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This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Roberto G.F., Lumini A., Neves L.A., do Nascimento M.Z. (2021). Fractal Neural Network: A new ensemble of fractal geometry and convolutional neural networks for the classification of histology images. EXPERT SYSTEMS WITH APPLICATIONS, 166, 1-11 [10.1016/j.eswa.2020.114103].

Availability:

This version is available at: <https://hdl.handle.net/11585/784605> since: 2020-12-17

Published:

DOI: <http://doi.org/10.1016/j.eswa.2020.114103>

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This is the final peer-reviewed accepted manuscript of:

Guilherme Freire Roberto, Alessandra Lumini, Leandro Alves Neves, Marcelo Zanchetta do Nascimento, Fractal Neural Network: A new ensemble of fractal geometry and convolutional neural networks for the classification of histology images, *Expert Systems with Applications*, Volume 166, 2021, 114103, ISSN 0957-4174,

The final published version is available online at:
<https://doi.org/10.1016/j.eswa.2020.114103>

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Fractal Neural Network: a new ensemble of fractal geometry and convolutional neural networks for the classification of histology images

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Abstract

Classification of histology images is a task that has been widely explored on recent computer vision researches. The most studied approach for this task has been the application of deep learning through CNN models. However, the use of CNN in the context of histological images classification has yet some limitations such as the need of large datasets, the slow training time and the difficult to implement a generalized model able to classify different types of histology tissue. In this paper, we propose an ensemble model based on handcrafted fractal features and deep learning that consists on fusing the classification of two CNN by applying the sum rule. We apply feature extraction to obtain 300 fractal features from different histological datasets. These features are reshaped into a $10 \times 10 \times 3$ matrix in order to compose an artificial image that is given as input to the first CNN. The second CNN receives as input the correspondent original image. After combining the results of both

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CNN, we were able to obtain accuracies that range from 89.66% up to 99.62% on five different datasets. Moreover, our model was able to classify images from datasets with imbalanced classes, without the need of images having the same resolution, and in a relative fast training time. We also verified that the obtained results are compatible with the most recent and relevant studies recently published in the context of histology image classification.

Keywords: deep learning, fractal features, classification ensemble, histology images

1. Introduction

Histopathology consists on the analysis of histological tissue and the study of how diseases affect the cells. Usually, a pathologist performs this analysis by observing histology slides through a digital microscope [7]. However, this task is prone to errors as evaluation is often subjective and dependent on the pathologist's experience, which may lead to misdiagnosis [38].

In order to provide support to pathologists, several computer vision techniques have been applied on images obtained from histology slides. These techniques consist on performing a series of evaluations on the input images and then provide a classification based on pre-defined classes, such as benign or malignant. This is a complex procedure, often referred as computer aided-diagnosis (CAD), which can be split into several stages, from image acquisition, going through pre-processing, segmentation, feature extraction, feature selection and classification [27]. Therefore, a CAD system is an important tool that provides a second view to the pathologist, increasing the diagnosis accuracy and reducing the amount of time and physicians required to label large amounts of medical exams [18]. In this paper, we focus on the feature extraction and classification stages of a CAD system for histological image analysis.

Different techniques can be applied to extract handcrafted features from these images. Among the most recently researched techniques, we can cite local binary pattern (LBP), gray level co-occurrence matrix (GLCM), speeded up robust features (SURF) or fractal geometry, which were applied for kidney tissue analysis [53], breast cancer classification [64], colon cell nuclei detection [2] and lymphoma classification [47], respectively. However, the main research focus for this area in recent years has been the application of

27 deep learning approaches, more specifically, the use of convolutional neural
28 networks (CNN).

29 CNN have shown to be efficient for the classification of objects, mainly
30 in multiclass problems [28, 24]. However, these relevant results are not as
31 often in the context of histological images [10, 59, 4]. One of the reasons
32 is that CNN require large sets for training, given that a major part of the
33 public histological datasets available contain a limited number of samples
34 [63]. To handle this situation, more data is generated for training by applying
35 rotation, mirroring or region cutting on the images. Nonetheless, this data
36 augmentation raises even more the high computational cost of CNN [32].

37 One of the possible solutions to reduce processing time consists in simpli-
38 fying the network architecture by reducing the amount of layers. However,
39 the removal of deeper layers may hinder the image analysis from a global
40 perspective [4], which may compromise the network performance. Some al-
41 ternative approaches, like hybrid networks, have been explored. These ap-
42 proaches associate non-deep learning techniques such as Gabor filters or LBP
43 operators with the convolution operations of CNN, which allows to replace
44 some of the network’s layers [28, 24]. Other approaches aim to achieve a
45 lower processing time by reducing the images’ dimensionality. In [29], the
46 authors applied Haar-wavelet decomposition on breast histology images and
47 used the decomposed images as input to a CNN.

48 Recent researches have shown that a fusion of handcrafted features with
49 deep learning models can enhance common approaches [40]. The application
50 of fractal features, which have provided relevant results in the context of
51 histological images classification [46, 48], could also be associated to hybrid
52 CNN. In [62], CNN were applied to extract values from an invariant fractal
53 dimension filter for detecting object curves in grayscale images. The authors
54 in [37] applied multifractal analysis to quantify and detect breast cancer,
55 classifying the generated feature vectors using deep learning. However, an
56 approach similar to the proposed by [29], wherein the CNN receives as input
57 secondary images generated by a specific technique has not yet been exper-
58 imented in the fractal geometry context. Moreover, methods that directly
59 associate fractal geometry with CNN through an ensemble for the classifica-
60 tion of histological images were not found in the literature.

61 In this paper, we propose a novel approach, which we name as Fractal
62 Neural Network (FNN), to classify histological images through the associ-
63 ation of fractal geometry and CNN. In our proposal, fractal features are
64 extracted from the histology images and then rearranged in order to gen-

65 erate an artificial RGB feature image. Both this artificial image and the
66 correspondent original image are given as input to a CNN ensemble, wherein
67 a classification based on the sum rule outputs the class prediction. This new
68 method provides the following contributions to the literature:

- 69 1. double-CNN classification ensemble wherein an image generated from
70 handcrafted fractal features and the respective regular image are given
71 as input to a CNN;
- 72 2. An adaptive method that is able to classify different sets of histological
73 images, including datasets with imbalanced classes, few samples and
74 varying image dimensions;
- 75 3. The combination of different fractal measures to provide a set of fea-
76 tures capable of describing the image’s properties;
- 77 4. A deep learning model that requires a small number of training epochs,
78 even when classifying new types of histology images.

79 In the second section of this paper, recent researches regarding the clas-
80 sification of histological images are discussed. In Section 3, we provide a
81 technical background on the use of fractal geometry for feature extraction of
82 color images. The proposed methodology is presented on Section 4, and in
83 Section 5, the results obtained by applying the method on the tested datasets
84 are presented and discussed. Finally, we conclude the paper at Section 6, with
85 an overview of the obtained results and suggestions for future researches.

86 **2. Related Work**

87 Plenty of advances have been achieved by researchers on the field of medi-
88 cal image classification recently, wherein deep learning approaches have been
89 playing a major role on such improvements mainly on the feature extraction
90 and classification stages of a CAD system.

91 *2.1. Breast Tumors Classification*

92 Breast cancer is a disease that initially starts with a tumor in the breast
93 area but can later grow to surrounding tissues. This is the most common
94 cancer type among women, although it also affects men. According to the
95 Nacional Cancer Institute, 276,480 new cases and 42,170 deaths are expected
96 in the United States for 2020 [17]. Due to high incidence, breast cancer
97 detection became an important focus on computer vision research.

98 In [13], an artificial neural network composed by two modules was built
99 to classify 58,000 patches with dimensions 15×15 of benign and malignant
100 breast tumors. The first module performs an unsupervised feature extraction
101 based on stacked denoising auto encoder. The second part, consists of a soft-
102 max classifier. This approach was able to provide accuracies of 98.27% and
103 90.54% for the detection of benign and malignant tumors, respectively. Mul-
104 tiple instance classification have also recently provided relevant results for the
105 classification of breast tumors. Using a spatial decomposition technique that
106 produces spatial and color components corresponding to 2nd and 3rd dimen-
107 sion of data tensors related to the input images, the authors in [44] were able
108 to achieve an accuracy of 84.67% using a multiple instance classifier. Their
109 method performed faster than other common approaches and could also ob-
110 tain an accuracy of 79.33% even with 90% of missing data. Handcrafted
111 image features have also been used as complementary to deep learning ap-
112 proaches. In [64], nuclei segmentation of breast tumors is performed through
113 the application of a CNN. Then, texture features obtained from different
114 handcrafted approaches are extracted from the segmented images and given
115 as input to an SVM classifier. After applying the Relief feature selection
116 method, the method was able to obtain an accuracy of 96.7%. In [31], the
117 authors used data-augmentation to significantly increase the number of sam-
118 ples of the breast cancer dataset by generating 112×112 sized patches. To
119 improve classification, the authors applied a simple six-layer CNN to remove
120 mislabeled patches. After associating multiscale feature extraction with a
121 CNN classifier, an accuracy of 100% was obtained.

122 *2.2. Colorectal Tumors Classification*

123 Colorectal cancer consists on the growth of malignant polyps in the colon
124 or rectum area. This is the fourth most common type of cancer, with 147,950
125 new cases and 53,200 deaths expected for 2020 in the United States [17].
126 Several researches have been published in recent years aiming to improve the
127 automated diagnosis of this type of cancer.

128 In [11], the authors used a 31-layers CNN to perform the classification of
129 colorectal histological images, achieving accuracies of 93.24% and 96.97% for
130 5-class and 2-class classification respectively. Similar results were obtained in
131 [51] when classifying 4 categories of colorectal tumors with a smaller network
132 (12 layers), wherein an accuracy of 93.28% was obtained after 400 epochs of
133 training. Furthermore, some researchers have been recently exploring ap-
134 proaches that consist of ensembles of different CNN models. The authors of

135 [5], for instance, first applied color normalization on the images of the col-
136 orectal dataset. Then, the normalized images were given as input to an U-
137 Net CNN in order to perform segmentation, aiming to remove non-glandular
138 areas. A different CNN model (GoogLeNet) was used to classify the seg-
139 mented images. This approach provided an accuracy of 85%. An ensemble
140 of different CNN was also published by [57] for the detection of colorectal
141 tumors. The authors developed an approach based on generative adversarial
142 networks (GAN) wherein the generator was implemented as an U-Net and
143 the discriminator is a standard CNN. With 3,000 patches of colorectal tumor
144 images available, the method provided an F-score of 0.940. According to the
145 authors, this approach deals well with class imbalance, due to its capacity
146 to retrain the network when new classes are added using the CNN Inception
147 v3.

148 *2.3. Non-Hodgkin Lymphomas Classification*

149 Lymphomas are a type of cancer that affects cells of the immunological
150 system, wherein the most common occurrence is the non-Hodgkin lymphoma
151 (NHL). According to statistics, 77,240 new cases and 19,940 deaths caused
152 by NHL are expected for 2020 in the United States [17]. Although it accounts
153 for only 3.3% of all cancer-related deaths, NHL are divided into categories,
154 each one requiring specific treatments. Therefore, computer methods that
155 are able to identify the NHL type are an important tool to provide support
156 to pathologists [43].

157 In [22], NHL images were split into several 36×36 patches which were
158 later cropped to 32×32 sub-patches using the Caffe framework, generating
159 825,000 training patches. These patches were given as input to a standard
160 AlexNet architecture and an accuracy of 96.58% was achieved with the use
161 of a voting scheme for classification. However, the use of deep learning tech-
162 niques is not mandatory to obtain relevant results for such task, as shown by
163 [25]. On this approach, the images were firstly converted into grayscale and
164 then, 130 non-overlapped patches with size 100×100 were extracted from
165 each image, resulting in a total of 48,620 patches. An unsupervised feature
166 extraction method was applied along with ordinary texture approaches to
167 extract 680 handcrafted features. These features were classified using a hi-
168 erarchical 2-stages machine learning method, which resulted in an accuracy
169 of 97.96%. In [6], the authors proposed a method that applies both deep
170 learning and handcrafted features for NHL classification. On this approach,
171 color, statistical and texture features were extracted from patches cropped

172 out of the original images and given as input at a random forest classifier.
173 These patches were also used to feed a GoogLeNet CNN. Both the random
174 forest and the CNN provided patch predictions which were processed using
175 weighted sum to generate a final classification prediction. The obtained ac-
176 curacy was of 99.10%. Fractal features have also provided relevant results
177 on NHL classification recently. In [36], fractal geometry was used to ex-
178 tract multiscale and multidimensional features from RGB and LAB colored
179 NHL images. The features extracted from the original images, without data-
180 augmentation, are given as input to a polynomial classifier. For binary class
181 classification, an accuracy of up to 97% was obtained.

182 *2.4. Gender and Age Classification*

183 Besides providing support to the diagnosis of diseases and differentiation
184 of tumors, computer vision techniques applied on histological images can
185 also serve as an indicator of age and gender. A set of images obtained from
186 mice liver tissue has been explored recently for this task. In [3], the au-
187 thors presented a novel deep learning approach named Texture-CNN. After
188 applying this approach along with a voting classification scheme, accuracies
189 of 99.1% and 98.2% were obtained for the classification of 2 gender and 4
190 aging classes respectively. However, handcrafted features have also provided
191 excellent results in this dataset. [12] applied 3 statistical approaches for grey
192 texture analysis, testing on different color spaces. After using a SVM to
193 classify the generated features, an accuracy of 100% was obtained for both
194 gender and aging classes. More recently, the authors in [39] proposed an
195 ensemble of handcrafted features and deep learning approaches. Moreover,
196 new data augmentation techniques based on principal component analysis
197 and discrete cosine transform were also presented. Using an ensemble of 6
198 CNN models trained with different data augmentation approaches and a set
199 of handcrafted features, the method was also able to obtain an accuracy of
200 100% for classifying gender and age from liver histological images.

201 Despite providing relevant results, most of these methods were imple-
202 mented for specific classification tasks. There are few computer vision ap-
203 proaches that were able to perform well on different histological image cate-
204 gories [48, 39, 19, 52]. Moreover, both handcrafted fractal features [46, 48, 49]
205 and CNN models [31, 6, 3] were able to provide high accuracy rates in several
206 CAD systems for histopathology tasks. Therefore, an ensemble method that
207 addresses both fractal geometry and deep learning, which is the core of our

208 proposal, could be able to improve these results when applied to different
209 histology datasets.

210 **3. Technical Background**

211 *3.1. Fractal Features*

212 Fractal geometry is a concept designed for the study of shapes that could
213 not be defined by euclidian geometry [35]. Shapes present in nature such as
214 a coastline, clouds, trees or lightnings are examples of structures that don't
215 have well-defined patterns. With fractal-based approaches, these structures
216 can be represented by observations through different scales. In computer
217 vision, such techniques are known as multiscale. Among the most common
218 ones, we can highlight the box-counting [41] and the gliding-box [21] algo-
219 rithms. The application of these algorithms consists in splitting the images
220 onto different scales and then extracting features from each sub-image. For
221 the representation of numerical features using fractal approaches, we have
222 fractal dimension (FD), lacunarity (LAC) and percolation (PERC) as three
223 of the most relevant. A multiscale and a multidimensional analysis of the
224 image are performed in order to obtain these features.

225 One of the approaches available in the literature for multiscale analysis
226 consists on the application of the gliding-box algorithm [21]. One of the main
227 advantages of this approach is that it can be applied on datasets containing
228 images with different resolutions, due to the fact that the output features are
229 given in relation to the scale instead of being absolute values. This algorithm
230 consists in placing a box β_i sized $L \times L$ on the left superior corner of the
231 image, wherein L is given in pixels. This box glides through the image, one
232 column and then one row at a time. After reaching the end of the image, the
233 box is repositioned at the starting point and the value of L is increased by
234 2. On an image sized $H \times W$, the total number T of boxes β_i for a scale L
235 is given by Equation 1:

$$T(L) = (H - L + 1) \times (W - L + 1) \quad | \quad L \leq \min(H, W). \quad (1)$$

236 For each time the box β_i is moved, a multidimensional analysis of color
237 similarity is performed for every pixel inside it. This is done by assigning the
238 center pixel to a vector $f_c = r_c, g_c, b_c$, where r_c, g_c and b_c correspond to the
239 color intensities of each of the RGB color channels of given pixel. The other
240 pixels in the box are assigned to a vector $f_i = r_i, g_i, b_i$ and compared to the

241 center pixel by calculating a color distance Δ . On the proposed approach,
 242 the Chessboard (Δ_h), Euclidian (Δ_e) and Manhattan (Δ_m) distances are
 243 calculated according to Equations 2-4.

$$\Delta_h = \max(|f_i(k_i) - f_c(k_c)|), k \in r, g, b. \quad (2)$$

$$\Delta_e = \sqrt{\sum_k (f_i(k_i) - f_c(k_c))^2}, k \in r, g, b. \quad (3)$$

$$\Delta_m = \sum_k |f_i(k_i) - f_c(k_c)|, k \in r, g, b. \quad (4)$$

244 If the value of Δ corresponding to the distance between f_i and f_c is less
 245 than or equal to the scale L , then f_i is labeled as 1, otherwise f_i receives the
 246 label 0. An example of the pixels' labelling when a distance Δ is calculated
 247 for a box sized 3×3 is illustrated on Figure 1.

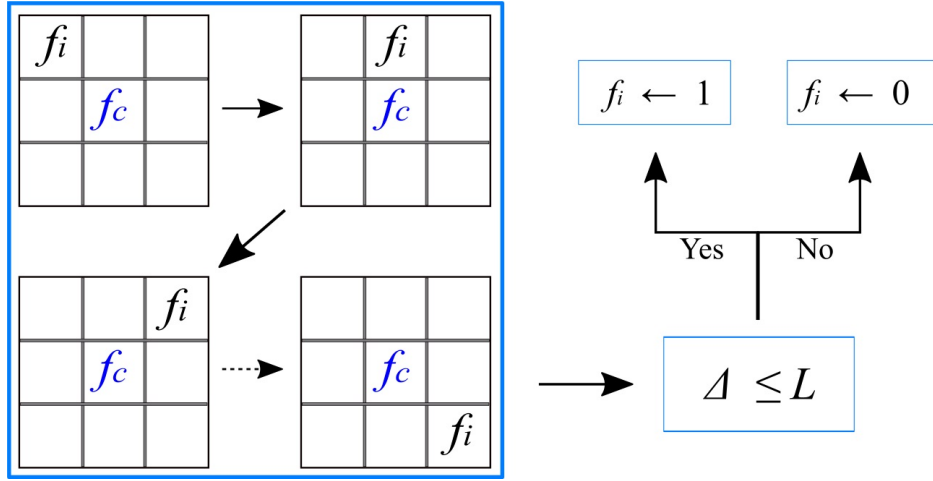


Figure 1: Labelling the pixels on a 3×3 by calculating a distance Δ .

248 This procedure converts a box that contains RGB values to one containing
 249 binary values. After performing this conversion for every box of every given
 250 L scale, a structure known as probability matrix is generated. Each element
 251 of the matrix corresponds to the probability P that m pixels on a scale L
 252 are labeled as 1 on each box. On Table 1, the visual representation of such
 253 matrix is presented. The matrix is normalized in a way that the sum of the
 254 elements in a column is equal to 1, as showed on Equation 5.

Table 1: Structure of the probability matrix.

	3	5	...	L_{max}
1	$P(1, 3)$	$P(1, 5)$...	$P(1, L_{max})$
2	$P(2, 3)$	$P(2, 5)$...	$P(2, L_{max})$
\vdots	\vdots	\vdots	\ddots	\vdots
L^2	$P(L^2, 3)$	$P(L^2, 5)$...	$P(L^2, L_{max})$

$$\sum_{m=1}^{L^2} P(m, L) = 1, \forall L. \quad (5)$$

255 Noteworthy here that the probability matrix does not have the shape of
 256 an ordinary rectangular matrix, as the number of rows grows exponentially
 257 for each value of L . After the matrix is complete, the FD and LAC local
 258 values can be obtained.

259 3.1.1. Fractal Dimension

260 FD is the most common technique to evaluate the fractal properties of an
 261 image. This is a measure for evaluating the irregularity and the complexity
 262 of a fractal.

263 To obtain local FD features from the probability matrix, for each value
 264 of L , the FD denominated $D(L)$ is calculated according to the Equation 6:

$$D(L) = \sum_{m=1}^{L^2} \frac{P(m, L)}{m}. \quad (6)$$

265 3.1.2. Lacunarity

266 LAC is a measure complementary to FD and allows to evaluate how the
 267 space of a fractal is filled [20]. From the probability matrix, first and second
 268 order moments are calculated with the Equations 7 and 8.

$$\mu(L) = \sum_{m=1}^{L^2} mP(m, L). \quad (7)$$

$$\mu^2(L) = \sum_{m=1}^{L^2} m^2P(m, L). \quad (8)$$

269 The value of LAC for a scale L is given by $\Lambda(L)$, which is obtained
 270 according to the Equation 9:

$$\Lambda(L) = \frac{\mu^2(L) - (\mu(L))^2}{(\mu(L))^2}. \quad (9)$$

271 *3.1.3. Percolation*

272 PERC is a physical phenomenon that consists on the study of fluid prop-
 273 erties on a porous media [15]. Such media is said to be percolating if a
 274 fluid can flow through the whole system, from the top to the bottom. In
 275 computer vision, this concept can be applied to verify the image porosity, or
 276 some cluster properties regarding pixel neighborhoods [49]. The first steps
 277 to obtain percolation features from a colored image follow the same proce-
 278 dures described for obtaining FD and LAC features. After calculating Δ , the
 279 generated binary matrices are given as input to a cluster labelling algorithm.
 280 Groups of nearby pixels that satisfied the criterion of the Δ distance are
 281 labelled in order to count the number of clusters on the image, as illustrated
 282 in Figure 2. The symbol * indicates pixels labelled as 1.

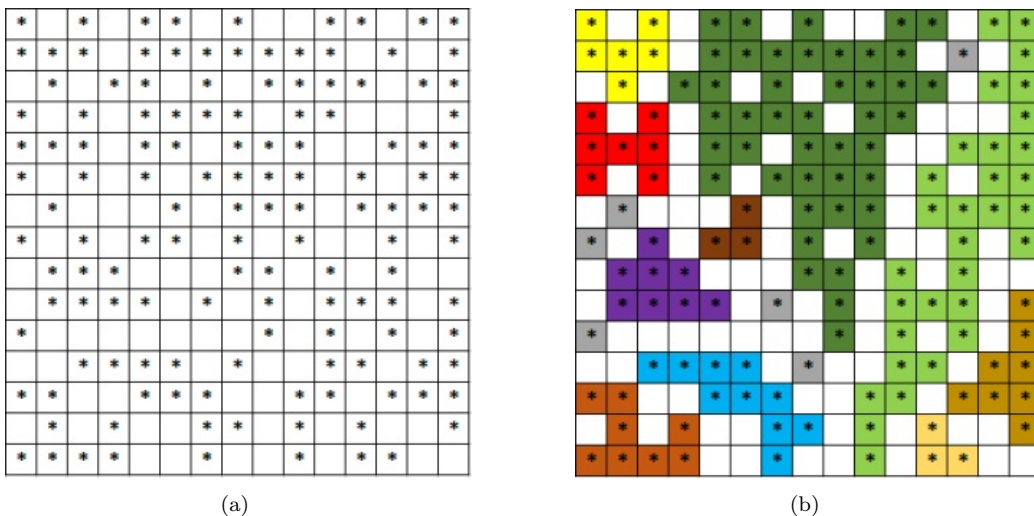


Figure 2: Matrix before (a) and after (b) the application of a cluster labelling algorithm.

283 Let c_i be the number of clusters on a box β_i , the feature $C(L)$ that
 284 represents the average number of clusters per box on a scale L is given by
 285 Equation 10

$$C(L) = \frac{\sum_{i=1}^{T(L)} c_i}{T(L)}. \quad (10)$$

286 Another feature that can be obtained consists on the average coverage
 287 area of the largest cluster in a box and is given by $M(L)$. Let m_i be the
 288 size in pixels of the largest cluster of the box β_i . The feature $M(L)$ is given
 289 according to Equation 11:

$$M(L) = \frac{\sum_{i=1}^{T(L)} \frac{m_i}{L^2}}{T(L)}. \quad (11)$$

290 We can also verify whether a box β_i is percolating. This can be achieved
 291 due to a property that states a percolation threshold for different types of
 292 structures. In squared matrices (digital images), this threshold has the value
 293 of $p = 0.59275$ [8], which means that if the ratio between pixels labeled as 1
 294 and pixels labeled as 0 is greater or equal than p , the matrix is considered as
 295 percolating. Let Ω_i be the number of pixels labeled as 1 in a box β_i with size
 296 $L \times L$, we determine whether such box is percolating according to Equation
 297 12:

$$q_i = \begin{cases} 1, & \frac{\Omega_i}{L^2} \geq 0.59275. \\ 0, & \frac{\Omega_i}{L^2} < 0.59275. \end{cases} \quad (12)$$

298 This results in a binary value for q_i , wherein 1 indicates that the box is
 299 percolating. The feature $Q(L)$ regards the average occurrence of percolation
 300 on a scale L and can be obtained as shown in Equation 13:

$$Q(L) = \frac{\sum_{i=1}^{T(L)} q_i}{T(L)}. \quad (13)$$

301 The number of obtained local features depends on the total of observation
 302 scales L . Considering that L ranges from 3 to L_{max} with an increment of 2,
 303 the amount of local features corresponds to $5 \times (\frac{L_{max}-3}{2} + 1)$ for each Δ . A
 304 summary of these features is shown in Table 2.

305 3.2. Convolutional Neural Networks

306 CNN are a special type of deep learning model that learns features from
 307 low- and high-level patterns on grid-shaped data [63]. The core of CNN

Table 2: Summary of the obtained local features.

FD	LAC	PERC		
$D(3)$	$\Lambda(3)$	$C(3)$	$Q(3)$	$M(3)$
$D(5)$	$\Lambda(5)$	$C(5)$	$Q(5)$	$M(5)$
\vdots	\vdots	\vdots	\vdots	\vdots
$D(L_{max})$	$\Lambda(L_{max})$	$C(L_{max})$	$Q(L_{max})$	$M(L_{max})$

308 are usually built from three types of layers: convolution; pooling; and fully
 309 connected layers. While the first two perform feature extraction, the later
 310 classifies these features and usually outputs a label to be assigned to the
 311 input data.

312 The convolution layers are the base structures of the network, hence the
 313 name CNN. These layers usually consist on a series of two operations. The
 314 first is convolution, a simple linear procedure that performs element-wise
 315 product between the input data and small arrays of numbers called kernels,
 316 which are the only learnable parameters in this type of layers. The second
 317 operation consists on passing the convolution output through a non-linear
 318 activation function. Different functions have been applied, although the Rec-
 319 tified Linear Unit (ReLU), which is given by $f(x) = \max(0, x)$, became the
 320 most popular as it tends to reduce training time [30].

321 Pooling layers provides a downsampling operation that reduces the data
 322 dimensionality. This is usually done by selecting the maximum or sometimes
 323 the average value of an element in a patch and feeding it to the following
 324 layer. These pooling operations are performed in order not only to decrease
 325 the number of features but also to introduce a small invariance to translation
 326 and distortion of structures in the input data.

327 The fully connected layers consist on a series of one or more layers wherein
 328 every output is connected to every input of the following layer by a learnable
 329 weight. Usually, the last fully connected layer has the same number of nodes
 330 as the number of classes of the training dataset. In classification problems,
 331 its output corresponds to class probabilities, which are obtained by applying
 332 an activation function, such as softmax. The network’s prediction is given
 333 by the class that obtained the highest probability value.

334 **4. Methodology**

335 *4.1. Image Databases*

336 We evaluated five histological image datasets. The first is the breast
337 cancer dataset provided by the Center of Bio-Image Informatics from the
338 University of California, Santa Barbara (UCSB) [14]. This dataset consists
339 of 58 breast tissue images split into two groups: benign (32) and malignant
340 (26). One example of each group is shown in Figure 3.

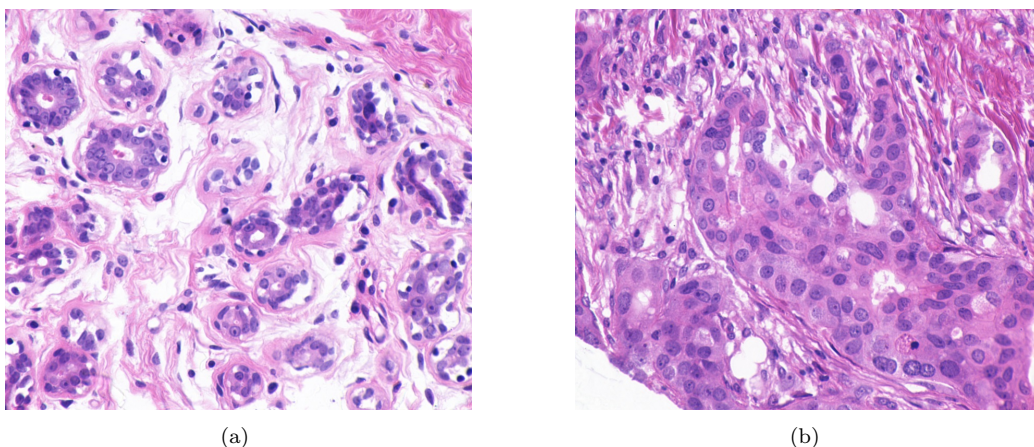


Figure 3: Samples of a benign (a) and a malignant (b) case from the UCSB dataset.

341 The second dataset (CR) consists of 165 colorectal tissue images [54], also
342 split into benign (74) and malignant (91) tumors. To acquire the images,
343 histological sections were digitally photographed with a Zeiss MIRAX MIDI
344 Slide Scanner with a scaled pixel resolution of $0.620\mu m$, which corresponds to
345 a magnification of 20x. On Figure 4, examples from each class are illustrated.

346 The third dataset (NHL) is composed by 173 non-Hodgkin Lymphoma
347 images divided into three classes: MCL - mantle cell lymphoma (99); FL
348 - follicular lymphoma (62); and CLL - chronic lymphocyte leukemia (12).
349 For the acquisition of the images, a light microscope Zeiss Axioscope with
350 a 20x objective and a colored digital camera (AXio Cam MR5) were used.
351 The obtained images were recorded without compression, with a resolution
352 of 1388×1040 pixels, a 24 bit quantization ratio and the RGB color model.
353 Regions of interest were later selected by a specialist [58]. This dataset was
354 made publicly available by the National Cancer Institute and the National
355 Institute on Aging [52].

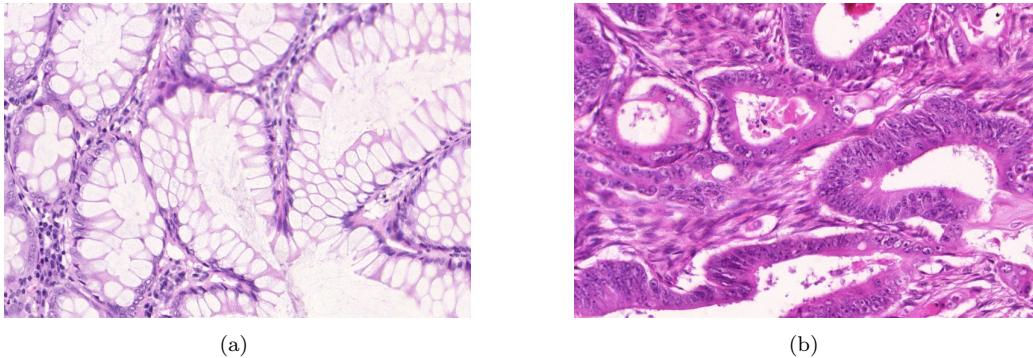


Figure 4: Samples of a benign (a) and a malignant (b) case from the CR dataset.

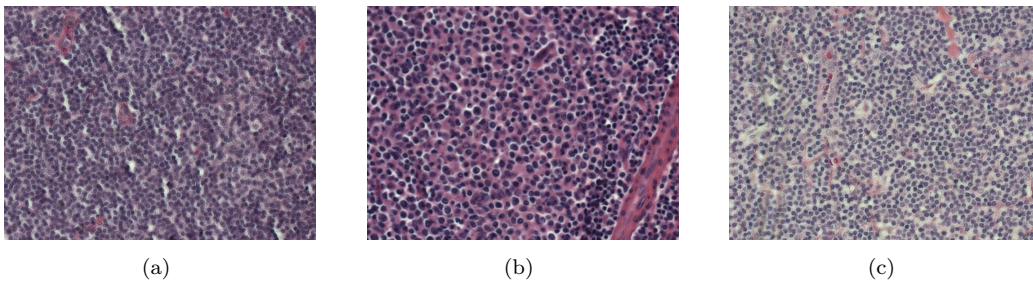
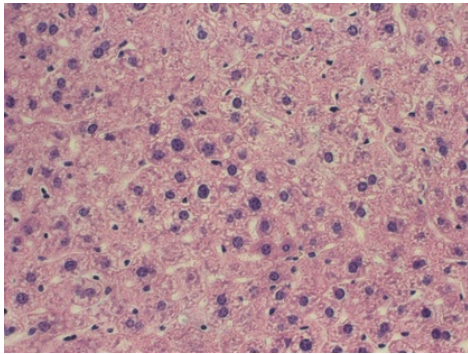
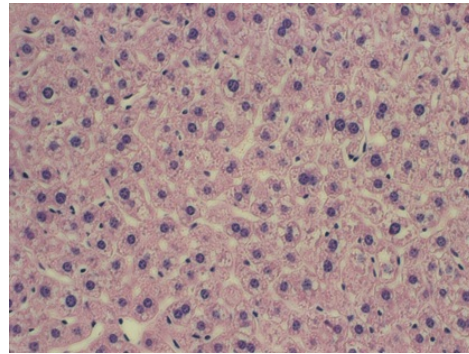


Figure 5: Samples of a CLL (a), a FL (b) and a MCL (c) case from the NHL dataset.

356 The two following datasets were both provided by the Atlas of Gene Ex-
 357 pression in Mouse Aging Project (AGEMAP) and are composed by liver
 358 tissue obtained from mice [42]. The images were acquired by a Carl Zeiss
 359 Axiovert 200 microscope and 40x objective. All images have the same res-
 360 olution of 417×312 pixels. The fourth dataset (LG) consists of 265 liver
 361 tissue images obtained from male (150) and female (115) mice on a caloric
 362 restriction diet. Examples of each class are illustrated on Figure 6. The fifth
 363 dataset (LA) consists of 529 images split in four classes, wherein each repre-
 364 sents a different age group of female mice on ad-libitum diets: one (100), six
 365 (115), 16 (162) and 24 (152) months old. On Figure 7, one example of each
 366 age group is illustrated. An overview of all these datasets is presented on Ta-
 367 ble 3. In all five datasets, the tissue samples were stained with Hematoxylin
 368 and Eosin (H&E).

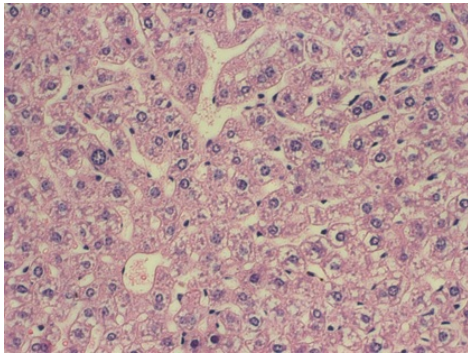


(a)

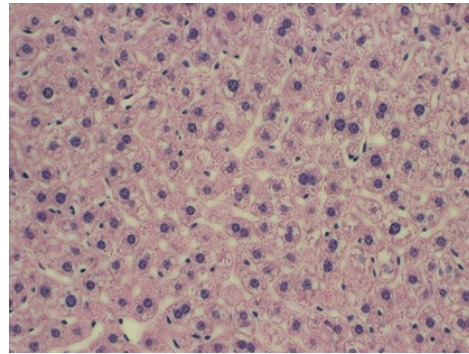


(b)

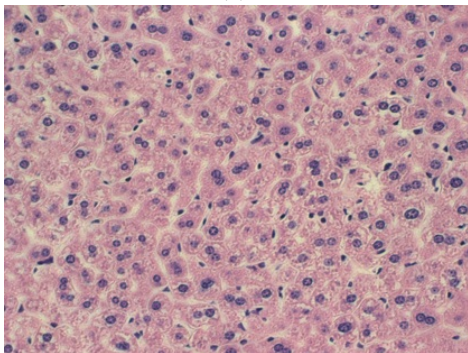
Figure 6: Samples of liver tissue from male (a) and female (b) mice from the LG dataset.



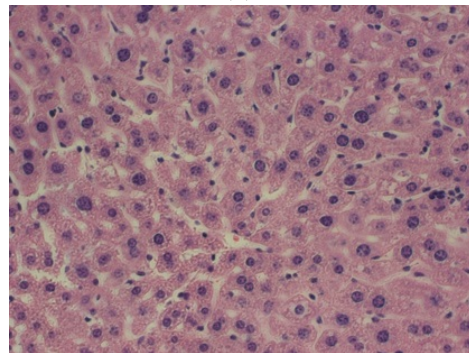
(a)



(b)



(c)



(d)

Figure 7: Samples of liver tissue from mice aged 1 month (a), 6 months (b), 16 months (c) and 24 months (d) from the LA dataset.

Table 3: Summary of the five tested datasets.

Dataset	Image	Classes	Samples	Resolution
UCSB [14]	Breast tumors	2	58	896×768
CR [54]	Colorectal tumors	2	165	from 567×430 to 775×522
NHL [52]	Non-Hodgkin Lymphoma	3	173	from 86×65 to 1388×1040
LG [42]	Liver tissue	2	265	417×312
LA [42]	Liver tissue	4	529	417×312

369 4.2. Method Overview

370 The proposed approach can be split into two modules. The first module
371 performs the extraction of local features by applying the fractal techniques
372 described in Section 3.1. The output of this module consist on a set of 300
373 features, which were obtained from calculating the FD, LAC and PERC local
374 values from each of the three distances Δ evaluated. The second module is
375 composed by 2 CNN whose goal is to perform classifications to obtain an
376 array of probabilities.

377 The input of the first CNN, henceforth named F-CNN, consists on an
378 artificial image generated from the features extracted on the first module.
379 The set of local features is reshaped into a $10 \times 10 \times 3$ RGB image, which is a
380 procedure based on [33]. The generated images are given as input to a CNN
381 for classification. The second CNN, henceforth named O-CNN, receives as
382 input the original image, wherein the class probabilities obtained from the
383 classification of such image are summed to the respective class probabilities
384 from the F-CNN. After this sum, the highest probability value indicates the
385 class prediction. An overview of this approach is presented on Figure 8. Each
386 step is described in details on the following sections.

387 4.3. Feature Extraction Module

388 The main stage of the proposed method consists in applying the tech-
389 niques based on fractal geometry, described in Section 3.1, on the images
390 under investigation. FD, LAC, and PERC local features are extracted using
391 multiscale and multidimensional approaches.

392 After being given as input to the FNN, the image is divided into different
393 scales, according to the gliding-box algorithm. Each perceptron of the first
394 layer represents a different scale with value L . This layer’s function consists
395 simply in generating a set of matrices for every region of the image and every
396 assigned value of L , which ranges from 3 to 41 with an increment of 2. We
397 chose this value for L_{max} as it generates the exact number of features required

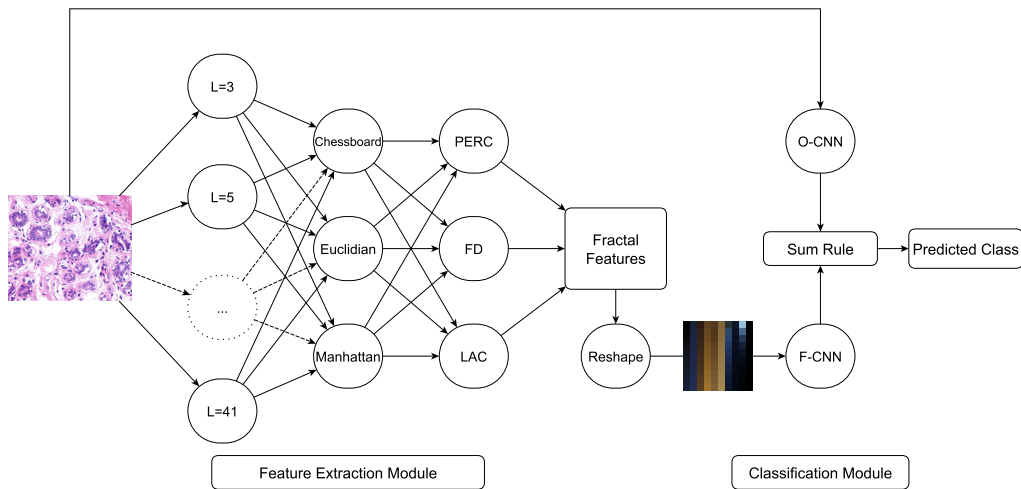


Figure 8: Overview of the proposed Fractal Neural Network model.

398 to provide a square image after applying the reshape procedure, which is
 399 ideal to avoid distortions when feeding the image to the F-CNN, and also
 400 due to the relevant classification results obtained with a similar value [46].
 401 The generated matrices are given as input to the second layer, which is a
 402 representation of the multidimensional approach of the methods described
 403 on Section 3.1. In the proposed architecture, each perceptron performs the
 404 calculation of a different type of distance Δ between the pixels of the image.

405 The output of each perceptron in the second layer consists in a set of
 406 binary matrices, wherein the values labeled as 1 are pixels that matched the
 407 Δ criteria. These matrices are given as input to the perceptrons of the third
 408 layer, wherein the techniques described on Section 3.1 for obtaining local FD,
 409 LAC and PERC values are finally applied. The resulting output consists on
 410 a set of 300 local features, which serve as input to the next module of the
 411 network. Prior to being given as input to both CNN, the original and the
 412 fractal images are resized in order to match the required input dimensions.

413 4.4. Classification Module

414 On the proposed FNN, classification is performed by two CNN. Both
 415 CNN are fine-tuned on the deepest layer, as we applied transfer learning
 416 using models pre-trained on the ImageNet database [50] in order to increase
 417 the accuracy whilst reducing the training time.

418 4.4.1. Fractal Features CNN - F-CNN

419 In order to serve as input for the incoming CNN classification, the feature
 420 vectors generated on the previous layers of the network must be converted
 421 into feature matrices. In order to do so, the set of 300 features obtained from
 422 the calculation of each of the three distances Δ are arranged to compose a
 423 different dimension of the matrix, aiming to simulate RGB color channels.
 424 Therefore, we split the feature vector into three sub-vectors containing 100
 425 features. These features are sequentially rearranged into a 10×10 matrix.
 426 The matrices generated by Δ_h , Δ_e and Δ_m correspond to the R, G and B
 427 color channels, respectively. In Figure 9, one example of each tested dataset
 428 is shown in order to illustrate the reshaping procedure.

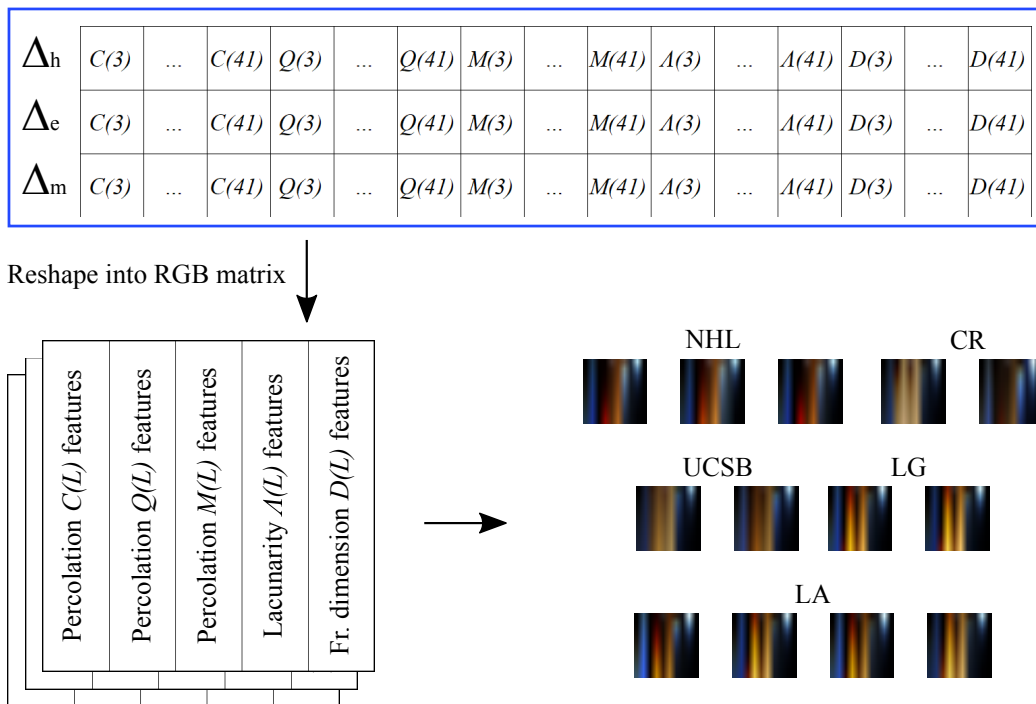


Figure 9: Illustration of the procedure to rearrange the local features in order to create a RGB image.

429 The generated images are given as input to the F-CNN, which outputs a
 430 score vector for each image indicating class probabilities.

431 *4.4.2. Original Images CNN - O-CNN*

432 In order to fully explore the classification power of a CNN, we chose to
 433 append a second CNN to the proposed architecture. The original images
 434 are given as input to this CNN and the class probabilities obtained from the
 435 output of the softmax layer are summed to the class probabilities obtained
 436 from the correspondent layer of the F-CNN where the images generated from
 437 fractal features were classified.

438 *4.4.3. Transfer Learning*

439 In order to reduce training time and achieve good results with few training
 440 epochs we chose to use transfer learning instead of training both CNN from
 441 scratch. Our proposed method applies network-based transfer learning [56],
 442 wherein the pre-trained network is partially reused and only the final layer
 443 is changed in order to match the number of classes. Therefore, we selected
 444 four CNN candidates that have provided relevant results in histology image
 445 classification recently [45, 34, 26] pre-trained on the ImageNet dataset. An
 446 overview of these four models is shown in Table 4.

Table 4: Selected pre-trained CNN models.

Model	Layers	Parameters	Input size
ResNet-50 [16]	50	2.6×10^7	$224 \times 224 \times 3$
ResNet-101 [16]	101	4.5×10^7	$224 \times 224 \times 3$
InceptionV3 [55]	48	2.4×10^7	$299 \times 299 \times 3$
Xception [9]	71	2.3×10^7	$299 \times 299 \times 3$

447 *4.5. Performance Evaluation*

448 In order to obtain the best possible results with the proposed method and
 449 properly evaluate these, we applied a testing approach divided in 4 stages.

450 Firstly, we evaluated which CNN model would be the most appropriate
 451 for the F-CNN and O-CNN slots in the proposed architecture. Then, we
 452 apply each of the CNN on the 5 datasets with the number of training epochs
 453 ranging from 1 to 10. This verification aims to determine the smaller number
 454 of epochs needed to obtain the highest accuracies. After these experiments,
 455 the proposed approach is applied on the datasets using the configuration
 456 results obtained from the previous tests. At last, we compare the proposed
 457 method with other common feature extraction techniques, analysing results

Table 5: Loss evaluation of different CNN models and time performance in seconds.

Dataset		ResNet-50	ResNet-101	InceptionV3	Xception
NHL	F-CNN	0.510	0.494	0.478	0.385
	O-CNN	0.767	0.585	0.497	0.409
	Time	42.69	85.79	87.58	77.01
CR	F-CNN	0.350	0.312	0.339	0.269
	O-CNN	0.018	0.022	0.045	0.043
	Time	50.21	91.26	93.82	83.37
UCSB	F-CNN	0.567	0.741	0.621	0.556
	O-CNN	0.318	0.271	0.305	0.606
	Time	21.99	39.65	39.01	29.76
LG	F-CNN	0.163	0.118	0.151	0.118
	O-CNN	0.005	0.017	0.005	0.041
	Time	67.25	133.84	139.99	128.66
LA	F-CNN	0.175	0.189	0.196	0.193
	O-CNN	0.048	0.128	0.031	0.051
	Time	122.47	247.67	259.65	247.22

458 obtained from using only the F-CNN as well as the ensemble with the O-
 459 CNN. To obtain these other features, we implemented the methods on Matlab
 460 R2019b, applied them on the same datasets and performed classification
 461 using the Rotation Forest classifier available at the software Weka 3.6.13. We
 462 chose this classifier due to its relevant results obtained from other researches
 463 on histology image classification [1, 48].

464 All tests were performed on a Intel Xeon Silver 4116 CPU at 2.10GHz
 465 with 128GB of RAM and a NVIDIA GeForce RTX 2080Ti embedded, using
 466 Matlab R2019b. Since some of the tested datasets have a small number of
 467 samples, we chose to apply 10-folds cross-validation in all testing stages in
 468 order to avoid problems such as overfitting.

469 5. Results and Discussion

470 Before testing the proposed model on its complete implementation, it was
 471 necessary to determine the CNN models to be assigned to the F-CNN and
 472 O-CNN slots. We tested the performance of four of the most popular CNN
 473 that have been applied on recent researches. On Table 5, the loss values for
 474 each dataset are presented as well as the average time in seconds required to
 475 train and classify the samples in 10 epochs.

476 We applied the Friedman non-parametrical test to verify whether the
 477 difference among the loss values were significant [23]. At $\alpha = 0.05$, we

Table 6: Accuracy values for the F-CNN with varying training epochs.

Epochs	NHL	CR	UCSB	LG	LA	Avg.
1	78.03%	77.58%	60.34%	68.68%	77.88%	72.50%
2	80.35%	78.79%	70.69%	81.13%	81.66%	78.52%
3	78.61%	83.03%	68.97%	91.32%	84.88%	81.36%
4	82.66%	83.64%	70.69%	88.68%	86.39%	82.41%
5	84.97%	89.09%	74.14%	93.21%	86.77%	85.63%
6	84.39%	86.67%	72.41%	89.81%	91.68%	84.99%
7	84.97%	88.48%	68.97%	90.94%	91.68%	85.01%
8	84.39%	88.48%	72.41%	91.70%	90.36%	85.47%
9	82.66%	86.06%	79.31%	95.09%	93.57%	87.34%
10	83.81%	86.06%	77.59%	95.47%	93.19%	87.23%

Table 7: Accuracy values for the O-CNN with varying training epochs.

Epochs	NHL	CR	UCSB	LG	LA	Avg.
1	83.82%	93.33%	56.90%	98.49%	92.82%	85.07%
2	87.28%	98.18%	58.62%	98.49%	95.27%	87.57%
3	89.02%	98.79%	68.97%	98.49%	96.03%	90.26%
4	90.75%	98.78%	72.41%	98.11%	96.68%	91.33%
5	90.75%	100.00%	75.86%	99.62%	98.11%	92.87%
6	88.44%	99.39%	79.31%	99.62%	97.16%	92.79%
7	90.17%	99.39%	74.14%	99.62%	98.49%	92.36%
8	93.64%	98.79%	81.03%	98.87%	98.68%	94.20%
9	89.60%	98.18%	82.76%	98.87%	99.05%	93.69%
10	88.44%	99.39%	75.86%	98.82%	99.43%	92.40%

478 obtained $P_k = 0.2073$ for the F-CNN and $P_k = 0.4144$ for the O-CNN, which
 479 indicates that there is not a significant difference when comparing the four
 480 tested CNN models. However, when comparing the time needed to perform
 481 training, the Friedman test indicated a significant difference ($P_k < 0.0001$)
 482 for all pairwise comparisons (Conover) involving the ResNet-50. Therefore,
 483 we chose the ResNet-50 to be assigned to both CNN slots of our proposed
 484 architecture not only due to its shorter training time, but also due to the
 485 relevant results recently obtained in the classification of histology images
 486 [45, 34, 60, 61].

487 Then, we tested the performance of each of the two CNN varying the
 488 number of training epochs. To prevent overfitting, and aiming to build a
 489 fast-training model, we chose to not go beyond 10 epochs for both CNN.
 490 The results are shown in Tables 6 and 7 for the F-CNN and the O-CNN
 491 respectively.

Table 8: Results obtained from the application of the proposed method.

	Accuracy	F-score
NHL	95.55%	0.864
CR	99.39%	0.994
UCSB	89.66%	0.895
LG	99.62%	0.996
LA	99.62%	0.996
Avg.	96.77%	0.949
SD.	4.334	0.058

492 From the results presented on Tables 6 and 7, it can be noted that the
 493 F-CNN is able to provide relevant results after 4 epochs. On the other hand,
 494 the O-CNN presented significant performance values with only 2 training
 495 epochs, providing accuracies above 85% for all datasets, with an exception for
 496 the breast tumor images, due to its small number of samples. Nevertheless,
 497 the best results were obtained with 9 and 8 training epochs for the F-CNN
 498 and O-CNN respectively. Therefore, these parameters were applied on the
 499 following tests.

500 We proceeded to apply the proposed FNN using the configuration pa-
 501 rameters obtained on the previous tests in order to evaluate the performance
 502 when applied to the five histology images dataset. The detailed results are
 503 shown on Table 8.

504 These results show that the proposed method is able to perform well on
 505 the classification of histology images. With exception for the UCSB dataset,
 506 accuracies above 95% were obtained, which can be a indicator of the method’s
 507 adaptability to different categories of histological tissue. Despite dealing with
 508 imbalanced classes on all datasets, the proposed method was also able to
 509 provide F-Measure values above 0.850 in all cases. It is also noteworthy the
 510 excellent results obtained for the CR, LG and LA, with performance values
 511 close to 1.0 for all evaluated metrics.

512 In order to verify how the proposed method fits among other computer
 513 vision approaches, we compare its performance with the results obtained by
 514 LBP, Haralick, PERC, LAC and FD features. It’s important to highlight
 515 that the fractal features used for comparison in this test consist of common
 516 feature vectors that are given as input to machine learning algorithms, which
 517 differs from our approach of reshaping the fractal features into a RGB image
 518 and feeding it to a CNN. Firstly, we compared the individual performance of

Table 9: Accuracy values obtained by different computer vision methods.

	NHL	CR	UCSB	LG	LA
LBP	72.83%	67.27%	79.31%	80.75%	71.46%
Haralick	74.57%	73.94%	81.03%	89.43%	88.28%
PERC	93.64%	87.27%	82.76%	95.09%	93.57%
LAC	89.60%	66.67%	79.31%	86.04%	83.93%
FD	78.03%	59.39%	62.07%	58.49%	50.47%
F-CNN	82.66%	86.06%	79.31%	95.09%	93.57%
O-CNN	93.64%	98.79%	81.03%	98.87%	98.68%

Table 10: Accuracy values obtained by the application of a classification ensemble between the O-CNN and other techniques.

	NHL	CR	UCSB	LG	LA
LBP	83.24%	91.52%	82.76%	93.58%	89.41%
Haralick	87.28%	92.12%	82.76%	95.47%	92.25%
PERC	94.22%	97.58%	86.21%	99.62%	99.24%
LAC	94.22%	98.18%	86.21%	99.62%	98.87%
FD	91.91%	98.79%	82.76%	99.25%	99.05%
FNN	95.55%	99.39%	89.66%	99.62%	99.62%

519 these techniques without using any classification fusion or ensemble approach.
 520 Thus, we did not performed the ensemble scheme between the F-CNN and
 521 the O-CNN, as it is originally intended for our proposal. The results are
 522 shown in Table 9.

523 Without using any ensemble approach, the O-CNN, which consists simply
 524 on using a ResNet-50 for classifying the original images, provided the best
 525 results. An exception is made for the UCSB dataset, wherein the best results
 526 were provided by the PERC features. Moreover, apart from the FD, the
 527 fractal features performed better than the LBP and Haralick descriptors in
 528 most cases. It can also be noted that the proposed F-CNN struggles to
 529 provide relevant results when applied on its own.

530 Thus, our method implements an ensemble between the F-CNN and the
 531 O-CNN. However, since a comparison among an ensemble method and non-
 532 ensemble approaches would not be fair, we included the O-CNN classification
 533 to compose an ensemble with the other compared methods. These results
 534 are shown in Table 10.

535 It can be noted that merging the classification results of both CNN not
 536 only improves the accuracy of the F-CNN, but also enhances the performance
 537 of the O-CNN. When compared to the other techniques, the proposed method
 538 provided better accuracies in all datasets. The LG dataset was the only
 539 one where the results obtained by our method could be matched by other
 540 techniques. In this case, the same accuracy value of 99.62% was obtained
 541 by PERC, LAC and the FNN. Besides, a significant difference among the
 542 compared techniques was indicated according to the Friedman test ($P_k <$
 543 0.0001 for $\alpha = 0.05$) in all pairwise comparisons (Conover). Our method
 544 also provided the highest average accuracy (96.8%) and smallest standard
 545 deviation (4.334), as can be seen on the graph presented on Figure 10.

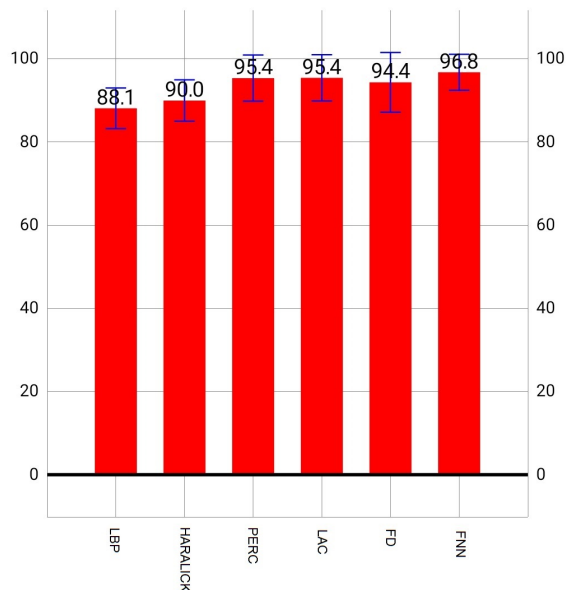


Figure 10: Average accuracy of the evaluated classification ensemble between the O-CNN and other techniques, applied to the five tested datasets.

546 An overview of the results obtained with the FNN in relation to other
 547 approaches in the context of histology image classification is shown in Table
 548 11. It can be noted that the methods that provided the best results on each
 549 classification task applied both deep learning (DL) and handcrafted (HC)
 550 features. Regarding the FNN, we were able to verify that its performance is
 551 compatible with recently published methods. Breast and colorectal cancer

552 classification remains as a challenging task in computer vision, since few
553 methods were able to obtain accuracies above 95% when classifying these
554 type of images. Nevertheless the FNN was able to achieve a remarkable
555 99.39% accuracy, ranking first among the compared methods in colorectal
556 cancer classification.

557 **6. Conclusion**

558 In this paper, we proposed an approach (FNN) that consists on the en-
559 semble of two CNN, wherein one of these receives as input images generated
560 from fractal features, to classify different categories of histological images.
561 We showed that our proposal was able to provide relevant results, with accu-
562 racies above 89%, for all tested histopathology challenges. Also, accuracies
563 greater than 99% were obtained for three out of the five evaluated datasets
564 (CR, LG and LA). Besides, we achieved these results with a training time
565 shorter than the required for other approaches such as [64, 51, 29] to obtain
566 similar performances. Therefore, we believe our proposal contributes to this
567 research area not only due to its adaptability to different types of histol-
568 ogy tissue and relatively low computing cost, but mainly due to the applied
569 feature vectors reshaping concept that allows the combined use of fractal fea-
570 tures and CNN. This approach has not yet been deeply explored and could
571 provide new insights on the combined power of handcrafted features and
572 deep learning. Nevertheless, there is still room for improvement, specially in
573 regard to the UCSB dataset classification, wherein hyper-parameter tuning
574 could play a major role to improve the model’s accuracy.

575 For future works, we propose the application of the FNN on other types
576 of histology tissue images, a study for optimizing the F-CNN and the O-
577 CNN parameters, the inclusion of fractal global features in the classification
578 ensemble and a deeper analysis of the fractal features reshaping procedure,
579 *e.g.* experimenting different ways to dispose the features or generating images
580 using a different 3-channel color model.

581 **7. Acknowledgment**

582 This study was financed in part by the Coordenação de Aperfeiçoamento
583 de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001 and by
584 the Programa Institucional de Internacionalização (PRINT/CAPES, Brazil),
585 project #88882.461704/2019-01. The authors gratefully acknowledge the

Table 11: Overview of the accuracy values obtained by different approaches in the context of histology image classification.

Images	Method	Approach	Accuracy
NHL	[6]	DL+HC	99,10%
	[24]	DL	97,96%
	[36]	HC	97,00%
	[22]	DL	96,58%
	FNN	DL+HC	95,55%
	[47]	HC	86,14%
Breast	[31]	DL+HC	100,00%
	[64]	DL+HC	96,67%
	[13]	DL	94,41%
	[29]	DL	91,00%
	FNN	DL+HC	89,66%
	[48]	HC	86,20%
	[44]	DL	84,67%
	[4]	DL	83,30%
Colorectal	[38]	HC	80,00%
	FNN	DL+HC	99,39%
	[11]	DL	96,97%
	[57]	DL	94,02%
	[51]	DL	93,28%
	[48]	HC	90,90%
	[7]	DL	87,50%
Liver (gender)	[5]	DL	85,00%
	[39]	DL+HC	100,00%
	[12]	HC	100,00%
Liver (age)	FNN	DL+HC	99,62%
	[3]	DL	99,10%
	[39]	DL+HC	100,00%
Liver (age)	[12]	HC	100,00%
	FNN	DL+HC	99,62%
	[3]	DL	98,20%

586 financial support of National Council for Scientific and Technological De-
587 velopment CNPq (Grant #427114/2016-0, Grant #304848/2018-2, Grant
588 #430965/2018-4 and Grant #313365/2018-0) and the State of Minas Gerais

589 Research Foundation - FAPEMIG (Grant #APQ-00578-18).

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