Table 1. The voxel based morphologic parameters based on 3D reconstruction

ID #	Long name	Short name	Symbol	Unit	Definition
1	Cell grid perimeter	CLGP	GP_c	µm	$GP_c = N_{s,cyto} a_{vxl}$ (1)
2	Cell surface area	CLSF	S_c (4)	µm²	$S_c = N_{s,cyto} s_{vxl}$ (2)
3	Cell volume	CLVM	V_c (3)	µm³	$V_c = (N_{v,cyto} + N_{v,nucl} + N_{v,mito}) v_{vxl}$ (3)
4	Cell surface to volume ratio	CLSV	SVr_c	µm⁻¹	$SVr_c = S_c / V_c$
5	Cell surface irregularity index	CLSI	SIi_c	µm⁻¹ᐟ²	$ISI_c = GP_c / \sqrt{V_c}$
6	Cell equivalent spherical radius	CLER	ER_c	µm	$ER_c = (\dfrac{3V_c}{4\pi})^{1/3}$
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	$<R_c>$	µm	$<R_c> = \sum\limits_{i=1}^{N_{s,cyto}} R_c(i) / N_{s,cyto}$ (4)
9	Standard deviation of R_c	CLDS	ΔR_c	µm	$\Delta R_c = \{\dfrac{1}{N_{s,cyto}} \sum\limits_{i=1}^{N_{s,cyto}} (R_c(i) - \langle R_c \rangle)^2\}^{1/2}$
10	Cell protrusion volume	CLPV	V_p	µm³	$V_{cp} = V_c - V_{c0}$ (5)
11	Cell protrusion number	CLPN	N_p	-	
12	Nuclear grid perimeter	NRGP	GP_n	µm	$GP_n = N_{s,nucl} a_{vxl}$
13	Nuclear surface area	NRSF	S_n	µm²	$S_n = N_{s,nucl} s_{vxl}$
14	Nuclear volume	NRVM	V_n	µm³	$V_n = N_{v,nucl} v_{vxl}$
15	Nuclear surface to volume ratio	NRSV	SVr_n	µm⁻¹	$SVr_m = S_m / V_m$
16	Nuclear surface irregularity index	NRSI	SIi_n	µm⁻¹ᐟ²	$ISI_n = GP_n / \sqrt{V_n}$
17	Nuclear equivalent spherical radius	NRER	ER_n	µm	$ER_n = (\dfrac{3V_n}{4\pi})^{1/3}$
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	$<R_n>$	µm	$<R_n> = \sum\limits_{i=1}^{N_{s,nucl}} R_n(i) / N_{s,nucl}$
20	Standard deviation of R_n	NRDS	ΔR_n	µm	$\Delta R_n = \{\dfrac{1}{N_{s,nucl}} \sum\limits_{i=1}^{N_{s,nucl}} (R_n(i) - \langle R_n \rangle)^2\}^{1/2}$
21	Mitochondrial grid perimeter	MNGP	GP_m	µm	$GP_m = N_{s,mito} a_{vxl}$
22	Mitochondrial surface area	MNSF	S_m	µm²	$S_m = N_{s,mito} s_{vxl}$
23	Mitochondrial volume	MNVM	V_m	µm³	$V_m = N_{v,mito} v_{vxl}$
24	Mitochondrial surface to volume ratio	MNSV	SVr_m	µm⁻¹	$SVr_m = S_m / V_m$
25	Mitochondrial surface irregularity index	MNSI	SIi_m	µm⁻¹ᐟ²	$ISI_m = GP_m / \sqrt{V_m}$
26	Mitochondrial equivalent spherical radius	MNER	ER_m	µm	$ER_m = 3 / SVr_m$
27	Nucleus-to-cell centroid distance	NCCD	CD_{nc}	µm	$D_{nc} = |\mathbf{r_{nc}} - \mathbf{r_{cc}}|$ (6)
28	Nucleus-to-cell volume ratio	NCVR	Vr_{nc}	-	$Vr_{nc} = V_n / V_c$
29	Mitochondrion-to-cell volume ratio	MCVR	Vr_{mc}	-	$Vr_{mc} = V_m / V_c$

(1) a_{vxl} = 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=0.5µm as the translation step size along z-axis, f_scale=0.87 is the correction factor for light refraction.

(2) $N_{s,xxxx}$ = number of surface or membrane voxels for the organelle xxxx, $s_{vxl} = 1.414 \cdot a_{vxl} d_z$ = 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) $N_{v,xxxx}$ = number of volume voxels for the organelle xxxx which includes the surface voxels and interior voxels, v_{vxl}=volume of voxel= $d_x d_y d_z$.

(4) $R_c = |\mathbf{r}_{cs}(i) - \mathbf{r}_{cc}|$ with $\mathbf{r}_{cs}(i) = (x_{cs}(i),\ y_{cs}(i),\ z_{cs}(i))d_{av}$ as the position vector of the ith voxel on the cell surface or membrane and $\mathbf{r}_{cc} = (x_{cc},\ y_{cc},\ z_{cc})d_{av}$ 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} = 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..
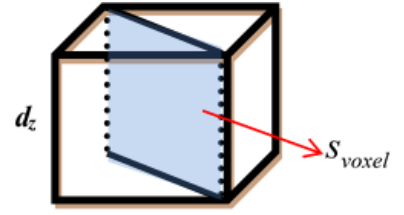
Table 2. The GLCM and pixel intensity parameters extracted from an input image

ID #	Long name	Short name	Definition [1]
1	Angular second moment (or energy or homogeneity)	ASM	$\sum_{i=0}^{G-1}\sum_{j=0}^{G-1}\{p(i,j)\}^2$
2	Contrast (or inertia)	CON	$\sum_{k=0}^{G-1}k^2 p_{x-y}(k)$
3	Correlation	COR	$\dfrac{\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(i-\mu_x)(j-\mu_y)p(i,j)}{\sigma_x\sigma_y}=\dfrac{\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(ij)p(i,j)-\mu_x\mu_y}{\sigma_x\sigma_y}$
4	Variance	VAR	$\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(i-\mu_x)^2 p(i,j)=\sum_{i=0}^{G-1}(i-\mu_x)^2 p_x(i)$
5	Inverse difference moment (or local homogeneity)	IDM	$\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}\dfrac{1}{1+(i-j)^2}p(i,j)$
6	Sum average (or mean value of 1st and 2nd gray-levels)	SAV	$\sum_{k=0}^{2G-2}kp_{x+y}(k)=\mu_x+\mu_y=2\mu_x$
7	Sum entropy	SEN	$-\sum_{k=0}^{2G-2}p_{x+y}(k)\cdot\log(p_{x+y}(k))$
8	Sum variance	SVA	$\sum_{k=0}^{2G-2}(k-SAV)^2 p_{x+y}(k)$
9	Entropy	ENT	$-\sum_{i=0}^{G-1}\sum_{j=0}^{G-1}p(i,j)\cdot\log(p(i,j))$
10	Difference entropy	DEN	$-\sum_{k=0}^{G-1}p_{x-y}(k)\cdot\log(p_{x-y}(k))$
11	Difference variance	DVA	$\sum_{k=0}^{G-1}k^2 p_{x-y}(k)-(\sum_{k=0}^{G-1}kp_{x-y}(k))^2$
12	Dissimilarity	DIS	$\sum_{i=0}^{G-1}\sum_{j=0}^{G-1}|i-j|\,p(i,j)$
13	Cluster shade	CLS	$\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(i+j-\mu_x-\mu_y)^3 p(i,j)=\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(i+j-2\mu_x)^3 p(i,j)$
14	Cluster prominence	CLP	$\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(i+j-\mu_x-\mu_y)^4 p(i,j)=\sum_{i=0}^{G-1}\sum_{j=o}^{G-1}(i+j-2\mu_x)^4 p(i,j)$
15	Maximum probability	MAP	$\max(p(i,j))$
16	Relative minimum pixel intensity	IMIN	$min(J(x,y))\,/\,mean((J(x,y))$
17	Relative maximum pixel intensity	IMAX	$max(J(x,y))\,/\,mean((J(x,y))$
18	Mean value of pixel intensity	IMEA	$mean((J(x,y))$

[1] J(x, y) is a 12-bit image before normalization, I(z, y) is the associated normalized 8-bit image as the input image for calculation of GLCM p(i, j). In addition, the following functions are used in the above definitions with i or j = 0,1,2,…,G-1 and G as the number of gray levels. G=255 for 8-bit gray level images I(x, y):

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

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