Quantitative characterization of airspace enlargement in emphysema

Harikrishnan Parameswaran, Arnab Majumdar, Satoru Ito, Adriano M. Alencar, and Béla Suki

Department of Biomedical Engineering, Boston University, Boston, Massachusetts

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EMPHYSEMA IS DEFINED AS the “abnormal permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis” (1, 33). In recent years, it has become widely accepted to use the mean linear intercept ($L_m$) (7, 38, 39) to confirm the presence of emphysema in various animal models (20, 23). The likely reason is that $L_m$ measures the linear dimensions of airspaces from histological sections and a variety of computer-generated test images. To this end, we developed an automated method for measuring linear intercepts from digitized images of tissue sections and calculate $L_m$ as their mean. We examined how the shape of airspaces and the variability of their sizes influence $L_m$ as well as the distribution of linear intercepts. We found that, for a relatively homogeneous enlargement of airspaces, $L_m$ was a reliable index for detecting emphysema. However, in the presence of spatial heterogeneities with a large variability of airspace sizes, $L_m$ did not significantly increase and sometimes even decreased compared with its value in normal tissue.

We also developed an automated method for measuring the area and computed an equivalent diameter of each individual airspace that is independent of shape. Finally, we introduced new indexes based on the moments of diameter that we found to be more reliable than $L_m$ to characterize airspace enlargement in the presence of heterogeneities.

METHODS

We analyzed various computer-generated geometric shapes as well as alveolar structures from images of hematoxylin and eosin-stained lung tissue sections fixed in formalin obtained from control and elastase-treated mice (17). First, the original image (Fig. 1A) was separated into tissue and airspace. To do this, the original image was thresholded to obtain a binary image, with black representing tissue and white representing airspace (Fig. 1B). The threshold level could be selected manually or computed automatically from the original image (26, 41).

Automated measurement of $L_m$. To estimate $L_m$, a uniform grid of horizontal and vertical lines was superimposed on the binary image (Fig. 1B). The air-tissue interfaces divide each grid line into chords that were either inside an airspace or inside tissue. The length of chords that were inside airspaces were measured and recorded as $L_m$.

Automated measurement of equivalent diameter. To measure air-space area and diameter, the binary image was first segmented into distinct airspaces using the watershed transform (4, 28). The process of segmenting the image can be described briefly as follows. From the binary image, first a distance map was calculated, such that every pixel representing air in the binary image was replaced by the negative of the Euclidean distance between that pixel and the nearest pixel representing tissue. Thus the resulting distance map had basins corresponding to airspaces as illustrated in Fig. 1C, where the pixels at the center of the airspace that were farthest from the boundary had the largest negative values (represented by darker shades of gray) and sometimes even decreased compared with its value in normal tissue.

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To systematically compare $L_m$ and $D_v$, we studied how these indexes characterize heterogeneous and uniform enlargement of a variety of idealized shapes. We also measured $L_m$ and $D_v$ from digitized images of histological sections and examined their effectiveness in distinguishing normal and emphysematous tissue.

**RESULTS**

We first focus our analysis on factors that determine the LI distribution and $L_m$. Specifically, we show that the LI distribution and $L_m$ are dependent on the shape of the airspaces. Next, we analyze the performance of $L_m$ under conditions of increasing variability in the size of airspaces and compare the results with those obtained using $D_v$. Finally, we present $L_m$ and $D_v$ measurements from images of normal and emphysematous lung tissue sections.

Shape dependence of $L_m$. The shape dependence of $L_m$ is laid out in the Crofton-Cauchy formula (21, 32), which relates $L_m$ to the area ($A$) and perimeter ($P$) of a two-dimensional object

$$P = \pi \frac{A}{L_m}$$

The three dimensional counterpart of Eq. 3 is given by

$$S = 4 \frac{V}{L_m}$$

where $S$ is the surface area and $V$ is the volume. Equations 3 and 4 make $L_m$ a useful method for estimating perimeter and surface area of a single object with known area and volume, respectively. To verify that Eq. 3 holds for airspaces in histological sections of the lung, we randomly selected airspaces from segmented images of lung tissue and computed $L_m$, perimeter, and area of the selected airspaces. When $L_m$ was plotted against the ratio of area to perimeter of the airspaces (Fig. 2A), we found a strong linear relationship with a slope close to $\pi$ (3.09 ± 0.01) and an intercept close to zero (−3.66 ± 0.41 μm). For a collection of airspaces (Fig. 2B), $L_m$ was found to be proportional to the ratio of total area to the total perimeter, with a slope of 2.97 ± 0.01 and an intercept of −2.9 ± 0.5 μm.

When $L_m$ is used as a measure of the linear dimensions of airspaces, using Eq. 3, it can be shown that $L_m$ depends not only on the dimensions of the object but also on its shape. Indeed, Eq. 3 implies that

$$L_m = \pi \frac{\sqrt{A}}{P} \sqrt{\frac{A}{P}} = \xi \sqrt{A}$$

where $\xi$ is a dimensionless quantity that depends only on shape.

To study how the shape influences the LI distribution, a simple test image containing a collection of randomly oriented identical ellipses was created. The shape of these ellipses was controlled by changing their eccentricity ($\epsilon$), defined as the ratio of the distance between the two focii of the ellipse to the length of its major axis. The first test image contained circles, which can be considered as ellipses with $\epsilon = 0$ (Fig. 3A). By increasing $\epsilon$, the circles were transformed into randomly oriented ellipses having the same area (Fig. 3B). The equivalent diameter in both cases was 65 pixels, but $L_m$ changed from 51 pixels ($\sigma = 14$) to 42 pixels ($\sigma = 18$). The corresponding LI

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**Fig. 1. Illustration of the method of segmentation. A: grayscale image. B: binary image. C: distance map. D: segmented image.**
distributions are shown in Fig. 3C, and their derivation is given in APPENDIX A. This clearly shows that the LI distribution as well as its mean and variance are sensitive to changes in shape. Another interesting observation here was the large spread of the LI distribution.

$L_m$ in Fig. 3B had a standard deviation that was 42% of the mean, although all the objects had identical dimensions. The high variability was entirely due to the shape of the objects.

These results indicate that the use of $L_m$ to characterize changes in dimensions of airspaces under various experimental conditions is only accurate when the shape of the airspaces does not change appreciably. Furthermore, even the LI distribution may not be used to calculate indexes of heterogeneity like the coefficient of variation (CV), defined as $\sigma/\mu$, because of its dependency on the shape of individual airspaces in the section. In contrast, the distribution of $d$ is by definition (Eq. 1) shape independent.

**Characterizing heterogeneous enlargement of airspaces.** We examined whether the mean airspace diameter ($D_0$) can detect airspace enlargement. An arithmetic mean gives equal weight to all the airspaces in the tissue section. Consequently, if there were many small airspaces accompanied by a few enlarged ones, then $D_0$ would have a value close to the dimensions of the smaller airspaces simply because there is a large number of them compared with the enlarged airspaces. One possible solution to this problem is to use a weighted mean measure, like $D_v$, where enlarged airspaces are weighted more than normal airspaces.

$D_v$ can be expressed as functions of the central moments of airspace diameters. Specifically, $D_1$ is a function of the mean ($\mu$) and variance ($\sigma^2$) of airspace diameters as:

$$D_1 = \frac{\langle d^2 \rangle}{\langle d \rangle} = \mu \left( 1 + \frac{\sigma^2}{\mu} \right)$$

and $D_2$ is a function of $\mu$, $\sigma^2$, and skewness ($\gamma$) of the diameter distribution

$$D_2 = \frac{\langle d^3 \rangle}{\langle d^2 \rangle^{3/2}} = \mu \left[ 1 + \frac{\sigma^2}{\mu^2} + \frac{\sigma^2 \gamma}{\mu} \right]$$

Equations 5 and 6 are derived in APPENDIX B. $D_v$ can therefore be thought of as a generalized measure of the airspace dimensions, which, unlike $L_m$, is independent of shape.

To analyze the effects of variability in airspace sizes on $L_m$ and $D_v$, we considered images consisting of a circle of radius $R$ surrounded by a symmetric packing of circles, each having a radius $r$. Starting from a configuration where $R = r$ (Fig. 4A), the ratio $R/r$ was increased in steps, such that the total area of the circles was unity. The number of circles of radius $r$ was chosen such that they provided a close packing around the circumference of the central circle (Fig. 4, A and B). For each step, we computed $L_m$, $D_0$, and $D_2$ for the corresponding image. In this case, since all the objects under consideration...
were of the same shape, \( L_m \approx D_1 \) (see DISCUSSION), and hence we plotted only \( L_m \) in Fig. 4C.

The variability in the sizes of the objects can be characterized by the CV of the areas. As the CV increased, the dimensions of the surrounding circles, which constitute the majority of objects, decreased. Consequently, both \( L_m \) (\( \bullet \) in Fig. 4C) and \( D_0 \) (\( \bigcirc \) in Fig. 4C) decreased. However, the enlargement of the central circle also influences \( \sigma^2 \) and \( \gamma \), both of which increased. Consequently, \( D_2 \) (\( \blacktriangledown \) in Fig. 4C) remained sensitive to the enlargement of the central circle and increased with CV.

**Analysis of tissue samples.** Figure 5 shows three typical images: a normal tissue section, an emphysematous tissue section with relatively homogeneous enlargement of airspaces, and an emphysematous tissue section showing spatially heterogeneous enlargement with a large variability in airspace sizes. To study the effectiveness of the different indexes in distinguishing normal and emphysematous tissue samples, \( L_m, D_1, \) and \( D_2 \) were calculated from 29 images of normal tissue sections and 41 images of emphysematous tissue sections. The indexes \( D_1 \) and \( D_2 \) were plotted against \( L_m \) (Fig. 6). For those sections, which exhibited a reasonably homogeneous enlargement of airspaces (Fig. 5B), \( L_m \) was able to distinguish between normal and emphysematous sections. However, for sections that had a more heterogeneous appearance (Fig. 5C), \( L_m \) even decreased compared with the normal sample (Fig. 5A). The overlap between normal and emphysematous samples on the \( L_m \) axis (Fig. 6) illustrates the inability of \( L_m \) to distinguish between normal and emphysematous tissue. On the \( D_1 \) and \( D_2 \) axes, however, normal and emphysematous samples were better separated, clearly indicating that these indexes are sensitive to abnormal enlargement of airspaces even in the presence of heterogeneity.
Pulmonary emphysema is a progressive disease characterized by tissue destruction and enlargement of distal airspaces (1, 33). Various methods including $L_m$ (38, 7, 39), destructive index (31), and airspace surface area per unit volume (9) have been used to quantitatively estimate the extent of emphysema through lung tissue sections. Despite its original definition as a destructive index (31), and airspace surface area per unit volume (9) have been used to quantitatively estimate the extent of emphysema in lung tissue sections. However, for emphysematous tissue, the automatically selected threshold was reliable and closely matched those chosen manually. We note, however, that for low-contrast images without a sharp air-tissue boundary, the choice of threshold could have a significant effect on the resulting measurements. Next, we measured LI as the chord lengths contained within the airspaces and bounded either by tissue or the image boundary. We computed $L_m$, using a method described by Oldmixon et al. (25) that corrects for the boundary effects. We note that, without this correction, $L_m$ was underestimated by $\sim 15\%$ on average. To measure airspace diameters, we segmented the image into separate airspaces using the watershed transform (28). This technique, however, introduces a second threshold that controls the degree of segmentation. Setting this threshold too low would result in an oversegmented output, and setting it too high would result in the removal of small airspaces. In this paper, this threshold was set by visually comparing the result of the segmentation procedure to the original image. Additionally, this method is not able to automatically identify large airways and unfilled blood vessels, which were excluded manually.

Using this automated image-processing technique, one can make unbiased measurement of the LI directly from stained images of lung tissue. Thus it is possible to characterize parenchymal structure using the full distribution of the chord lengths of alveolar sizes or linear intercept lengths rather than just $L_m$. Our results, however, indicate that the distribution of LI itself is also sensitive to the shape of individual airspaces. Therefore, the distribution of LI is not very reliable for studying the changes in variability and other higher order moments of airspace dimensions that characterize the heterogenous nature of emphysematous tissue structure.

Apart from the enlargement of airspaces, another important structural change observed in emphysema is the loss of internal surface area or air-tissue interface. Being a function of shape, $L_m$ is also sensitive to changes in surface area. Previous studies (7, 21) have shown that $L_m$ for a three-dimensional object is proportional to the ratio of volume and surface area, which in two dimensions reduces to the ratio of area and perimeter (Fig. 2). Therefore, at a fixed lung volume, $L_m$ is inversely proportional to the internal surface area of the lung. Thurlbeck et. al. (37) made extensive internal surface area measurements in the human lung and observed that, in centrilobular emphysema and also in cases of “mild” emphysema, the internal surface area did not significantly decrease below the range found in normal lungs. In many cases studied, however, subjective visual assessment always identified the tissue samples as emphysematous. This finding suggests that the presence of a few abnormally enlarged airspaces among many normal ones might be a more reliable morphological indicator of emphysema than the total change in internal surface area and hence $L_m$. It has also been recently reported that, in an elastase-induced mouse model of mild emphysema, both the mean size of the airspaces and their CV significantly increased compared with those observed in control lungs (16). Thus a poor correlation between $L_m$ and various measures of lung function (27) may be a consequence of the fact that $L_m$ does not take into account the large variability of airspace sizes in tissue sections. In certain experimental conditions, this may also result in the identification of the wrong mechanism or missing the right mechanism.

Alveolar diameters, unlike the LI, depend only on size, and therefore they can be used to calculate indexes of airspace enlargement like weighted mean diameters. The use of a

**DISCUSSION**

For images with a high contrast between the air and tissue regions, the samples, however, appear better separated on the $D_1$ axis and completely separated on the $D_2$ axis (dotted line).

**Fig. 6.** $L_m$, $D_1$, and $D_2$ measurements from tissue samples. A: $D_1$ plotted against $L_m$. B: $D_2$ plotted against $L_m$. The overlap between normal and emphysematous samples on the $L_m$ axis illustrates the inability of $L_m$ to distinguish between normal and heterogenous samples of emphysematous tissue. The samples, however, appear better separated on the $D_1$ axis and completely separated on the $D_2$ axis (dotted line).
weighted mean to characterize abnormal enlargement of airspaces in emphysema is not new. In fact, $L_m$ is itself a weighted mean measure similar to $D_1$:

$$L_m = k \frac{\langle A \rangle}{\langle P \rangle} \propto \frac{\langle d^3 \rangle}{\langle d \xi \rangle}$$  \hspace{1cm} (7)

where $k$ is the constant of proportionality from Fig. 2B. Thus, although $L_m$ is a weighted mean measure of airspace dimensions, the weight of each airspace depends on its shape due to the shape factor $\xi$. The indexes $D_i$ also have simple physical interpretations. For example, $D_2$ can be expressed as

$$D_2 = \frac{\langle d^3 \rangle}{\langle d^2 \rangle} = \sum_i \left( \frac{A_i}{\sum_j A_j} \right) d_i$$  \hspace{1cm} (8)

Therefore, $D_2$ is a weighted mean measure where every airspace is weighted by the fraction of the total area occupied by it. In a homogeneous and narrow distribution of alveolar sizes, as observed in normal lung tissue samples, the area weighted mean is very close to the arithmetic mean since the fractional area occupied by airspaces is nearly constant. When the distribution of airspace sizes becomes wider with abnormally large airspaces surrounded by many smaller ones, the large airspaces will be weighted significantly more in the calculation of $D_2$ than in the calculation of $L_m$ since they occupy a higher fraction of the total area than the smaller airspaces. This makes $D_2$ more sensitive to the presence of enlarged airspaces in a tissue section than $L_m$ or $D_0$ (Fig. 6).

Computed tomography (CT) provides physicians with a noninvasive tool for assessing alterations in lung structure induced by various disease processes. Many studies have been undertaken to detect and quantify pulmonary emphysema using CT (3, 8, 10, 13). Low attenuation areas (LAA) on CT scans have been shown to represent emphysematous changes in the lungs of patients (3, 24). It has been reported that the cumulative distribution of LAA cluster sizes ($A$) follows a power law $P(A) \propto A^{-\alpha}$ (22). The exponent $\alpha$ was found to be sensitive to small changes in structure in early emphysema (6, 22). When the LAA cluster sizes follow a power law distribution, it can be shown that $D_2$ of the LAA clusters is a function of the power law exponent. This suggests that the area of LAA clusters in a CT image could be used to calculate an area-weighted mean diameter value similar to $D_2$ measured from tissue sections. Thus our new index $D_2$ may prove useful to characterize the progression of emphysema from macroscopic CT images as well. Nevertheless, the relation between $D_2$ of LAA, which indicates changes in structure at the scale of a CT voxel, and $D_2$ from histological sections, which measures changes at the scale of individual alveoli, needs further investigation.

In conclusion, $L_m$ that is currently the most widely accepted index for detecting and quantifying abnormally enlarged airspaces in emphysema is not reliable, especially in the presence of spatially heterogeneous tissue destruction. The weighted mean diameter on the other hand is a robust measure of size and is sensitive to airspace enlargement, even in the presence of heterogeneities. Finally, since emphysema is currently defined as an abnormal increase in airspace dimensions, our findings may have implications for the very definition and the quantitative characterization of the progression of emphysema.

**APPENDIX A**

**Probability Density Function of LI**

In this appendix, we derive the probability density function of $L_I$ for circles and ellipses. First, we consider a circle of diameter $D$ with intercepts of length $\lambda$, where $\lambda \leq D$. Because a circle possesses rotational symmetry, it is sufficient to consider only horizontal intercepts to obtain the probability density function $\Pi(\lambda)$ of intercept lengths. In addition, due to the symmetry between the upper and lower halves of the circle, we calculate the intercepts only in the upper half. The horizontal intercepts are evenly spaced with a density of $\rho$ intercepts per unit length, such that the total number of intercepts $v$ is given by

$$v = \int_0^{D/2} dh \rho = \frac{D}{2} \rho$$  \hspace{1cm} (A1)

Figure 7A shows that, at a distance $h$ from the center, the intercept length $\lambda$ satisfies

$$\left(\frac{\lambda}{2}\right)^2 + h^2 = \left(\frac{D}{2}\right)^2$$  \hspace{1cm} (A2)

Thus the lengths of the intercepts $\lambda$ can be written as a function of $h$ as

$$\lambda(h) = \sqrt{D^2 - 4h^2}$$  \hspace{1cm} (A3)

The probability density function $\Pi(\lambda)$ of the intercept length $\lambda$ is defined as

**Fig. 7. Illustrations of horizontal intercepts of length $\lambda$ at distances between $h$ and $h + \Delta h$ from the center of a circle with diameter $D$ (A) and maximum length of the horizontal intercept $\lambda_0$ and maximum height of an ellipse at angle $\theta$ (B).**
\[ \Pi(\lambda) \Delta \lambda = P[\lambda \leq \hat{h} \leq \lambda + \Delta \lambda] \]  

(A4)

which is the probability of finding an intercept with length \( \hat{h} \) between \( \lambda \) and \( \lambda + \Delta \lambda \). Using Eq. A3, these intercepts can be found between \( h \) and \( h - \Delta h \) in the upper semicircle, which satisfies the relations

\[ \lambda = \sqrt{D^2 - 4h^2} \]  

(A5a)

\[ \lambda + \Delta \lambda = \sqrt{D^2 - 4(h - \Delta h)^2} \]  

(A5b)

where \( 0 < h \leq D/2 \). Thus the probability density function \( \pi(\lambda) \) can be written as

\[ \Pi(\lambda) \Delta \lambda = P[h \leq \hat{h} \leq h - \Delta h] \]  

(A6)

\[ = \frac{\rho \Delta h}{\nu} \]  

(A7)

\[ = \frac{2\Delta h}{D} \]  

(A8)

where the last step is obtained by using Eq. A1. Equations A5 can now be used to express \( \Delta h \) in terms of \( \Delta \lambda \)

\[ \Delta h = \frac{\lambda \Delta \lambda}{2 \sqrt{D^2 - \lambda^2}} \]  

(A9)

and thus

\[ \Pi(\lambda) = \frac{\lambda}{D \sqrt{D^2 - \lambda^2}} \]  

(A10)

\( L_m \) can then be calculated as

\[ L_m = \langle \lambda \rangle = \int_0^D d\lambda \lambda \pi(\lambda) \]  

(A11)

\[ = \frac{\pi}{4} D \approx 0.785D \]  

(A12)

and the variance of LI is given by

\[ \sigma^2(\lambda) = \langle \lambda^2 \rangle - \langle \lambda \rangle^2 \]  

(A13)

\[ = \left( \frac{2}{3} - \frac{\pi^2}{16} \right) D^2 = (0.223D)^2 \]  

(A14)

For an ellipse with major axis \( 2a \) and minor axis \( 2b \), the calculation of \( \pi(\lambda) \) is complicated by the lack of rotational symmetry. We first find the conditional probability density function of horizontal intercept lengths for an ellipse with a particular tilt \( \theta \), which can be derived similar to that for a circle, and thus

\[ \Pi(\lambda | \theta) = \frac{1}{\lambda_0} \frac{\lambda}{\sqrt{\lambda_0^2 - \lambda^2}} \]  

(A15)

where \( \lambda_0 \) is the maximum length of a horizontal intercept, given by

\[ \lambda_0 = D \frac{(1 - \varepsilon^2)^{1/4}}{\sqrt{1 - \varepsilon^2 \cos^2 \theta}} \]  

(A16)

where \( \varepsilon \) is the eccentricity of the ellipse and \( D = 2\sqrt{ab} \) is its equivalent diameter. We note that the total number of lines intersecting a tilted ellipse depends on the angle \( \theta \), and is given by

\[ \nu(\theta) = \rho \frac{\sqrt{1 - \varepsilon^2 \cos^2 \theta}}{(1 - \varepsilon^2)^{1/4}} \]  

(A17)

where \( \rho \) is the density of intercepts. Figure 7B illustrates \( \lambda_0 \) and \( \nu(\theta) \). The probability density function of LI is thus given by

\[ \Pi(\lambda) = \frac{1}{\nu \sigma^2(\lambda)} \int_{0}^{\nu} \nu(\theta) \Pi(\lambda | \theta) \]  

(A18)

which can be calculated numerically. \( L_m \) and the variance of intercept lengths for an ellipse can, however, be calculated exactly as

\[ L_m = \frac{\pi^2}{8} \left[ \frac{(1 - \varepsilon^2)^{3/4}}{E(\varepsilon^2)} \right] D \]  

(A19)

\[ \sigma^2 = \frac{1}{3} \frac{K(\varepsilon^2)E(\varepsilon^2) - \pi^2}{64} D^2 \]  

(A20)

where \( K(\ldots) \) and \( E(\ldots) \) are the complete elliptic integrals of the first and second kind, respectively. When \( D = 65 \) pixels for circles with \( \varepsilon = 0 \), \( L_m = 51.0 \) pixels with a standard deviation of intercept lengths \( \sigma_a = 14.5 \) pixels, and for ellipses with \( \varepsilon = 0.9 \), \( L_m = 45.2 \) pixels with \( \sigma_a = 18.7 \) pixels. These values closely match the numerical measurements from Fig. 3.

**APPENDIX B**

**Relating \( D \) to the Diameter Distribution**

Let \( \mu \) be the arithmetic mean of the diameter distribution. The equivalent diameter of any airspace in the tissue section can be expressed as \( d_i = \mu + \delta_i \). By definition, \( \langle \delta^2 \rangle = 0 \) and \( \langle \delta^2 \rangle = \sigma^2 \), the standard deviation of airspace diameters. The \( n \)th moment of \( d_i \) can be calculated as

\[ \langle d^n \rangle = \sum_{n=0}^{\infty} \binom{n}{m} \mu^m \sigma^{n-m} \]  

(B1)

Using Eq. B1, we can relate \( D \) to \( \nu + 1 \) and lower order moments of the diameter distribution. Specifically, for \( \nu = 1, 2 \)

\[ D_1 = \langle d^2 \rangle \frac{\langle d^2 \rangle}{\langle d \rangle} = \mu^2 + \sigma^2 \]  

\[ D_2 = \langle d^4 \rangle \frac{\langle d^4 \rangle}{\langle d^2 \rangle} = \mu^4 + \frac{2}{3} \left( \frac{\langle d^4 \rangle}{\langle d^2 \rangle} - \frac{\langle d^2 \rangle}{\langle d \rangle} \right) + \frac{1}{3} \left( \frac{\langle d^2 \rangle}{\langle d \rangle} \right)^2 \]  

where \( \gamma = \langle \delta^2 \rangle / \sigma^4 \) is the skewness of the diameter distribution.

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