with Grey Level Co-occurrence Matrix (GLCM) for Positron

Emission Tomography (PET) Image Analysis

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ABSTRACT

Background:

Quantification of heterogeneous radiotracer uptake in PET has the potential to be used as a biomarker of prognosis. Textural features accounting for both spatial and intensity information have recently been applied to FDG-PET images and used to predict treatment response. However, textural features have been predicted to strongly depend on volume. Other factors affecting textural features such as segmentation and quantization have previously been investigated on clinical data while image contrast and noise have not been assessed systematically. This study aims to investigate the relationships between textural features and these factors using phantom data.

Methods:

The torso NEMA phantom was first filled with 18F solutions to yield different contrasts between the six hot spheres (0.5-27 cm3) and the colder uniform background (2:1, 4:1, 8:1) and scanned on the TrueV PET-CT scanner for 120min. Images were reconstructed using OSEM (4 iterations, 21 subsets) for different scan durations (15-120min) and smoothed with a 4-mm Gaussian filter. The phantom with two heterogeneous spherical inserts (8.2 and 18.8 cm3) was then scanned and reconstructed using same protocol for contrast 4:1 only. All spheres were delineated using three approaches 1) the exact boundaries based on their known diameters, 2) 40% fixed threshold and 3) adaptive threshold. Textural features were derived from the co-occurrence matrix using different quantization levels (8-256).

Results:

Some textural features (contrast, dissimilarity, entropy, correlation) increase while others (homogeneity, energy) decrease with quantization at different rates depending on sphere
volume. When using the exact delineation, contrast and scan duration (noise) have a lesser effect on textural features than sphere volume. When applying the same exact regions on the uniform background (no partial volume), the relationships between textural features and volume are comparable to when applied to the respective spheres except for correlation. Textural features are indirectly related to noise and contrast via segmentation with adaptive threshold being superior compared to the fixed threshold.

Conclusion:

Among the six textural features, homogeneity and dissimilarity are the most suitable for measuring PET tumour heterogeneity with quantization 64 if regions are segmented using methods that are robust to noise and contrast variations. To use these textural features as prognostic biomarkers, changes in textural features between baseline and treatment scans should always be reported along with the changes in volumes.

Keywords: Radiomics; PET tumour heterogeneity; texture analysis; GLCM; noise and contrast; segmentation.


**Introduction**

PET radiotracer uptake in tumour is often heterogeneous due to different biological characteristics of tumour cells (e.g., cell proliferation, cell death, differential metabolic activity, vascular structure etc.). Heterogeneity defines the aggressiveness and therapeutic resistance of the tumour and makes the effective treatment strategies challenging (1). Because of this reason, accurate quantification of intra-tumour heterogeneity has the potential to be used as a person specific tumour staging and prognostic biomarker (2-5). A large amount of quantitative features representing heterogeneity can be extracted from these images which is termed as radiomics (6). Artificial intelligence (AI) assisted accurate classification of these tumour radiomic features can make tumour staging and prognostic biomarker more robust (7, 8).

Among a number of heterogeneity features (2, 9-12), textural features (homogeneity, correlation, energy, contrast, dissimilarity and entropy) – a second order heterogeneity metric extracted from quantifier based grey level co-occurrence matrices (GLCMs) (13) accounting for both spatial and intensity information have shown to be capable of staging tumour (14) as well as to predict response (15, 16) for FDG PET images at varying levels.

GLCMs are generated using quantized or resampled intensities within a volume of interests (VOIs) (16) where intensities are resampled in an integer number of bins with the number of bins being power of 2. Textural features extracted from these GLCMs have been reported to be strongly dependent on the metabolically active volume (MATV) using simulated data (17) and confirmed on clinical data (18-23). Intensity quantization substantially affects the texture indices and thus should be chosen carefully (18, 24). Reducing quantization always decreases homogeneity (25) and prognostic impact of the textural features is influenced by quantization level (26). Several groups have suggested using either quantization level 32 (18) or 64 (16,
Quantization level 150 or higher also has been proposed in other studies (17, 19). No statistically significant differences have been reported in another study (16). Three textural features - homogeneity, dissimilarity and entropy are found to be robust to delineation method and partial volume effects (PVE) (21). A separate study suggested that smoothing and segmentation have only a small effect compared to quantization (24). Relationships of textural features with tumour heterogeneity using different parameters and methods reported in literature are summarized in supplementary Table S1.

Non uniform selections of parameters and methods across studies make the choice of best textural feature based on MATV, quantization and segmentation challenging and its relationship with the tumour biological characteristics indistinguishable (18, 20). Relationship between volume and quantization has not been explicitly investigated in these studies. Likewise, effects of other parameters such as image contrast and noise on segmentation and textural features have not been reported systematically. This study aims to investigate the relationships of textural features with these parameters using phantom data.

**Materials and Methods**

The torso NEMA phantom (Figure 1) containing six spheres (0.52, 1.15, 2.57, 5.58, 11.49 and 26.52 ml or cm³) was filled with $^{18}$F solutions to yield three different contrasts between the hot spheres and the colder uniform background (2:1 and 4:1). The activity ratio between spheres and background are shown in Table 1
Table 1. Activity concentration of the spheres and background

| Attributes       | 2:1 (kBq/ml) | 4:1 (kBq/ml) |
|------------------|--------------|--------------|
| Sphere           | 1668.52      | 2775.43      |
| Background       | 838.59       | 697.24       |
| Measured Ratio   | 1.99:1       | 3.98:1       |

The phantom data were acquired in 3D mode on the TrueV PET-CT scanner (Siemens, USA) for 120 minutes which provides 109 image planes or slices covering a 21.6 cm axial FOV (field of view). Images were reconstructed into a 256×256×109 matrix with voxel dimensions of 2.67×2.67×2.00 mm using OSEM reconstruction algorithm with 4 iterations and 21 subsets for five different scan durations (900, 1200, 2000, 4000 and 7200 seconds [15, 20, 33.3, 66.6 and 120 minutes]) to represent different levels of noise. The starting time of each static frame were shifted to reconstruct five different overlapping realizations for the first four durations. All the reconstructed images were then smoothed with a 4-mm FWHM (full width at half maximum) Gaussian filter after applying decay correction. The details of the full reconstruction can be found in (27).

In a separate scan, data were acquired by replacing the six spheres with two separate spheres with volumes of 8.18 and 18.82 ml corresponding to 25 and 33 mm diameter respectively (Figure 1). Each of these sphere also contains another smaller sphere of volume 1.15 ml (13 mm diameter) within it to create two separate compartments. The wall thickness kept at 2 mm. When these two compartments are filled with different level of activity, they represent a tumour which has a deprived core and a hot rim. 3D printing technology was utilized to create the two hot rim tumours. The background and inner spheres were filled with 564 kBq/ml and the outer rims of the spheres were filled with 2564.5 kBq/ml activity respectively to create a contrast of 4:1 between the hot rim, inner core and background.
Figure 1: (a) Torso NEMA phantom for PET with six fillable spheres and a cold insert in the middle, (b) The diameter of each of the six spheres, (c) CAD drawing of the lead with the heterogeneous insert and (d) CAD drawing showing the two spheres to create a hot rim and cold core. The diameter of the inner sphere is 13 mm. The outer sphere diameters are 25 and 33 mm for two separate inserts.

All the spheres (both homogeneous and heterogeneous) were delineated using three different segmentation methods. First volume of interest (VOI_{true}) was estimated using the calculated boundaries based on the known diameter and position of each sphere. The second delineation method was a fixed threshold set to 40% ($I_{40T}$) of the maximum intensity ($I_{max}$) within the sphere giving a VOI noted as VOI$_{40T}$ (28)

$$I_{40T} = 0.4 \times I_{max} \quad (1)$$

Voxels having activity more than $I_{40T}$ were included in the VOI$_{40T}$.

The final volume of interest (VOI$_\alpha$) was estimated using an adaptive threshold based method as described by Schaefer et al (29), where the threshold intensity (I$_\alpha$) is given by

$$I_{\alpha} = (\alpha \times I_{70}) + (\beta \times I_{bg}) \quad (2)$$

$I_{70}$ is the mean intensity in a contour containing all voxels with a value greater than 70% of the $I_{max}$ in the sphere and $I_{bg}$ is the mean background intensity within a sphere of size 26.52 ml located away from all the spheres to avoid partial volume effect (PVE). Both the threshold based methods were applied separately on each roughly delineated VOI containing a sphere to generate the corresponding VOIs. The $\alpha$ and $\beta$ parameters for the adaptive threshold were
calculated using the mean value of optimal cutoff intensities ($I_{optimal}$) of five realizations using all contrasts for each acquisition duration. $I_{optimal}$ of each hot sphere is calculated using optimal threshold ($T_{optimal}$) and $I_{max}$. $T_{optimal}$ is estimated as the percentage threshold value of $I_{max}$ which provides the best matched thresholded volume with the VOI$_{true}$ for the uniform sphere phantom.

To investigate the individual effect of size and segmentation on GLCM features, six similar size spheres were also placed on the background away from the hot spheres to remove the variability arising from inconsistent segmentation of VOI. For investigating the effects of shape, three different shapes (cylinder, ellipsoid and spheres) with same volumes of 2.57 and 26.52 cm$^3$ were placed in the background (Figure 1).

Quantization of intensities of each VOI was carried out by normalizing the intensities (between 0 and 1) and multiplying the normalized intensities by different quantized values, ($Q= 8, 16, 32, 64, 128$ and $256$)

$$N(x) = D \times \left( \frac{I(x) - [I(x)]_{min}}{[I(x)]_{max} - [I(x)]_{min}} \right)$$  \hspace{1cm} (3)

where

$I(x)$ is the intensity of voxel $x$ in the original image

$[I(x)]_{min}$ and $[I(x)]_{max}$ are the minimum and maximum value in the VOI

$D$ is the quantization level (4, 8, 16, 32, 64, 128 and 256)

Grey level co-occurrence matrix (GLCM) was derived for each normalized and quantized VOI data. Several textural features (homogeneity, correlation, energy, contrast, dissimilarity
and entropy), a second order heterogeneity measures, were then estimated from these GLCM data. The textural features are given as

\[
\text{Homogeneity} = \sum_{i,j} \frac{1}{1-(i-j)^2} p(i,j)
\]

\[
\text{Correlation} = \sum_{i,j} \frac{(i-\mu_i)(j-\mu_j)p(i,j)}{\sigma_i \sigma_j}
\]

\[
\text{Energy} = \sum_{i,j} p(i,j)^2
\]

\[
\text{Contrast} = \sum_{i,j} |i-j|^2 p(i,j)
\]

\[
\text{Dissimilarity} = \sum_{i,j} |i,j| p(i,j)
\]

\[
\text{Entropy} = -\sum_{i,j} p(i,j) \log(p(i,j))
\]

where

\((i,j)\) indicates cell location of the GLCM matrix,

\(p(i,j)\) is the cell value at \((i,j)\),

\(\mu\) and \(\sigma\) are mean and standard deviation respectively.

The ranges of homogeneity, energy and entropy is \([0,1]\). The GLCM homogeneity is high or 1 if GLCM concentrates along the diagonal meaning that there are a lot of pixels with the same or very similar grey level values. Therefore, high homogeneity refers to textures that contain ideal repetitive structures. Low homogeneity refers to a big variation in both, texture elements and their spatial arrangements. An ‘inhomogeneous texture’ refers to an image that has almost no repetition of texture elements and spatial similarity is absent. The larger the changes in grey values, the lower the GLCM homogeneity.
Solid tone image would have an entropy value of 0. A completely random distribution would have very high entropy. On the other hand, Energy is 1 for a constant image. Energy is a measure of local homogeneity and therefore represents the measure opposite to entropy.

The range of correlation value is \([-1,1]\). It returns a measure of how correlated a pixel to its neighbor over the whole image. Correlation is 1 or -1 for a perfectly positively or negatively correlated image and ‘\(NaN\)’ for a constant image.

Contrast and dissimilarity range is \([0, (\text{size}(GLCM) - 1)^2]\) and \([0, \infty]\) respectively. Both contrast and dissimilarity are 0 for a constant or perfectly homogeneous image and low if the neighbouring pixels are very similar in their grey level values indicating soft texture but the measure value is differently weighed. For heavy texture, both contrast and dissimilarity values are high with maximum values being \((\text{size}(GLCM) - 1)^2\) and \(\infty\) respectively.

**Results**

One representative slice for both homogeneous and heterogeneous spheres for both contrasts and three different acquisition durations (900, 2000 and 7200 seconds) are shown in Figure 2.

All the textural features are dependent on the quantization value. Figure 3 shows the relationships between mean textural features of five realizations and quantization values for \(\text{VOI}_{\text{true}}\). Homogeneity exponentially decreases with the increase of quantization levels. Separations among homogeneity for different spheres remain unchanged for different quantization levels. Correlation remains constant with quantization for all spheres from quantization level 32 onwards. However, there are clear separations among correlations for
different spheres. Contrast and dissimilarity increase approximately linearly with the increase of quantization levels. Separation among the spheres increases with the increase of quantization levels. Energy decreases and entropy increases with quantization levels. For volumes less than 5.58 cm$^3$ both entropy and energy remain unchanged after quantization 32. However, it keeps on changing with quantization for bigger spheres and requires higher quantization level to remain unaffected. Higher quantization level would make volumes appear as heterogeneous. On the contrary, low quantization level would make them appear as homogeneous. A compromise is required while choosing appropriate quantization level. Considering all six textural features, quantization level 64 or 32 appears to provide the best compromise. Quantization level 64 has been chosen in this study to generate all the textural features unless mentioned otherwise.

**Figure 2:** One reconstructed slice of the NEMA PET phantom with homogeneous spheres for contrast 2:1 (first row: a to c) and 4:1 (second row: d to f). The heterogeneous spherical inserts with cold inner core (third row: g to i). First column (a, d & g) for 900 seconds, second column (b, e & h) for 2000 seconds and third column (c, f & i) for 7200 seconds reconstructions. Red circles represent $\text{VOI}_{\text{true}}$ and green circles represent spherical background lesions with different volumes. (j, k & l) represent cylindrical, ellipsoidal and spherical shaped objects with the same volumes that were placed in the uniform background.

Figure 4 shows the relationships between textural features and acquisition duration for $\text{VOI}_{\text{true}}$ for contrast 2:1. All the features remain unchanged with acquisition durations and are reproducible if the true volume is known except for the smallest one. There are clear separations among volumes for all six textural features. Standard Deviation (SD) reduces with the increase of volume of sphere with energy and entropy being the most reproducible.
Dependency of textural feature on sphere volume for contrast 4:1 is shown in Figure 5. Features for the spheres located at the background also show dependency on the volumes. Homogeneity and entropy increase with volumes, whereas contrast, dissimilarity and energy decrease. There are subtle differences between the spheres and backgrounds for homogeneity, contrast and dissimilarity showing their dependency on the volume edge. Entropy and energy are robust to edge as shown by very good agreement between the sphere and background. The separation between sphere and background for correlation indicates that it is more dependent on the intensity variations. All the features reaches plateau with the increase of volume at varying rates. The features do not vary with the contrast if VOI_true is known (Figure 6).

**Figure 3:** Mean six textural features (a to f) of five realizations against quantization for VOI_true for all six spheres. The features shown here are for 4:1 contrast and 900 seconds acquisition duration.

**Figure 4:** Six textural features (a to f) vs. acquisition durations for VOI_true, contrast 2:1 and quantization level 64.

**Figure 5:** Six textural features (a to f) vs. True Volume (VOI_true) for contrast 4:1, 900 seconds acquisition and quantization level 64 for both sphere and background.

**Figure 6:** Six textural features (a to f) vs. image contrast for VOI_true for acquisition duration 900 seconds and quantization level 64.
Volumes estimated from all three methods for all three contrasts are shown in Figure 7. VOI\textsubscript{40T}, estimated using I\textsubscript{40T}, are always smaller compared to VOI\textsubscript{true} for 8:1 contrast and high noise. VOI\textsubscript{40T} for contrast 4:1 are similar to VOI\textsubscript{true} especially for volumes bigger than 5.58 cm\(^3\) and less dependent on noise, indicating that I\textsubscript{40T} is optimal for 4:1 contrast. VOI\textsubscript{40T} are always overestimated for contrast 2:1 for all noise levels for volumes less than 5.58 cm\(^3\). For bigger volumes VOI\textsubscript{40T} are underestimated for high noise cases for contrast 2:1. As the contrast goes down, the dependency on the volume and noise increases and the discrepancies between VOI\textsubscript{A} and VOI\textsubscript{true} become noticeable especially for smaller volumes and higher noise.

Figure 8 and 9 compare the relationships between textural features and acquisition durations for VOI\textsubscript{true} with VOI\textsubscript{40T} and VOI\textsubscript{A} respectively for contrast 2:1. Textural features derived using VOI\textsubscript{40T} are significantly different than those of VOI\textsubscript{40T} for smaller volumes (Figure 8). As the volume increases the differences between them reduces. The textural features also vary with the noise as the VOI\textsubscript{40T} vary with the noise. With an adaptive segmentation method, all textural features become independent of noise for volume greater than 2.57 cm\(^3\) and match closely with the features generated using VOI\textsubscript{true} (Figure 9).

**Figure 7:** Log of volumes vs. acquisition durations for all six spheres for three segmentation methods (true volume (VOI\textsubscript{true}), 40% threshold (VOI\textsubscript{40T}) and adaptive threshold (VOI\textsubscript{A})) for contrast 2:1 (a) and 4:1 (b).

**Figure 8:** Six textural features (a to f) vs. acquisition durations for two different segmented volumes (VOI\textsubscript{true} and VOI\textsubscript{40T}) for contrast 2:1 and quantization level 64.
**Figure 9:** Six textural features (a to f) vs. acquisition durations for two different segmented volumes (VOI\textsubscript{true} and VOI\textsubscript{A}) for contrast 2:1 and quantization level 64.

Figure 10 shows the six textural features for 2.57 and 26.52 cm\textsuperscript{3} cylindrical, ellipsoidal and spherical volumes. The results indicate that energy and entropy are more sensitive to change in volumes compared to the other four textural measures. However, for similar volumes, none of the textural feature shows any dependency on the shape of the volume.

**Figure 10:** Six textural features (a to f) vs. lesions with different shapes and volumes placed in the background for contrast 2:1 and quantization level 64. C-2.57, E-2.57 and S-2.57 represents 2.57 cm\textsuperscript{3} cylindrical, ellipsoidal and spherical volumes respectively. C-26.52, E-26.52 and S-26.52 represents 26.52 cm\textsuperscript{3} cylindrical, ellipsoidal and spherical volumes respectively.

Figure 11 shows the textural features comparison between the six homogenous spheres of contrast 4:1 with the two heterogeneous spheres of the same contrast for three different segmentation methods. Due to PVE the smaller heterogeneous sphere appears less heterogeneous in the reconstructed image for 900 seconds acquisition durations (Figure 2). Because of that, all the textural features generated using VOI\textsubscript{true} for smaller heterogeneous sphere agrees with the homogeneous spheres of similar volumes except correlation, which is dependent on the intensity. Homogeneity, contrast and dissimilarity measures are different for the bigger heterogeneous sphere compared to the homogenous ones of similar volumes. Though being 123% bigger than the smaller one, the bigger heterogeneous sphere shows little differences in these three textural features for VOI\textsubscript{true} indicating that the volume effect is compensated by heterogeneity. They are even more similar for VOI\textsubscript{A} for both the heterogeneous spheres because adaptive threshold only able to segment the hot rim of the
bigger sphere. However, these three measures for VOI_A are different from VOI_true because their VOIs are also different. Both the heterogeneous spheres show similar entropy and energy measures for both VOI_true and VOI_A to that of the homogeneous spheres. For VOI_{40T}, they are also similar as volumes delineated by this method for these two heterogeneous spheres are similar indicating that these two heterogeneity measures are more dependent on volume than heterogeneity itself compared to the former three measures. Since VOI_{40T} is able to delineate the whole bigger sphere (hot rim and the deprived core) unlike VOI_A, the other heterogeneity measures for VOI_{40T} are different for two heterogeneous spheres. However, VOI_{40T} for both the spheres are much bigger than the VOI_true.

**Figure 11:** Six textural features (a to f) vs. volumes for all six homogeneous spheres for VOI_true and for two heterogeneous spheres for VOI_true, VOI_{40T} and VOI_A. Contrast and quantization level were kept fixed at 4:1 and 64 respectively.

**Discussion**

To use textural features as a tumour staging and prognostic biomarker better understanding of relationships of textural features with MATV, quantization and segmentation are very important. Investigation of spheres filled with same homogeneous activity reveals that bigger the volume wider the range of intensities making quantization sensitive to the volume of lesions. In such cases, higher quantization makes bigger homogeneous spheres appear as heterogeneous compared to the smaller ones. Lower quantization level removes the dependency on volume by forcing the intensities to be homogeneous and eliminating the heterogeneity information. Considering the characteristics of all the textural features for the homogeneous spheres over a range of volumes, it appears that quantization level 32 or 64 should be preferred and the findings are similar to the finding of previous studies (16, 18).
All six textural features are dependent on volumes at varying degrees with entropy and energy being the most sensitive ones. Spheres of similar volumes placed in the background reveals that PVE effect on textural features is far smaller than the effect of volume. Dependency of entropy on MATV significantly reduces for volumes greater than $45 \text{ cm}^3$ for quantization 256 (19). However, a different study suggested to use volume greater than $10 \text{ cm}^3$ (23) for quantization 64. Dependency of quantization on volume investigated in this study explains the reason for finding two different cutoff volumes. Investigation on heterogeneous spheres suggested that if response occurs as a result of combined changes in volume and heterogeneity, entropy and energy are only able to display changes in volumes (not heterogeneity), making them unsuitable for prognostic biomarkers of heterogeneity. High sensitivity of correlation to intensity also makes it less suitable to report changes in heterogeneity.

Two threshold based delineation methods (40% fixed and adaptive) were employed to investigate the effects of segmentation on textural features. It has been found that fixed threshold can only be optimal for a certain contrast for all noise levels and remains sensitive not only to contrast and volume but also to noise. With an adaptive approach, the dependency on contrast and noise is reduced and becomes less sensitive to contrast and noise. However, for the case of clinical setting where the acquisition duration is generally 15 minutes or 900 seconds, the adaptive threshold performance is not optimal particularly when the volume is small and contrast is low. The volumes generated using these two methods are substantially different. Since VOIs delineated using 40% threshold are different from each other, textural features generated using these VOIs are also different with the actual lesion volumes being the same. However, since VOIs generated using adaptive threshold matches with the VOI\textsubscript{true}, textural features are closer to the true textural features compare to VOI\textsubscript{40T}. These results suggested that texture indices are highly sensitive to the segmentation method due to the
erroneous inclusion or exclusion of the boundary or the edges of the lesion. These findings are confirmed by the consistent textural measures provided by the different shapes with the same volumes placed in the uniform background. The results are also consistent with the previously published findings (18, 21, 30).

Volume delineated by a robust segmentation method is capable of generating textural features such as homogeneity, contrast and dissimilarity that are capable of capturing tracer uptake heterogeneity if the volume changes between scans are minimal. Since homogeneity directly related to volume, it can only be used as a feature of image heterogeneity if the changes of volume and homogeneity are in opposite directions, i.e., if the combined multiplicative changes of volumes and homogeneity are either zero or negative. On the other hand, as contrast and dissimilarity are inversely related to volume they can be used as an image heterogeneity feature if the combined multiplicative changes of volumes and homogeneity are either zero or positive. Since contrast is approximately two times more sensitive to volumes compared to dissimilarity, homogeneity and dissimilarity are the two textural features that should be used to measure heterogeneity. These two features also provide complementary heterogeneity information which can be used for cross validation.

**Conclusions**

Homogeneous regions appear heterogeneous on PET images as quantified by textural features. Textural features generated using GLCM depends on quantization, volume and segmentation method. Since these features differentially vary with volume, regions should be segmented using methods are that are robust to variations in contrast and noise using quantization level 64. Small scale heterogeneity phantom studies suggest that homogeneity and dissimilarity are the most suitable textural features to be used as heterogeneity measures.
where there are combined changes in both heterogeneity and volume due to treatment. Further investigations are required with more complex heterogeneous phantoms representing real clinical scenario to fully understand the volume and segmentation effects on the reproducibility of these textural indices. Nonetheless, to use these textural features as prognostic biomarkers, changes in textural features between baseline and treatment scans should always be reported along with the changes in volumes.

Declarations

• Ethics approval and consent to participate:

Not applicable.

• Consent for publication:

Not applicable.

• Availability of data and material:

The datasets used during the current study are available from the corresponding author on reasonable request.

• Competing interests:

The author declares that he has no conflict of interest.

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- **Authors' information:**

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