

Article

# Propositions for Confidence Interval in Systematic Sampling on Real Line

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**Abstract:** Systematic sampling on real line ( $\mathbb{R}$ ) when using the different probes is very attractive method within which the biomedical imaging is consulted by a surgery, etc. This study is an extension of [16], and an exact calculation method is proposed for the calculation of constant  $\lambda_q$  of confidence interval for the systematic sampling. If the smoothness constant  $q$  of measurement function ( $MF$ ) is estimated to be enough small mean square error, we can make the important remarks for the design-based stereology. The  $MF$  is occurred by slicing the three dimensional object systematically. The systematic design is used as a method to get the quantitative results from the tissues and the radiological images. Synthetic data in systematic sampling principle can support the results of real data. The currently used covariogram model proposed by [28] is tested for the different measurement functions to see the performance on the variance estimation. The exact value of constant  $\lambda_q$  is examined for the different measurement functions as well.

**Keywords:** biomedical imaging; covariogram; design-based stereology; estimation of volume; systematic sampling

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## 1. Introduction

The important improvements in non-invasive scanning techniques, such as X-ray, computed tomography, magnetic resonance known as medical imaging tools, support to explore and apply the stereological methods. Magnetic resonance imaging is an important tool for the imaging of human body. The main aim at imaging of human body is to understand deeply the structure, function, life cycle and diagnosis of a disease, an evaluation of treatment. Making a right decision is an important step for these reasons given above. A researcher wants to estimate not only the variance of systematic sampling but also construct the confidence interval of volume parameter  $Q$  in order to check whether a tumor, cerebral hemorrhage, etc have exceeded a specific threshold.

The systematic sampling is used as a design-based approach for estimating a parameter  $Q$  of a geometrical quantities, such as volume, area, surface area, length [13,16,17,23,31]. In systematic sampling principle, stereological objects are sampled with probes, such as lines, regular grid, or designed patterns. The probes superimposed on the stereological objects are tools for us to get the quantitative values of geometrical quantities. The chosen design is an important step to have unbiased estimates for the geometrical quantities. The regular systematic sampling design is used at most of time, because it is widely accepted design for estimating the parameter  $Q$ . From the statistics, we know that if we have a sampling on parameter  $Q$ , we will have the estimated values for this parameter for each replication of sampling. It is surprisingly nice that the estimated values of each replication for the sampling on the geometrical objects produce a fluctuation. This fluctuation is modelled by Fourier transformation technique proposed by [27,28]. To show the mathematical discussion of the Matheron's theory, a brief introduction is expressed by Section 2. Since we have the estimated values, the variance estimation is needed. For the one-dimensional systematic sampling (also known as Cavalieri sampling), previous studies have shed some light on the variance estimation of the one-dimensional systematic sampling, such as [8,15,18,19,24–26,29]. Main source in these studies is of inspiration in Matheron's theory. Matheron proposed his covariogram model intuitively. In this study, we aim to focus on testing the performance of this covariogram model for the different

measurement functions proposed arbitrary by us. No study has been addressed the performance evaluation of the covariogram model for the different measurement functions.

As implied by the previous paragraph, we have the estimated values for the parameter  $Q$ . The variance estimation has been tried to accomplish, however the confidence interval for the estimated values was studied by [16]. [16] proposes two approaches for the coefficient of confidence interval in the statistical inference. The first one is based on the statistical theory. In this study, the second proposition of [16] is examined and our aim is to find a calculation method for the constant  $\lambda_q$  given in [16]. It is nicely said that an exact calculation method to evaluate the constant  $\lambda_q$  is considered, so we will have more accurate information for the confidence intervals. We will test the performance of the covariogram model for the different measurement functions at same time for our exact values of the constant  $\lambda_q$ , because the direction of the sampling axis produces the different measurements function, depending on the the shape of 3-dimensional objects, such as ellipsoidal, quasi-ellipsoidal, star-like, etc, as implied by [16].

The true variance, the empirical true variance, the variance approximation, and the confidence interval for systematic sampling on  $\mathbb{R}$  with variance approximation formula are introduced briefly, because some tools will be used to evaluate the exact value of the constant  $\lambda_q$ . The connection between measurement function approach done by [15] and Matheron's transitive theory based on the Fourier transform is given in [15]. In this study, tools will be used and we introduce briefly the results of these two approach, finally, a proposition is offered to find  $\lambda_q$  exactly.

Since the true measurement function is not known, we do not get the true variance of systematic sampling on  $\mathbb{R}$ . The variance approximation known as a variance extension term is given in the two forms coming from Fourier transformation basically given in [8] and the properties of measurement functions. Some definitions expressed in [15] and [16] will be given to get the values of constant  $\lambda_q$  in the section of confidence interval. As a conclusion, we attempt to give a proposition for the confidence interval and the suggestions for researchers who work the application field of design-based stereology and biomedical imaging.

The organization of the paper is the following form. Section 2 introduces the materials in the systematic sampling and describes the exact calculation method for constant  $\lambda_q$  as well. A simulation study and real data examples are given at Section 3. A section 4 is considered for the discussions on results.

## 2. Materials and Methods

### 2.1. Exact and Empirical Variance of Systematic Sampling on $\mathbb{R}$ and its Approximation

The object which will be estimated is a volume parameter  $Q$  of a fixed, bounded, nonvoid with piecewise smooth boundary of finite surface area  $Q_S$ , except fractals. Volume estimation with Cavalieri planes called the measurement function  $f$  is also known as the systematic sampling on  $\mathbb{R}$ ,

$$\hat{Q} = T \sum_{j=0}^{n-1} f((\mathbf{u} + j)T). \quad (1)$$

$T$  is a constant distance among the sections obtained from three-dimensional object.  $\mathbf{u}$  is an uniform random variable in the interval  $[0, T)$ .

The problem is about predicting  $Var(\hat{Q}) = \mathbb{E}(\hat{Q} - Q)^2 = \mathbb{E}(\hat{Q}^2) - Q^2$ . Since the uniform distribution defined at  $[0, T)$  is used,  $\mathbb{E}(\hat{Q}^2) = 1/T \int_0^T \hat{Q}(u)^2 du$ .

The empirical true variance of systematic sampling on  $\mathbb{R}$  is calculated by the formula given below,

$$Var(\hat{Q}) = \frac{1}{m} \sum_{r=1}^m (\hat{Q}_r - Q)^2, \quad (2)$$

where  $m$  is the number of resampling for the systematic sampling on  $\mathbb{R}$ .  $\hat{Q}_r$  is an estimated value at a random starting point for  $u$  for the volume.  $Q$  is the exact value for the area under the measurement function.  $\hat{Q}$  is the estimator of  $Q$  [6,7,32].

The empirical true variance of systematic sampling on  $\mathbb{R}$  is

$$CE^2(\hat{Q}) = Var(\hat{Q}/Q). \quad (3)$$

The empirical true coefficient of error is calculated by

$$CE(\hat{Q}) = \sqrt{Var(\hat{Q})/Q^2}. \quad (4)$$

In the simulation section, Eq. (4) is used to test the performance of variance approximation formula in Eq. (23). The true variance is calculated by a formula given below. A calculation of the true variance by means of Eq. (5) is intractable (see [8] for more details).

$$Var(\hat{Q}) = T \sum_{k=-\infty}^{\infty} g(kT) - \int_{-\infty}^{\infty} g(h)dh, \quad (5)$$

where

$$g(h) = \int_{\mathbb{R}} f(x) \cdot f(x+h)dx, h \in \mathbb{R} \quad (6)$$

$g(h)$  is a covariogram function of the measurement function  $f$ . It is proposed by Matheron's transitive theory and is known to be convolution of  $f$  with its reflection,  $G(t) = \mathcal{F}_1 g = (\mathcal{F}_1 f)(\mathcal{F}_1 f)$ ,  $\mathcal{F}_1$  expresses Fourier transform defined as

$$G(t) = \mathcal{F}_1 g(h) = \int_{-\infty}^{\infty} g(h)exp(-2\pi i t h)dh. \quad (7)$$

Some measurement functions are used to represent the biological objects very efficiently. They are given with following forms and the function  $f$  has positive values for each values of variable  $x$ , namely  $f : \mathbb{R} \rightarrow \mathbb{R}^+$ ,  $q$  is a smoothness constant.

$$f(x) = (1 - x^2)^q, x \in [-1, 1], q \in [0, 1], \quad (8)$$

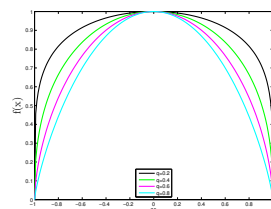
$$f(x) = ((1 - \cos(x))(1 - x^2))^q, x \in [-1, 1], q \in [0, 1], \quad (9)$$

and

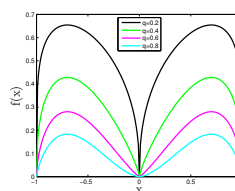
$$f(x) = exp(-sin(-x^3)), x \in [-38\pi/100, 53\pi/100] \quad (10)$$

$$f(x) = (5/112)(-54x^4 - 25x^3 + 48x^2 + 25x + 6), x \in [-1, 1] \quad (11)$$

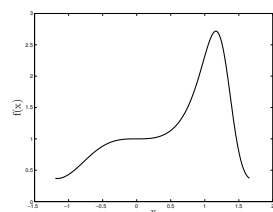
They represent the area measured on an each slices of the three dimensional object. The measurement functions in Eqs. (8) and (11) are used by [15,21].



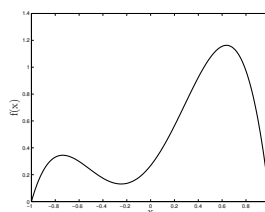
(a) MF of Eq. 8



(b) MF of Eq. (9)



(a) MF of Eq. (10)



(b) MF of Eq. (11)

Since the covariogram function  $g$  of measurement functions which represents the biological objects, etc. can not be calculable to get the integral values, a model for the covariogram function of them should be proposed. In this sense,  $g$  can be modelled by a polynomial with the fractional power,

$$g(h) = b_0 + b_j|h|^j + b_2h^2, \quad j = 2q + 1, \quad q \in \mathbb{R}. \quad (12)$$

Eq. (12) is defined to be a covariogram model.

The true variance comprises from three components which are the variance extension term, Zitterbewegung and the higher-order terms, respectively. These terms were gotten in García-Fiñana & Cruz-Orive [15] (see section 6 for detailed expressions).

Now since  $g$  is the convolution of  $f$  with its reflection,  $G(t) = \mathcal{F}_1g = (\mathcal{F}_1f)(\bar{\mathcal{F}}_1f)$ , so we finally get

$$\begin{aligned} \text{Var}(\hat{Q}(u)) &= T^{-1} \int_0^T \hat{Q}(u)^2 du - Q^2 \\ &= \sum_{k=-\infty}^{\infty} G(k/T) - G(0) \\ &= 2 \sum_{k=1}^{\infty} G(k/T) \end{aligned} \quad (13)$$

where  $G(0)$  comes from the properties of covariogram function (Detailed expressions are given in [8]).

The variance extension term of systematic sampling on  $\mathbb{R}$  is obtained by using the formula given in Eq. (9.1) and Eq. (9.2) in the study of Cruz-Orive [8] as follow,

$$\begin{aligned} \mathcal{F}_1h^j &= b(j,1)q^{-(j+1)}, \quad (j > -1, \text{non-even}) \\ b(j,1) &= \frac{\pi^{-j-1/2} \Gamma(\frac{j+1}{2})}{\Gamma(-\frac{j}{2})} \end{aligned} \quad (14)$$

which is the Fourier transformation of  $h^j$ .

By using Eq. (13) and Eq. (14), Eq. (15) can be found.

$$\begin{aligned} \text{Var}_E(\hat{Q}) &= 2b_j b(j,1) T^{j+1} \zeta(j+1) \\ \text{Var}_E(\hat{Q}) &= \alpha(q)(3g(0) - 4g(T) + g(2T)) \\ \text{Var}_E(\hat{Q}) &= \alpha(q)(3C_0 - 4C_1 + C_2) T^2 \end{aligned} \quad (15)$$

where

$$\alpha(q) = \frac{2\pi^{-(2q+3/2)}\Gamma(q+1)\zeta(2q+2)}{(2^{2q+1}-4)\Gamma(-\frac{2q+1}{2})}, \quad q \in \mathbb{R} \quad (16)$$

$$\hat{g}(kT) = TC_k \quad (17)$$

Eq. (16) is gotten according to Fourier transformation basically given in [8].

$$\alpha(q) = \frac{\Gamma(2q+2)\zeta(2q+2)\cos(q\pi)}{(2\pi)^{2q+2}(1-2^{2q-1})}, \quad q \in \mathbb{R} \quad (18)$$

$$\text{Var}_E(\hat{Q}) = \frac{2\pi^{-(2q+3/2)}\Gamma(q+1)\zeta(2q+2)}{(2^{2q+1}-4)\Gamma(-\frac{2q+1}{2})}(3C_0-4C_1+C_2)T^2 \quad (19)$$

Eq. (18) is found according to the refined Euler Mac-Laurin which can be used to approximate integrals by finite sums. It is given in [15]. Note that Eq. (16) and Eq. (18) give same results.

### 2.1.1. The Formula of Smoothness Constant $q$

The formula of smoothness constant  $q$  is proposed by [15]. In the subsection, we will get it in the framework of Fourier transformation. The same formula for  $q$  is obtained. The covariogram model  $g$  can be declared by integer  $k$  values. If  $h = iT$  is near zero, Eq. (7) has more information. By using Eq. (15),

$$g(iT) = b_0 + b_{2q+1}(|iT|)^{2q+1} + b_2(iT)^2, \quad i = 0, k, 2k,$$

$$\text{Var}_E(\hat{Q}) = 2b_{2q+1}b(2q+1,1)T^{2q+2}\zeta(2q+2) \quad (20)$$

$$\begin{aligned} \text{Var}_E(\hat{Q}) &= 2\pi^{-(2q+3/2)} \frac{\Gamma(q+1)}{\Gamma(-\frac{2q+1}{2})} \zeta(2q+2) \\ &\quad \frac{T \cdot 3g(0) - 4g(kT) + g(2kT)}{k^{2q+1}(2^{2q+1}-4)} \end{aligned}$$

can be obtained. By using Eq. (19) and Eq. (20),

$$\frac{1}{k^{2q+1}} \cdot [3g(0) - 4g(kT) + g(2kT)] = [3g(0) - 4g(T) + g(2T)] \quad (21)$$

is obtained and then

$$\begin{aligned} k^{2q+1} &= \frac{3g(0) - 4g(kT) + g(2kT)}{3g(0) - 4g(T) + g(2T)} \\ q &= \frac{1}{2\log(k)} \cdot \log\left(\frac{3g(0) - 4g(kT) + g(2kT)}{3g(0) - 4g(T) + g(2T)}\right) - \frac{1}{2}, \end{aligned}$$

where,  $k = 2, 3, \dots$

can be obtained. By using Eq. (17),

$$\hat{q} = \frac{1}{2\log(k)} \cdot \log\left(\frac{3C_0 - 4C_k + C_{2k}}{3C_0 - 4C_1 + C_2}\right) - \frac{1}{2}, \quad k = 2, 3, \dots \quad (22)$$

the estimator  $\hat{q}$  is gotten when the measurement function is obtained by planimetry.

We calculate the estimated coefficient of error for the systematic sampling on  $\mathbb{R}$  by means of Eq. (23) given below,

$$\begin{aligned} \text{var}_E(\hat{Q})/Q^2 &= \alpha(q)(3C_0 - 4C_1 + C_2)T^2/Q^2 \\ \hat{c}e(\hat{Q}) &= \sqrt{\alpha(q)(3C_0 - 4C_1 + C_2)} \left(\sum_{i=1}^n f_i\right)^{-1} \end{aligned} \quad (23)$$

where

$$C_k = \sum_{i=1}^{n-k} f_i \cdot f_{i+k}, \quad k = 0, 1, \dots, n-1. \quad (24)$$

This is defined to be a coefficient of error of Matheron's covariogram model. Eq. (6) and Eq.(24) have in fact inheritance.  $n \geq 2k + 1$  observations are required due to Eq. (24) [8–10, 14,15,28]. The estimation values of smoothness constant from exact  $(1 - x^2)^q$ ,  $((1 - \cos(x))(1 - x^2))^q$ ,  $\exp(-\sin(-x^3))$  and  $(5/112)(-54x^4 - 25x^3 + 48x^2 + 25x + 6)$  measurement functions will be obtained at the simulation section. [2–5,17,19,20,22,23,30,32–35] currently used this model for the different measurement functions. We aim to show the performance of the covariogram model for the different measurement functions. In other words, the capability of fitting performance on the different measurement functions is tested, so the information gained is displayed by the simulation results. The simulation results for the estimation of the smoothness constant formula is given into appendix section.

## 2.2. Confidence Interval in Systematic Sampling on $\mathbb{R}$

The variance of Cavalieri sampling changes with a fractional power of  $T$  [15,16]. It is given that the behavior of the variance of the Cavalieri estimator is strongly connected to analytical properties of the measurement function  $f$ . An aspect coming from Matheron's transitive theory is given in [8]. That there is a fractional power for  $T$  is not pointed out by [25,26]. [15] is an extension of [25].

We will give an exact calculation of  $\lambda_q$  found in a generalized version of the refined Euler Mac-Laurin summation formula with a fractional power of measurement functions to be smoothness constant  $q$ . A brief introduction, and some definitions will be given for the smoothness conditions of measurement function  $f$  to get the formulae of  $\lambda_q$  for confidence interval.

A bounded interval for the difference  $(\hat{Q} - Q)$  defined a generalized version of the refined Euler Mac-Laurin summation formula is

$$|\hat{Q} - Q| \leq T^{q+1} P_{q+1}^* \sum_{i=1}^N |Sf^{(q)}(a_i)| \quad (25)$$

where

$$P_{q+1}^* = \max_{\{\Delta, \beta\}} \left\{ \left| \frac{-2}{(2\pi)^{q+1}} \sum_{j=1}^{\infty} \frac{1}{j^{q+1}} \cos(2\pi\Delta j - \frac{\pi}{2}(q+1) + \beta) \right| \right\}, \quad (26)$$

$\Delta \in [0, 1)$  and  $\beta \in [0, 2\pi]$  (For detailed expressions, see [16]).

The preliminaries were given. Now, we will use the tools in [16]. After some straightforward calculation, the formula of  $\lambda_q$  will be obtained in the following steps.

By means of Cauchy Schwarz inequality  $(\sum_{i=1}^N |x_i|)^2 \leq N \sum_{i=1}^N x_i^2$ , where  $x_i = Sf^{(q)}(a_i)$ ,

$$\left( \sum_{i=1}^N |Sf^{(q)}(a_i)| \right)^2 \leq N \sum_{i=1}^N (Sf^{(q)}(a_i))^2. \quad (27)$$

When Eq. (25) and Eq. (27) are used,

$$\begin{aligned} \frac{|\hat{Q} - Q|}{T^{q+1}P_{q+1}^*} &\leq \sum_{i=1}^N |Sf^{(q)}(a_i)| \\ |\hat{Q} - Q| &\leq T^{q+1}P_{q+1}^* \sqrt{N} \sqrt{\sum_{i=1}^N (Sf^{(q)}(a_i))^2} \end{aligned} \quad (28)$$

is obtained.

Eq.(29) given in [15] is

$$\text{Var}_E(\hat{Q}) = T^{2q+2} \frac{P_{2q+2,T}(0)}{\cos(\pi q)} \sum_{i=1}^N (Sf^{(q)}(a_i))^2 \quad (29)$$

When  $\sum_{i=1}^N (Sf^{(q)}(a_i))^2$  in Eq. (29) is written in the Eq. (28), Eq. (30) is obtained.

$$\begin{aligned} |\hat{Q} - Q| &\leq P_{q+1}^* \sqrt{N} \sqrt{\frac{\cos(\pi q)}{P_{2q+2,T}(0)}} \sqrt{\text{Var}_E(\hat{Q})}, \\ |\hat{Q} - Q| &\leq \lambda_q \sqrt{\text{Var}_E(\hat{Q})}, \end{aligned} \quad (30)$$

where

$$\lambda_q = P_{q+1}^* \sqrt{N} \sqrt{\frac{\cos(\pi q)}{P_{2q+2,T}(0)}}, \quad q \in \mathbb{R} \quad (31)$$

$\lambda_q$  is a function of  $q$  and  $N$ . In the following steps, we will give a definition for the function  $P_{k,T}$  in [1]. The function  $P_{q+1}^*$  is required to apply Theorem 2.1.

From Eq. (30), for true parameter  $Q$  a bounded interval (or 100% confidence interval) is given as [15,16]

$$\left( \hat{Q} - \lambda_q \sqrt{\text{Var}_E(\hat{Q})}, \hat{Q} + \lambda_q \sqrt{\text{Var}_E(\hat{Q})} \right) \quad (32)$$

The equations to get the values of constant  $\lambda_q$  are given below [1,15],

$$P_{k,T}(x) = P_k \left( \frac{x}{T} - \left[ \frac{x}{T} \right] \right) = \frac{-2}{(2\pi)^k} \sum_{j=1}^{\infty} \frac{\cos(2\pi j(x/T) - (1/2)\pi k)}{j^k}, \quad (33)$$

where  $x \in \mathbb{R}$ ,  $k = 2, 3, \dots$

From Eq.(33),  $P_{2q+2,T}(0)$  is obtained,

$$\begin{aligned} P_{2q+2,T}(0) &= \frac{-2}{(2\pi)^{2q+2}} \sum_{j=1}^{\infty} \frac{\cos(2\pi j(0/T) - (1/2)\pi(2q+2))}{j^{2q+2}} \\ P_{2q+2,T}(0) &= \frac{2}{(2\pi)^{2q+2}} \zeta(2q+2) \cos(\pi q). \end{aligned}$$

We will give the following theorem to get the values  $P_{q+1}^*$  exactly.

**Theorem 2.1.** 1. Supposing that we have a right-open side interval  $[a, b)$ , the maximum value of the interval is

$$\lim_{h \rightarrow 0} (b - h) = \lim_{h \rightarrow \infty} (b - 1/h)$$

2. Supposing that we have a left-open side interval  $(a, b]$ , the maximum value of the interval is

$$\lim_{h \rightarrow 0} (a + h) = \lim_{h \rightarrow \infty} (a + 1/h)$$

3. Supposing that we have the left-open side and right-open side interval  $(a, b)$ , the maximum value of the interval is

$$\lim_{h \rightarrow 0} (a + h) = \lim_{h \rightarrow \infty} (a + 1/h)$$

$$\lim_{h \rightarrow 0} (b - h) = \lim_{h \rightarrow \infty} (b - 1/h)$$

In order to calculate  $P_{q+1}^*$  exactly,  $\Delta$  is replaced with  $1 - h$ . When  $h \rightarrow 0$ , we get the result:

$$P_{q+1}^* = \lim_{h \rightarrow 0} \left| \frac{-2}{(2\pi)^{q+1}} \sum_{j=1}^{\infty} \frac{1}{j^{q+1}} \cos(2\pi(1-h)j - \frac{\pi}{2}(q+1) + 2\pi) \right| \quad (34)$$

Now we can explain how to get the values of constant  $\lambda_q$  below.

When  $N$  and  $P_{2q+2,T}(0)$  given in the Eq. (31) are replaced with 2 and the Eq. (34), respectively, we get an equation,

$$\lambda_q = P_{q+1}^* \cdot \sqrt{2} \cdot \sqrt{\frac{(2\pi)^{2q+2}}{2\zeta(2q+2)}} \quad (35)$$

The codes written in Mathematica 7 or higher versions 8 and 9 do not compute the value of  $\lambda_0$  and gives infinity. So, for the calculation of  $q = 0$ , we use Eq. (36) in order to get the result.

By means of Eq. (35), we get  $\lambda_0$ :

$$P_{q+1}^* = \lim_{h \rightarrow 0} \left| \frac{-2}{(2\pi)} \sum_{j=1}^{\infty} \frac{1}{j} \cos(2\pi(1-h)j + \frac{3\pi}{2}) \right| = 1/2 \quad (36)$$

$$\lambda_0 = \frac{1}{2} \cdot \sqrt{\frac{(2\pi)^2}{\zeta(2)}} = 2.44949$$

For  $q = 0.1$ ,

$$\begin{aligned} \lambda_{0.1} &= \lim_{h \rightarrow 0} \left| \frac{-2}{(2\pi)^{0.1+1}} \sum_{j=1}^{\infty} \frac{1}{j^{0.1+1}} \cos(2\pi(1-h)j \right. \\ &\quad \left. - \frac{\pi}{2}(0.1+1) + 2\pi) \right| \cdot \sqrt{\frac{(2\pi)^{2.2}}{\zeta(2.2)}} \\ &= 2.71243 \end{aligned} \quad (37)$$

is gotten. For other  $q$  values, similar procedure is proceeded. By using the formula given in Eq. (31), the values at Table 1 are obtained for  $N = 2, N = 3$  and  $N = 4$  [12].

It is attested that  $\lim_{h \rightarrow \infty} (1 - 1/h)$  and  $\lim_{h \rightarrow 0} (1 - h)$  give the same values for  $\lambda_q$ , which is used to define the right-open side interval.

Moreover, in order to construct the confidence interval,

$$\hat{Q} - \lambda_q \cdot \hat{c}e(\hat{Q}) \cdot \hat{Q} \leq Q \leq \hat{Q} + \lambda_q \cdot \hat{c}e(\hat{Q}) \cdot \hat{Q} \quad (38)$$



**Table 1.**  $q$  and its exact  $\lambda_q$  values for different  $N$  values

$q$	$\lambda_q (N = 2)$	$\lambda_q (N = 3)$	$\lambda_q (N = 4)$
0	2.44949	-	-
0.1	2.71243	3.32203	3.83595
0.2	2.93821	3.59855	4.15525
0.3	3.12464	3.82689	4.41891
0.4	3.26925	4.004	4.62342
0.5	3.36968	4.12699	4.76544
0.6	3.42394	4.19345	4.84218
0.7	3.43064	4.20165	4.85165
0.8	3.38906	4.15073	4.79285
0.9	3.29929	4.04079	4.6659
1	3.16228	3.87298	4.47214

**Table 2.**  $q$  and its computational  $\lambda_q$  values for  $N = 2$ 

$q$	$\lambda_q (Seq_1)$	$\lambda_q (Seq_2)$	$\lambda_q (Seq_3)$	$\lambda_q (Seq_4)$
0	2.402871	2.418465	-	-
0.1	2.671264	-	-	-
0.2	2.89612	-	-	2.926749
0.3	3.07818	3.105091	3.111937	3.114245
0.4	3.216635	-	-	3.258353
0.51	3.323898	-	-	3.365038
0.6	3.397839	3.408876	3.412577	3.414001
0.7	3.418973	-	-	3.426855
0.8	3.383912	-	3.38736	3.387638
0.9	3.297052	3.29831	3.298648	3.298765
1	3.161317	-	-	-

are used, where  $\lambda_q$  is the confidence interval coefficient.  $\hat{c}e$  is an estimated coefficient of error [14,16,17].

We got the values of  $\lambda_q$  for different  $q$  values by using the exact calculation approach calculated via the Mathematica 7 or higher versions 8 and 9. One can get the values of constant  $\lambda_q$  for the different  $q$  values with  $N = 2$ ,  $N = 3$ , and  $N = 4$ .

When the number of sequence in codes revised is increased, the computational values convergence the values calculated by the exact approach (see Table 1 and Table 2). Because the getting of computational  $\lambda_q$  values for  $N = 2$  would be unlikely to be useful, we give up computing some of them.  $Seq_i$ : The number of sequence increased by an user,  $i : 1, 2, 3, 4$ .

### 3. Results

This section will give the simulation results for the estimation of smoothness constant  $q$  in variance formulae in Eq. (23). Together with the estimated  $q$  with  $k = 2$ , it is planned to see whether or not the confidence interval includes the true volume value for the approximate variance based on Matheron's covariogram model (CEMC) and empirical true variance (ETCE) estimations as well. Real data examples are given to test the performance of confidence interval.

#### 3.1. Simulation

In the simulation performed, the number of resampling is 3000 and the number of systematic sampling on  $\mathbb{R}$  is 20 for the measurement functions in Eqs. (8)-(11).

As implied by p.31 into [8], it is obvious the changing of measurement function affects the variance extension term given in Eq. (15), which leads to confidence level is more accurate. The covariogram model in Eq. (12) can be adopted for the general measurement functions. The simulation results in Tables 5 – 16 show that the model can be used for the measurement functions given in Eqs. (8)- (11) even if they are not the true covariogram function of them. It can be said that the model is a good approximation for the covariogram functions of the measurement functions. Note that the integral of function in Eq. (9) is computed by means of the numerical integration with in MATLAB 2013a, but the integral of function in Eq. (8), (10) and (11) are computed by means of the 'int' function which is a function for the exact calculation of integral in MATLAB 2013a.  $N$  in  $\lambda_q$  is taken to be 2.

It is interesting that the covariogram model in Eq. (12) is proposed and it can be a good approximation for the covariogram function of  $f$  in Eqs. (8) - (11). We want to use it to be able to check the performance of covariogram model in Eq. (12). The estimation of  $q$  can be said an open problem for the the measurement functions in Eqs. (8)- (11). It is observed from the simulation results that the performance of the smoothness constant  $q$  formula depends on the covariogram model in Eq. (12), proposed by [27,28].

It is seen that Eqs. (10) and (11) does not have the smoothness constant  $q$  parameter, but we want to estimate it to get the values of variance estimation precisely for the measurement functions without parameter  $q$ . The true parameter values are accepted to be  $q = 0.95, q = 0.9$ , respectively, because the estimated values of  $q$  parameter is around those values.

The theoretical percentage was 100. In this sense, the confidence interval includes the true volume as a percentage 100; but according to the empirical true variance, the percentage can not be 100. We can say that the empirical true variance can include the true volume values ( $Q$ ) satisfactorily. Finally, the simulation supports the theory. The fluctuation of  $ETCE$  is expected results which occur when the idea of systematic sampling in Eq. (1) is used.  $CEMC$  can be good approximation to  $ETCE$ , and so the percentage of them,  $PEMCE$  and  $PETCE$ , can be thought to have similar values, which shows the our investigation on the performance of  $\lambda_q$  values would be reasonable. In other words, when we look at the performance of confidence interval as to including the true value, we should focus on  $PEMC$  and  $PETCE$  must give similar results together. In this point, the trustiness of confidence interval is acceptable, because the  $PETCE$  is at least 95 approximately.

The estimated values for the measurement function in Eq. (8) with  $q = 0.4$  and  $q = 0.8$  and also Eq. (9) with  $q = 0.4$  and  $q = 0.8$  would be around the true parameter values. It is seen that the covariogram model in Eq. (12) could not be representative for the covariogram functions for these  $q$  values of the measurement function in Eq. (8). However, when it is thought on the performance of variance estimation, the variance estimation for the systematic sampling of Eq. (8) gives the satisfactorily results. The measurement function in Eq. (9) could not be represented by the covariogram model in Eq. (12). However, for the variance estimation on systematic sampling of Eq. (9), it is seen that satisfactory efficient results are produced by the covariogram model in Eq. (12). The efficiency for the systematic sampling of measurement function in Eq. (10) is not as good as that in Eq. (11).

As a final comment, this model can be used. However, the proposed measurement functions, such as Eqs. (8) - (11), should be systematically sampled so that one can get the more precise decision on the application for the biomedical imaging.  $CEMC$ ,  $ETCE$ ,  $PEMC$  and  $PETCE$  are the abbreviations for the coefficient of error of Matheron's covariogram model, the empirical true coefficient of error, the percentage for coefficient of error of Matheron's covariogram model and the percentage for empirical true coefficient of error, respectively.  $\widehat{Var}(\hat{q})$  and  $\widehat{MSE}(\hat{q})$  are the simulated variance and simulated mean square error of the estimator  $\hat{q}$ , respectively.  $n$  is the number of systematic sampling.

**Table 3.** 5 Sheep brain volumes from automatic pixel counting ( $mm^2$ ) after determining border of slices with 5 mm thickness and their confidence intervals for  $N = 2$ : arithmetic mean of  $\hat{q}$  values with  $k = 2, 3, 4, 5, 6, 7$  in Eq. (22)

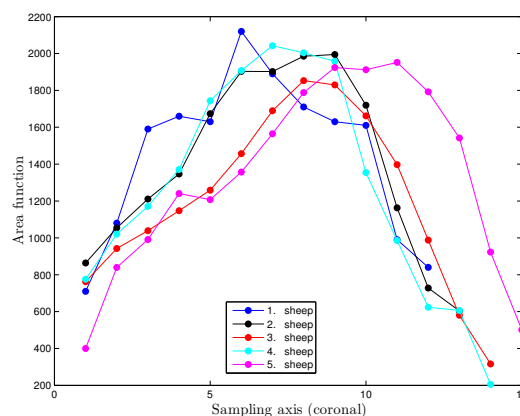
Brains	Q	$\hat{Q}$	$\hat{q}$	$\hat{c}e$	$\hat{Q}_{lower}$	$\hat{Q}_{upper}$	Num.Sec.
1	85000	87300	.20	.0234	81289.05	93310.95	12
2	94000	90738	.34	.0106	87731.40	93744.60	13
3	83000	84608	.50	.0066	82722.64	86493.36	14
4	88000	88846	.42	.0087	86318.13	91372.87	14
5	100000	99675	.67	.0039	98351.66	100998.34	15

**Table 4.** 5 Sheep brain volumes from automatic pixel counting ( $mm^2$ ) after determining border of slices with 5 mm thickness and their confidence intervals for  $N = 2$ :  $\hat{q}$  values with  $k = 2$  in Eq. (22)

Brains	Q	$\hat{Q}$	$\hat{q}$	$\hat{c}e$	$\hat{Q}_{lower}$	$\hat{Q}_{upper}$	Num.Sec.
1	85000	87300	-.06	.0234	82646.98	91953.02	12
2	94000	90738	.18	.0131	87249.31	94226.69	13
3	83000	84608	.41	.0075	82464.84	86751.16	14
4	88000	88846	.28	.0105	85934.10	91756.90	14
5	100000	99675	.63	.0041	98283.46	101066.54	15

### 3.2. Real Data

Five different sheep brain which were 12-18 months old were removed from their skull via the craniotomy in the laboratory for anatomy. These brains immersed in formalin (5%) for 10 days. Brains scanned with standard  $T2$ -weighted 0.5 tesla MRI in the coronal plane with 5 mm slice thickness. The real volume of each brain was obtained by using the Archimedean principle repeated in 6 times. The mean of 6 results for each brain was used as an exact volume of a brain. They were estimated by the slices in coronal plane. The results are given in Tables 3-4. The area values of each slice obtained from the coronal axis are depicted at the figure 3.



**Figure 3.** Area functions for each brain.

When  $N$  in Eq. (31) is replaced with 3,  $\lambda_{q=0.3} = 3.82689$  and  $\lambda_{q=0.34} = 3.90405$  are found. The confidence intervals of brain 2 for  $q = 0.3$  and  $q = 0.34$  are (87055.68,94420.32) and (86981.44, 94494.56), respectively. These confidence intervals include the exact volume of the brain 2.

In table 4, when  $q$  with  $k = 2$  is taken, the confidence interval includes the true volumes of each non-vivo brains. For brain 2, the volume value is included by the confidence interval. It is seen that estimating accurately the parameter  $q$  affects the variance estimation and the confidence interval as

well. For this reason,  $\lambda_q$  values for  $N = 2, 3, 4$  in Table 1 are computed, however, the simulation results show that  $N = 2$  should be taken. Tables 3-4 show the true volume ( $Q$ ), the estimated volume ( $\hat{Q}$ ), the estimated smoothness constant ( $\hat{q}$ ), the estimated coefficient of error ( $\hat{c}\hat{e}$ ), the lower bound of the estimated volume ( $\hat{Q}_{lower}$ ), the upper bound of the estimated volume ( $\hat{Q}_{upper}$ ) and the number of sections (Num. Sec.).

#### 4. Conclusions and Discussions

In this study, a method showing how to calculate constant  $\lambda_q$  is proposed. It is expected that this method can be used as a new tool in Mathematics when it is needed. A program written in MATLAB 2013a package give the lower and upper levels of confidence and the values of quantitative values of stereology when the data obtained from a single replication is supplied. The program can be supplied on a request. The estimation of  $q$  is open problem even if we know the exact form of the measurement functions. In other perspective of our discussion, the covariogram model can not be so good approximation for the measurement functions. However, when we make a comparison between *CEMC* and *ETCE*, *CEMC* can be regarded as a good approximation to *ETCE* for each the number of sampling.

As implied by [10,14,15], the estimation of  $q$  is important to avoid the biasedness of the variance of systematic sampling on  $\mathbb{R}$ . Unbiasedness of variance estimate leads to have the accurate lower and upper bounds of confidence interval for the systematic sampling on  $\mathbb{R}$ . It is observed from the simulation results that the covariogram model in Eq. (12) gives the satisfactorily results for the variance estimation if *CEMC* and *ETCE* have an approximate values. Variance estimation based on covariogram model and the values of *PCEMC* *PETCE* are an another criteria to approve the performance of exact values of the constant  $\lambda_q$ , as observed from the simulation results.

A numerical computation for the constant  $\lambda_q$  of confidence interval for the systematic sampling was done by [10]. The more precise values of the constant  $\lambda_q$  means the more precise confidence interval. It is obvious that the exact calculation proposition should be preferred, because the computation of the constant  $\lambda_q$  proposed by [10] is not as good as the results displayed by Tables 1 and 2. The [8,15,18,19,24–26,29] studies focused on the variance estimation for the systematic sampling. In this study, we proceed the same steps especially inspired from Matheron's theory, however the covariogram model in Eq. (12) can be thought to pass testing on the performance evaluation when we cross checking with *ETCE*.

For the real data, since the measurement functions used can not be represented by exactly similar manner, we should prefer to use different  $N$  values. Eq. (22) can produce the negative estimated  $\hat{q}$  values for the area function of real data given in figure 3. The constant  $\lambda_q$  values for different  $N$  values must be given, because the real data shows that we can need constant  $\lambda_q$  values with the different  $N$ . The Mathematica codes which are used to get the  $\lambda_q$  values can be sent on a request.

It is observed that the synthetic data generated from a class of exact measurement functions can approve the real data for non-vivo brains when the real data have an exactly similar form with the synthetic data. Generally, the covariogram model in Eq. (12) gives the satisfactory results for the measurement functions used in this study. However, the proposed measurement functions should be systematically sampled while conducting a research on the biomedical imaging to increase the information in the decision rule.

## Appendix

**Table 5.**  $(1 - x^2)^q$ :  $q = 0.4$ 

$n$	$\hat{q}$	$\widehat{Var}(\hat{q})$	$\widehat{MSE}(\hat{q})$
5	0.469211	0.000755	0.005545
6	0.449412	0.001009	0.003450
7	0.438921	0.000994	0.002509
8	0.430876	0.000992	0.001945
9	0.426702	0.001029	0.001742
10	0.422139	0.001089	0.001580
11	0.419202	0.001029	0.001398
12	0.417282	0.001049	0.001348
13	0.414414	0.001213	0.001421
14	0.413815	0.001090	0.001281
15	0.411180	0.001210	0.001335
16	0.411575	0.001060	0.001194
17	0.409010	0.001232	0.001314
18	0.409631	0.001119	0.001211
19	0.409595	0.001086	0.001178
20	0.408593	0.001079	0.001153

**Table 6.**  $(1 - x^2)^q$ :  $q = 0.8$ 

$n$	$\hat{q}$	$\widehat{Var}(\hat{q})$	$\widehat{MSE}(\hat{q})$
5	0.798607	0.014187	0.014189
6	0.821274	0.015347	0.015800
7	0.827312	0.016704	0.017450
8	0.838035	0.016471	0.017918
9	0.835330	0.017350	0.018599
10	0.840301	0.017530	0.019154
11	0.840649	0.017641	0.019294
12	0.839555	0.018128	0.019693
13	0.842700	0.017997	0.019821
14	0.837016	0.018080	0.019450
15	0.838411	0.018319	0.019794
16	0.840756	0.018341	0.020002
17	0.837451	0.018479	0.019881
18	0.831963	0.019301	0.020323
19	0.839645	0.019642	0.021214
20	0.835757	0.019321	0.020599

**Table 7.**  $(1 - x^2)^q$ :  $q = 0.4$ 

$n$	<i>CEMC</i>	<i>ETCE</i>	<i>PEMCE</i>	<i>PETCE</i>
5	0.031387	0.027150	100.0	98.8
6	0.024935	0.021804	100.0	99.1
7	0.020275	0.017246	100.0	99.1
8	0.016988	0.014385	100.0	99.3
9	0.014433	0.011948	100.0	98.7
10	0.012535	0.010502	100.0	99.1
11	0.011000	0.009178	100.0	99.5
12	0.009751	0.008085	100.0	99.0
13	0.008768	0.007458	100.0	99.0
14	0.007891	0.006564	100.0	99.1
15	0.007211	0.006121	100.0	99.3
16	0.006562	0.005408	100.0	99.3
17	0.006069	0.005181	100.0	99.2
18	0.005580	0.004672	100.0	99.5
19	0.005167	0.004271	100.0	99.4
20	0.004820	0.003961	100.0	99.3

**Table 8.**  $(1 - x^2)^q$ :  $q = 0.8$ 

$n$	<i>CEMC</i>	<i>ETCE</i>	<i>PEMCE</i>	<i>PETCE</i>
5	0.018256	0.022835	100.0	100.0
6	0.012532	0.016332	100.0	100.0
7	0.009405	0.012425	100.0	100.0
8	0.007190	0.009670	100.0	100.0
9	0.005913	0.007842	100.0	100.0
10	0.004853	0.006570	100.0	100.0
11	0.004053	0.005437	100.0	100.0
12	0.003491	0.004684	100.0	100.0
13	0.003021	0.004037	100.0	100.0
14	0.002674	0.003554	100.0	100.0
15	0.002380	0.003191	100.0	100.0
16	0.002116	0.002814	100.0	100.0
17	0.001885	0.002528	100.0	100.0
18	0.001702	0.002280	100.0	100.0
19	0.001549	0.002043	100.0	100.0
20	0.001429	0.001903	100.0	100.0

**Table 9.**  $((1 - \cos(x))(1 - x^2))^q$ :  $q = 0.4$ 

$n$	$\hat{q}$	$\widehat{Var}(\hat{q})$	$\widehat{MSE}(\hat{q})$
5	-0.059737	0.009231	0.220590
6	0.257864	0.001882	0.022085
7	0.412975	0.000590	0.000758
8	0.483350	0.000779	0.007726
9	0.501458	0.000922	0.011216
10	0.507921	0.001314	0.012961
11	0.507945	0.000837	0.012489
12	0.507897	0.001435	0.013076
13	0.503777	0.000699	0.011469
14	0.501835	0.001445	0.011816
15	0.497033	0.000737	0.010153
16	0.494786	0.001527	0.010511
17	0.489366	0.000710	0.008696
18	0.488828	0.001432	0.009323
19	0.483590	0.000714	0.007702
20	0.481851	0.001531	0.008230

**Table 10.**  $((1 - \cos(x))(1 - x^2))^q$ :  $q = 0.8$ 

$n$	$\hat{q}$	$\widehat{Var}(\hat{q})$	$\widehat{MSE}(\hat{q})$
5	-0.127902	0.025653	0.886655
6	0.259307	0.009587	0.301935
7	0.471353	0.008843	0.116851
8	0.591335	0.008365	0.051906
9	0.667866	0.009158	0.026618
10	0.712836	0.010045	0.017643
11	0.743469	0.010628	0.013824
12	0.769775	0.011272	0.012186
13	0.782195	0.012278	0.012595
14	0.794971	0.013111	0.013137
15	0.802343	0.013406	0.013412
16	0.810423	0.013491	0.013599
17	0.814130	0.013994	0.014194
18	0.822037	0.014498	0.014984
19	0.822426	0.014351	0.014854
20	0.822911	0.015298	0.015823

**Table 11.**  $((1 - \cos(x))(1 - x^2))^q$ :  $q = 0.4$ 

$n$	<i>CEMC</i>	<i>ETCE</i>	<i>PEMCE</i>	<i>PETCE</i>
5	0.136986	0.035193	100.0	94.6
6	0.075842	0.056090	100.0	97.4
7	0.048192	0.022847	100.0	98.0
8	0.035892	0.036584	100.0	99.1
9	0.029172	0.017402	100.0	98.3
10	0.024801	0.026910	100.0	99.5
11	0.021386	0.013797	100.0	98.6
12	0.018852	0.020350	100.0	99.4
13	0.016763	0.010922	100.0	98.9
14	0.015121	0.016248	100.0	99.7
15	0.013697	0.009184	100.0	98.5
16	0.012545	0.013334	100.0	99.4
17	0.011526	0.007842	100.0	98.9
18	0.010623	0.011027	100.0	99.7
19	0.009865	0.006687	100.0	98.5
20	0.009211	0.009652	100.0	99.6

**Table 12.**  $((1 - \cos(x))(1 - x^2))^q$ :  $q = 0.8$ 

$n$	<i>CEMC</i>	<i>ETCE</i>	<i>PEMCE</i>	<i>PETCE</i>
5	0.179574	0.070757	100.0	95.8
6	0.098853	0.058929	100.0	98.7
7	0.056666	0.040635	100.0	100.0
8	0.037906	0.035454	100.0	100.0
9	0.027210	0.025762	100.0	100.0
10	0.021142	0.023491	100.0	100.0
11	0.016973	0.018652	100.0	100.0
12	0.014014	0.016925	100.0	100.0
13	0.011669	0.013700	100.0	100.0
14	0.010083	0.012682	100.0	100.0
15	0.008732	0.010624	100.0	100.0
16	0.007799	0.010070	100.0	100.0
17	0.006862	0.008591	100.0	100.0
18	0.006093	0.008067	100.0	100.0
19	0.005530	0.007070	100.0	100.0
20	0.005030	0.006753	100.0	100.0



**Table 13.**  $\exp(-\sin(-x^3))$ :  $q = 0.95$ 

$n$	$\hat{q}$	$\widehat{Var}(\hat{q})$	$\widehat{MSE}(\hat{q})$
5	-0.088096	0.050826	1.128469
6	0.041988	0.031897	0.856384
7	0.189917	0.018652	0.596379
8	0.320166	0.008843	0.405534
9	0.449291	0.007235	0.257945
10	0.549659	0.004972	0.165245
11	0.639576	0.002916	0.099279
12	0.714919	0.001908	0.057171
13	0.776112	0.001817	0.032055
14	0.827798	0.001763	0.016697
15	0.868178	0.001724	0.008419
16	0.899500	0.001604	0.004154
17	0.928089	0.001326	0.001806
18	0.942607	0.001128	0.001183
19	0.959425	0.001025	0.001114
20	0.967014	0.000817	0.001106

**Table 14.**  $\exp(-\sin(-x^3))$ :  $q = 0.95$ 

$n$	<i>CEMC</i>	<i>ETCE</i>	<i>PEMCE</i>	<i>PETCE</i>
5	0.123899	0.042779	100.0	100.0
6	0.096852	0.020019	100.0	100.0
7	0.068757	0.008892	100.0	100.0
8	0.046235	0.003329	100.0	100.0
9	0.031395	0.001138	100.0	100.0
10	0.022537	0.000614	100.0	100.0
11	0.016419	0.000538	100.0	100.0
12	0.012289	0.000462	100.0	100.0
13	0.009477	0.000366	100.0	100.0
14	0.007494	0.000282	100.0	100.0
15	0.006081	0.000220	100.0	100.0
16	0.005047	0.000184	100.0	100.0
17	0.004236	0.000158	100.0	100.0
18	0.003677	0.000132	100.0	100.0
19	0.003202	0.000117	100.0	100.0
20	0.002850	0.000103	100.0	100.0

**Table 15.**  $(5/112)(-54x^4 - 25x^3 + 48x^2 + 25x + 6) : q = 0.9$ 

$n$	$\hat{q}$	$\widehat{Var}(\hat{q})$	$\widehat{MSE}(\hat{q})$
5	0.119701	0.021089	0.629956
6	0.349198	0.018577	0.321959
7	0.506408	0.017147	0.172062
8	0.607155	0.017009	0.102768
9	0.677396	0.017249	0.066802
10	0.720912	0.016863	0.048935
11	0.765776	0.016458	0.034474
12	0.786878	0.015944	0.028741
13	0.815932	0.015711	0.022778
14	0.838310	0.015351	0.019157
15	0.856894	0.015623	0.017481
16	0.865002	0.016006	0.017231
17	0.883260	0.015086	0.015367
18	0.887106	0.015674	0.015840
19	0.896326	0.015430	0.015444
20	0.904643	0.014824	0.014845

**Table 16.**  $(5/112)(-54x^4 - 25x^3 + 48x^2 + 25x + 6) : q = 0.9$ 

$n$	CEMC	ETCE	PEMCE	PETCE
5	0.131979	0.061047	100.0	97.7
6	0.076664	0.044234	100.0	100.0
7	0.047065	0.031891	100.0	100.0
8	0.032165	0.024913	100.0	100.0
9	0.023411	0.019979	100.0	100.0
10	0.018146	0.015962	100.0	100.0
11	0.014053	0.013222	100.0	100.0
12	0.011617	0.011093	100.0	100.0
13	0.009464	0.009315	100.0	100.0
14	0.007890	0.007985	100.0	100.0
15	0.006690	0.006992	100.0	100.0
16	0.005872	0.006274	100.0	100.0
17	0.005015	0.005386	100.0	100.0
18	0.004499	0.004952	100.0	100.0
19	0.003983	0.004410	100.0	100.0
20	0.003544	0.003891	100.0	100.0

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