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REVIEW

Application of fractal and textural analysis in medical physiology, pathophysiology and pathology

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Summary

Fractal and textural analyses represent a rapidly developing class of computational and mathematical methods with potential wide applications in medicine and biology. In recent years, they have been successfully used for the evaluation of subtle alterations in cell and tissue morphology associated with various physiological and pathological processes. It has been shown that cells in early stages of apoptosis exhibit changes in chromatin fractal and textural features. Cellular senescence is also sometimes associated with changes in textural patterns in some cell populations. So far, artificial intelligence approaches based on co-occurrence matrix textural data were successfully implemented in predicting cell damage in in vitro conditions, with artificial neural networks achieving the best performance. In the future, several methodological issues and challenges related to the use of fractal and textural methods will have to be resolved before their introduction into contemporary clinical practice. This concise review focuses on the recent research on the application of fractal and textural methods in experimental physiology and related fields.

Key words: fractal, texture, signal, artificial intelligence.

INTRODUCTION

Fractal and textural analyses represent a rapidly developing class of computational and mathematical methods with potential wide application in medicine and biology. Since their introduction in the second half of the 20th century, they have been implemented in both fundamental and clinical medical fields and they have contributed to the better understanding of various physiological and pathological processes. The examples include the utilization of fractal computations to describe self-similarity nature of nuclear chromatin, as well as the use of textural features to detect changes of tissue structural entropy during the process of physiological aging. These methods also have a potentially significant diagnostic value in medicine since they may be used to enhance objectivity and the level of automation of various protocols and techniques during pathohistological analysis of tissues and cells (1-5).

Both fractal and textural methods can be used for analyzing various signals in medicine (3-5). These mostly include two-dimensional data such as the ones associated with digital micrographs. One-dimensional signals such as the ones obtained during electroencephalography and electromyography can also be evaluated. Some fractal features of three-dimensional computer models can also be successfully quantified in order to better understand different levels of structural organization related to complex biological systems. In essence, there are very few methodological constraints that limit the use of these techniques in both fundamental and applied medical sciences, and it is estimated that these methods will become important additions to many conventional research protocols in future (1-3).

In recent years, there have been many attempts to integrate these methods with machine learning algorithms in order to develop artificial intelligence systems capable of classification and prediction of biological processes (6, 7). Quantifications of cell textural features can be used to train various machine learning models such as the ones based on a binomial logistic regression, decision trees and random forests. Support vector machines as a supervised machine learning approach also use fractal input data during the model training and testing for classification and prediction accuracy. Finally, numerous artificial neural networks can be created to use these types of data. The examples include relatively simple multilayer perceptron networks, but also complex Bayesian and convolutional neural networks for computer vision in pathology and other medical fields (7-10).

This concise review focuses on recent research on the application of fractal and textural methods to experimental physiology and related fields. We primarily focus on fractal box counting algorithm and textural gray level co-occurrence matrix (GLCM) algorithm since they are probably most frequently used in medical research. We also cover the use of discrete wavelet transform mathematical analysis as a common addition to GLCM. Finally, we discuss our recent results on the potential use of these methods in the development of artificial intelligence models in fundamental and clinical medicine.

FRACTAL AND TEXTURAL INDICATORS

The most important fractal indicators are fractal dimension and lacunarity (11-15). There are numerous ways to calculate fractal dimension from a signal, but today, standard box counting method is most widely implemented. When evaluating a two-dimensional signal, the structure, which is usually binarized, is covered by a series of boxes on different scales, after which the partially or fully filled boxes are counted (15). Subsequently, the software forms a log-log regression line based on these numbers and respective scales, and the value of fractal dimension is computed from the slope of the line. This value for the binarized 2D structure is usually between 1 and 2 and it represents an indirect quantification of complexity and the level of detail. Lacunarity, on the other hand, represents the degree of "gappiness" in the fractal architecture, and it is computed from a variation coefficient of the number of resolution units per box. The values of fractal dimension and lacunarity may be in a strong statistical association for some signals but this is not always the case (13-15).

Textural indicators are computed based on higher mathematical operations and the second order statistical analysis is often required (16-19). Gray level co-occurrence matrix approach is often used for this although today there are many different alternatives. In two-dimensional signals, gray intensity values are allocated to the resolution units after which the value pairs are analyzed taking into account the distance between the units and the orientation (i.e. horizontal, vertical, diagonal). Probably most important textural features that are subsequently calculated are angular second moment, inverse difference moment, entropy, and contrast (16, 17). Angular second moment is often a representation of textural uniformity, whereas inverse difference moment greatly depends on the local homogeneity of resolution units. Entropy depends on the level of chaos and disorder of texture, while the contrast is an indirect quantification of textural heterogeneity. Most textural features are mathematically interrelated although the strength of correlation may vary due to many contributing factors (16-19).

Today, in medicine and biology, as an addition to the traditional GLCM analysis, mathematical wavelet analysis is also sometimes performed. This analysis is based on the mathematical concept of wavelet signals and, among numerous different approaches, Harr discrete wavelet transform probably has the biggest potential in medical research (20, 21). Wavelet coefficient energies computed using this technique are often indirect indicators of textural

heterogeneity and can be used to provide a more detailed insight and explanations on the nature of GLCM changes.

FRACTAL DIMENSION AND TEXTURAL FEATURES OF NUCLEAR CHROMATIN

Nuclear chromatin is a complex macromolecule and many aspects of its structural organization and biophysical principles that govern it are not entirely understood (22-26). The most fundamental level of chromatin organization is based on nucleosomes, a complex of DNA and histone proteins, where the DNA is wrapped around a protein octamer, and forms the so-called beads-on-a-string structure. The nucleosomes with the help of other histones and nonhistone proteins then coil into a filamentous helical system, 30 nm in diameter, designated as chromatin fiber. Chromatin fibers can form large swaths of transcriptionally inactive heterochromatin, but they can also uncoil to the basic beads-on-a-string form and become more active as euchromatin. Higher levels of coiling are also possible and may occur during cell division or other processes (22-26).

When looking at monomer attraction forces within a polymer such as chromatin and their interaction with repulsion forces, traditional models assumed the creation of an equilibrium state, or equilibrium globule as a transition from an initial coil-globule condition (27-29). This equilibrium model of chromatin architecture has long been a dominant view in some scientific circles. At the beginning of the 21st century, an alternative model, based on the fractal globule, has been proposed, and some evidence point to it as being the correct interpretation. Fractal globule possesses some characteristics of self-similarity, a hallmark trait of fractals. In the fractal globule, a distinct territorial organization is observed (unlike mixed structure in equilibrium), and many similar globules can be observed on different scales. Fractal dimension of euchromatin and heterochromatin differ, with euchromatin usually having a higher level of fractal complexity (29). Probably the most important works that in detail explain arguments for the equilibrium and fractal models of chromatin architecture are the ones by Mirny, Kwon and Sung (27, 28).

Textural features of chromatin can be successfully quantified using the above-mentioned gray level co-occurrence matrix method. This technique can be applied both in conventional light microscopy and transmission electron microcopy evaluation of chromatin architecture. So far three most frequently quantified chromatin GLCM indicators have been angular second moment, inverse difference moment and entropy. They are potentially capable of detecting subtle alterations in chromatin distribution during various physiological and pathological processes even if these changes cannot be visualized by an experienced histologist or pathologist (30-32).

Programmed cell death may be followed by pronounced changes in chromatin fractal and textural indicators. One of the first studies describing these changes was published by Losa and Castelli (2005) in human breast cancer cells, where apoptosis was induced by the chemical agent calcimycin (33). It was shown that during the early stages of cell death, a significant loss of chromatin complexity occurs demonstrated by reduction in the fractal dimension. Furthermore, this is followed by a significant increase of GLCM sum entropy and some other textural features. Both fractal and GLCM methods seem to be more sensitive than conventional cytofluorometric techniques in detection of early apoptosis (33).

Some other proapoptotic substances can also change chromatin distribution inside the nucleus which then reflects on GLCM features. The example is oxidopamine, a potent neurotoxin that in certain conditions induces cell death in many different cell populations. In some previous works, it was demonstrated that this compound even in small, sublethal concentrations leads to the reduction of nuclear angular second moment and inverse difference moment (30, 31). These changes are probably related to DNA and chromatin damage that takes place due to the effects of reactive oxygen species and oxidative stress as it has been hypothesized recently (34).

There are three potential explanations for the changes of GLCM and fractal parameters of chromatin in different experimental settings. First, condensation of chromatin that usually occurs during the early stages of cell death may influence both chromatin complexity and texture (33, 34). Condensed, inactive chromatin can probably have lower values of fractal dimension and high values of uniformity and local homogeneity quantified by angular second moment and inverse difference moment, respectively. Second, chromatin marginalization, that is also sometimes present during cell damage and death, may also change chromatin fractality and entropy (35). Finally, subtle changes in euchromatin/heterochromatin ratio that are independent of chromatin condensation and marginalization may also affect fractal dimension of the nucleus particularly knowing that these two forms of chromatin, when considered separately, have different values of complexity (36, 37). Previously, it was demonstrated that within a single cell population such as the hepatocytes, the cells that have very discrete differences in gene expression (periportal versus perivenous hepatocytes) have significantly different values of GLCM chromatin indicators, even though these differences are not visible during conventional microscopy (32). In future, it remains to be seen if fractal and GLCM methods will have a practical application in terms of being used as a part of sensing systems to detect cell damage and death.

FRACTAL AND TEXTURAL ANALYSIS IN AGING RESEARCH

One of the first works to introduce the chaos theory and fractality in aging and senescence research was by Lipsitz and Goldberger (1992), which suggested that the reduction of fractal complexity during aging contributes to the decreased ability of the organism to adapt to physiological stress (38). Since then, there have been numerous studies confirming such loss of complexity in various tissues and cell populations. In many tissues, the reduction of fractal dimension is sometimes followed by an increase in structural degradation and deterioration, which can be indirectly quantified with some textural features such as GLCM entropy. Nowadays fractal and textural methods are frequently used to demonstrate age-related changes in tissue cytoarchitecture, intercellular communication and even individual cells and their organelles (39, 40).

One of the examples where fractal analysis method was used to describe complexity loss of cytoarchitecture during aging is our study on spleen hematopoietic tissue in mice (41). Here we obtained spleen tissue from 64 male Swiss albino mice and divided them into 8 separate age groups. The hematopoietic tissue was stained with nucleic acid specific toluidine blue dye and the results indicated that during aging the fractal dimension of the tissue decreased while the lacunarity increased. Another study which used toluidine blue technique was done with liver tissue, however, here instead of quantifying tissue fractal parameters, we opted for calculation of fractal descriptors of chromatin organization (42). As expected, we showed that there was an age-dependent reduction of the fractal dimension. Age-related changes in tissue and cell fractal parameters are not necessarily present solely in old animals. Postnatal development is also sometimes characterized by a similar reduction of complexity as it was shown in the previous work on Giemsa-stained chromatin in mice spleen follicular cells (43).

Regarding the textural indicators, to the best of our knowledge, the first study in the field of aging research to use the GLCM approach was done by Shamir et al. (2009) on the animal model of Caenorhabditis elegans (44). Here the authors analyzed age-associated changes in muscle tissue and demonstrated changes in entropy and directionality, probably due to structural degradation. The particularly interesting observation of this study was the agreement of the detected changes with gene expression findings, demonstrating the ability of GLCM method to indirectly predict epigenetic processes in cells. This work also discussed two different theories of aging, one focused on stochastic accumulation of damage and the other focused on changes in developmental pathways, as well as the ability of textural analysis to provide indirect evidence supporting the latter (44).

Similarly to the work of Shamir and associates, in 2012, textural entropy increase due to aging was quantified in mice spleen hematopoietic tissue (45). However, in this case, the focus of the study was on cell nuclei rather than on tissue cytoarchitecture. Apart from changes in textural entropy, it was shown that local textural homogeneity of the nuclei (quantified as inverse difference) significantly decreased. Two potential explanations of the changes were provided: one focused on DNA damage accumulation, and the other on epigenetic dysregulation.

Regarding more recent works on the use of GLCM analysis in aging research, one must mention the work of Imakubo et al. (2021) done on Caenorhabditis elegans oocytes. Age related changes of oocyte appearance were evaluated by quantifying various textural features and GLCM correlation feature proved to be a sensitive indicator. This study showed the potential of GLCM algorithm to be used as a part of future biosensors capable of objectively assessing oocyte quality and potentially reducing errors in fertilization (46).

Future applications of fractal and textural analyses in experimental gerontology will mainly be focused on testing the ability of these methods to detect and quantify age-associated accumulation of DNA damage and changes in gene expression. Also, we will need to evaluate the effects of numerous chemical mediators related to aging on fractal and textural characteristics of cells and tissues. Finally, future work will need to include the standardization, validity testing and other aspects of quality assurance of these methods. Both fractal and GLCM algorithms will have to be implemented in different experimental settings, and inter-observer and intra-observer reliability will have to be assessed. Only then will we be able to draw definite conclusions on the scientific value of these methods in aging research.

ARTIFICIAL INTELLIGENCE BASED ON FRACTAL AND TEXTURAL DATA

Artificial intelligence (AI) in essence represents a large group of computation methods, models and algorithms where a machine learns or acquires the ability to perform cognitive functions that at least partially resemble those of a human. There are various types of machine learning (ML) some of which are supervised while others are unsupervised (48, 49). Machine learning in medicine and biology offers new and exciting possibilities of automation and autonomy of numerous diagnostic and research protocols and methods. Even today, various ML-based computer automated diagnostic systems are implemented in both fundamental and clinical medicine, and it is estimated that in future, artificial intelligence will become an important part of decision making in almost every medical discipline (48, 49).

Fractal and textural analyses offer an abundance of data and most of them can be used to train and test AI models. These models can be developed with the aim of
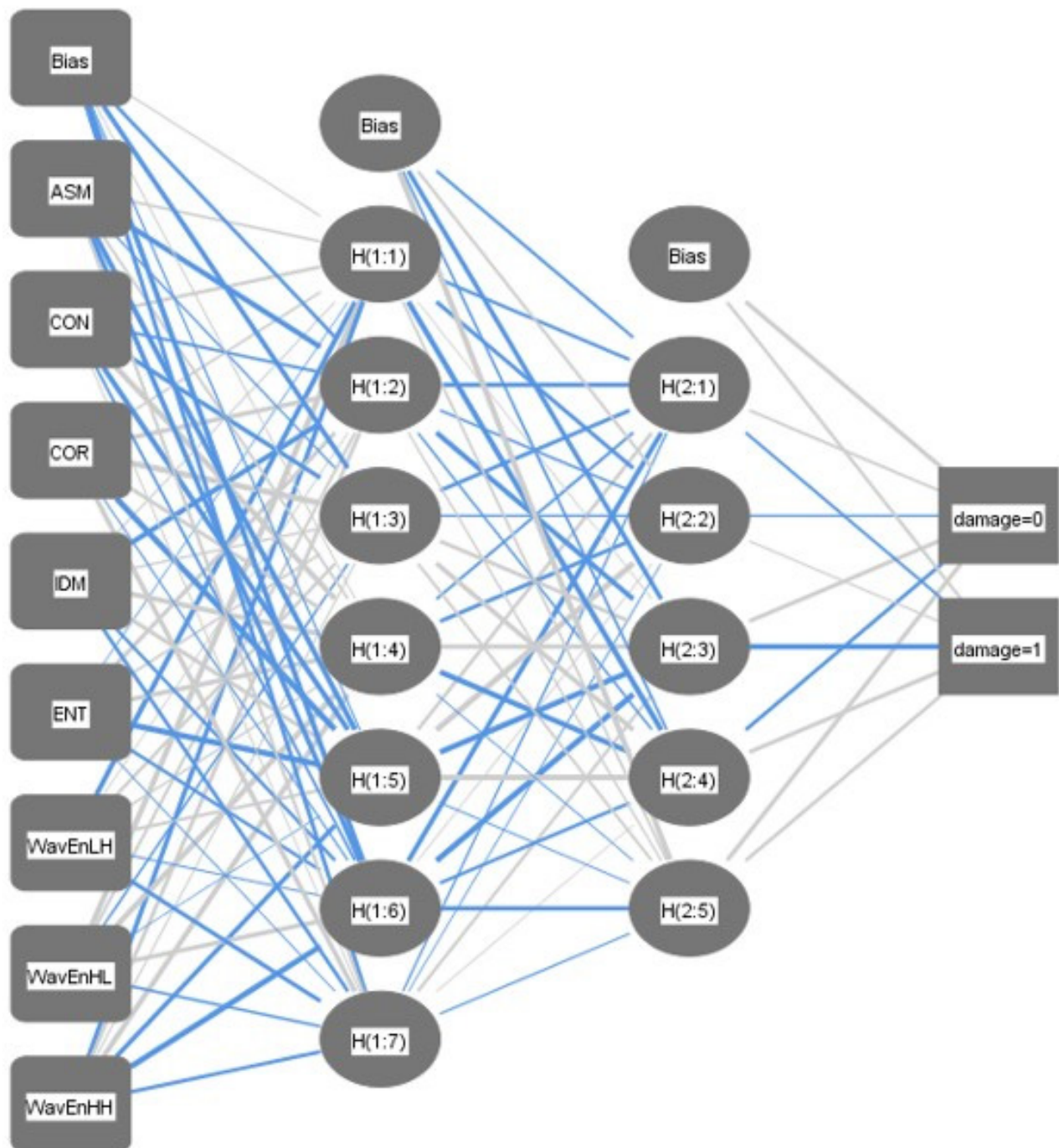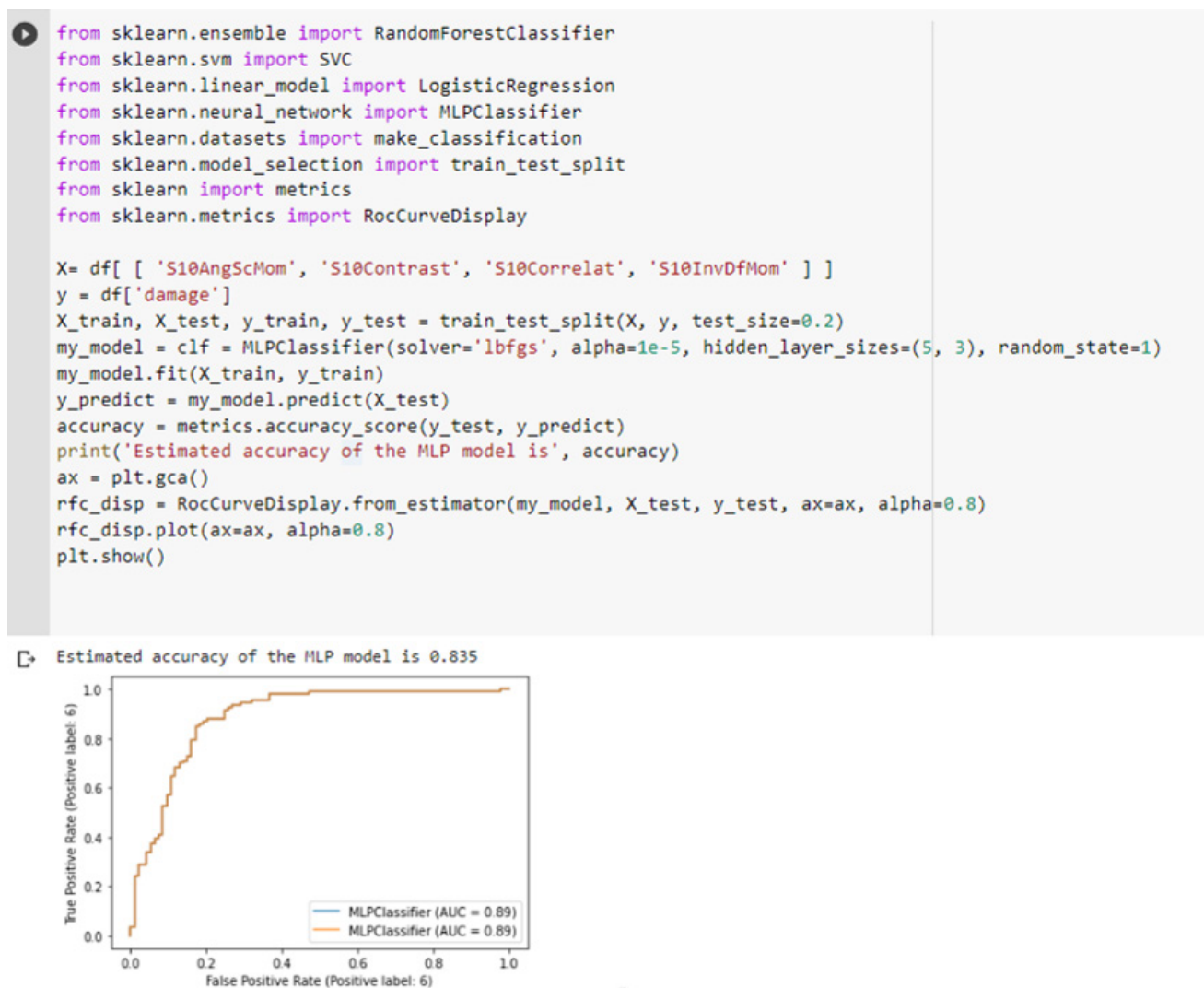
Figure 1. Example of an artificial neural network architecture with 2 hidden layers of neurons that uses GLCM (ASM as angular second moment, CON as contrast, COR as correlation, IDM as inverse difference moment, ENT as entropy) and wavelet coefficient energies (WavEnLH, WavEnHL, WavEnHH) as input data. The network is used to classify damaged (damage=0 as output) and intact cells (damage=1 as output).

classifying biological systems (i.e. cells) based on their physiological properties. They can be also created with the ability of prediction of physiological or pathological phenomena. The common approach would be to use fractal indicators such as fractal dimension and GLCM indicators such as angular second and inverse moments as input data during training. The output data can be a class of cells or tissues formed based on a hallmark trait, or a biochemical parameter as a variable (6-8).

Probably the most feasible AI application of fractal and textural data is their use in training supervised machine learning algorithms. During this type of training, the machine is exposed to the series of input data (i.e. fractal dimension, inverse difference moment etc.) and the resulting output data which is usually binary (6, 7). After many repetitions, the machine learns to associate certain values from the input with the result. In artificial neural networks this learning is done by weight adjustment in hidden layers of neurons **(figure 1)**. Neural networks to this date probably remain the most efficient supervised learning approach to GLCM data. These include simple multilayer perceptrons which, are relatively

```
from sklearn.ensemble import RandomForestClassifier
from sklearn.svm import SVC
from sklearn.linear_model import LogisticRegression
from sklearn.neural_network import MLPClassifier
from sklearn.datasets import make_classification
from sklearn.model_selection import train_test_split
from sklearn import metrics
from sklearn.metrics import RocCurveDisplay

X= df[ [ 'S10AngScMom', 'S10Contrast', 'S10Correlat', 'S10InvDfMom' ] ]
y = df['damage']
X_train, X_test, y_train, y_test = train_test_split(X, y, test_size=0.2)
my_model = clf = MLPClassifier(solver='lbfgs', alpha=1e-5, hidden_layer_sizes=(5, 3), random_state=1)
my_model.fit(X_train, y_train)
y_predict = my_model.predict(X_test)
accuracy = metrics.accuracy_score(y_test, y_predict)
print('Estimated accuracy of the MLP model is', accuracy)
ax = plt.gca()
rfc_disp = RocCurveDisplay.from_estimator(my_model, X_test, y_test, ax=ax, alpha=0.8)
rfc_disp.plot(ax=ax, alpha=0.8)
plt.show()
```

Estimated accuracy of the MLP model is 0.835

Figure 2. Example of the programming code for the multilayer perceptron AI model that uses GLCM angular second moment, inverse difference moment, correlation and contrast features as input data. The model has the classification accuracy of 83% in separating damaged from intact cells and area under the ROC curve of 0.89. The code was written in Python programming language and Scikit-learn library.

easy to develop in contemporary programming languages **(figure 2)**, and also convolutional neural networks frequently used form computer vision. Other possible supervised learning algorithms include the ones based on decision trees **(figure 3)**, random forest, support vector machines, principal component analysis or binomial logistic regression (6, 7).

Our recent publication on the application of artificial intelligence methods focused on the ability of GLCM-trained machine learning models to identify cell damage caused by sublethal doses of ethanol (7). As input data, we used GLCM contrast, GLCM correlation, angular second moment, inverse difference moment and GLCM variance. Three AI approaches were evaluated: multilayer perceptron neural network, binomial logistic regression, and random trees. The results indicated that the multilayer perceptron had the highest classification accuracy and the area under the receiver operating characteristic curve suggesting that this approach had the highest discriminatory power when separating damaged from intact cells (7).

In future, before using AI algorithms based on fractal and GLCM data in practice, one will have to resolve several limitations related to training, testing and validity of these methods. Many AI algorithms are essentially "black box" models meaning that it is difficult, if not impossible to interpret the inner mechanisms that govern the model (apart from input and output data). This may especially be true of artificial neural networks, but it may also be applied to support vector machines and random forests. Second, rigorous quality assurance of both fractal and GLCM method, as well as the future biosensors based on AI must be performed. Finally, issues regarding data validity and sample size must be resolved particularly knowing that in some medical scientific areas it may be difficult to obtain data large enough form training a machine learning model. Only after these challenges are adequately resolved, we will be able to include GLCM and fractal-based AI algorithms in clinical practice.
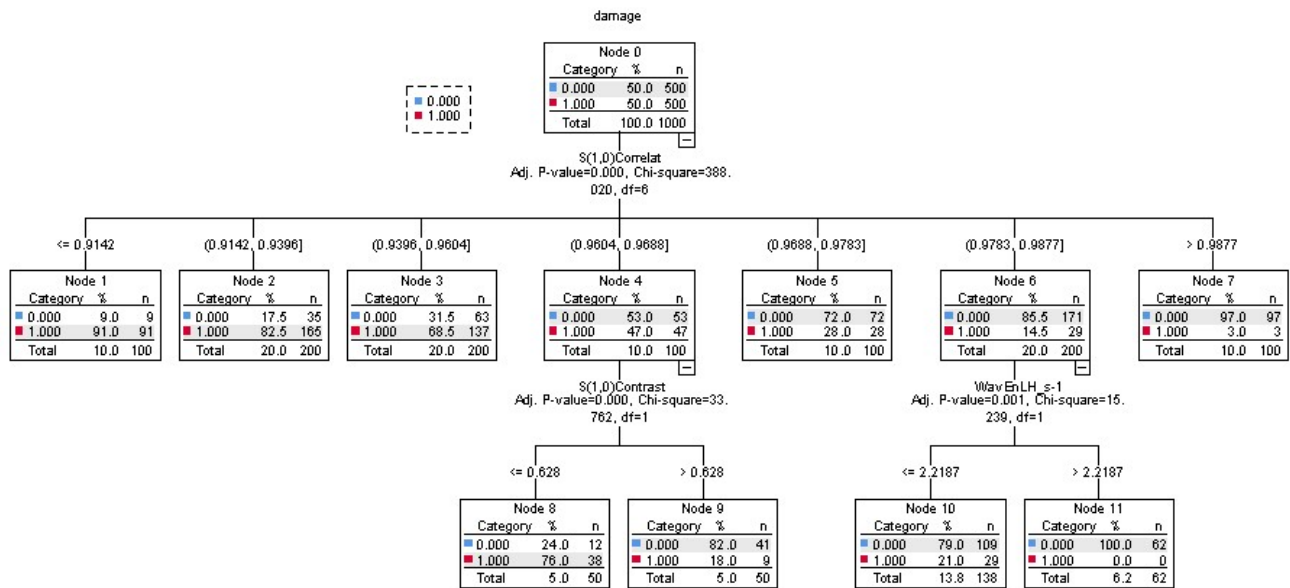
Figure 3. Machine learning model based on decision tree that uses chi-square automatic interaction detection to make decisions from GLCM and wavelet data.

CONCLUSION

Fractal and textural analyses are contemporary and innovative computational approaches with potentially wide application in signal analysis. Previously, they have been successfully applied in detecting subtle changes in cell morphology and intercellular communication associated with aging and apoptosis. Data obtained from fractal and textural analyses can be used for training and evaluation of various machine learning models. So far, artificial intelligence approaches based on co-occurrence matrix data were successfully implemented in predicting cell damage in *in vitro* conditions, with artificial neural networks achieving the best performance. In future, several methodological issues and challenges related to the use of fractal and textural methods will have to be resolved before their introduction to contemporary clinical practice.

Conflict of interest

The authors declared no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

Author Contributions

IP conceptualized the manuscript, JPP and SRŠ did literature screening. All authors participated in manuscript writing and provided critical intellectual input.

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PRIMENA FRAKTALNE I TEKSTURALNE ANALIZE U MEDICINSKOJ FIZIOLOGIJI, PATOFIZIOLOGIJI I PATOLOGIJI

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Sažetak

Fraktalna i teksturalna analiza predstavljaju klasu računarskih i matematičkih metoda koje se brzo razvijaju, i koje se odlikuju potencijalno širokom primenom u medicini i biologiji. Poslednjih godina se uspešno koriste za procenu diskretnih promena u morfologiji ćelija i tkiva povezanih sa različitim fiziološkim i patološkim procesima. Prethodno je pokazano da se pojedine ćelije u ranim fazama apoptoze odlikuju promenama u fraktalnim i teksturalnim karakteristikama jedarnog hromatina. Ćelijsko starenje je takođe ponekad povezano sa promenama teksturalnih obrazaca u nekim ćelijskim populacijama. Do sada su algoritmi veštačke inteligencije zasnovani na teksturalnim podacima dobijenim iz matriksa simultanog pojavljivanja sivih intenziteta rezolucionih jedinica, uspešno primenjeni za predviđanje oštećenja ćelija u in vitro uslovima, pri čemu su neuronske mreže postigle najbolje performanse. U budućnosti će morati da se reši nekoliko metodoloških pitanja i izazova u vezi sa upotrebom fraktalnih i teksturalnih metoda pre njihovog uvođenja u savremenu kliničku praksu. Ovaj kratki pregledni rad se fokusira na nedavna istraživanja o primeni fraktalnih i teksturalnih metoda u eksperimentalnoj fiziologiji i srodnim oblastima.

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