

**Table 1. The list of morphologic parameters based on confocal imaging**

ID #	Full Name	Short name	Symbol	Unit	Definition
1	Cell grid perimeter	CLGP	$GP_c$	$\mu\text{m}$	$GP_c = N_{s,cyto} a_{vxl}$ <sup>(1)</sup>
2	Cell surface area	CLSF	$S_c$ <sup>(4)</sup>	$\mu\text{m}^2$	$S_c = N_{s,cyto} S_{vxl}$ <sup>(2)</sup>
3	Cell volume	CLVM	$V_c$ <sup>(3)</sup>	$\mu\text{m}^3$	$V_c = (N_{v,cyto} + N_{v,nucl} + N_{v,mito}) v_{vxl}$ <sup>(3)</sup>
4	Cell surface to volume ratio	CLSV	$SVr_c$	$\mu\text{m}^{-1}$	$SVr_c = S_c / V_c$
5	Cell surface irregularity index	CLSI	$SIi_c$	$\mu\text{m}^{-1/2}$	$SIi_c = GP_c / \sqrt{V_c}$
6	Cell equivalent spherical radius	CLER	$ER_c$	$\mu\text{m}$	$ER_c = (\frac{3V_c}{4\pi})^{1/3}$
7	Cell volume sphericity index	CLVS	$VSi_c$	-	$VSi_c = 4\pi ER_c^2 / S_c = (36\pi V_c^2)^{1/3} / S_c$
8	Average distance of cell membrane voxels to centroid	CLDM	$\langle R_c \rangle$	$\mu\text{m}$	$\langle R_c \rangle = \sum_{i=1}^{N_{s,cyto}} R_c(i) / N_{s,cyto}$ <sup>(4)</sup>
9	Standard deviation of $R_c$	CLDS	$\Delta R_c$	$\mu\text{m}$	$\Delta R_c = \{ \frac{1}{N_{s,cyto}} \sum_{i=1}^{N_{s,cyto}} (R_c(i) - \langle R_c \rangle)^2 \}^{1/2}$
10	Cell protrusion volume	CLPV	$V_p$	$\mu\text{m}^3$	$V_{cp} = V_c - V_{c0}$ <sup>(5)</sup>
11	Cell protrusion number	CLPN	$N_p$	-	
12	Nuclear grid perimeter	CLGP	$GP_n$	$\mu\text{m}$	$GP_n = N_{s,nucl} a_{vxl}$
13	Nuclear surface area	NRSF	$S_n$	$\mu\text{m}^2$	$S_n = N_{s,nucl} S_{vxl}$
14	Nuclear volume	NRVM	$V_n$	$\mu\text{m}^3$	$V_n = N_{v,nucl} v_{vxl}$
15	Nuclear surface to volume ratio	NRSV	$SVr_m$	$\mu\text{m}^{-1}$	$SVr_m = S_m / V_m$
16	Nuclear surface irregularity index	NRSI	$SIi_n$	$\mu\text{m}^{-1/2}$	$SIi_n = GP_n / \sqrt{V_n}$
17	Nuclear equivalent spherical radius	NRER	$ER_n$	$\mu\text{m}$	$ER_n = (\frac{3V_n}{4\pi})^{1/3}$
18	Nuclear volume sphericity index	NRVS	$VSi_n$	-	$VSi_n = 4\pi ER_n^2 / S_n = (36\pi V_n^2)^{1/3} / S_n$
19	Average distance of nuclear membrane voxels to centroid	NRDM	$\langle R_n \rangle$	$\mu\text{m}$	$\langle R_n \rangle = \sum_{i=1}^{N_{s,nucl}} R_n(i) / N_{s,nucl}$
20	Standard deviation of $R_n$	NRDS	$\Delta R_n$	$\mu\text{m}$	$\Delta R_n = \{ \frac{1}{N_{s,nucl}} \sum_{i=1}^{N_{s,nucl}} (R_n(i) - \langle R_n \rangle)^2 \}^{1/2}$
21	Mitochondrial grid perimeter	MNGP	$GP_m$	$\mu\text{m}$	$GP_m = N_{s,mito} a_{vxl}$
22	Mitochondrial surface area	MNSF	$S_m$	$\mu\text{m}^2$	$S_m = N_{s,mito} S_{vxl}$
23	Mitochondrial volume	MNVm	$V_m$	$\mu\text{m}^3$	$V_m = N_{v,mito} v_{vxl}$
24	Mitochondrial surface to volume ratio	MNSV	$SVr_m$	$\mu\text{m}^{-1}$	$SVr_m = S_m / V_m$
25	Mitochondrial surface irregularity index	MNSI	$SIi_m$	$\mu\text{m}^{-1/2}$	$SIi_m = GP_m / \sqrt{V_m}$
26	Mitochondrial equivalent spherical radius	MNER	$ER_m$	$\mu\text{m}$	$ER_m = 3 / SVr_m$
27	Nucleus-to-cell centroid distance	NCCD	$CD_{nc}$	$\mu\text{m}$	$D_{nc} =  \mathbf{r}_{nc} - \mathbf{r}_{cc} $ <sup>(6)</sup>
28	Nucleus-to-cell volume ratio	NCVR	$Vr_{nc}$	-	$Vr_{nc} = V_n / V_c$
29	Mitochondrion-to-cell volume	MCVR	$Vr_{mc}$	-	$Vr_{mc} = V_m / V_c$

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- (1)  $a_{vxl} = \text{voxel side length} = d_x = d_y \approx d_z$ , where  $d_x$  and  $d_y$  is the pixel size along x- and y-axis, respectively, while  $d_z$  is the distance between two neighboring interpolated slices. The side length  $d_z$  is obtained by requiring  $d_z \cdot (N_{int} + 1) \approx z\_step \cdot f\_scale$  with  $N_{int}$  as the integer number of interpolated slices between two raw slices and  $z\_step = 0.5 \mu\text{m}$  as the translation step size along z-axis,  $f\_scale = 0.87$  is the correction factor for light refraction.
- (2)  $N_{s,xxxx} = \text{number of surface or membrane voxels for the organelle } xxxx$ ,  $s_{vxl} = 1.414 \cdot a_{vxl} d_z = \text{area of the diagonal plane of one voxel}$  (see figure below) as the average surface area of the membrane voxels. A surface voxel of a specific organelle is defined as the one which has at least one of the six neighboring voxels belong to another organelle or the host medium outside of the cell.
- (3)  $N_{v,xxxx} = \text{number of volume voxels for the organelle } xxxx$  which includes the surface voxels and interior voxels,  $v_{vxl} = \text{volume of voxel} = d_x d_y d_z$ .
- (4)  $R_c = |\mathbf{r}_{cs}(i) - \mathbf{r}_{ce}|$  with  $\mathbf{r}_{cs}(i) = (x_{cs}(i), y_{cs}(i), z_{cs}(i)) d_{av}$  as the position vector of the  $i$ th voxel on the cell surface or membrane and  $\mathbf{r}_{ce} = (x_{cc}, y_{cc}, z_{cc}) d_{av}$  as the position vector of the cell centroid,  $d_{av} = (d_x + d_y + d_z)/3$ . The component coordinates of  $\mathbf{r}_{cc}$  are defined as  $x_{cc} = \sum_{i=1}^{N_{v,cell}} x(i) / N_{v,cell}$  with  $N_{v,cell} = N_{v,cyto} + N_{v,nucl} + N_{v,mito}$ , etc..
- (5)  $V_{c0} = \text{cell volume after removing the protrusions through the opening morphology operation}$  (an erosion followed by a dilation using the same structuring element for both operations) on the confocal image slices.
- (6)  $\mathbf{r}_{nc} = (x_{nc}, y_{nc}, z_{nc}) d_{av}$  is the position vector of the nuclear centroid with its components defined as  $x_{nc} = \sum_{i=1}^{N_{v,nucl}} x(i) / N_{v,nucl}$ , etc..

**Table 2. The list of image parameters extracted from one diffraction image with GLCM**

ID #	Full Name	Short name	Definition <sup>(1)</sup>
1	Correlation	COR	$\frac{\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i - \mu_x)(j - \mu_y) p(i, j)}{\sigma_x \sigma_y} = \frac{\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (ij) p(i, j) - \mu_x \mu_y}{\sigma_x \sigma_y}$
2	Dissimilarity	DIS	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1}  i - j  p(i, j)$
3	Contrast (or inertia)	CON	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i - j)^2 p(i, j)$
4	Inverse Difference Moment (or local homogeneity)	IDM	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} \frac{1}{1 + (i - j)^2} p(i, j)$
5	Entropy	ENT	$-\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} p(i, j) \cdot \log(p(i, j))$
6	Sum entropy	SEN	$-\sum_{k=0}^{2G-2} p_{x+y}(k) \cdot \log(p_{x+y}(k))$
7	Difference entropy	DEN	$-\sum_{k=0}^{G-1} p_{x-y}(k) \cdot \log(p_{x-y}(k))$
8	Angular Second Moment (or energy or homogeneity)	ASM	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} \{p(i, j)\}^2$
9	Variance	VAR	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i - \mu_x)^2 p(i, j)$
10	Sum variance	SVA	$\sum_{k=0}^{2G-2} (k - SEN)^2 p_{x+y}(k)$
11	Difference variance	DVA	$\frac{1}{G-1} \sum_{k=0}^{G-1} (p_{x-y}(k) - \bar{p}_{x-y})^2$
12	Mean	MEA	$\sum_{i=0}^{G-1} i \sum_{j=0}^{G-1} p(i, j) = \mu_x$
13	Sum average	SAV	$\sum_{k=0}^{2G-2} k p_{x+y}(k)$
14	Cluster shade	CLS	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i + j - \mu_x - \mu_y)^3 p(i, j)$ $= \sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i + j - 2\mu_x)^3 p(i, j)$
15	Cluster prominence	CLP	$\sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i + j - \mu_x - \mu_y)^4 p(i, j)$ $= \sum_{i=0}^{G-1} \sum_{j=0}^{G-1} (i + j - 2\mu_x)^4 p(i, j)$
16	Maximum probability	MAP	$\max(p(i, j))$
17	Minimum probability	MIP	$\min(p(i, j))$
18	relative minimum pixel intensity	IMIN	$\min(J(x, y)) / \text{mean}(J(x, y))$
19	relative maximum pixel intensity	IMAX	$\max(J(x, y)) / \text{mean}(J(x, y))$

(1)  $J(x, y)$  is a 12-bit diffraction image before normalization,  $I(z, y)$  is the associated normalized 8-bit diffraction image as the input image to obtain GLCM  $p(i, j)$ . In addition, the following functions are used in calculating the GLCM parameter with  $i$  or  $j = 0, 1, 2, \dots, G-1$  and  $G$  as the number of gray levels.  $G=255$  for 8-bit gray level images  $I(x, y)$ :

$$p_x(i) = \sum_{j=0}^{G-1} p(i, j), \quad p_y(j) = \sum_{i=0}^{G-1} p(i, j), \quad p_{x+y}(k) = \sum_{i=0}^{G-1} \sum_{\substack{j=0 \\ i+j=k}}^{G-1} p(i, j), \quad p_{x-y}(k) = \sum_{i=0}^{G-1} \sum_{\substack{j=0 \\ |i-j|=k}}^{G-1} p(i, j), \quad \mu_x = \sum_{i=0}^{G-1} i p_x(i),$$

$$\sigma_x^2 = \sum_{i=0}^{G-1} (p_x(i) - \mu_x)^2, \quad \mu_y = \sum_{j=0}^{G-1} j p_y(j), \quad \sigma_y^2 = \sum_{j=0}^{G-1} (p_y(j) - \mu_y)^2.$$