



SVM Classification of Cell Survival/Apoptotic Death for Color Texture Images of Survival Receptor Proteins

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ABSTRACT: In recent years, considerable interests have been developed for the development of small cell inhibitors of protein kinases. Different combinations are undertaken human trials for the medical care of cancer, inflammatory diseases, and other symptoms, while some of them are validated for clinical purpose only. Apoptosis and necrosis are two different types of cell death. In necrosis, serious health problems and inflammatory responses occurs due to uncontrolled cell death while in apoptosis there is a control on cell death. Cancer arises from the dysfunction in the apoptotic pathway. Apoptosis or cell death is a general component for the evolution of multicellular organisms. In this paper a CAD system is designed for the classification (survival or apoptotic death) of survival receptor proteins (EGF and Insulin) using Discrete Wavelet transform for colour texture classification problem. In this article all the work has been done on the color images which has not done till yet by other researchers. The maximum accuracy of 93.33% is obtained using Support vector machine (SVM) classifier while the minimum accuracy of 13.33% is obtained.

Keywords: Computer aided diagnostic system, EGFR, Insulin receptors, Wavelet functions, texture features, SVM classifier.

I. INTRODUCTION

Traditional biomedical engineering works on different research areas like physiological monitoring, imaging systems, radiotherapy, and the development of therapeutic and assistive devices [1, 2]. It requires the use of engineering principles for the design of lifecycle. In maximum cases the interconnection starts from whole body through the guts to tissue level which let us know for cell survival/ death. In all organisms, cells die due to various reasons it can be intentionally or unintentionally [3]. During the early phase of development in mammals, a complex program of cell death is required to develop various parts of normal size and function. Unintended cellular's can also lead to cell death like any system react with chemical agents or ultraviolet light [4, 5]. The growth factors like insulin and epidermal growth factor (EGF) exhibit survival effects and programmed cell death TNF- α function as apoptosis cues [6, 7]. Many proteins help in this process which interacts systematically regulating a specific cross talk or pathway with other proteins of other pathways [8, 9]. This results in activation of different pathways that may lead to different physiological and biological changes inside the cell. The final outcome of cell survival/ death is decided by the different concentration of market proteins among the pathways. The EGF binds with its receptor to form EGF receptor (EGFR) which inturn binds with Src homology 2 (SH2) leading to the activation of the phosphatidylinositol 3 kinase (PI3K) pathway, RAS/extracellular signal regulated kinase (ERK) pathway, and the activator of transcription (JAK/ STAT) pathway. The receptor of EGF binds at the outer side of cell membrane (while receptor if insulin binds at the inner side) and phosphorylates the residues into sub-units (tyrosine). Insulin binds with its receptor IRS on cell membranes leads to the transduction to cell

death/ survival. IRS also leads to different downstream pathways [10-12].

In this paper a diagnostic system is outlined for the detection of cell survival/ death using different receptor proteins. Images are taken from heat map given by Gaudet *et al.* [1]. Each image is further divided into 13 parts ranging from 0-24 hr. Discrete wavelet transform [13] is used for the extraction of features which are classified by SVM classifier [14, 15]. The major contribution of our proposed system is a critical study of different error functions for different SVM classification and regression functions with a study how to use 1D and 2D data (image/ signal) with SVM. The novelty of our model lies in the analysis with seven different texture feature vectors for every wavelet function.

Organization of this article is as follows: section 2 explains the proposed methodology for the classification of survival proteins with detailed study of SVM [16,17], section 3 explains the results and discussion using different wavelets by considering seven different texture feature vectors followed by conclusion and future work.

II. PROPOSED COMPUTER AIDED DIAGNOSTIC (CAD) TOOL

The main target of this work is to design a CAD system for identification of cell survival / death for different receptor proteins images. There are different steps which were involved in designing a CAD: Data Set Collection, Data Pre-processing, Feature Extraction, and Data Classification [18]. Fig. 1 shows the different steps of proposed system for the diagnosis of cell absent or present using different receptor proteins.

To develop a CAD system, it is important that the classifiers used in the classification module of the CAD system are trained with an image database that contains representative images from each subclass.

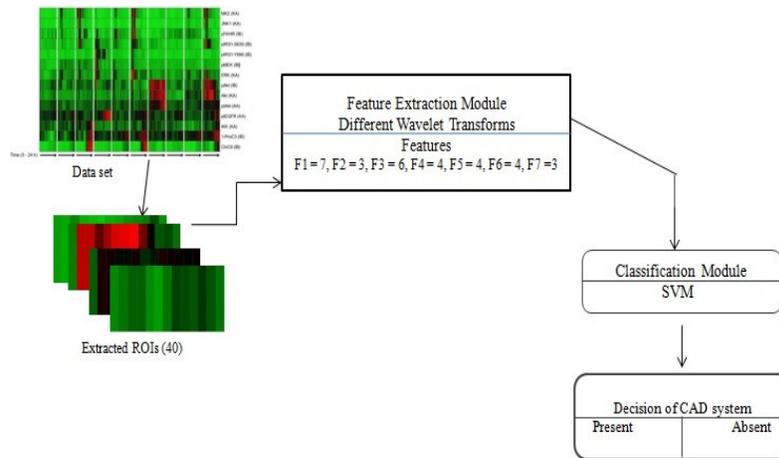


Fig. 1. Computer Aided Diagnostic system.

Proposed work is done on images taken from Gaudet *et al.* The data consists of different images but in this paper images of EGFR, IRS and IEK are considered. The features can be extracted using shape based and textural based [13, 14]. There are different types of analysis. Time domain analysis is carried out by Shannon Nyquist Theorem, frequency analysis is analyzed by Fourier Transform, Short-Time Fourier Transform is analyzed by Gabor Wavelet and the last is Wavelet Transform. In this paper analysis has been done by using Wavelet transform. There is a difference between Fourier analysis and wavelet transform. Fourier analysis involves the splitting of any signal into sinusoidal waves of different frequencies while wavelet transform consists of splitting of a signal into shifted and scaled version of the original wavelet which is known as mother wavelet. The scaled (dilated) and shifted (translated) value for the wavelet function $\psi(x)$ and scaling function $\phi(x)$ of the basis function is represented by Eq. (1) and Eq. (2) respectively at the j^{th} level.

$$\psi_k^j(x) = \psi_{j,k}(x) = 2^{j/2} \psi(2^j x - k) \quad (1)$$

$$\phi_k^j(x) = \phi_{j,k}(x) = 2^{j/2} \phi(2^j x - k) \quad (2)$$

for $j = 0, \dots$ and $k = 0, 1, \dots, 2^j - 1$. Also the subscripts j defines the scaling of value and k defines the shifting of value. The scaling function and wavelet function at $(j + 1)^{\text{th}}$ level can be obtained by replacing j with $j + 1$ in Eq. (1) and Eq. (2) which is represented by Eq. (3) and Eq. (4).

$$\phi_{j+1,k}(x) = 2^{(j+1)/2} \phi(2^{j+1} x - k) = 2^{j/2} \sqrt{2} \phi_{j,k}(2^j x - k) \quad (3)$$

$$\psi_{j+1,k}(x) = 2^{(j+1)/2} \psi(2^{j+1} x - k) = 2^{j/2} \sqrt{2} \psi_{j,k}(2^j x - k) \quad (4)$$

The linear integration of the scaling function at j level can be expressed for the next $j+1$ level is represented by Eq. (5) and Eq. (6) respectively.

$$\phi_{j,k}(x) = \sum_m u(m-2k) \cdot \phi_{j+1,m}(x) \quad (5)$$

$$\psi_{j,k}(x) = \sum_m v(m-2k) \cdot \phi_{j+1,m}(x) \quad (6)$$

where scaling filter is represented as $u(m)$ and the wavelet filter is represented as $v(m)$.

Any signal which has to be decomposed is passed through two filters wavelet filter v^* / high pass filter (HPF)

(n) and scaling filter $u^*(n)$ / low pass filter (LPF). For every wavelet the HPF's and LPF's are different.

We get Approximation ($A / c_{j+1}(k)$) decomposition after LPF with $c_0(x) = f(x)$, where $f(x)$ is expressed by Eq. (7) and Details ($D / d_{j+1}(k)$) decomposition after HPF which is represented by Eq. (8) and Eq. (9) respectively.

$$f(x) = \sum_k c_{j0}(k) \phi_{j0,k}(x) + \sum_{j=0}^{\infty} \sum d_j(k) \psi_{j,k}(x) \quad (7)$$

$$c_{j+1}(k) = \sum_x c_j(x) \cdot u^*(x-2k) \quad (8)$$

$$d_{j+1}(k) = \sum_x c_j(x) \cdot v^*(x-2k) \quad (9)$$

Down sampling of columns results in cA and cD decomposition. The row sampling of cA yields horizontal decomposition; CH and approximation decomposition; CA and while row sampling of cD yields diagonal decomposition; CD and vertical decomposition; CV. All the data studied so far is for one dimension. Likewise, two dimensional wavelet transform has its significance. In two-dimension (2D) scaling function; $\phi(x, y)$ is expressed as $\phi(x) \times \phi(y)$ and 2D wavelet function can be represented as:

1. CV2 or $\psi_1(x, y)$ is the representation of the vertical decomposition and expressed as $\phi(x) \times \psi(y)$,
2. CH2 or $\psi_2(x, y)$ is the representation of the horizontal decomposition and expressed as $\psi(x) \times \phi(y)$,
3. CD2 or $\psi_3(x, y)$ is the representation of the diagonal decomposition and expressed as $\psi(x) \times \psi(y)$.

The scaled and shifted value for the $\phi(x, y)$ is represented by Eq. (10).

$$\phi_{k,l}^j(x, y) = 2^{j/2} \phi \left(\left(2^j x - k \right), \left(2^j y - l \right) \right) \quad (10)$$

For the 2D image, the four decomposed transforms values can be expressed by Eq. (11) to Eq. (14).

$$CA_i(x, y) = \sum_{c=-\infty}^{\infty} \sum_{r=-\infty}^{\infty} u(c-2x) \cdot u(c-2y) f_i(c, r) \quad (11)$$

$$CH_i(x, y) = \sum_{c=-\infty}^{\infty} \sum_{r=-\infty}^{\infty} v(c-2x) \cdot u(r-2y) f_i(c, r) \quad (12)$$

$$CV_i(x, y) = \sum_{c=-\infty}^{\infty} \sum_{r=-\infty}^{\infty} u(c-2x) \cdot v(r-2y) f_i(c, r) \quad (13)$$

$$CD_j(x,y) = \sum_{c=-\infty}^{\infty} \sum_{r=-\infty}^{\infty} v(c-2x).v(r-2y)f_j(c,r) \quad (14)$$

Normalized energy is calculated for each sub image. For approximate sub image at j^{th} level of decomposition is represented by Eq. (15).

$$\text{Normalized Energy} = \frac{\|CA_i\|_F^2}{\text{area}(CA_i)} \quad (15)$$

For detailed sub image at i^{th} level of decomposition

$$\text{Normalized Energy} = \frac{\|Cx_i\|_F^2}{\text{area}(Cx_i)} \quad (16)$$

where F : forbenius normalization, x can be vertical (V) diagonal (D) or horizontal (H) decomposition.

There are different types of normalization techniques : Euclidean normalization, forbenius normalization (forb norm) and Generalized vector p-norm. Forb norm of an $m \times n$ matrix X is define by Eq. (17)

$$\|X\|_F = \sqrt{\sum_{i=1}^m \sum_{j=1}^n |a_{i,j}|^2} \quad (17)$$

In this paper 10 different wavelet transforms are considered such as haar (db1), daubechies (db4 and db6), coiflet (coif1, coif2); symlet (sym3, sym5); biorthogonal (bior3.1, bior3.3, bior4.4). Each wavelet transforms consists of seven different texture feature vector (TFV) which are tabulated in Table 1.

Table 1: Wavelet energy descriptors for seven TFV.

Texture feature vector	Wavelet energy descriptors	Length (l)
TFV1	$\left(\frac{\ CA_2\ _F^2}{\text{area}(CA_2)}, \frac{\ CH_2\ _F^2}{\text{area}(CH_2)}, \frac{\ CV_2\ _F^2}{\text{area}(CV_2)}, \frac{\ CD_2\ _F^2}{\text{area}(CD_2)}, \frac{\ CH_1\ _F^2}{\text{area}(CH_1)}, \frac{\ CV_1\ _F^2}{\text{area}(CV_1)}, \frac{\ CD_1\ _F^2}{\text{area}(CD_1)} \right)$	7
TFV2	$\left(\frac{\ CH_1\ _F^2}{\text{area}(CH_1)}, \frac{\ CV_1\ _F^2}{\text{area}(CV_1)}, \frac{\ CD_1\ _F^2}{\text{area}(CD_1)} \right)$	3
TFV3	$\left(\frac{\ CH_2\ _F^2}{\text{area}(CH_2)}, \frac{\ CV_2\ _F^2}{\text{area}(CV_2)}, \frac{\ CD_2\ _F^2}{\text{area}(CD_2)}, \frac{\ CH_1\ _F^2}{\text{area}(CH_1)}, \frac{\ CV_1\ _F^2}{\text{area}(CV_1)}, \frac{\ CD_1\ _F^2}{\text{area}(CD_1)} \right)$	6
TFV4	$\left(\frac{\ CH_1\ _F^2}{\text{area}(CH_1)}, \frac{\ CV_1\ _F^2}{\text{area}(CV_1)}, \frac{\ CD_1\ _F^2}{\text{area}(CD_1)}, \frac{\ CD_2\ _F^2}{\text{area}(CD_2)} \right)$	4
TFV5	$\left(\frac{\ CA_2\ _F^2}{\text{area}(CA_2)}, \frac{\ CH_1\ _F^2}{\text{area}(CH_1)}, \frac{\ CV_1\ _F^2}{\text{area}(CV_1)}, \frac{\ CD_1\ _F^2}{\text{area}(CD_1)} \right)$	4
TFV6	$\left(\frac{\ CA_2\ _F^2}{\text{area}(CA_2)}, \frac{\ CH_2\ _F^2}{\text{area}(CH_2)}, \frac{\ CV_2\ _F^2}{\text{area}(CV_2)}, \frac{\ CD_2\ _F^2}{\text{area}(CD_2)} \right)$	4
TFV7	$\left(\frac{\ CH_2\ _F^2}{\text{area}(CH_2)}, \frac{\ CV_2\ _F^2}{\text{area}(CV_2)}, \frac{\ CD_2\ _F^2}{\text{area}(CD_2)} \right)$	3

There are different types of classifiers. Mainly they are *linear classifiers* and *SVM classifiers*. Linear classifiers are linearly separable (preceptor) while SVM classifiers have wide margin, cost function etc. In this research paper SVM classifier is used which classify the unknown testing images based on training images. There are different types of SVM that can be consider for minimising the error function using different training algorithm. Type 1 SVM Classification (SVC)/ C- SVC, Type 2 SVC/ ν (nu)- SVC, one-class SVC, Type 1 SVM Regression (SVR)/ epsilon- SVR and Type 2 SVR / ν - SVR are different classes of SVM. The error functions of different SVM's are

a. For Linear Separable :

$$\text{Distance between } \Rightarrow \frac{|wx+b|}{\|w\|} = \frac{1}{\|w\|}, \text{ Total is } \frac{2}{\|w\|} = \frac{2}{\sqrt{w^T w}} \quad (18)$$

$$\Rightarrow \frac{\max 2}{\|w\|} = \min \frac{w^T w}{2} \quad (19)$$

$$\Rightarrow \min_{w,b} \frac{1}{2} (w^T w) \text{ subject to } (w^T x + b) \geq 1 \text{ for } i = 1, 2, \dots, l$$

b. For Non linear separable / C-SVC : This classification minimizes the error function using Eq. (20)

$$\Rightarrow \min_{w,b,\xi} \frac{1}{2} (w^T w) + C \sum_{i=1}^l \xi_i \quad (20)$$

$$\Rightarrow \text{subject to } y_i (w^T \phi(x_i) + b) \geq 1 - \xi_i \text{ for } i = 1, 2, \dots, l \text{ and } \xi_i \geq 0$$

where C is the capacity constant or large penalty parameter, ξ_i is the parameter which handles non separable data inputs.

c. nu-SVC: This classification minimizes the error function using Eq. (21)

$$\Rightarrow \min_{w,b,\xi} \frac{1}{2} (w^T w) - \nu \rho + \frac{1}{l} \sum_{i=1}^l \xi_i \quad (21)$$

$$\Rightarrow \text{subject to } y_i (w^T \phi(x_i) + b) \geq \rho - \xi_i \text{ for } i = 1, 2, \dots, l, \xi_i \geq 0 \text{ and } \rho \geq 0$$

In a regression SVM, the independent and dependent variables are expressed by a function f including the noise also. This can be represented as $y = f(x) + \text{noise}$. The two types of SVR models can be expressed by Eq. (22)

1. SVR 1 : The error function for SVR1 is expressed by Eq. (22)

$$\Rightarrow \min_{w,b,\xi} \frac{1}{2} (w^T w) + C \sum_{i=1}^l \xi_i + C \sum_{i=1}^l \xi_i^* \quad (22)$$

$$\begin{aligned} &\text{subject to } (w^T \phi(x_i) + b) - y_i \leq \varepsilon + \xi_i^* \\ &y_i - w^T \phi(x_i) - b \leq \varepsilon + \xi_i \quad \text{and} \\ &\xi_i, \xi_i^* \geq 0 \text{ for } i = 1, 2, \dots, l \end{aligned}$$

2. SVR 2: The error function for SVR 2 is expressed by Eq. (23)

$$\frac{1}{2} \omega^T \omega - C \left[\nu \varepsilon + \frac{1}{N} \sum_{i=1}^N (\xi_i + \xi_i^*) \right] \quad (23)$$

subject to:

$$\begin{aligned} &(w^T \phi(x_i) + b) - y_i \leq \varepsilon + \xi_i^* \\ &y_i - (w^T \phi(x_i) + b) \leq \varepsilon + \xi_i \\ &\xi_i, \xi_i^* \geq 0, i=1, \dots, N, \varepsilon \geq 0 \end{aligned}$$

Different kernel functions (linear, Gaussian, RBF etc) are used to train SVM. The results obtained with linear kernels are faster because it uses C- regression parameter optimization while other kernel uses γ parameter optimization.

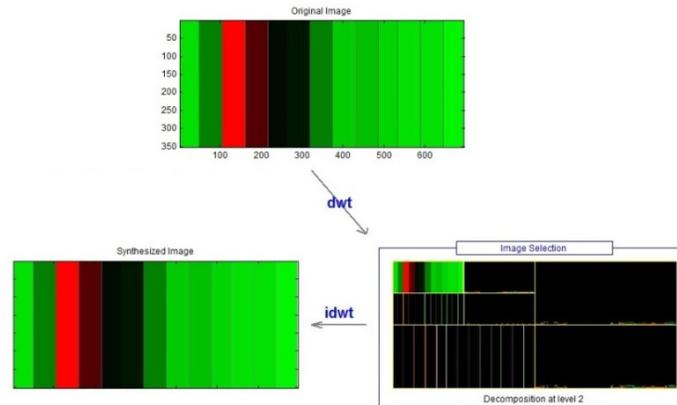


Fig. 2. DWT and IDWT using HAAR wavelet.

III. RESULTS AND DISCUSSIONS

In this research paper, CAD system is designed to classify the cell death/ survival for the survival receptor proteins. Different images from [1] were analyzed using MATLAB 2016a. All the collected images (colored) were converted into gray level images. First level decomposition values for different wavelet filters using symmetrical mode were computed. Later second level decomposition (CA2, CD2, CV2, CH2) for different

wavelet filters are analyzed. Fig. 2 shows the decomposed image using DWT and also the inverse DWT (IDWT) considering HAAR wavelet. Different length features were evaluated for different decomposed levels using Forb norm. Table 2 tabulates the seven different texture features and different wavelet functions with maximum and minimum accuracy using SVM classifier. Table 3 tabulates the confusion matrix showing maximum and minimum accuracy.

Table 2: Performance analysis for receptor proteins using SVM classifiers of TFV1-TFV7.

TFV (l)	Maximum Accuracy	Different wavelet transforms	Minimum Accuracy	Different wavelet transforms
TFV1 (7) (CH1, CV1, CD1, CA2, CH2, CV2, and CD2)	93.33%	bior3.1, bior 3.3,db1	13.33%	bior 3.1, coif1,db4, db6,sym3
TFV2 (3) (CH1, CV1, CD1)	93.33%	db6, sym5	20%	bior 3.1, bior4.4
TFV3 (6) (CH1, CV1, CD1, CH2, CV2, and CD2)	93.33%	db1, db4	13.33%	db6,sym3,sym5
TFV4 (4) (CH1, CV1, CD1, and CD2)	93.33%	db4	13.33%	bior 3.3, sym3, sym5
TFV5 (4) (CH1, CV1, CD1, and CA2)	93.33%	bior 4.4, db4,db6	13.33%	bior 3.1, bior3.3, sym3, sym5
TFV6 (4) (CA2, CH2, CV2, and CD2)	86.67%	db1, bior 4.4,	13.33%	bior 3.1, bior3.3, coif1,coif 2, db6, sym3, sym5
TFV7 (3) (CH2, CV2, and CD2)	93.33%	bior4.4, db1, sym5	13.33%	db6

Table 3: Confusion matrix showing maximum accuracy and minimum accuracy.

Maximum Accuracy Confusion Matrix			Minimum Accuracy Confusion Matrix				
	a	b		a	b		
c	70	0	93.33%	c	20	50	13.33%
d	10	70		d	80	0	

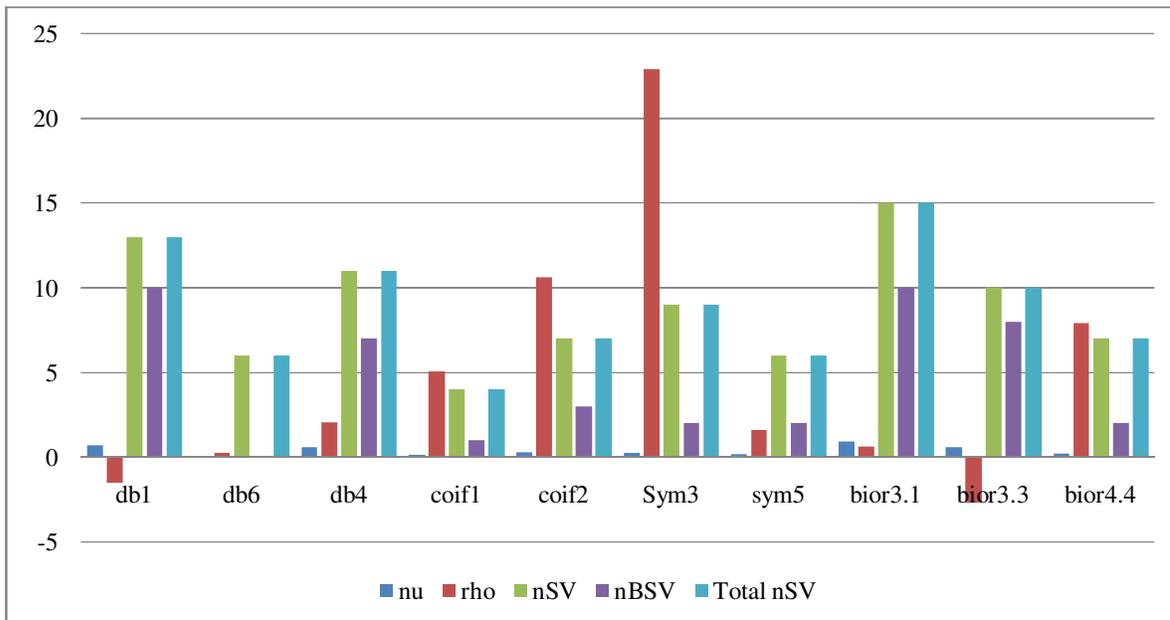


Fig. 3. Different Parameters of various wavelet transforms using SVM.

The maximum accuracy of 93.33% and the minimum accuracy of 13.33% is obtained using different wavelet transforms. Different parameters were calculated when using LibSVM classifier [19] as shown in Fig 3. In Fig 3 *obj* signifies the optimal objective value of the dual SVM, *rho* defines *b* in the decision function, *nSV* defines number of support vectors, and *nBSV* defines bounded support vectors (i.e., $\alpha_i = C$).

CONCLUSION

In this research article, a CAD system is designed for the classification of cell survival/ death using survival receptor proteins for different discrete wavelet transforms. By various experiments it was concluded that, for the characterization of different receptors the highest OCA of 93.3% using different wavelet transforms for different TFV is obtained. Therefore, the results obtained of the CAD system help doctors for the different diagnosis of presence and absence of receptor protein (EGFR and IRS) pathways. The results obtain will give information on how the input signals inducing cell death should be modulated to achieve desire outputs and thus helps the experimentalists to design proposals regarding possible improvement to cell death. Till yet no work has been done on this topic. Different feature extraction techniques were applied in future so as to get better accuracy.

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