}, \mathbf{w}) + k(\mathbf{w}, \mathbf{z})) d\mathbf{w} d\mathbf{z} dh \end{aligned} \quad (84)$$

where $A_{\mathbf{z}} = b(\mathbf{z}, r) \cap \Omega$. We then used a finite difference algorithm with respect to the variable h ($n_h = \frac{3r}{dh}$ steps of size $dh = 0.001$) coupled with a Monte-Carlo sampling of $\mathbf{x}$ and $\mathbf{z}$ in each $A_{h_j} = j \cdot dh$ for $1 \leq j \leq n_h$ ($n_{\mathbf{x}} = n_{\mathbf{z}} = 1000$ random draws $\mathbf{x}_i, \mathbf{z}_p$, $1 \leq i, p \leq n$) as well as a sampling of $\mathbf{w}$ in each $A_{\mathbf{z}_p}$ related to each random draw $\mathbf{z}_p$ ($n_{\mathbf{w}} = 1000$ random draws $\mathbf{w}_k$, $1 \leq k \leq n_{\mathbf{w}}$) and approximate

$$\begin{aligned} &\int_0^{3r} \int_{A_h} (k(\mathbf{x}, h) + k(h, \mathbf{x})) d\mathbf{x} \int_{A_h} (k(\mathbf{z}, h) + k(h, \mathbf{z})) \int_{A_z} (k(\mathbf{z}, \mathbf{w}) + k(\mathbf{w}, \mathbf{z})) d\mathbf{w} d\mathbf{z} dh \\ &\approx \sum_{j=1}^{n_h} \frac{A_{h_j}}{n_{\mathbf{x}}} \sum_i^{n_{\mathbf{x}}} (k(h_j, \mathbf{x}_i) + k(\mathbf{x}_i, h_j)) \\ &\quad \frac{A_{h_j}}{n_{\mathbf{z}}} \sum_{p=1}^{n_{\mathbf{z}}} \left\{ (k(h_j, \mathbf{z}_p) + k(\mathbf{z}_p, h_j)) \frac{A_{\mathbf{z}_p}}{n_{\mathbf{w}}} \sum_{k=1}^{n_{\mathbf{w}}} (k(\mathbf{z}_p, \mathbf{w}_k) + k(\mathbf{w}_k, \mathbf{z}_p)) \right\} dh, \end{aligned} \quad (85)$$

leading to

$$I_5 \approx a^4 \beta^3 \left(1 + 0.0153 \frac{ur}{a} \right). \quad (86)$$

Finally, reinjecting Monte-Carlo approximation of I_5 in Eq. (83), we obtain

$$\mathbb{E}\{S_4^3\} \approx \tilde{\alpha}_4 \beta^3 0.002 \frac{ur}{a}, \quad (87)$$

leading to

$$\mathbb{E}\{S_4\} \approx 24 \mathbb{E}\{S_4^3\} = 24 \tilde{\alpha}_4 \beta^3 0.002 \frac{ur}{a}, \quad (88)$$

3.3 Conclusion

Finally, because $\int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = 0$, we have

$$\mathbb{E}\{S_5\} = 12\alpha_5 \int_{\Omega^3} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{r}) \int_{\Omega^2} \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{z}, \mathbf{w}) = 0, \quad (89)$$

and

$$\mathbb{E}\{S_6\} = \alpha_6 \int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) \int_{\Omega^2} \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{z}, \mathbf{w}) \int_{\Omega^2} \phi_0(\mathbf{r}, \mathbf{u}) d(\mathbf{r}, \mathbf{u}) = 0. \quad (90)$$

Consequently, using expressions of $\mathbb{E}\{S_2\}$ (Eq. (58)), $\mathbb{E}\{S_3\}$ (Eq. (74)) and $\mathbb{E}\{S_4\}$ (Eq. (88)) in Eq. (50) we obtain

$$\begin{aligned} \mathbb{E}\left\{(K(r, n) - \mathbb{E}\{K(r, n)\})^3\right\} &= \frac{a^3}{(n(n-1))^3} \sum_{j=2}^{j=4} \mathbb{E}\{S_j\} \\ &= \frac{4a^3}{(n(n-1))^2} \left[\beta \left(1 + 0.76 \frac{ur}{a}\right) + \beta^2 \left(\left(-3 + 1.173 \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2}\right) + \left(-0.915 + \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2} 0.414\right) \frac{ur}{a} \right) \right. \\ &\quad \left. + \beta^3 \left(-2 \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2} + 0.012 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} \frac{ur}{a} \right) \right], \end{aligned} \quad (91)$$

which simplifies for $n \gg 1$ to

$$\begin{aligned} &\mathbb{E}\left\{(K(r, n) - \mathbb{E}\{K(r, n)\})^3\right\} \\ &= \frac{4}{\lambda^3} \left(\frac{\beta}{n} \left(1 + 0.76 \frac{ur}{a}\right) + \beta^2 \left(1.173 + 0.414 \frac{ur}{a}\right) + \beta^3 \left(-2 + 0.012n \frac{ur}{a}\right) \right). \end{aligned} \quad (92)$$

4 computation of $\mathbb{E}\left\{(K(r, n) - \mathbb{E}\{K(r, n)\})^4\right\}$

We have

$$\mathbb{E}\left\{(K(r, n) - \mathbb{E}\{K(r, n)\})^4\right\} = \frac{a^4}{(n(n-1))^4} \mathbb{E}\left\{\left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y})\right)^4\right\}, \quad (93)$$

and following the method of section 3, we expand $\mathbb{E}\left\{\left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y})\right)^4\right\}$ as

$$\mathbb{E}\left\{\left(\sum_{\mathbf{x} \neq \mathbf{y}} \phi_0(\mathbf{x}, \mathbf{y})\right)^4\right\} = \sum_{j=2}^8 \mathbb{E}\{\tilde{S}_j\} \quad (94)$$

where $\tilde{S}_j$ is the sum of the terms containing j different points:

$$\tilde{S}_2 = \tilde{a}_2 \sum_{\mathbf{x} \neq \mathbf{y}} \phi_0^4(\mathbf{x}, \mathbf{y}), \quad (95)$$

$$\begin{aligned} \tilde{S}_3 &= a_3^1 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0^3(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) + a_3^2 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0^2(\mathbf{x}, \mathbf{z}) \\ &\quad + a_3^3 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{y}), \end{aligned} \quad (96)$$

$$\begin{aligned}
\tilde{S}_4 &= \tilde{a}_4^1 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0^3(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) + \tilde{a}_4^2 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0^2(\mathbf{z}, \mathbf{w}) \\
&+ \tilde{a}_4^3 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) + \tilde{a}_4^4 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{w}) \\
&+ \tilde{a}_4^5 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) + \tilde{a}_4^6 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{w}) \\
&+ \tilde{a}_4^7 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{y}, \mathbf{z}), \tag{97}
\end{aligned}$$

$$\begin{aligned}
\tilde{S}_5 &= \tilde{a}_5^1 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{r}) + \tilde{a}_5^2 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{z}, \mathbf{r}) \\
&+ \tilde{a}_5^3 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{r}) \\
&+ \tilde{a}_5^4 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{y}, \mathbf{r}) \\
&+ \tilde{a}_5^5 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{w}, \mathbf{r}) \\
&+ \tilde{a}_5^6 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{w}) \phi_0(\mathbf{z}, \mathbf{r}), \tag{98}
\end{aligned}$$

$$\begin{aligned}
\tilde{S}_6 &= \tilde{a}_6^1 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u}} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) \\
&+ \tilde{a}_6^2 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) \\
&+ \tilde{a}_6^3 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) \\
&+ \tilde{a}_6^4 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{w}, \mathbf{r}) \phi_0(\mathbf{w}, \mathbf{u}), \tag{99}
\end{aligned}$$

$$\tilde{S}_7 = \tilde{a}_7 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u} \neq \mathbf{s}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{w}, \mathbf{r}) \phi_0(\mathbf{u}, \mathbf{s}) \tag{100}$$

and

$$\tilde{S}_8 = \tilde{a}_8 \sum_{\mathbf{x} \neq \mathbf{y} \neq \mathbf{z} \neq \mathbf{w} \neq \mathbf{r} \neq \mathbf{u} \neq \mathbf{s} \neq \mathbf{r}} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) \phi_0(\mathbf{s}, \mathbf{r}). \tag{101}$$

4.1 computation of coefficients $\tilde{a}_2, \tilde{a}_3^1, \dots, \tilde{a}_8$

Computing the number of terms in each sum of Eq. (94), we get that

$$(n(n-1))^4 = \tilde{a}_2 \tilde{\alpha}_2 + \sum_{j=1}^3 \tilde{a}_3^j \tilde{\alpha}_3 + \sum_{j=1}^7 \tilde{a}_4^j \tilde{\alpha}_4 + \sum_{j=1}^6 \tilde{a}_5^j \tilde{\alpha}_5 + \sum_{j=1}^4 \tilde{a}_6^j \tilde{\alpha}_6 + \tilde{a}_7 \tilde{\alpha}_7 + \tilde{a}_8 \tilde{\alpha}_8, \tag{102}$$

where $\tilde{\alpha}_i = n(n-1) \dots (n-i+1)$ is the number of ways to choose an ordered subset of i different points among n . Expanding Eq. (102) and identifying polynomial coefficients, we obtain that

$$\tilde{a}_2 = 8, \sum_{j=1}^3 \tilde{a}_3^j = 208, \sum_{j=1}^7 \tilde{a}_4^j = 652, \sum_{j=1}^6 \tilde{a}_5^j = 576, \sum_{j=1}^4 \tilde{a}_6^j = 188, \tilde{a}_7 = 24 \text{ and } \tilde{a}_8 = 1. \tag{103}$$

Using similar counting arguments as in sub-section 3.1, we further obtain that

$$\tilde{a}_3^1 = 64, \tilde{a}_3^2 = 48 \text{ and } \tilde{a}_3^3 = 96 \text{ which verify } \sum_{j=1}^3 \tilde{a}_3^j = 208, \quad (104)$$

$$\begin{aligned} \tilde{a}_4^1 = 16, \tilde{a}_4^2 = 12, \tilde{a}_4^3 = \tilde{a}_4^4 = 96, \tilde{a}_4^5 = 192, \tilde{a}_4^6 = 48 \text{ and } \tilde{a}_4^7 = 192, \\ \text{which verify } \sum_{j=1}^7 \tilde{a}_4^j = 652, \end{aligned} \quad (105)$$

$$\begin{aligned} \tilde{a}_5^1 = 96, \tilde{a}_5^2 = 48, \tilde{a}_5^3 = 16, \tilde{a}_5^4 = 192, \tilde{a}_5^5 = 32 \text{ and } \tilde{a}_5^6 = 192, \\ \text{which verify } \sum_{j=1}^6 \tilde{a}_5^j = 576, \end{aligned} \quad (106)$$

and

$$\tilde{a}_6^1 = 12, \tilde{a}_6^2 = 32, \tilde{a}_6^3 = 96 \text{ and } \tilde{a}_6^4 = 48 \text{ which verify } \sum_{j=1}^4 \tilde{a}_6^j = 188. \quad (107)$$

4.2 computation of $\mathbb{E}\{\tilde{S}_j\}$ for $2 \leq j \leq 8$

4.2.1 computation of $\mathbb{E}\{\tilde{S}_2\}$

Assuming a uniform distribution of the points inside Ω we have

$$\mathbb{E}\{\tilde{S}_2\} = 8 \int_{\Omega^2} \phi_0^4(\mathbf{x}, \mathbf{y}) d\alpha_2(\mathbf{x}, \mathbf{y}), \quad (108)$$

where $\alpha_2 = n(n-1)a^{-2}\mu_4$ (see Eq. (3)), that we expand as

$$\begin{aligned} \mathbb{E}\{\tilde{S}_2\} &= 8\alpha_2 \int_{\Omega^2} (\phi^4(\mathbf{x}, \mathbf{y}) - 4\beta\phi^3(\mathbf{x}, \mathbf{y}) + 6\beta^2\phi^2(\mathbf{x}, \mathbf{y}) - 4\beta^3\phi(\mathbf{x}, \mathbf{y}) + \beta^4) d(\mathbf{x}, \mathbf{y}) \\ &= 8\alpha_2 \left(\int_{\Omega^2} \phi^4(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) - 4\beta I_3 + 6\beta^2 I_1 - 4\beta^3 I_0 + a^2 \beta^4 \right). \end{aligned} \quad (109)$$

We are thus left with the computation of $\int_{\Omega^2} \phi^4(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y})$ that we numerically evaluate to

$$\int_{\Omega^2} \phi^4(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) \approx a^2 \beta \left(1 + 1.44 \frac{ur}{a} \right). \quad (110)$$

Finally, using Supplementary Table **S1** in Eq. (109), we obtain

$$\mathbb{E}\{\tilde{S}_2\} \approx 8\tilde{\alpha}_2 \left(\beta \left(1 + 1.44 \frac{ur}{a} \right) - 4\beta^2 \left(1 + 0.76 \frac{ur}{a} \right) + 6\beta^3 \left(1 + 0.305 \frac{ur}{a} \right) \right) \quad (111)$$

4.2.2 computation of $\mathbb{E}\{\tilde{S}_3\}$

Because $\tilde{a}_3^1 = 64$, $\tilde{a}_3^2 = 48$ and $\tilde{a}_3^3 = 96$, we can re-write $\mathbb{E}\{\tilde{S}_3\}$ as

$$\mathbb{E}\{\tilde{S}_3\} = 64\mathbb{E}\{\tilde{S}_3^1\} + 48\mathbb{E}\{\tilde{S}_3^2\} + 96\mathbb{E}\{\tilde{S}_3^3\}, \quad (112)$$

with

$$\mathbb{E}\{\tilde{S}_3^1\} = \alpha_3 \int_{\Omega^3} \phi_0^3(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}), \quad (113)$$

$$\mathbb{E} \left\{ \tilde{S}_3^2 \right\} = \alpha_3 \int_{\Omega^3} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0^2(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}), \quad (114)$$

and

$$\mathbb{E} \left\{ \tilde{S}_3^3 \right\} = \alpha_3 \int_{\Omega^3} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}). \quad (115)$$

Accounting for Ω boundaries at leading order and using Monte-Carlo numerical approximations (see sections 2 and 3), we find that

$$\mathbb{E} \left\{ \tilde{S}_3^1 \right\} \approx 0, \quad (116)$$

$$\mathbb{E} \left\{ \tilde{S}_3^2 \right\} \approx \tilde{\alpha}_3 \left(\beta^2 \left(1 + 0.7 \frac{ur}{a} \right) - 2\beta^3 \left(1 + 0.3 \frac{ur}{a} \right) \right). \quad (117)$$

and

$$\mathbb{E} \left\{ \tilde{S}_3^3 \right\} \approx \tilde{\alpha}_3 \left(\beta^2 \left(1 - \frac{3\sqrt{3}}{4\pi} \right) + 0.47 \frac{ur}{a} - \beta^3 \left(2.17 + 0.72 \frac{ur}{a} \right) \right), \quad (118)$$

leading to

$$\mathbb{E} \left\{ \tilde{S}_3 \right\} = \tilde{\alpha}_3 \left(\beta^2 \left(104.3 + 78.7 \frac{ur}{a} \right) - \beta^3 \left(304.3 + 97.9 \frac{ur}{a} \right) \right). \quad (119)$$

4.2.3 computation of $\mathbb{E} \left\{ \tilde{S}_4 \right\}$

We decompose the computation of $\tilde{S}_4$ as follows

$$\mathbb{E} \left\{ \tilde{S}_4 \right\} = \sum_{j=1}^7 \tilde{a}_4^j \mathbb{E} \left\{ \tilde{S}_4^j \right\} \quad (120)$$

where coefficients $\tilde{a}_4^j$ are given by Eq. (105) and,

$$\mathbb{E} \left\{ \tilde{S}_4^1 \right\} = \alpha_4 \int_{\Omega^4} \phi_0^3(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (121)$$

$$\mathbb{E} \left\{ \tilde{S}_4^2 \right\} = \alpha_4 \int_{\Omega^4} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0^2(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (122)$$

$$\mathbb{E} \left\{ \tilde{S}_4^3 \right\} = \alpha_4 \int_{\Omega^4} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (123)$$

$$\mathbb{E} \left\{ \tilde{S}_4^4 \right\} = \alpha_4 \int_{\Omega^4} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (124)$$

$$\mathbb{E} \left\{ \tilde{S}_4^5 \right\} = \alpha_4 \int_{\Omega^4} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (125)$$

$$\mathbb{E} \left\{ \tilde{S}_4^6 \right\} = \alpha_4 \int_{\Omega^4} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}), \quad (126)$$

and

$$\mathbb{E} \left\{ \tilde{S}_4^7 \right\} = \alpha_4 \int_{\Omega^4} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{y}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}). \quad (127)$$

First $\int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = 0$ leading to $\mathbb{E}\{\tilde{S}_4^1\} = 0$. Then, we have $\mathbb{E}\{\tilde{S}_4^2\} = \alpha_4 (I_1 - a^2 \beta^2)^2$ leading to (see Supplementary Table **S1**),

$$\mathbb{E}\{\tilde{S}_4^2\} \approx \tilde{\alpha}_4 \left(\beta \left(1 + 0.305 \frac{ur}{a} \right) - \beta^2 \right)^2. \quad (128)$$

Expansion and numerical integration near the boundary of $\mathbb{E}\{\tilde{S}_4^3\}$, $\mathbb{E}\{\tilde{S}_4^4\}$ and $\mathbb{E}\{\tilde{S}_4^5\}$ gives $\mathbb{E}\{\tilde{S}_4^3\} \approx \mathbb{E}\{\tilde{S}_4^4\} \approx \mathbb{E}\{\tilde{S}_4^5\} \approx 0$. Conversely, expansion of $\mathbb{E}\{\tilde{S}_4^6\}$ yields

$$\begin{aligned} \mathbb{E}\{\tilde{S}_4^6\} &\approx \alpha_4 \left\{ \int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{y}, \mathbf{z}) \phi(\mathbf{z}, \mathbf{w}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}) \right. \\ &\quad \left. - 4\beta I_5 + 4\beta^2 a I_2 - a^4 \beta^4 \right\} \end{aligned} \quad (129)$$

and we are left with the computation of

$$I_6 = \int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{y}, \mathbf{z}) \phi(\mathbf{z}, \mathbf{w}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}). \quad (130)$$

First, for $\mathbf{x}$ such that $|\mathbf{x} - \partial\Omega| > 3r$, there is no boundary correction and we decompose $I_6 = I_6^{in} + I_6^{border}$ where

$$\begin{aligned} I_6^{in} &= \int_{\Omega^4} \mathbf{1}_{\{|\mathbf{x} - \partial\Omega| > 3r\}} \mathbf{1}_{\{|\mathbf{x} - \mathbf{y}| < r\}} \mathbf{1}_{\{|\mathbf{x} - \mathbf{w}| < r\}} \left\{ \mathbf{1}_{\{|\mathbf{y} - \mathbf{z}| < r\}} \mathbf{1}_{\{|\mathbf{w} - \mathbf{z}| < r\}} d\mathbf{z} \right\} d(\mathbf{x}, \mathbf{y}, \mathbf{w}) \\ &= (a - 3ur) \int_{\Omega^3} \mathbf{1}_{\{|\mathbf{x} - \mathbf{y}| < r\}} \mathbf{1}_{\{|\mathbf{x} - \mathbf{w}| < r\}} \left\{ \mathbf{1}_{\{|\mathbf{y} - \mathbf{z}| < r\}} \mathbf{1}_{\{|\mathbf{w} - \mathbf{z}| < r\}} d\mathbf{z} \right\} d\mathbf{w} d\mathbf{y}, \end{aligned} \quad (131)$$

and

$$\begin{aligned} I_6^{border} &= \frac{u}{16} \int_0^{3r} \int_{A_h} \int_{A_h} (k(h, \mathbf{y}) + k(\mathbf{y}, h)) (k(h, \mathbf{w}) + k(\mathbf{w}, h)) \\ &\quad \left\{ \mathbf{1}_{\{|\mathbf{y} - \mathbf{z}| < r\}} \mathbf{1}_{\{|\mathbf{w} - \mathbf{z}| < r\}} (k(\mathbf{y}, \mathbf{z}) + k(\mathbf{z}, \mathbf{y})) (k(\mathbf{w}, \mathbf{z}) + k(\mathbf{z}, \mathbf{w})) d\mathbf{z} \right\} d\mathbf{w} d\mathbf{y} dh. \end{aligned} \quad (132)$$

We then rewrite I_6^{in} as

$$I_6^{in} = (a - 3ur) (\pi r^2)^2 \Pr\{|\mathbf{y} - \mathbf{z}| < r \text{ and } |\mathbf{w} - \mathbf{z}| < r \text{ given that } (\mathbf{y}, \mathbf{w}) \in b(\mathbf{x}, r)\}. \quad (133)$$

Denoting $d(\mathbf{y}, \mathbf{w}) = |\mathbf{y} - \mathbf{w}|$, and $\mathbf{z}$ being uniformly distributed in Ω , we have

$$\begin{aligned} &\Pr\{|\mathbf{y} - \mathbf{z}| < r \text{ and } |\mathbf{w} - \mathbf{z}| < r \text{ given that } (\mathbf{y}, \mathbf{w}) \in b(\mathbf{x}, r)\} \\ &= \frac{1}{(\pi r^2)^2} \int_{b(\mathbf{x}, r)^2} |b(\mathbf{y}, r) \cap b(\mathbf{w}, r)| d\mathbf{y} d\mathbf{w} = \frac{1}{(\pi r^2)^2} \int_{b(\mathbf{x}, r)^2} A(d(\mathbf{y}, \mathbf{w}), r) d\mathbf{y} d\mathbf{w} \end{aligned} \quad (134)$$

where $A(d(\mathbf{y}, \mathbf{w}), r)$ is given by Eq. (69)

$$A(d(\mathbf{y}, \mathbf{w}), r) = 2r^2 \cos^{-1} \left(\frac{(d(\mathbf{y}, \mathbf{w}))}{2r} \right) - \frac{(d(\mathbf{y}, \mathbf{w}))}{2} \sqrt{4r^2 - (d(\mathbf{y}, \mathbf{w}))^2}. \quad (135)$$

$\mathbf{y}$ and $\mathbf{w}$ are uniformly distributed in $b(\mathbf{x}, r)$ and we can thus consider local polar coordinates: $\mathbf{y}(0 \leq r_{\mathbf{y}} \leq r, 0 \leq \theta_{\mathbf{y}} \leq 2\pi)$ and $\mathbf{w}(0 \leq r_{\mathbf{w}} \leq r, 0 \leq \theta_{\mathbf{w}} \leq 2\pi)$ around $\mathbf{x}(0, 0)$ leading to

$$d(\mathbf{y}, \mathbf{w}) = d(r_{\mathbf{y}}, r_{\mathbf{w}}, \Theta) = \sqrt{r_{\mathbf{y}}^2 + r_{\mathbf{w}}^2 - 2r_{\mathbf{y}}r_{\mathbf{w}}\cos(\Theta)}, \quad (136)$$

and re-write I_6^{in} as

$$I_6^{in} = (a - 3ur) 2\pi \int_{r_{\mathbf{y}}=0}^r \int_{r_{\mathbf{w}}=0}^r \int_{\Theta=0}^{2\pi} A(d(r_{\mathbf{y}}, r_{\mathbf{w}}, \Theta), t) r_{\mathbf{y}} r_{\mathbf{w}} d(r_{\mathbf{y}}, r_{\mathbf{w}}, \Theta). \quad (137)$$

Finally, a numerical integration of I_6^{in} with a finite differences scheme in $r_{\mathbf{y}}$, $r_{\mathbf{w}}$ and Θ gives

$$I_6^{in} \approx (a - 3ur)0.46(a\beta)^3. \quad (138)$$

Furthermore, we approximate numerically I_6^{border} as

$$I_6^{border} \approx 3ur(a\beta)^3 0.53 \frac{ur}{a}, \quad (139)$$

leading to

$$I_6 = I_6^{in} + I_6^{border} \approx a^4 \beta^3 \left(0.46 + 0.21 \frac{ur}{a} \right). \quad (140)$$

and using Supplementary Table **S1** in Eq. (129) we obtain

$$\mathbb{E} \left\{ \tilde{S}_4^6 \right\} \approx \tilde{\alpha}_4 \left(\beta^3 \left(0.46 + 0.21 \frac{ur}{a} \right) - \beta^4 \right). \quad (141)$$

Finally, numerical integration of $\mathbb{E} \left\{ \tilde{S}_4^7 \right\}$ gives $\mathbb{E} \left\{ \tilde{S}_4^7 \right\} \approx 0$, and reinjecting Eq. (141) and Eq. (128) in Eq. (120), we obtain

$$\mathbb{E} \left\{ \tilde{S}_4 \right\} \approx \tilde{\alpha}_4 \left(12 \left(\beta \left(1 + 0.305 \frac{ur}{a} \right) - \beta^2 \right)^2 + 48\beta^3 \left(0.46 + 0.21 \frac{ur}{a} \right) - 48\beta^4 \right), \quad (142)$$

that is

$$\mathbb{E} \left\{ \tilde{S}_4 \right\} \approx \tilde{\alpha}_4 \left(\beta^2 \left(12 + 7.32 \frac{ur}{a} + 1.116 \left(\frac{ur}{a} \right)^2 \right) + \beta^3 \left(-1.92 + 2.69 \frac{ur}{a} \right) - 36\beta^4 \right) \quad (143)$$

4.2.4 computation of $\mathbb{E} \left\{ \tilde{S}_5 \right\}$

We decompose the computation of $\mathbb{E} \left\{ \tilde{S}_5 \right\}$ as follows

$$\mathbb{E} \left\{ \tilde{S}_5 \right\} = \sum_{j=1}^6 \tilde{\alpha}_5^j \mathbb{E} \left\{ \tilde{S}_5^j \right\} \quad (144)$$

where coefficients $\tilde{\alpha}_5^j$ are given by Eq. (106) and,

$$\mathbb{E} \left\{ \tilde{S}_5^1 \right\} = \alpha_5 \int_{\Omega^5} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}), \quad (145)$$

$$\mathbb{E} \left\{ \tilde{S}_5^2 \right\} = \alpha_5 \int_{\Omega^5} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{z}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}), \quad (146)$$

$$\mathbb{E} \left\{ \tilde{S}_5^3 \right\} = \alpha_5 \int_{\Omega^5} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{x}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}), \quad (147)$$

$$\mathbb{E} \left\{ \tilde{S}_5^4 \right\} = \alpha_5 \int_{\Omega^5} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{y}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}), \quad (148)$$

$$\mathbb{E} \left\{ \tilde{S}_5^5 \right\} = \alpha_5 \int_{\Omega^5} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{w}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}), \quad (149)$$

and

$$\mathbb{E} \left\{ \tilde{S}_5^6 \right\} = \alpha_5 \int_{\Omega^5} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{y}, \mathbf{w}) \phi_0(\mathbf{z}, \mathbf{r}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}). \quad (150)$$

First $\int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = 0$ leads to $\mathbb{E} \left\{ \tilde{S}_5^1 \right\} = \mathbb{E} \left\{ \tilde{S}_5^5 \right\} = 0$. Then, we have

$$\mathbb{E} \left\{ \tilde{S}_5^2 \right\} = \alpha_5 (I_1 - a^2 \beta^2) (I_2 - a^3 \beta^2) \quad (151)$$

that is, using Supplementary Table **S1**

$$\mathbb{E} \left\{ \tilde{S}_5^2 \right\} \approx \tilde{\alpha}_5 \beta^3 \left(1 + 0.305 \frac{ur}{a} \right) 0.0066 \frac{ur}{a} \quad (152)$$

Finally, expansion and numerical integration near the boundary of $\mathbb{E} \left\{ \tilde{S}_5^3 \right\}$, $\mathbb{E} \left\{ \tilde{S}_5^4 \right\}$ and $\mathbb{E} \left\{ \tilde{S}_5^6 \right\}$ gives $\mathbb{E} \left\{ \tilde{S}_5^3 \right\} \approx \mathbb{E} \left\{ \tilde{S}_5^4 \right\} \approx \mathbb{E} \left\{ \tilde{S}_5^6 \right\} \approx 0$. leading to

$$\mathbb{E} \left\{ \tilde{S}_5 \right\} \approx \tilde{\alpha}_5^2 \mathbb{E} \left\{ \tilde{S}_5^2 \right\} \approx 48 \tilde{\alpha}_5 \beta^3 \left(1 + 0.305 \frac{ur}{a} \right) 0.0066 \frac{ur}{a}, \quad (153)$$

that is

$$\mathbb{E} \left\{ \tilde{S}_5 \right\} \approx \tilde{\alpha}_5 \beta^3 \left(0.317 \frac{ur}{a} + 0.0966 \left(\frac{ur}{a} \right)^2 \right). \quad (154)$$

4.2.5 computation of $\mathbb{E} \left\{ \tilde{S}_6 \right\}$

We decompose the computation of $\mathbb{E} \left\{ \tilde{S}_6 \right\}$ as follows

$$\mathbb{E} \left\{ \tilde{S}_6 \right\} = \sum_{j=1}^4 \tilde{a}_6^j \mathbb{E} \left\{ \tilde{S}_6^j \right\} \quad (155)$$

where coefficients $\tilde{a}_6^j$ are given by Eq. (107) and,

$$\mathbb{E} \left\{ \tilde{S}_6^1 \right\} = \alpha_6 \int_{\Omega^6} \phi_0^2(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}, \mathbf{u}), \quad (156)$$

$$\mathbb{E} \left\{ \tilde{S}_6^2 \right\} = \alpha_6 \int_{\Omega^6} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{x}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}, \mathbf{u}), \quad (157)$$

$$\mathbb{E} \left\{ \tilde{S}_6^3 \right\} = \alpha_6 \int_{\Omega^6} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{y}, \mathbf{z}) \phi_0(\mathbf{z}, \mathbf{w}) \phi_0(\mathbf{r}, \mathbf{u}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}, \mathbf{u}), \quad (158)$$

and

$$\mathbb{E} \left\{ \tilde{S}_6^4 \right\} = \alpha_6 \int_{\Omega^6} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{w}, \mathbf{r}) \phi_0(\mathbf{w}, \mathbf{u}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}, \mathbf{u}), \quad (159)$$

Because $\int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = 0$, $\mathbb{E} \left\{ \tilde{S}_6^1 \right\} = \mathbb{E} \left\{ \tilde{S}_6^2 \right\} = \mathbb{E} \left\{ \tilde{S}_6^3 \right\} = 0$, and we are thus left with the computation of $\mathbb{E} \left\{ \tilde{S}_6^4 \right\}$ that reads

$$\begin{aligned} \mathbb{E} \left\{ \tilde{S}_6^4 \right\} &= \alpha_6 \int_{\Omega^6} \phi_0(\mathbf{x}, \mathbf{y}) \phi_0(\mathbf{x}, \mathbf{z}) \phi_0(\mathbf{w}, \mathbf{r}) \phi_0(\mathbf{w}, \mathbf{u}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w}, \mathbf{r}, \mathbf{u}) \\ &= \alpha_6 (I_2 - a^3 \beta^2)^2 \approx \tilde{\alpha}_6 \beta^4 \left(0.0066 \frac{ur}{a} \right)^2. \end{aligned} \quad (160)$$

and we have that

$$\mathbb{E} \left\{ \tilde{S}_6 \right\} = \tilde{a}_6^4 \mathbb{E} \left\{ \tilde{S}_6^4 \right\} \approx \tilde{\alpha}_6 \beta^4 0.0021 \left(\frac{ur}{a} \right)^2. \quad (161)$$

4.2.6 Conclusion

Because $\int_{\Omega^2} \phi_0(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y}) = 0$, $\tilde{S}_7 = \tilde{S}_8 = 0$, and

$$\mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^4 \right\} = \frac{a^4}{(n(n-1))^4} \sum_{j=2}^6 \mathbb{E} \left\{ \tilde{S}_j \right\}. \quad (162)$$

Reinfecting expressions of $\mathbb{E} \left\{ \tilde{S}_j \right\}$, for $2 \leq j \leq 6$ (Eq. (111), (119), (143), (154) and (161)), we have

$$\begin{aligned} \mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^4 \right\} &= \frac{a^4}{(n(n-1))^3} \left(\beta \left(8 + 11.52 \frac{ur}{a} \right) \right. \\ &+ \beta^2 \left(\left(-32 + 104.3 \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2} + 12 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} \right) + \left(-24.32 + 78.7 \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2} + 7.32 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} \right) \frac{ur}{a} \right. \\ &+ \left. 1.116 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} \left(\frac{ur}{a} \right)^2 \right) \\ &+ \beta^3 \left(\left(48 - 304.3 \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2} - 1.92 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} \right) + \left(14.784 - 97.9 \frac{\tilde{\alpha}_3}{\tilde{\alpha}_2} + 2.69 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} + 0.317 \frac{\tilde{\alpha}_5}{\tilde{\alpha}_2} \right) \frac{ur}{a} \right. \\ &+ \left. \frac{\tilde{\alpha}_5}{\tilde{\alpha}_2} 0.0966 \left(\frac{ur}{a} \right)^2 \right) \\ &+ \left. \beta^4 \left(-36 \frac{\tilde{\alpha}_4}{\tilde{\alpha}_2} + 0.0021 \frac{\tilde{\alpha}_6}{\tilde{\alpha}_2} \left(\frac{ur}{a} \right)^2 \right) \right), \end{aligned} \quad (163)$$

which simplifies for $n \gg 1$ to

$$\begin{aligned} \mathbb{E} \left\{ (K(r, n) - \mathbb{E} \{K(r, n)\})^4 \right\} &= \frac{1}{\lambda^4} \left(\frac{\beta}{n^2} \left(8 + 11.52 \frac{ur}{a} \right) \right. \\ &+ \frac{\beta^2}{n} \left((104.3 + 12n) + (78.7 + 7.32n) \frac{ur}{a} + 1.116n \left(\frac{ur}{a} \right)^2 \right) \\ &+ \frac{\beta^3}{n} \left((-304.3 - 1.92n) + (-97.9 + 2.69n + 0.317n^2) \frac{ur}{a} + n^2 0.0966 \left(\frac{ur}{a} \right)^2 \right) \\ &+ \left. \beta^4 \left(-36 + 0.0021n^2 \left(\frac{ur}{a} \right)^2 \right) \right). \end{aligned} \quad (164)$$

5 Computation of $\gamma \left(\tilde{K}_M(r) \right)$ and $\kappa \left(\tilde{K}_M(r) \right)$

We defined in the main manuscript the mean statistic

$$\tilde{K}_M(r) = \frac{1}{M} \sum_{j=1}^M \tilde{K}^j(r, n_j) \quad (165)$$

where $\tilde{K}^j(r, n_j)$ is the modified Ripley's K function that is evaluated on the j^{th} field of view. Thus,

$$\gamma \left(\tilde{K}_M(r) \right) = \frac{\mathbb{E} \left\{ \left(\frac{1}{M} \sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^3 \right\}}{\left(\text{var} \left\{ \frac{1}{M} \sum_{j=1}^M \tilde{K}^j(r, n_j) \right\} \right)^{\frac{3}{2}}}. \quad (166)$$

For $i \neq j$, $\tilde{K}^j$ is independent of $\tilde{K}^i$ and for all $1 \leq j \leq M$, $\text{var} \left\{ \tilde{K}^j(r, n_j) \right\} = 1$, thus,

$$\text{var} \left\{ \frac{1}{M} \sum_{j=1}^M \tilde{K}^j(r, n_j) \right\} = \frac{1}{M^2} \sum_{j=1}^M \text{var} \left\{ \tilde{K}^j(r, n_j) \right\} = \frac{1}{M}, \quad (167)$$

and we rewrite

$$\gamma\left(\tilde{K}_M(r)\right) = \frac{1}{M^{\frac{3}{2}}} \mathbb{E} \left\{ \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^3 \right\} \quad (168)$$

Then, we decompose

$$\begin{aligned} & \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^3 = \sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^3 \\ & + 3 \sum_{j \neq i} \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^2 \left(\tilde{K}^i(r, n_j) - \pi r^2 \right) \\ & + 6 \sum_{j \neq i \neq k} \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \left(\tilde{K}^i(r, n_j) - \pi r^2 \right) \left(\tilde{K}^k(r, n_j) - \pi r^2 \right), \end{aligned} \quad (169)$$

and because $\mathbb{E} \left\{ \tilde{K}^j(r, n_j) - \pi r^2 \right\} = 0$, we have

$$\mathbb{E} \left\{ \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^3 \right\} = \sum_{j=1}^M \mathbb{E} \left\{ \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^3 \right\}, \quad (170)$$

that is

$$\mathbb{E} \left\{ \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^3 \right\} = \sum_{j=1}^M \gamma \left(\tilde{K}^j(r, n_j) \right), \quad (171)$$

which leads to

$$\gamma \left(\tilde{K}_M(r) \right) = \frac{1}{M^{\frac{3}{2}}} \sum_{j=1}^M \gamma \left(\tilde{K}^j(r, n_j) \right). \quad (172)$$

Similarly, we have

$$\kappa \left(\tilde{K}_M(r) \right) = \frac{1}{M^2} \mathbb{E} \left\{ \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^4 \right\}, \quad (173)$$

and we decompose

$$\begin{aligned} & \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^4 = \sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^4 \\ & + 4 \sum_{j \neq i} \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^3 \left(\tilde{K}^i(r, n_j) - \pi r^2 \right) \\ & + 3 \sum_{j \neq i} \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^2 \left(\tilde{K}^i(r, n_j) - \pi r^2 \right)^2 \\ & + 6 \sum_{j \neq i \neq k} \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^2 \left(\tilde{K}^i(r, n_j) - \pi r^2 \right) \left(\tilde{K}^k(r, n_j) - \pi r^2 \right) \\ & + 24 \sum_{j \neq i \neq k \neq l} \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \left(\tilde{K}^i(r, n_j) - \pi r^2 \right) \left(\tilde{K}^k(r, n_j) - \pi r^2 \right) \left(\tilde{K}^l(r, n_j) - \pi r^2 \right) \end{aligned} \quad (174)$$

which leads to

$$\begin{aligned} & \mathbb{E} \left\{ \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^4 \right\} = \sum_{j=1}^M \mathbb{E} \left\{ \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^4 \right\} \\ & + 3 \sum_{j \neq i} \mathbb{E} \left\{ \left(\tilde{K}^j(r, n_j) - \pi r^2 \right)^2 \right\} \mathbb{E} \left\{ \left(\tilde{K}^i(r, n_i) - \pi r^2 \right)^2 \right\}, \end{aligned} \quad (175)$$

that is

$$\mathbb{E} \left\{ \left(\sum_{j=1}^M \left(\tilde{K}^j(r, n_j) - \pi r^2 \right) \right)^4 \right\} = \sum_{j=1}^M \kappa \left(\tilde{K}^j(r, n_j) \right) + 3M(M-1). \quad (176)$$

Reinjecting Eq. 176 in Eq. 173, we obtain

$$\kappa \left(\tilde{K}_M(r) \right) = \frac{1}{M^2} \sum_{j=1}^M \kappa \left(\tilde{K}^j(r, n_j) \right) + 3 \frac{M-1}{M}. \quad (177)$$

Table S1: Numerical approximations of major integrals

Denotation	Formula	Numerical approximation
I_0	$\int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y})$	$a^2 \beta$
I_1	$\int_{\Omega^2} \phi(\mathbf{x}, \mathbf{y})^2 d(\mathbf{x}, \mathbf{y})$	$a^2 \beta \left(1 + 0.305 \frac{ur}{a}\right)$
I_2	$\int_{\Omega^3} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z})$	$a^3 \beta^2 \left(1 + 0.0066 \frac{ur}{a}\right)$
I_3	$\int_{\Omega^2} \phi^3(\mathbf{x}, \mathbf{y}) d(\mathbf{x}, \mathbf{y})$	$a^2 \beta \left(1 + 0.76 \frac{ur}{a}\right)$
I_4	$\int_{\Omega^3} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{x}, \mathbf{z}) \phi(\mathbf{y}, \mathbf{z}) d(\mathbf{x}, \mathbf{y}, \mathbf{z})$	$a^3 \beta^2 \left(1 - \frac{3\sqrt{3}}{4\pi} + 0.207 \frac{ur}{a}\right)$
I_5	$\int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{y}, \mathbf{z}) \phi(\mathbf{z}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w})$	$a^4 \beta^3 \left(1 + 1.0051 \frac{ur}{a}\right)$
I_6	$\int_{\Omega^4} \phi(\mathbf{x}, \mathbf{y}) \phi(\mathbf{y}, \mathbf{z}) \phi(\mathbf{z}, \mathbf{w}) \phi(\mathbf{x}, \mathbf{w}) d(\mathbf{x}, \mathbf{y}, \mathbf{z}, \mathbf{w})$	$a^4 \beta^3 \left(0.46 + 0.21 \frac{ur}{a}\right)$

References

- [1] Ripley B (1988) Statistical inference for spatial processes. Cambridge University Press.
- [2] Getis A, Franklin J (1987) Second-order neighborhood analysis of mapped point patterns. Ecology 68: 473-477.
- [3] Weisstein E. URL <http://mathworld.wolfram.com/Circle-CircleIntersection.html>.
- [4] de Chaumont F, Dallongeville S, Chenouard N, Hervé N, Pop S, et al. (2012) Icy: an open bioimage informatics platform for extended reproducible research. Nat Methods 9: 690-6.
- [5] Olivo-Marin JC (2002) Extraction of spots in biological images using multiscale products. Pattern Recognition 35: 1989-1996.