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A modified artificial immune system based pattern recognition approach -- an application to clinic diagnostics

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Abstract

Objective—This paper introduces a modified artificial immune system (AIS)-based pattern recognition method to enhance the recognition ability of the existing conventional AIS-based classification approach and demonstrates the superiority of the proposed new AIS-based method via two case studies of breast cancer diagnosis.

Methods and materials—Conventionally, the AIS approach is often coupled with the k nearest neighbor (k -NN) algorithm to form a classification method called AIS- k NN. In this paper we discuss the basic principle and possible problems of this conventional approach, and propose a new approach where AIS is integrated with the radial basis function – partial least square regression (AIS-RBFPLS). Additionally, both the two AIS-based approaches are compared with two classical and powerful machine learning methods, back-propagation neural network (BPNN) and orthogonal radial basis function network (Ortho-RBF network).

Results—The diagnosis results show that: (1) both the AIS- k NN and the AIS-RBFPLS proved to be a good machine learning method for clinical diagnosis, but the proposed AIS-RBFPLS generated an even lower misclassification ratio, especially in the cases where the conventional AIS- k NN approach generated poor classification results because of possible improper AIS parameters. For example, based upon the AIS memory cells of “replacement threshold = 0.3”, the average misclassification ratios of two approaches for study 1 are 3.36% (AIS-RBFPLS) and 9.07% (AIS- k NN), and the misclassification ratios for study 2 are 19.18% (AIS-RBFPLS) and 28.36% (AIS- k NN); (2) the proposed AIS-RBFPLS presented its robustness in terms of the AIS-created memory cells, showing a smaller standard deviation of the results from the multiple trials than AIS- k NN. For example, using the result from the first set of AIS memory cells as an example, the standard deviations of the misclassification ratios for study 1 are 0.45% (AIS-RBFPLS) and 8.71% (AIS- k NN) and those for study 2 are 0.49% (AIS-RBFPLS) and 6.61% (AIS- k NN); and (3) the proposed AIS-RBFPLS classification approaches also yielded better diagnosis results than two classical neural network approaches of BPNN and Ortho-RBF network.

Conclusion—In summary, this paper proposed a new machine learning method for complex systems by integrating the AIS system with RBFPLS. This new method demonstrates its satisfactory effect on classification accuracy for clinical diagnosis, and also indicates its wide potential applications to other diagnosis and detection problems.

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Keywords

artificial immune system; radial basis function; partial least square regression; pattern recognition; breast cancer; clinical diagnosis

1. Introduction

Breast cancer is one of the most common cancers in women, which approximately affects 10% of all women at some stage of their life in the western world [1]. While there are many different diagnostic approaches to detect breast cancer in early stages, the fine needle aspiration (FNA) biopsy method is a reliable and standard test and can be used as a definitive diagnosis method [2]. The information from the extracted biological sample can be examined by pathologists to confirm whether the abnormality is a benign breast disorder or a malignant tumor requiring further testing and treatment. In most cases no single feature or characteristic of the extracted material can separate benign samples from malignant samples [3], and so a reliable diagnosis depends on years of training for a pathologist to identify groups of cancer signature features. As more automated tests are performed, we can consider how computer-aided pattern recognition can increase precision and accuracy of diagnosis by using sophisticated machine learning processes.

An early pattern recognition study of FNA-based breast cancer diagnosis was reported in 1990, where nine cytological characteristics of benign and malignant breast fine-needle aspirates were employed to establish a classification model for breast cancer diagnosis [3]. The same data set was then used to investigate the diagnosis effect of an instance-based learning strategy [4]. As we can see, with the development of computation and artificial intelligence techniques, a variety of machine learning methods have been developed for clinical diagnosis. For example, discrimination analysis is a typical tool for building multivariate diagnosis models, especially for linear systems [5–6]. Multilayer forward neural networks including the back-propagation neural networks have become a most widely used powerful diagnosis tool for complex nonlinear systems. [7–8]. Other approaches such as the fuzzy classifier [9] and self-organization map neural network [10] have also been applied to clinical diagnosis.

Recently, a novel artificial intelligence method termed the artificial immune system (AIS) has been applied to different application areas especially in the pattern recognition field, since it emerged in the 1990s as a bio-inspired computational research tool [11–14]. The main concept of this approach is to use a supervised learning process to create core (representative) data points to represent and cover the sample distribution space of each class. Then, these representative data points will be used to create a model for future prediction. K nearest neighbor (k -NN) is widely used as a follow-up method to form an AIS- k NN classification approach [12–13]. However, the success of this approach depends on the core data points selected by the AIS system. Once the AIS creates memory cells (i.e., core points), the k -NN model only uses these points for new sample prediction without further considering any other useful information of the entire existing data, which may result in an unreliable prediction. A detailed principle description of these involved methods will be given in the following sections.

In this paper, we integrate the AIS process with the radial basis function – partial least square regression to form an AIS-RBFPLS approach. By employing two independent clinical diagnosis data sets, we aim to demonstrate the advantage of the proposed AIS-RBFPLS approach over the conventional AIS- k NN approach, compare with the two widely

used neural network models, and provide suggestions for future applications of our new approach.

2. Material description

The first data set for this study is the FNA samples to establish a model for separating malignant breast tumor samples from benign samples. The FNA method was used to collect breast tissue materials from patients with a known clinical outcome, and the samples were then mounted on a microscope slide. The samples were then scored by pathologists according to the major cytological characteristics found in the sample. The data for this study was originally from the Clinical Sciences Center at the University of Wisconsin, Madison. The nine cytological characteristics employed for breast cancer detection were: clump thickness, uniformity of cell size, uniformity of cell shape, marginal adhesion, single epithelial cell size, bare nuclei, bland chromatin, normal nucleoli, and mitoses. A detailed description of these data can be found at UC Irvine Machine Learning Repository [15]. The sampling process covered two years from 1989 to 1991, in which 699 tissue samples (Benign: 458, Malignant: 241) were analyzed. The objective for this sample collection and data-base creation was to establish a diagnosis model using the nine cytological characteristics.

The second data set for this study is the mammography data for breast cancer screening. It contains the patient personal information (age) and three Breast Imaging-Reporting and Data System (BI-RADS) attributes (shape, margin, and density) for 516 benign and 445 malignant masses. The data were originally collected at the Institute of Radiology of the University Erlangen-Nuremberg between 2003 and 2006. The detailed description of this data set can be referred to the above mentioned Machine Learning Repository and literature [16].

3. Method description

3.1 Artificial immune system

Artificial immune systems are a recently developed bio-inspired machine learning method mimicking the response of natural immune systems to pathogen invasion [11]. Basically, when a pathogen invades the human body, special cells circulating within the body called “B-cells” generate antibodies specific to the antigens derived from the pathogen. Each B-cell can only produce one particular antibody. Once a B-cell gets sufficiently stimulated because of the close affinity to a presented antigen, it rapidly produces clones of itself. At the same time, the B-cell surface antigens will mutate to match the antigen as closely as it can, and this process is repeated many times in the human body. After a successful defense against the invading pathogen, a small number of “memory B-cells” stay in the body for sufficiently long periods of time to prevent reinfection. For future pathogen invasions, these memory B-cells can rapidly and efficiently recognize an antigen which is similar to those that the immune system previously fought against. Figure 1 shows a flowchart of the principle of this learning process. A brief description of the AIS algorithm that effectively mimics this biological process is shown below [12, 14]:

3.1.1 Initialization—We define the major terminologies of the AIS algorithm using vocabulary associated with the biological immune system. In the AIS algorithm, antigens refer to training data, classes indicate the origins of the antigens (i.e., category of each data point), memory cells are the representative data points, and artificial recognition balls (ARB) denote a group of candidate memory cells.

- 0) This is a preprocessing and initialization step for the algorithm. All sample data vectors are normalized so that the distances between any two data vectors – either used as antigen or ARB members – is in the range [0, 1]. We then randomly generate an initial memory cell population and ARB population. For each antigen (i.e., training sample), we then perform the following three steps.

3.1.2 ARB generation

- 1) Identify the memory cell (mc) which is from the same class as the antigen (ag) and the most stimulated by the antigen. Stimulation is defined as “ $1 - \text{dist}(\text{ag}, \text{mc})$ ”, where “dist” is the Euclidean distance between the two vectors. The smaller the distance, the higher the stimulation. The identified memory cell is denoted as mc_match.
- 2) Clone the identified memory cell at a predefined clone-rate (μ). Meanwhile, as memory cells have the same data structure and the same dimension number as training data, each variable (feature) of the new clones can be mutated with a user defined mutation rate (ζ) to keep the diversity of memory cell candidates. Then add these new clones to the ARB population.

3.1.3 Nomination of new memory cell—The key issue of this section is that all the ARB population members compete to generate a new memory cell.

- 3) A resource (ψ) allocation process is applied to the ARB population, which is dictated by the stimulation of each ARB member to the current antigen. An ARB member with higher stimulation will be given more of the limited resource. This process will result in the death of some ARB members with lower stimulation responses, which can in turn control the ARB population.
- 4) Calculate the average stimulation of the ARB population of each class. If the average stimulation for each class is higher than a user-defined threshold value (δ), then the learning process for this antigen is halted.
- 5) Otherwise, clone and randomly mutate the surviving ARB members with a probability which is proportional to their stimulation levels and then return to step 3).

3.1.4 Update memory cell pool

- 6) Select the ARB member which has the highest stimulation (i.e., the memory cell candidate: mc_cand) from the class of the antigen. If this highest stimulation is above the stimulation of the previously identified memory cell (mc_match) to the antigen, we add the mc_cand to the memory cell pool. Moreover, if the distance between mc_cand and mc_match is less than a user defined threshold value termed “*replacement threshold*” (γ), then mc_cand replaces mc_match.

Running the above learning process for all the antigens (training samples) will generate a final memory cell pool which theoretically can represent and cover the entire space distribution of the training sample set and will be used for the classification of new samples (antigens). A detailed description of this entire process can be found in the literature [12, 14].

3.2 k nearest neighbor (k -NN)

A typical and widely reported method to use the AIS memory cells to create a classification model for future prediction is the k -NN algorithm [12, 14, 17]. Briefly, a new sample is classified based on a majority vote of its k nearest neighbors (i.e., memory cells or

representative points). The new object is assigned to the class which contains the majority of the k memory cells. This is an efficient and easy-to-use classification approach, but there is one potentially-serious problem. Once the AIS creates memory cells (representative points), the k -NN model only uses these representative points for new sample prediction without further considering any other useful information from the entire training set. It is very likely that this approach can decrease the classification effect. Therefore, this paper aims to introduce a machine learning process which not only uses the AIS created memory cells but also employs the entire training sample set in an effort to increase the effect of the AIS-based classification approaches.

3.3 Radial basis function – partial least square regression (RBFPLS)

The method we integrated with the AIS to increase the classification results was the radial basis function – partial least square regression (RBFPLS). Basically, RBF-based methods use a kernel function to transfer the original sample space to a transitional space which is then correlated with the final output through a linear regression process [18–19]. A typical radial basis function is a Gaussian function expressed as:

$$a_{ij} = \exp\left(\frac{-\|\mathbf{x}_i - \mathbf{c}_j\|^2}{\sigma_j^2}\right) \quad (1)$$

where $\mathbf{x}_i$ is an input vector, $\mathbf{c}_j$ is the radial basis center, σ_j is the radial basis width and a_{ij} is the output of radial basis center j to input vector i . In our proposed approach, the AIS generated representative data points were used as the radial basis centers $\mathbf{c}_j$. This integration made it possible to employ all the training samples for the AIS-based machine learning processes. Supposing there are n training samples and m radial basis vectors (i.e., the AIS generated representative data points), the output of the hidden layer composed of all the radial basis functions is an n by m matrix:

$$\mathbf{A} = \begin{bmatrix} a_{11} & \dots & a_{1m} \\ \vdots & \vdots & \vdots \\ a_{n1} & \dots & a_{nm} \end{bmatrix} \quad (2)$$

In the conventional RBF approach, a linear regression will be applied to establish a map from matrix $\mathbf{A}$ to the outputs of the training samples $\mathbf{y} = (y_1 \ y_2 \ \dots \ y_n)^T$ and the regression coefficients (i.e., the weights between the hidden and output layers) can be used for future prediction.

Due to the possible similarity of the AIS created representative points, there could be a co-linearity in the outputs of the hidden layer constructed with the representative points. Therefore, we further applied partial least square regression (PLSR) instead of conventional linear regression to create a relationship between $\mathbf{A}$ and the output $\mathbf{y}$. Integrating PLS with RBF has been successfully applied to other studies [20–21]. The PLSR approach extracts uncorrelated latent variables from the original variable data. A general linear model is $\mathbf{Q} = \mathbf{X}\mathbf{B} + \mathbf{E}$, where $\mathbf{B}$ is the regression coefficients and $\mathbf{E}$ is the residual matrix. In PLSR, $\mathbf{X}$ can be decomposed into $\mathbf{X} = \mathbf{T}\mathbf{P}^T$, where $\mathbf{T}$ is PLS components (score matrix). Let $\mathbf{W}$ be the inverse of $\mathbf{P}^T$: $\mathbf{W} = (\mathbf{P}^T)^{-1}$, so $\mathbf{T}$ can be expressed as $\mathbf{T} = \mathbf{X}\mathbf{W}$. Then the regression equation turns to be $\mathbf{Q} = \mathbf{X}\mathbf{W}\mathbf{P}^T\mathbf{B} + \mathbf{E} = \mathbf{T}\mathbf{A} + \mathbf{E}$, where $\mathbf{A} = \mathbf{P}^T\mathbf{B}$. Thus, the regression between $\mathbf{X}$ and $\mathbf{Q}$ becomes the regression between PLS components $\mathbf{T}$ and $\mathbf{Q}$. The prediction of new independent data $\mathbf{X}_n$ can be easily determined with $\mathbf{Q}_n = \mathbf{X}_n\mathbf{W}\mathbf{A}$. The details of PLSR are

well discussed in the literature [22]. By incorporating all of these concepts together, we have presented a new AIS-based machine learning approach, called AIS-RBFPLS, in this paper.

3.4 Back propagation neural network (BPNN)

Both two AIS-based approaches, the AIS- k NN and the AIS-RBFPLS, were also compared with another traditional machine learning method, the BPNN, to examine differences among the models for clinical diagnosis effects. The BPNN is one of the most widely used neural network models, which has been extensively applied to pattern recognition and function approximation. Typically, the BPNN is composed of three layers: input, hidden, and output. A sigmoid function is widely used as an activation function for each hidden and output neuron. During the training process, the prediction error of one training sample is propagated backward to adjust the connecting weights. A detailed description can be referred to the literature [23], and this traditional BPNN approach provides a baseline comparison to benchmark our novel AIS-RBFPLS approach.

3.5 Orthogonal radial basis function neural network (Ortho-RBFN)

In addition to BPNN, another classical machine learning method for complex systems, named Ortho-RBFN, was employed to compare with our proposed approach. Briefly, the learning process of Ortho-RBFN is to construct a three-layer forward neural network by selecting necessary and sufficient radial basis vectors through a Gram-Schmidt method. The learning process of the Ortho-RBFN is a deterministic process without being influenced by initial network weight values, which is its advantage over BPNN, but both of these two types of neural networks have become widely used machine learning methods for complex systems. The details of Ortho-RBFN can be found in the literature [18]. All the computing work in this study was performed on Matlab (version: 7.6.0).

4. Results of case study 1

4.1 Data pretreatment and experimental design

In this study, 699 tissue samples (458 benign, 241 malignant) were employed for breast cancer diagnosis modeling. Each sample was composed of 9 cytological characteristics described earlier. There are 16 samples that contain missing characteristic values, and so these samples were excluded from our analysis to prevent the missing values from disturbing the diagnosis effect comparison. The remaining 683 samples were randomly and evenly divided into 3 groups which were respectively used for model training, validating and blind testing. As described earlier, the data were normalized before the AIS searching process began.

Briefly, the entire framework of the analysis was to: 1) use the AIS algorithm to create representative data points from the training data; 2) employ the validation data to determine the proper parameters for the AIS follow-up classification models (k NN and RBFPLS); and 3) test the diagnosis accuracies of the complete AIS-based pattern recognition approaches (AIS- k NN and AIS-RBFPLS) on the blinded testing data. Specifically, as to the proposed AIS-RBFPLS approach, after the AIS selected the representative data points from the training samples, we used these representative points to construct the radial basis kernel functions. Then, the entire training sample set was applied to determine the other parameters such as PLS component number and PLS regression coefficients. To avoid a possible over-fitting problem, we applied the model generated from the training set to the validating set. The model with the parameters which yielded a lowest error on the validating set was chosen as the final model to test on the blind testing set. A flow-chart of this experimental framework is shown in Figure 2.

4.2 Results of AIS- k NN

The major parameters for the AIS in this study were set to be: 5 for the clone-rate (μ), 100 for permit resources (ψ), 0.3 for the mutation rate (ζ), and 0.95 for the stimulation threshold (δ). Similar values can be found in other reported studies [17]. A thorough investigation of the optimal parameter values is beyond the main scope of this paper. To compare the robustness and effect of the two subsequent classification methods (k -NN and RBFPLS) following the AIS selected representative data points, we gave four different values to an important parameter: the *replacement threshold* (γ). This parameter directly controls the replacement of the existing memory cells and the final memory cell pool, i.e., the representative data points. The four different *replacement threshold* values were 0.05, 0.1, 0.2, and 0.3, providing a platform to compare the two AIS-based machine learning approaches. For each different *replacement threshold*, we ran AIS on the training samples 6 independent times. The results of the created memory cells are listed in Table 1. We observed that the number of memory cells increased along with a decrease on the *replacement threshold* because a lower *replacement threshold* allowed the AIS to keep more existing memory cells. The representative data points that the AIS algorithm created from the training samples were then used to establish a classification model through the follow-up pattern recognition approaches.

For the AIS- k NN approach, the next step was to use k -NN to create a pattern recognition method for future prediction through these AIS memory cells (representative points). The key issue for k -NN is to determine a proper k value. There have been some suggestions for this issue in the literature [24]. In general, a larger value of k is frequently observed to reduce the influence of outliers or system noise, but it could generate clouded class boundaries, so usually small k values are suggested [19, 24]. In this study the validating sample set was used to determine a proper k value, and eventually the k -NN with the determined k value was applied to the testing sample set. Figure 3 shows a typical relationship between k value and the misclassification ratio on the validating sample set, using the results of the first AIS run (with the *replacement threshold* = 0.05). The model with $k = 6$ yielded the lowest misclassification ratio, so $k = 6$ was determined as a proper k value for this case and was then applied to examine the classification effect on the blind testing set. A similar k value determination process was applied to the validating sample sets of all the 24 cases (4 threshold values * 6 repeats) and then the proper k values were used to examine their classification effects on the corresponding testing sets. Table 2 shows the classification results of AIS- k NN for all 24 cases.

The AIS- k NN classification results of all the 24 cases in Table 2 are acceptable, but the results of the *replacement threshold* value = 0.3 are clearly worse than the other AIS- k NN results. One main reason could be that the large *replacement threshold* value did not keep enough memory cells and the final remaining memory cells actually did not adequately cover or represent the sample space. Even within the AIS- k NN results of the *replacement threshold* value = 0.3, the misclassification ratio based on the 4th AIS run is multiple times of the results of the other 5 runs. The k -NN approach, which follows AIS, was a deterministic machine learning process, so the big difference between two runs (i.e., 26.32% of the 4th run versus 3.95% of the 5th run) indicated a possible question of the representativeness of the AIS memory cells. Since we can not fully guarantee and control the result of a stochastic process such as the AIS learning process, we need to be armed to handle possible questionable results from the AIS process. This encouraged us to test if integrating the AIS with RBFPLS would make the classification more robust and lead to a further model improvement.

4.3 Results of AIS-RBFPLS

The same AIS created memory cells as listed in Table 1 were employed to examine if a RBFPLS approach would improve the classification results. Briefly, for each case of Table 1, the memory cells (representative points) created by the AIS were used as the radial basis centers and all the training samples were used to establish a RBFPLS model.

There two key parameters to control the modeling effect of RBFPLS: the Gaussian width (i.e., the radial basis center width: σ_j) and a proper PLS component number. Ideally, we would employ optimization tools to find the best Gaussian widths. For example, genetic algorithms can help find the optimum Gaussian width for each radial basis center in the literature [25]. However, this could be a very time consuming process. Meanwhile, some reported studies have demonstrated that a Gaussian width of $\sigma_j = 1$ could be a reasonable choice for general uses [20, 26], so in this paper we also used $\sigma_j = 1$ for our studies.

The proper PLS component number for each case in Table 1 was determined by examining the classification effect of the AIS-RBFPLS models on the independent validating samples which were randomly selected from the total data set. Figure 4 show a typical relationship between the PLS component number and the misclassification ratio on the validating samples, using the results of the second AIS run (with the *replacement threshold* = 0.05). We found that PLS = 5 yielded the lowest misclassification ratio on the validating sample set. Therefore, PLS = 5 was chosen as a reasonable value for our modeling strategy for this case. This determination process was applied to all 24 cases (4 *replacement threshold* values * 6 repeats), and we tested the resulting RBFPLS models to examine their classification effects on the testing sets. The classification results of AIS-RBFPLS for all 24 cases are also listed in Table 2 with the results of AIS-kNN.

Using the AIS algorithm to generate representative points is a stochastic process, and so it is better for a robust and systematic modeling effect comparison to examine the average classification results between different model runs. Figure 5 shows a cross comparison between the AIS-kNN and AIS-RBFPLS results in Tables 2. It can be seen from this figure that for all the *replacement threshold* values but the case of *replacement threshold* = 0.2, AIS-RBFPLS has a lower or equal average misclassified ratios than or to AIS-kNN and a systematically lower standard deviation of the misclassified ratios than AIS-kNN. Especially when the *replacement threshold* value = 0.3, the classification process of the AIS-RBFPLS was not disturbed by this potentially improper AIS parameter while the classification effect of AIS-kNN was clearly degraded. This leads us to believe that the AIS-RBFPLS is a more robust process than the traditional AIS-kNN, even when model parameters have not been fully optimized. The superior results from the AIS-RBFPLS model are mainly due to: (1) the radial basis centers are better able to deal with possible nonlinearity among the system by utilizing the Gaussian function; and (2) RBFPLS further makes use of the information of all the training samples to make the model an even better fit within the sample distribution space and make the modeling process less disturbed by possible improper AIS memory cells.

4.4 Results of other classical methods

The two AIS-based approaches described above were then compared with the classical BPNN and Ortho-RBF model. One key parameter for a BPNN model is the number of hidden neurons. In this study, we adopted a typical estimation method to determine an adequate first estimate of this hidden neuron number [27]. Assuming there are S training samples and the dimensions of input and output vectors are p and q respectively, the

estimate of the hidden neuron number is $Nh = INT[\frac{S \times q - q}{p + q + 1}]$, where $INT[\bullet]$ denotes a

nearest integer function. In this study, $S = 227$ (training samples), $p = 9$ (cytological characteristics) and $q = 1$ (either benign or malignant), and the resulting hidden neuron number was calculated to be 21. We also examined the BPNN modeling results with $Nh = 16$ and 26 (which is 25% less and more than the estimated number) to cover a relatively wide range for a possible proper hidden neuron number. For each Nh , we ran the BPNN on the training samples a total of 6 times, and then chose the model that yielded a lowest error on the validating samples to predict the blind testing samples.

One key issue of the Ortho-RBF is to determine the number of radial basis vectors. In this study, we gradually increased the number of radial basis vectors to construct the Ortho-RBF models from the training samples. As suggested in the literature [20, 26], the Gaussian width for each radial basis vector was also set to be 1. Among these models, the one that yielded the lowest misclassification ratio was selected as the final model to predict the testing samples.

The results from the BPNN and Ortho-RBF modeling are listed in Table 3. Comparing these results with the average results of the AIS-RBFPLS in Table 2, we can see that: (1) the AIS-RBFPLS systematically shows a lower misclassification ratio than the BPNN, and (2) when the *replacement threshold* value = 0.1 and 0.05, the AIS-RBFPLS shows a lower misclassification ratio than the Ortho-RBF network and in the other two cases the AIS-RBFPLS still generated a result comparable to the Ortho-RBF network. This demonstrates the AIS created memory cells (representative points) have the potential to cover and capture the majority of space distribution information of the initial sample set.

One of the most cited references working on the same data set was from the Clinical Sciences Center at the University of Wisconsin, Madison where the data for this study was originally generated [3]. In that study, the sample set was split into only two parts: 66.7% for training and 33.3% for testing. The testing error of a multi-surface-based classification method was found to be 4.1%, which is slightly higher compared to the results of the methods proposed in this present study. The higher misclassification ratio of the reported multi-surface method may indicate there could be nonlinearities within the data system.

5. Results of case study 2

5.1 Data pretreatment and experimental design

In this study case, 961 mammography samples (516 benign, 445 malignant) were employed for breast cancer screening analysis. Each sample was composed of 4 variables including patient age and three Breast Imaging-Reporting and Data System (BI-RADS) attributes: shape, margin, and density. After excluding the 131 samples that contain missing characteristic values, we retained 830 samples (427 benign, 403 malignant) for analysis. Like what we did in the first study, the remaining 830 samples were randomly and evenly divided into 3 groups which were respectively used for model training, validating and blind testing. The same machine learning processes and result comparison methods as in the first study were applied to this topic.

5.2 Results of AIS-kNN

In this case study, the *replacement threshold* was also given four different values: 0.05, 0.1, 0.2, and 0.3, aiming to provide a platform to compare the two AIS-based machine learning approaches. For each different *replacement threshold*, we ran AIS on the training samples 6 independent times. The results of the created memory cells are listed in Table 4. The number of memory cells increases along with a decrease on the *replacement threshold* as a lower *replacement threshold* allows the AIS to keep more memory cells. These representative data

points were then used to establish a classification model through the follow-up pattern recognition approaches.

For the AIS- k NN approach, we still adopted the same k -value determination strategy as in the first case study. The k -value which yielded the lowest misclassification ratio in the validating set was selected as the final k -value for blind testing. The testing results of all the 24 cases (4 threshold values * 6 repeats) are listed in Table 5. It is clear that the average misclassification ratio is sensitive to the value of *replacement threshold* and its generated representative data points, which suggests possible unstableness of the AIS- k NN approach.

5.3 Results of AIS-RBFPLS

The AIS created memory cells as listed in Table 4 were employed to further examine if a RBFPLS approach would improve the classification results. Briefly, for each of the 24 cases of Table 4, the memory cells (representative points) created by the AIS were used as the radial basis centers and all the training samples were used to establish a RBFPLS model. Also the Gaussian width σ_j was also set to be 1, a generally suggested value, for this case study. The proper PLS component number for each case was determined by examining the classification effect of the AIS-RBFPLS models on the independent validating samples. The classification results of AIS-RBFPLS on the testing samples for all the 24 cases are also listed on Table 5 with the AIS- k NN results. .

A comparison between the AIS- k NN and AIS-RBFPLS for this study is shown in Figure 6. Clearly, AIS-RBFPLS not only has a lower misclassification ratio but also has a much smaller result standard deviation. Also, AIS-RBFPLS shows its robustness in terms of the values of *replacement threshold*. All these results presented an obvious advantage of AIS-RBFPLS over the AIS- k NN.

5.4 Results of other classical methods

In this section, the two AIS-based approaches were also compared with the classical BPNN and Ortho-RBF model. Using the same modeling and validating process as defined in the first case study, the results from the BPNN and Ortho-RBF modeling are listed in Table 6. Comparing these results with the AIS-RBFPLS results in Table 5 indicates that the AIS-RBFPLS systematically shows a lower misclassification ratio than both BPNN and Ortho-RBF network. This further presents the ability of the AIS created memory cells (representative points) to capture the majority of space distribution information of the original sample set.

6. Discussion

This paper integrated the AIS algorithm with the RBFPLS model to improve the effect of the classification model of the current AIS- k NN. The Gaussian width (radial basis center width) is a key issue for the RBFPLS approach, controlling the response field of each radial basis function. In this study, a feasible Gaussian width suggested for general uses was applied. For future studies, we can employ optimization methods to find the optimal value of the Gaussian width for each radial basis center to further improve the classification effect of the AIS-RBFPLS.

The AIS-RBFPLS approach also demonstrated its robustness on the AIS results. For example, an overly large *replacement threshold* value could result in the final memory cells being unable to cover and represent the entire sample distribution space, and this consequently resulted in the failure of the k -NN classification method in this study. However, the RBFPLS presented its robustness on this aspect, by employing the AIS created representative samples as the radial basis centers of Gaussian kernel functions and using all

the training samples to systematically build a classification model. Radial basis function help the model handle possible nonlinearity in the system and PLS resolved another potential problem, i.e., possible co-linearity among the outputs of the kernel functions constructed with the AIS created representative samples. In addition, unlike BPNN which requires an iterative learning process, RBFPLS is a one-step deterministic learning process once we set up the parameters. An increase on training sample size will not dramatically increase the computation time of RBFPLS.

Considering the unbalance between the benign and malignant samples in the first case study (FNA breast tissue samples), we also examined the diagnosis sensitivity and specificity on the testing set to avoid a possible overwhelming of one category over the other. The average values of the sensitivity and specificity of the AIS-*k*NN approach are: 83.54% and 94.93% (replacement threshold $\gamma = 0.3$), 99.58% and 96.06% ($\gamma = 0.2$), 97.08% and 96.85% ($\gamma = 0.1$), and 97.50% and 96.85% ($\gamma = 0.05$). The average value of the sensitivity and specificity of the AIS-RBFPLS approach are: 95.63% and 97.19% ($\gamma = 0.3$), 95.63% and 97.41% ($\gamma = 0.2$), 96.67% and 97.19% ($\gamma = 0.1$), and 96.67% and 97.30% ($\gamma = 0.05$). In this study, the balance between sensitivity and specificity supported the reliability of the systematical classification accuracy on this unbalanced sample set.

In addition to the above major objectives, this paper also demonstrated the proposed AIS-RBFPLS classification approach could yield a better result than two classical machine learning methods: BPNN and Ortho-RBF network, which further indicate a wide and promising future application of the proposed method.

This proposed AIS-RBFPLS classification approach can be applied to other data and sensor outputs such as those for non-invasive diagnosis and hazardous chemical detection. The AIS algorithm can create representative points (memory cells) for multiple (≥ 2) classes, so the AIS-RBFPLS also provides an efficient classification method for a multiple-class problem. Also, the AIS learning process is a stochastic process, so it is always reasonable to perform the AIS for enough repeated times to generalize a reliable result.

7. Conclusion

This paper proposed a novel AIS-based machine learning approach by integrating the AIS with the RBFPLS. The results of two case studies show that: (1) both the conventional AIS-*k*NN and our newly proposed AIS-RBFPLS models can generate a satisfactory diagnosis accuracy; (2) the AIS-RBFPLS presented an even lower misclassification ratio and higher diagnosis stability than the AIS-*k*NN; (3) AIS-RBFPLS was found to be robust in terms of the AIS created memory cells, ultimately yielding a good classification result even in the case where the AIS was provided with less-than-ideal parameter values; and (4) the proposed AIS-RBFPLS approach presented better diagnosis results than the classical BPNN and Ortho-RBF network, demonstrating the ability of the AIS created memory cells (representative points) to cover sample spaces. The successful application of our newly proposed method to clinical diagnosis also indicates wide potential applications to a variety of artificial intelligence fields.

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Figure 1.
Flowchart of the AIS learning process

Figure 2.
Flowchart of the modeling and validating process

Figure 3.
Relationship between k value and misclassified ratio on the validating samples

Figure 4. Relationship between PLS component number and misclassified ratio on the validating samples

Figure 5. Comparison of classification results of AIS-kNN and AIS-RBFPLS on the FNA breast tissue samples. kNN: AIS-kNN, RP: AIS-RBFPLS and 1–4: indicating four different replacement threshold values (1:0.3, 2:0.2, 3:0.1, and 4:0.05)

Figure 6.

Comparison of classification results of AIS-kNN and AIS-RBFPLS on the mammography samples. kNN: AIS-kNN, RP: AIS-RBFPLS and 1–4: indicating four different *replacement threshold* values (1:0.3, 2:0.2, 3:0.1, and 4:0.05)

Table 1

The number of memory cells for different replacement threshold values (FNA breast tissue samples)

run index	replacement threshold			
	0.3	0.2	0.1	0.05
1	9	18	53	87
2	10	18	58	87
3	8	19	57	90
4	8	18	53	92
5	7	19	50	92
6	9	22	58	84

Table 2

Misclassification ratio [%] of the AIS-kNN (A-k) and AIS-RBFPLS (A-RP) using the AIS memory cells generated with the different replacement threshold values (FNA breast tissue samples)

run index	replacement threshold							
	0.3		0.2		0.1		0.05	
	A-k	A-RP	A-k	A-RP	A-k	A-RP	A-k	A-RP
1	5.26	3.07	2.19	3.07	2.63	3.07	2.19	3.07
2	5.26	3.07	2.63	3.95	3.51	3.07	2.63	3.51
3	9.65	3.07	3.07	3.51	3.51	2.19	3.95	3.07
4	26.32	3.95	2.63	2.63	2.19	3.07	3.51	2.63
5	3.95	3.07	2.19	2.63	3.51	3.51	2.19	2.63
6	3.95	3.95	3.51	3.51	3.07	3.07	3.07	2.63
Mean (std)	9.07 (8.71)	3.36 (0.45)	2.70 (0.51)	3.22 (0.53)	3.07 (0.56)	3.00 (0.43)	2.92 (0.72)	2.92 (0.36)

Table 3

Misclassification ratio [%] of BPNN with different hidden neuron numbers and Ortho-RBF model (FNA breast tissue samples)

	BPNN			Ortho-RBF
No. of hidden neurons / radial basis vectors	16	21	26	14
Misclassification ratio [%]	4.39	3.95	4.39	3.07

Table 4

The number of memory cells for different replacement threshold values (mammography data)

run index	replacement threshold			
	0.3	0.2	0.1	0.05
1	7	18	46	57
2	8	16	47	69
3	6	18	53	60
4	6	22	46	66
5	6	16	42	69
6	6	18	43	59

Table 5

Misclassification ratio [%] of the AIS-kNN (A-k) and AIS-RBFPLS (A-RP) using the AIS memory cells generated with the different replacement threshold values (mammography data)

run index	replacement threshold							
	0.3		0.2		0.1		0.05	
	A-k	A-RP	A-k	A-RP	A-k	A-RP	A-k	A-RP
1	22.3	19.78	24.46	19.42	22.66	18.71	20.5	18.71
2	33.81	19.78	23.38	18.71	19.42	19.42	20.86	19.42
3	25.18	19.06	23.38	19.06	20.86	18.71	20.14	18.71
4	20.86	18.71	20.86	18.35	21.22	19.42	22.66	18.71
5	30.58	19.06	19.78	19.06	20.86	19.06	47.48	19.42
6	37.41	18.71	20.5	18.71	20.5	18.71	42.81	18.35
Mean (std)	28.36 (6.61)	19.18 (0.49)	22.06 (1.91)	18.89 (0.37)	20.92 (1.05)	19.01 (0.35)	29.08 (12.57)	18.89 (0.44)

Table 6

Misclassification ratio [%] of BPNN with different hidden neuron numbers and Ortho-RBF model (mammography data)

	BPNN			Ortho-RBF
No. of hidden neurons / radial basis vectors	35	46	58	101
Misclassification ratio [%]	21.22	20.86	21.58	23.02