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AISAC: An Artificial Immune System for Associative Classification Applied to Breast Cancer Detection

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Abstract: Early breast cancer diagnosis is crucial, as it can prevent further complications and save the life of the patient by treating the disease at its most curable stage. In this paper, we propose a new artificial immune system model for associative classification with competitive performance for breast cancer detection. The proposed model has its foundations in the biological immune system; it mimics the detection skills of the immune system to provide correct identification of antigens. The Wilcoxon test was used to identify the statistically significant differences between our proposal and other classification algorithms based on the same bio-inspired model. These statistical tests evidenced the enhanced performance shown by the proposed model by outperforming other immune-based algorithms. The proposed model proved to be competitive with respect to other well-known classification models. In addition, the model benefits from a low computational cost. The success of this model for classification tasks shows that swarm intelligence is useful for this kind of problem, and that it is not limited to optimization tasks.

Keywords: swarm intelligence; artificial immune systems; classification; breast cancer

1. Introduction

Evolutionary computation (EC) is an active research area with several successful applications in a variety of domains [1–3]. Evolutionary methods have exhibited impressive performances when compared to other approaches.

One branch of evolutionary methods, known as swarm intelligence (SI), has shown the ability to find accurate solutions to numerous problems, such as computer vision [4], feature selection [5], clustering [6], network routing [7], and resource planning [8], among others.

However, regarding supervised classification, SI has been applied mainly for parameter optimization of classifiers (Support Vector Machines [9], Gamma [10], fuzzy rule-based classifiers [11]), for training set instance selection (for neural networks [12], k-nearest neighbors [13], and Support Vector Machines [14]), and in other optimization problems: attribute and instance selection [15,16], and the selection of optimal parameter values [17]. Despite the rich application of SI in the field, there is currently no algorithm based on SI that correctly classifies any presented dataset, as a consequence of the no free lunch theorem [18].

Although some works have been developed in this area, such as immune system models [19], immune networks [20], and, more recently, endocrine systems [21], this is an under-researched area.

For this reason, we propose a new model based on the biological immune system designed explicitly for classification. The aim of this system is to overcome the limitations of previous models and be competitive with well-known classification models. Our model constitutes a contribution to the state of the art on novel pattern classifiers, and tackles some challenges in the field of evolutionary pattern recognition and related applications.

The main contribution of this research is a model of immune system classification which is statistically significantly better than other immune-based classifiers. The proposed model is also competitive with respect to classifiers such as multilayer perceptron [22], Support Vector Machines [23], C4.5 [24], and random forest [25]. In addition, it has a low computational cost, is highly configurable, and performs well for an impactful application area: the early detection of breast cancer.

The rest of the paper is structured as follows. In Section 2, a review of the related works is presented. General elements of the human immune system are detailed in Section 3, as well as the new Artificial Immune System for Associative Classification (AISAC). Then, Section 4 details the experiments where the proposed model is applied to medical data analysis, in particular to the detection of breast cancer, as well as other types of cancer. The results obtained are compared to other classification models based on immune systems, in addition to other well-known classification systems. Furthermore, empirical studies are performed in order to determine the adequate parameter values for the proposed AISAC, which are detailed in Section 4.2. In Section 5, a discussion of the results is presented. The paper finishes by offering conclusions and future lines of work in the Conclusions section.

2. Related Works

We compared ten learning classification systems to our AISAC model. We selected three immune-based classification algorithms (AIRS1 [26], Immunos1 [27], and CLONALG [28]), as well as six well-known algorithms, considered among the best general-purpose classifiers (Support Vector Machines [23], multilayer perceptron [22], nearest neighbor [29], RIPPER [30], C4.5 [24], naïve Bayes [31], and random forest [25]).

All the algorithms were available in Weka [32], including the immune-based algorithms, which were released by Jason Brownlee in 2011, with a recent update in 2013 [27]. We manually explored the best parameter configuration for each algorithm. In the following paragraphs we offer a brief description of the learning algorithms.

2.1. Supervised Classifier

In the literature there are several classification algorithms, belonging to different approaches. In this section we will address seven of them; these algorithms represent vector support machines, neural networks, distance-based classifiers, decision trees, probabilistic classifiers, rule-based classifiers, and classifier committees.

Support Vector Machines (SVM) [23] are algorithms which construct a model that linearly separates classes using a hyperplane. The classification performance depends on the separation done by the hyperplane. This algorithm is designed to work with two classes, so in order to use a multiclass dataset, other strategies have been used, such as multi-splitting the classes or constructing more than one model to cover all the classes. Finding the right kernel is not easy, so the results may vary. SVM models suffer from a lack of interpretability. We used the Weka implementation of IMO due to its low computational cost.

Multilayer perceptron (MLP) [22] is an artificial neural network model which maps a set of inputs to get a defined set of outputs. This model has multiple layers and nodes representing neurons that are connected in each layer. Back propagation is an algorithm used to train multilayer neural networks by changing the weights in each connection using the error of the outputs, which is propagated to each previous layer. Training can become a very expensive process, since it requires a long time and a large amount of data to be trained; in addition, the generated model is not very interpretable.

The nearest neighbor (NN) [29] algorithm computes the distances between the test pattern and all the training patterns, and chooses the dominant class among the k-nearest patterns. This algorithm is one of the simplest machine learning algorithms; despite this fact, the performance of this algorithm is one of the highest for some datasets. This algorithm suffers from high memory consumption, since the training set is kept in memory at all times.

Repeated Incremental Pruning to Produce Error Reduction (RIPPER) [30] is an algorithm based on generating association rules for reducing the error when pruning. The generation of rules is made by applying a pruning operator to delete conditions or rules in order to obtain the greatest reduction of error. The output model is easy to understand.

C4.5 [24] is a decision tree for pattern classification. The information entropy is used to choose the node splits to generate the tree, where each node represents an attribute of the data. This algorithm may become stuck at a local minimum and would need additional processes to avoid this. The output model is easy to understand.

Naïve Bayes [31] is a classifier based on the Bayes theorem and assumes the independency of each attribute. This algorithm requires a small quantity of training data to generate the model used for classification.

Random forest [25] is a classifier ensemble based on a random combination of tree classifiers, such that each tree depends on the values of an independently tested random classification tree. It is a small modification of bagging that builds a long collection of uncorrelated trees and then averages the results.

2.2. Classification Systems Based on Immune Systems

The Artificial Immune Recognition System (AIRS) [26] is inspired by the immune system and uses memory cells, resource competition, affinity maturation, and clonal selection, based on the functioning of the biological immune system. This algorithm has four stages, which are data normalization and initialization, memory cell identification and artificial recognition balls generation, competition for resources, and conversion of candidate memory cells into memory cells.

Immunos1 [27] is a model based on the immune system that exhibits dynamic learning and assumes no data reduction. The training population is partitioned and allows independent and parallel management in the classifier. The cells compete by calculating the affinity using Euclidean distance and calculating the avidity.

CLONALG [28] is based on the clonal selection principle, which allows the cells that correctly recognize the antigens to proliferate. It has the ability to perform parallel search and is used for pattern recognition and optimization problems using each antibody as a candidate for the optimal solution.

Our proposal differs from other classification algorithms due to the use of stochastic methodologies, which make it possible to find solutions to non-polynomial problems. Likewise, this behavior allows the algorithm to explore and find optimal solutions to perform the corresponding classification.

3. Our Proposal: An Artificial Immune System for Associative Classification

3.1. The Human Immune System

The immune system is a biological system that protects an organism against pathogens, such as biological, chemical, or intern hazards [33]. The immune system has two main functions: to recognize substances foreign to the body (also called antigens), and to react against them. These substances may be microorganisms that cause infectious diseases, transplanted organs or tissues of another individual, or tumors. The proper functioning of the immune system provides protection against infectious diseases and can protect a person from cancer.

An antigen is any substance that causes the body to create antibodies. It is a substance capable of inducing an immune response. Among the properties of antigens, the following can be highlighted [34]:

1. They have to possess the quality of strangers to the human body. That is, the antigens may come from outside (exogenous) or they may be generated in our body (endogenous);
2. Not all trigger an immune response, because of the amount of inoculum that is introduced. A considerable proportion is needed to trigger a response;
3. The immune response is under genetic control. Because of this, the immune system decides whether to respond or not, and against whom it will respond and against whom it will not;
4. The basic structure has an important relevance. This is because T and B lymphocytes are involved in cell-mediated immunity: T lymphocytes regulate the entire immune response, and B lymphocytes are secondary;
5. Some antigens must be recognized by the T lymphocytes to give a response, which are called antigens of thymus-dependent type; there are others that do not—it is enough for them to reach the B lymphocyte to be recognized as such. These are called thymus-independent antigens.

Antigenic macromolecules have two fundamental elements: the antigenic carrier, which is a macroprotein, and the antigenic determinants (epitopes), which are small molecules attached to them with a particular spatial configuration that can be identified by an antibody; therefore, the epitopes are responsible for the specificity of the antigen for the antibody.

Thus, the same antigenic molecule can induce the production of as many different antibody molecules as different antigenic determinants it possesses. For this reason, antigens are said to be polyvalent. Generally, an antigen has between five and ten antigenic determinants on its surface (although some have 200 or more), which may be different from each other so that they may react with different types of antibodies.

The immune system is divided into two subsystems: the innate immune system and the adaptive immune system. The innate immune system can detect antigens inside the system, while the adaptive immune system is more complex, since it exhibits a response which can be modified to answer back to specific antigens. This response is improved by the repeated presence of the same antigen.

The innate immune system has an immediate response, but this is not specific and there are no memory cells involved. In contrast, the adaptive immune system response takes more time to be activated but is specific to the antigen because memory cells are involved.

Adaptive immunity or acquired immunity is the ability of the immune system to adapt, over time, to the recognition of specific pathogens with greater efficiency [35]. Immunological memory is created from the primary response to a specific pathogen and allows the system to develop a better response to eventual future encounters.

Antibodies are chemicals that help destroy pathogens and neutralize their toxins. An antibody is a protein produced by the body in response to the presence of an antigen, and it is able to combine effectively with it. An antibody is essentially the complement of an antigen.

The specific adjustment of the antibody to the antigen depends not only on the size and shape of the antigenic determinant site, but also on the site corresponding to the antibody, more similar to the analogy of a lock and key. An antibody, as well as an antigen, also has a valence. While most of the antigens are polyvalent, the antibodies are bivalent or polyvalent. Most human antibodies are bivalent.

Various cell types carry out immune responses by way of the soluble molecules they secrete. Although lymphocytes are essential in all immune responses, other cell types also play a role [35]. Lymphocytes are a special group of white blood cells: they are the cells that intervene in the defense mechanisms and in the immune reactions of the organism.

There are two main categories of lymphocytes: B and T [35].

B lymphocytes, which represent between 10% and 20% of the total population, circulate in the blood and are transformed into antibody-producing plasma cells in the event of infection. They are responsible for humoral immunity. T lymphocytes are divided into two groups that perform different functions:

a. T lymphocyte killers (killer cells or suppressor cells) are activated by abnormal cells (tumor or virus-infected); they attach to these cells and release toxic substances called lymphokines to destroy them;
b. T helper cells (collaborators) stimulate the activity of T-killer cells and intervene in other varied aspects of the immune reaction.

Macrophages (from Greek "big eaters") are cells of the immune system that are located within tissues. These phagocytic cells process and present the antigens to the immune system. They come from precursors of bone marrow that pass into the blood (monocytes) and migrate to sites of inflammation or immune reactions. They differ greatly in size and shape depending on their location. They are mobile, adhere to surfaces, emit pseudopodia, and are capable of phagocytosis-pinocytosis or have the capacity to store foreign bodies.

When macrophages phagocyte a microbe, they process and secrete the antigens on their surface, which are recognized by helper T lymphocytes, which produce lymphokines that activate B lymphocytes. This is why macrophages are part of the antigen-presenting cells. Activated B lymphocytes produce and release antibodies specific for the antigens presented by the macrophage. These antibodies adhere to the antigens of the microbes or cells invaded by viruses, and thus attract with greater avidity the macrophages to phagocyte them [34].

Subsequently, the regulation phase controls the cells generated in the immune response in order to avoid damaging the system itself and preventing autoimmune responses. Finally, in the resolution phase, the harmful agent is removed and the cells generated to destroy the antigen die, only storing the memory cells.

The immune system has been the inspiration for numerous researchers in order to develop learning classifier systems [36–39]. Similarly, the immune system inspired the model proposed in this paper, the Artificial Immune System for Associative Classification, which is described in the next section.

3.2. AISAC: Artificial Immune System for Associative Classification

The main goal of classifier systems is to assign or predict a class label for an unseen pattern according to its attributes after training it with similar patterns [40].

Many classifier systems are based on two steps: model construction and model operation [41]. Model construction is a representation of the training set, which is used to generate a structure to classify the patterns presented. Model operation classifies data whose class labels are not known using the previously constructed model. In this paper, the classification problem is addressed by proposing a new model based on the immune system. Although numerous computational models have been developed based on the human immune system [42], this research presents a new model that incorporates additional elements of the immune response. The model is called Artificial Immune System for Associative Classification (AISAC). This model is proposed within the supervised classification paradigm, and therefore constitutes a new supervised classifier.

Among the characteristics of the proposed model, it can be highlighted that it is an eager classifier, since it generates internal data structures to classify the new instances. Thus, the training set is replaced by other structures. The proposed artificial immune system model includes two types of functions: the acquired (adaptive) immune response, and the innate immune response. The acquired immune response consists of five phases:

1. Detection of antigenic macromolecules;
2. Activation of B lymphocytes;
3. Immune response regulation;
4. Development of adaptive immunity;
5. Resolution of the threat.

The innate immune response has only one phase:

1. Resolution of the threat.

In general, the acquired immunological response begins with the detection of antigenic macromolecules by macrophages. Each macrophage will phagocytose a number of antigenic determinants of the antigenic molecule in which it specializes. Subsequently, each macrophage will present the antigenic determinants that it phagocytosed to the T lymphocyte helpers.

In Phase 2, these lymphocytes will generate an immune response, activating a certain number of B lymphocytes. Activated B lymphocytes will produce and release specific antibodies to the antigens presented by the macrophage. Then, the immune response will be monitored (Phase 3). If the immune response is satisfactory, the generated antibodies are conserved. Otherwise, a readjustment of the generated antibodies is performed so that they are able to combine with the antigenic determinants presented.

To guarantee the development of adaptive or acquired immunity (Phase 4), each of the antibodies will undergo a reconstitution phase so that it is capable of improving its immune response. Finally, in Phase 5, the antigenic macromolecules are completely removed and the antigens are stored in the immune memory.

In the case of the innate immune response a set of antibodies is already in memory; when an antigen is present, it is automatically detected and eliminated.

Metaphor-Free AISAC

The proposed artificial immune system-based model is indeed a classification algorithm. The acquired immune response corresponds to the model construction phase of the classifier, and the innate immune response corresponds to the model operation phase of the algorithm.

Thus, the training phase consists of five steps:

1. Detection of antigenic macromolecules. For each class (antigenic macromolecule), a selected number of instance bags (macrophages) will be computed. Then, the instances of the class will be randomly assigned to the bags;
2. Activation of B lymphocytes. For each bag of each class, a prototype (B lymphocyte) will be computed, considering the mean of the instances in the corresponding bag;
3. Immune response regulation. The prototypes computed in phase 2 are moved in the space by using the training set classification performance as an adaptability function;
4. Development of adaptive immunity. The prototypes are cloned, to obtain the desired number of candidate closed prototypes. Then, the best performed clone is kept;
5. Resolution of the threat. The final prototypes are stored as training data, and the original training set is deleted.

The innate immune response has only one phase:

1. Resolution of the threat. In here, the instance to classify is assigned to the class of its closets prototype.

The complete pseudocode of the model construction (adaptive immune response) in the proposed AISAC model is shown below in Figure 1. In this model, the following assumptions are made. First, we have a set of labeled training data $U = \{u_1, \ldots, u_n\}$, where each instance is represented by a vector of attributes, features, or characteristics, $u_i = [u_{i1}, \ldots, u_{im}] \in \mathbb{R}^m$. This data set constitutes the antigenic determinants (instances), of the antigens to be detected. Each instance is associated with a single class to which it belongs, which is denoted as $l(u_i)$.

Adaptive immune response	
Inputs:	Training Set U, Number of iterations G, Number of prototypes f, Percentage of training α, Update rate lr, Number of adjustments I
Outputs:	Immune memory IM

Initialization:

Divide the training set U, using the Hold Out method, into two sets: a training set EU, and a test set PU. For this purpose, the percentage of instances to be used for training defined by the user will be considered (α).

Phase 1: Detection of antigenic macromolecules

1. Determine the number of bags necessary to represent the classes, as $f_{count} = \frac{f}{|L|}$
2. For each class L_i, determine the number of instances to be assigned to each bag as $count_i = \frac{f_{count}}{|L_i|}$
   - 2.1. For each bag of the class mac_{ij}
     - 2.1.1. Randomly assign the corresponding $count_i$ instances
     - 2.1.2. Present the list of assigned instances to the merging procedure

Phase 2: Activation of B lymphocytes

3. For each list of assigned instances $linf_{ij}$ to the merging procedure
   - 3.1. Apply the merging procedure
     - 3.1.1. The merging procedure will obtain a center instance $\bar{a}_{ij}$, computed as the mean of the instances in the list $linf_{ij}$
   - 3.2. Add the merged prototype $\bar{a}_{ij}$ to the set of antibodies A
4. $it = 0$;
5. While $it < G$

Phase 3: Control of the immune response

- 5.1. Calculate the fitness evaluation, considering the detection rate of the instances of the test set PU, by using the existing set of antibodies $A = \{\bar{a}_1, \ldots, \bar{a}_f\}$.
- 5.2. Adjust the prototype set so that they are able to correctly classify the instances in PU. This is done using the function $Adapt(A, PU)$.
- 5.3. If the new set of prototypes produced by the adjustment $A' = \{\bar{a'}_i, \ldots, \bar{a'}_f\}$ has a better performance (fitness evaluation) than the set of antibodies A, then $A \leftarrow A'$

Phase 4: Development of adaptive immunity

- 5.4. An initially empty set of prototypes is considered, $Ac = \emptyset$
- 5.5. For each prototype $\bar{a}_i$
  - 5.5.1. Generate the clones, considering that they will have a random mutation by increasing or decreasing a randomly chosen value between the limits of each attribute of the prototype.
  - 5.5.2. Obtain a new prototype $\overline{ac}_i$ by averaging all clones, and add it to the set Ac
- 5.6. If the new set of prototypes produced by cloning $Ac = \{\overline{ac}_i, \ldots, \overline{ac}_f\}$ has a better performance than the set of antibodies A, then $A \leftarrow Ac$
- 5.7. $it = it + 1$

Phase 5. Threat resolution

6. Store the prototypes in the immune memory, $IM \leftarrow A$

Figure 1. Pseudocode of the adaptive immune response in the Artificial Immune System for Associative Classification (AISAC) model.

The set of all classes within U is denoted as $L = \{l_1, \ldots, l_k\}$. Each of these classes is considered a microprotein-carrying antigenity. The data of the test set $P = \{p_1, \ldots, p_t\}$ is described by the same attributes or characteristics as the training data; thus, a test object is denoted by $p_i = [p_{i1}, \ldots, p_{im}] \in \mathbb{R}^m$.

The pseudocode of the adjustment in the adaptive immune response in the AISAC model is shown below, in Figure 2.

Adjusting the immune response	
Inputs:	Prototype Set A Test Set PU
Outputs:	Adjusted prototype set A'

1. $it = 0; A' = \emptyset$
2. While $it < I$
   - 2.1. For each instance $ag \in PU$
     - 2.1.1. Determine the corresponding prototype ca, which is the closest to ag de according to a Euclidean distance
     - 2.1.2. For each component j of the prototype ca, the modified prototype ca' is computed as follows:

$$ca'_{ij} = \begin{cases} ca_{ij} + \left(lr * \left(ag_j - ca_{ij}\right)\right), & if\ l(ca) = l(ag) \\ ca_{ij} - \left(lr * \left(ag_j - ca_{ij}\right)\right), & if\ l(ca) \neq l(ag) \end{cases}$$

     - 2.1.3. Add the modified prototype ca' to the set A'
   - 2.2. $lr = lr * 0.9$
   - 2.3. Permute the instances in PU randomly.
   - 2.4. $it = it + 1$
3. Return A'

Figure 2. Pseudocode of the adjustment in the adaptive immune response in the AISAC model.

This adjustment has the possibility to explore the neighbors closest to each of the prototypes, which allows us to obtain a set of prototypes that best represents the test set patterns.

The complete pseudocode of the innate immune response (model operation) in the proposed AISAC model is shown below, in Figure 3.

Innate immune response	
Inputs:	Unknown instance d
Outputs:	Class mac

Phase 1: Threat resolution

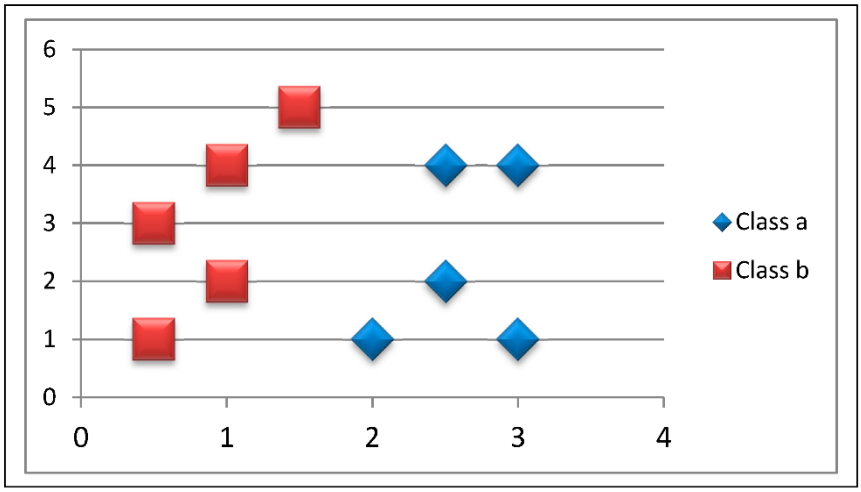
1. For each prototype of the immune memory $a \in IM$
   - 1.1. Calculate the affinity of prototype with the unknown instance, such as $aff_a(d) = Euclidean(a, d)$, where $Euclidean$ is the Euclidean distance function.
2. Return the class of the closed prototype, such as $mac = \underset{a \in IM}{\operatorname{argmin}}\{aff_a(d)\}$

Figure 3. Pseudocode of the innate immune response in the AISAC model.

The last phase of the proposed algorithm is based on finding the most similar prototypes to each of the patterns of the test set, that is, assigning the class of the pattern most similar to each of the patterns whose class is unknown.

3.3. AISAC Graphic Example

The following is an example of adaptive and innate immune responses in the proposed model. Suppose we have a training set that has 10 two-dimensional patterns, evenly distributed among two classes, as shown in Figure 4. Let us also consider that our immune system has six macrophages.



x	y	Class
2.5	4	a
2	1	a
3	4	a
2.5	2	a
3	1	a
0.5	3	b
0.5	1	b
1.5	5	b
1	4	b

Figure 4. Example of a training set containing 10 patterns (antigenic determinants), from two classes (antigenic macromolecules), a and b.

The adaptive immune response is developed as follows.

Phase 1: Detection of antigenic macromolecules

The adaptive immune response begins by determining the number of macrophages necessary to phagocyte the antigenic determinants of each antigenic macromolecule, such as:

$$f\_count = \left\lfloor \frac{\text{f (quantity of bags (macrophages))}}{\text{L (number of clases (antigenic macromolecules))}} \right\rfloor.$$

Thus, the macrophages are divided in such a way that they can phagocyte equitably to the antigenic determinants. Later, these antigenic determinants are presented to the T-Helper lymphocytes. In the example of Figure 4, we have two antigenic macromolecules, which correspond to two classes. Thus:

$$f_{count} = \left\lfloor \frac{\text{f (quantity of bags (macrophages))}}{\text{L (number of clases (antigenic macromolecules))}} \right\rfloor = \lfloor 6/2 \rfloor = 3.$$

Accordingly, three bags (macrophages) will be assigned to phagocyte the antigenic determinants of each antigenic macromolecule, that is, to group the class data, through random sampling without replacement. In the example, two instances (antigenic determinants) of class a (antigenic macromolecule a) will be assigned to bag (macrophage) 1, two will be assigned to bag 2, and the remainder to bag 3. This process will be repeated for class b (antigenic macromolecule b) (Figure 5).

The initial training patterns are shown in Figure 4. We have a balanced distribution of five patterns belonging to class a, and five patterns of class b. These patterns are kept in consistent figures; however, it is important to keep in mind what the ten initial patterns are.

In Figure 5, the training patterns are grouped into equally distributed bags for each class, that is, all classes will have the same number of bags. As a consequence of the above, each class will be represented by the same number of prototypes.

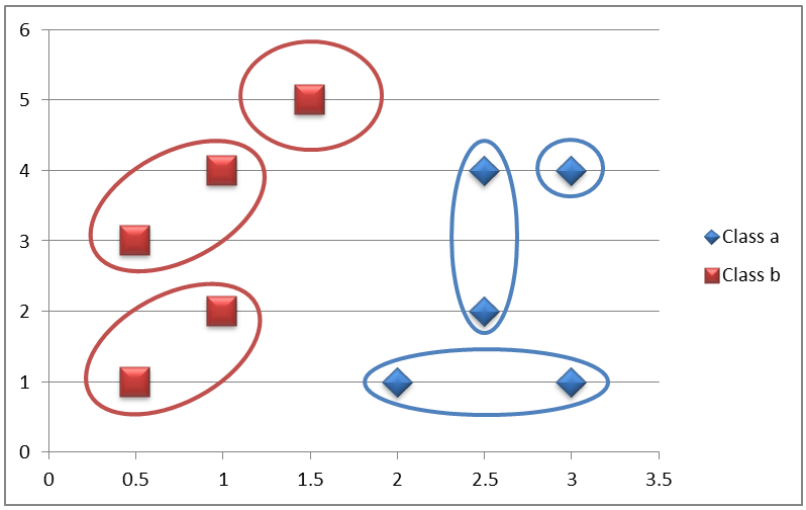
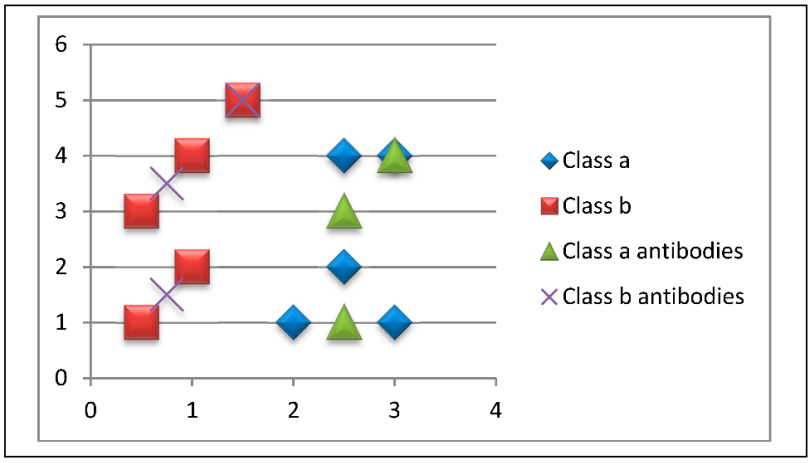


Figure 5. Macrophages phagocytosing the corresponding antigenic determinants. Ellipses represent the macrophage.

Phase 2: Activation of B lymphocytes

Subsequently, each bag (macrophage) activates the corresponding merging procedure (B lymphocyte), which will release a prototype (antibody) $\bar{a}_i$ corresponding to the instances (antigenic determinants) presented by the macrophage, which is determined by the mean of the instances (Figure 6).



x	y	Class
2.5	3	a
2.5	1	a
3	4	a
0.75	3.5	b
0.75	1.5	b
1.5	5	b

Figure 6. Generation of initial antibodies for each B lymphocyte.

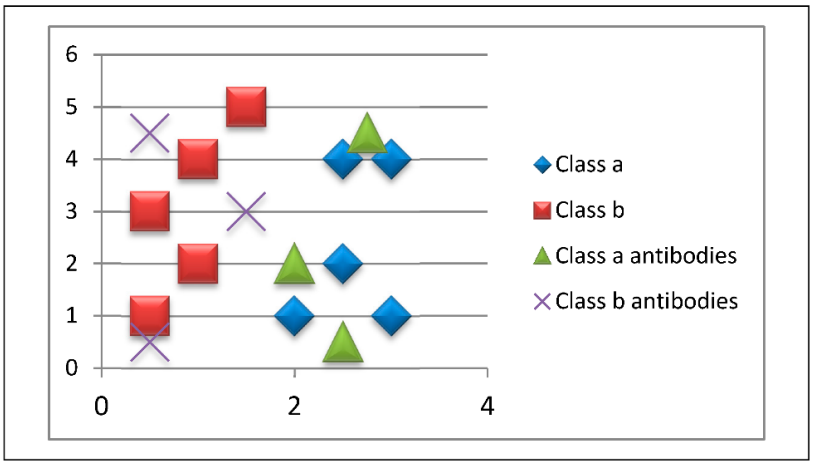
At this stage, a unique prototype is generated with the mean value of the patterns of each bag. In this example, three prototypes are created for each class. As we can notice, there are two prototypes similar to an original training pattern; this is because in their respective bag there was only one pattern to average their values.

Phase 3: Control of the immune response

Estimation of the current prototypes' (antibodies) ability is performed by calculating the weighted performance in order to reduce bias a little due to the possible imbalance in the data set. To do this, the instances (antigenic determinants) of the validation set are presented to the prototypes. Each prototype responds to its nearest instance (antigenic determinant).

The immune response is then adjusted so that the prototypes (antibodies) are able to correctly classify the instances (to combine with the antigenic determinants presented). To do this, the prototypes

"approach" the instances of the corresponding class, and "move away" from the instances of other classes. Thus, the prototypes move in the search space, so that they obtain a better performance compared to being in their previous positions. If the new prototypes (antibodies) have a better immune response than the previous antibodies, they are replaced. This process is shown in Figure 7.

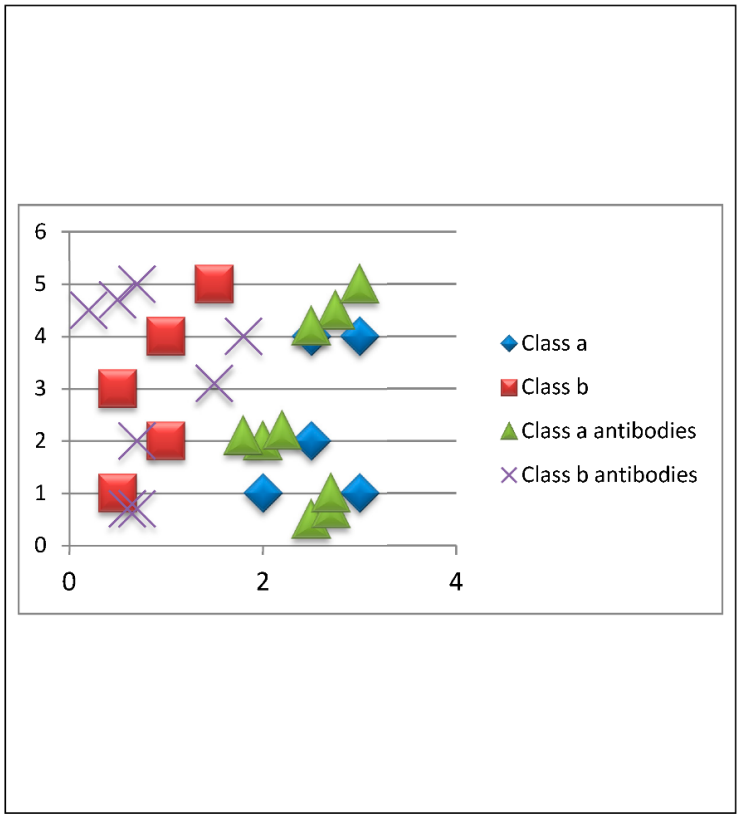


x	y	Class
2	2	a
2.5	0.5	a
2.75	4.5	a
0.5	4.5	b
1.5	3	b
0.5	0.5	b

Figure 7. Immune response adjustment process.

Phase 4: Development of adaptive immunity

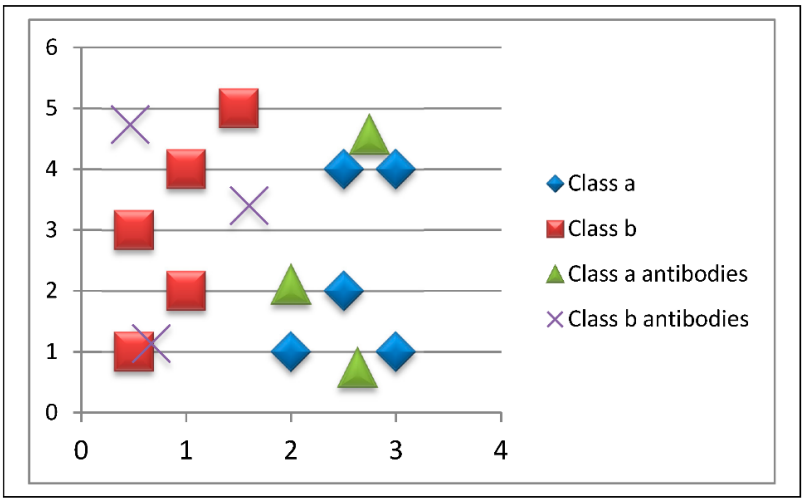
To develop the adaptive response, the prototypes (antibodies) are cloned. This allows the algorithm to explore the search space. To achieve this, the position of the prototype is slightly modified. This process is shown in Figure 8, where two clones are generated for each prototype (antibody).



	x	y	Class
Original	2	2	a
Clone	2.2	2.2	a
Clone	1.8	2.1	a
Original	2.5	0.5	a
Clone	2.7	0.7	a
Clone	2.7	1	a
Original	2.75	4.5	a
Clone	2.5	4.2	a
Clone	3	5	a
Original	0.5	4.5	b
Clone	0.5	4.7	b
Clone	0.7	5	b
Original	1.5	3	b
Clone	1.8	4	b
Clone	1.5	3.1	b
Original	0.5	0.5	b
Clone	0.7	2	b
Clone	0.6	0.7	b

Figure 8. Cloning of antibodies.

Subsequently, the antibody survival phase is performed, where a mean of the clones generated from each prototype (antibody) is obtained so that we return to the six antibodies (three from class a and three from class b). This survival process is shown in Figure 9.



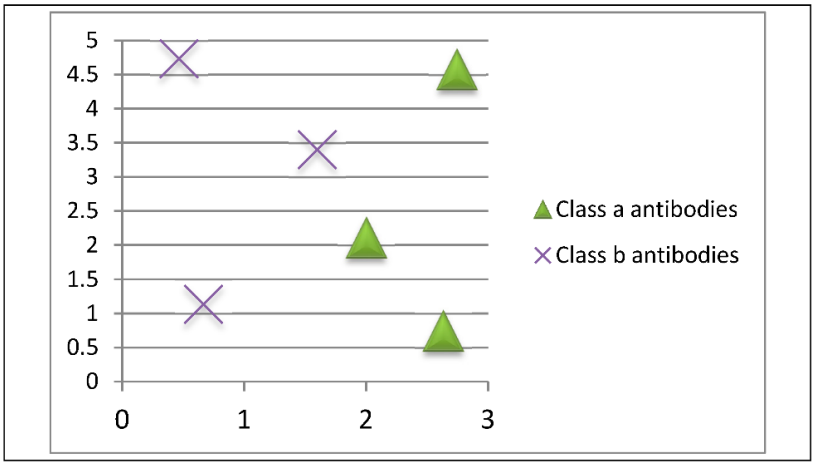
x	y	Class
2	2.1	a
2.63	0.73	a
2.75	4.56	a
0.46	4.73	b
1.6	3.4	b
0.66	1.13	b

Figure 9. Survival of antibodies.

If the new clones of the prototypes (antibodies) exhibit a better immune response than the previous antibodies, they are replaced. This process is iterative and elitist because it only retains the best antibodies generated. Then, these prototypes are used in the immune response. Phases 3 and 4 are repeated for a predefined number of iterations.

Phase 5: Threat resolution

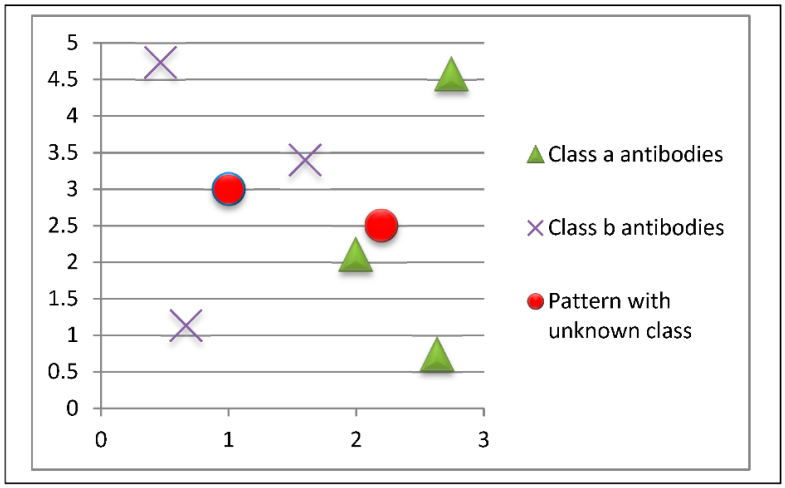
At this stage, the final prototypes (antibodies) are stored in the immune memory (Figure 10).



x	y	Class
2	2.1	a
2.63	0.73	a
2.75	4.56	a
0.46	4.73	b
1.6	3.4	b
0.66	1.13	b

Figure 10. Final antibodies in immune memory.

Upon completion of the model construction phase (adaptive immune response), it is possible to perform the classification or model operation (innate immune response). In this case, let us suppose that we have two new patterns whose classes are unknown, as shown in Figure 11. These patterns correspond to unknown classes (antigenic determinants), and we want to respond to this threat using the prototypes (antibodies) previously stored in the immune memory.

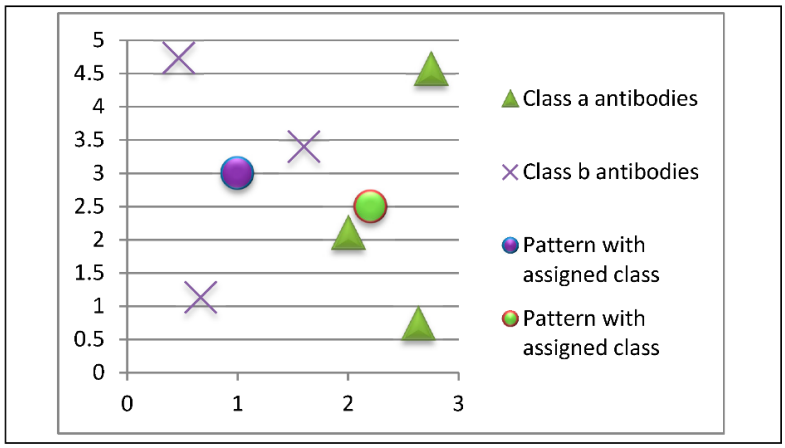


x	y	Class
1	3	Unknown
2.2	2.5	Unknown

Figure 11. Distribution of new antigenic determinants whose classes are unknown.

Antibodies stored in memory will be used to classify new patterns whose class is unknown. In this example, three class a patterns and three class b patterns are stored, so each class is represented by the same number of prototypes.

The innate immune response will look for the most closely related prototypes (antibodies) to each unknown instance (antigenic determinant), so the classification would be as shown in Figure 12.



x	y	Class
1	3	b
2.2	2.5	a

Figure 12. Phase of resolution of the threat in the innate immune response.

In this example, the pattern at coordinates (1.0, 3.0) would be classified as class b, while the pattern at coordinates (2.2, 2.5) would be classified as class a.

The proposed AISAC model is a contribution to the state-of-art of artificial immune systems. It provides a new modeling of the biological behavior of the immune system, and has a low computational cost. In addition, AISAC is simple and able to fit the training data using few antibodies. We consider that this model enhances the frontier of classification systems. In the next section, we test the performance of the AISAC model in a very important scenario: cancer detection.

4. Results

In this section the results obtained in this investigation are presented and discussed. First, Section 4.1 briefly describes the datasets that were used in the comparison of results. In Section 4.2, considerations related to the configuration of the parameters of the AISAC model are issued. Then, in Section 4.3 an evaluation of the running time of the proposed algorithm as well as the results of the evaluation is carried out.

Finally, in Section 4.4, the performance evaluation and the comparison of what AISAC produces with the different learning algorithms are presented and discussed.

4.1. Datasets

We decided to test the performance of the AISAC model for the cancer detection problem. We selected 10 cancer-related datasets, available from international repositories (Table 1). The datasets used were:

(a) Breast Cancer Digital Repository (BCDR) [43]. This is a dataset of real Portuguese patients provided by the Faculty of Medicine of the University of Porto, Portugal;
(b) Breast Cancer Wisconsin (Original) Data Set (BCWO) [44,45]. The University of Wisconsin, Madison by Dr. William H. Wolberg, provided this dataset;
(c) Breast Cancer Wisconsin (Diagnostic) Data Set (BCWD) [45]. This dataset was created by Wolberg, Nick, and Mangasarian from the University of Wisconsin, and was donated to the UCI repository in November 1995;
(d) Breast Cancer Wisconsin (Prognostic) Data Set (BCWP) [45]. This is a different version of the former;
(e) Breast Cancer SEER (BCSEER) [46]. This dataset was requested to the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program;
(f) Mammographic Mass Data Set (MMDS) [47]. Matthias Elter donated this dataset to the UCI repository in October 2007. It contains patients' age and attributes collected from digital mammograms of patients between 2003 and 2006 at the Institute of Radiology of the University Erlangen-Nuremberg;
(g) Breast Cancer Data Set (BCDS) [45]. This dataset was provided by M. Zwitter and M. Soklic and obtained at the University Medical Centre, Institute of Oncology, Ljubljana, Yugoslavia. This dataset contains clinic data of the patients, such as age and menopause status, in addition to data corresponding to the breast tumor and recurrence;
(h) Lung Cancer Data Set (LCDS) [45]. This dataset was published in Hong et al.'s work in 1991 and later donated by Stefan Aeberhard in May 1992. It describes three types of lung cancers;
(i) Haberman's Survival Data Set (HSDS) [45]. Tjen-Sien Lim donated this dataset in March 1999. It contains cases from a study of patients who had a surgery for breast cancer at the Hospital of the University of Chicago;
(j) Thoracic Surgery Data Set (TSDS) [48]. Lubicz, Pawelczyk, Rzechonek, and Kolodziej in Wroclaw, Poland created this dataset, and Maciej Zieba and Jakub Tomczak donated it in November 2013. It contains data from patients who had lung cancer and eventually a major lung resection in the 2007 to 2011 years at the Wroclaw Thoracic Surgery Centre.

Table 1. Datasets.

Dataset	Classes	Attributes		Missing Values	Imbalance Ratio
		Numeric	Categorical		
BCDR	2	38	0	Yes	1.06
BCDS	2	1	8	Yes	2.36
BCWO	2	9	0	Yes	1.9
BCSEER	2	5	0	No	5.41
HSDS	2	3	0	No	2.77
LCDS	3	56	0	Yes	1.44
MMDS	2	5	0	Yes	1.15
TSDS	2	2	14	No	5.71
BCWD	2	30	0	No	1.68
BCWP	2	33	0	Yes	3.21

4.2. Parameter Configuration

It is well-know that swarm intelligence algorithms suffer from having many parameters to tune. Finding the appropriate values is crucial, since it can increase the performance of the algorithms. However, this is not a trivial process.

To avoid overfitting, we carried out several empirical studies of the proposed algorithm in order to determine the optimal parameters (number of iterations and the number of antigens) for each dataset.

The empirical studies allowed us to determine which parameter values were sufficient for the algorithm to obtain the best performances. Unlike the trial and error approach, empirical studies of the number of antibodies and iterations necessary for a good classification allowed us to find in a sequential way the parameters that obtained the best performance in the classification of each dataset. It is necessary to mention that the empirical studies of the number of antibodies and iterations were performed for each dataset.

Shown below is an example of a test done with the Breast Cancer Wisconsin (Prognostic) dataset (BCWP) to obtain the number of iterations and the number of antigens for the dataset.

The test for the iterations was done by using 100 antibodies and running the classification process using 100 iterations. This means that the model was tested each time and the performance after each iteration was saved. For the BCWP dataset, the results for this test are shown in Figure 13.

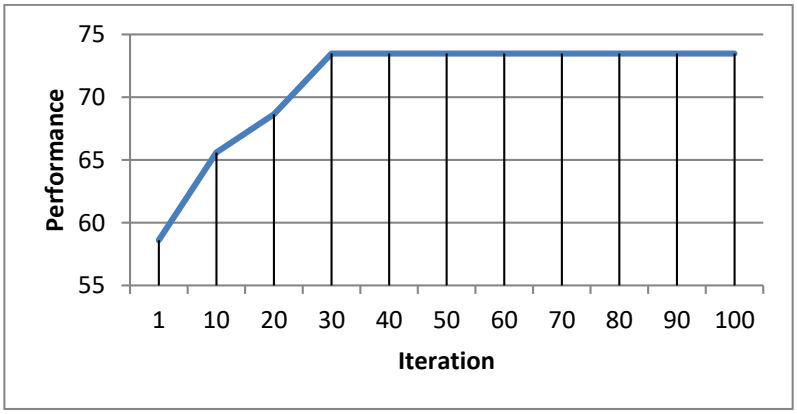


Figure 13. Iteration empirical study test results for the Breast Cancer Wisconsin (Prognostic) (BCWP) dataset.

We can observe that the maximum performance was obtained using 30 iterations and increasing the number of iterations did not increase the performance, so 30 iterations were finally used for this dataset.

Regarding to the number of antibodies needed to obtain the better performances, we set the number of iterations at 100, and varied the number of antibodies from 2 to 100 antibodies. This means the model was tested 99 times, varying the number of antibodies in independent runs. For the BCWP dataset, the results for this test are shown in Figure 14.

We can observe that the best performance was reached using 90 antibodies; therefore, for this dataset 90 antibodies were used in classification.

In conclusion, for the BCWP dataset, 90 antibodies and 30 iterations were used. This process was repeated for each dataset individually.

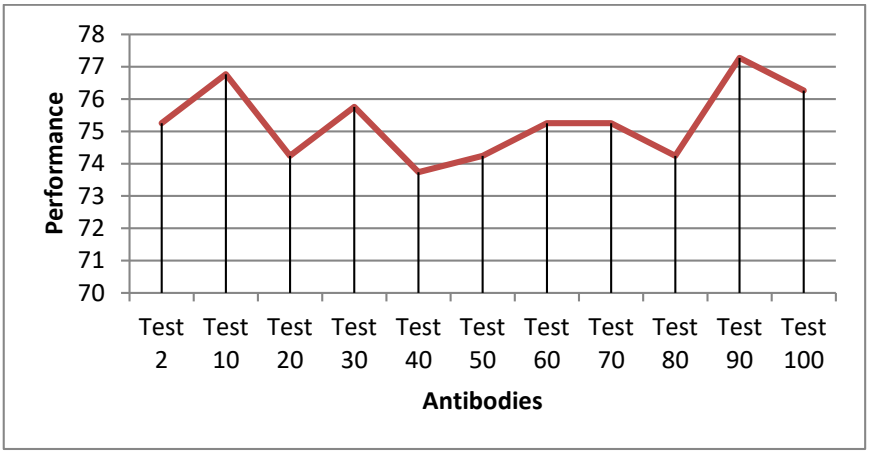


Figure 14. Antibodies empirical study test results for the BCWP dataset.

Finally, in Table 2 we present the values obtained by the empirical studies for each dataset.

Table 2. Hommel values of the compared learning algorithms.

Dataset	Antibodies	Iterations
BCDR	40	30
BCDS	50	50
BCWO	10	20
BCSEER	20	10
HSDS	40	90
LCDS	80	20
MMDS	100	20
TSDS	20	30
BCWD	30	10
BCWP	90	30

The values obtained show that a maximum of 100 antibodies and 90 iterations are enough for the proposed model to obtain competitive performances for classification.

This is important because 90 iterations do not represent a huge investment of time in evolutionary algorithms; likewise, representing a dataset with only 100 antibodies implies a reduction of the computational cost of classification and the cost of storing the models.

In some classification models, such as k-nearest neighbors (KNN), the training set is completely stored. This means that if the training set contains 3000 patterns, we need to store them all. In contrast, with the proposed model, we only need to store 100 antibodies for further classification.

4.3. Running Time Evaluation

Similarly, an empirical study was carried out to determine the computational cost of the algorithm, obtaining the results presented in Table 3. Table 3 refers to the running time of the algorithm in each of the datasets.

As presented in the table, the proposed algorithm obtained an average running time of 26.31 s for all datasets, with the shortest time 3.1 s and the greatest 39.4 s. It is important to highlight that less than half a minute to perform breast cancer detection is a relevant result.

Table 3. Average running time of the classification algorithm.

Dataset	Average Time (S)
BCDR	25.1
BCDS	29.1
BCWO	4.7
BCSEER	3.1
HSDS	38.8
LCDS	22.5
MMDS	30.0
TSDS	39.4
BCWD	35.0
BCWP	35.4

4.4. Performance Evaluation

We used the five-fold stratified cross-validation (5-scv) procedure, due to the imbalance ratio of some datasets [49]. As a performance measure, we used the average classifier accuracy of the folds. The process was repeated 10 times.

This algorithm was implemented and tested in a personal computer with the following specifications: Intel Core i7 970 3.20 Ghz, 24Gb RAM memory, Windows 8.1 Pro 64bits, Hard drive 1 TB.

We tested the AISAC model in two scenarios: with respect to other immune-based learning classification systems (Section 4.4.1) and with respect to well-known learning classification systems (Section 4.4.2). In both scenarios, we used the Wilcoxon test [50] to establish the existence or lack thereof of significant differences in performance among the compared algorithms. We used a significance level of 0.1, for a 90% confidence interval. This particular statistical comparison was suggested in [51].

4.4.1. Comparison of AISAC versus Immune-Based Learning Algorithms

Table 4 shows the performance of the AISAC and other immune-based algorithms over the 10 cancer-related datasets. The best results are highlighted in bold.

Table 4. Average performances obtained by the immune-based learning algorithms. The best results are highlighted in bold.

Dataset	AIRS1	Immunos1	CLONALG	AISAC
BCDR	**73.204**	56.077	57.735	64.360
BCWO	96.710	84.692	94.135	**97.420**
BCSEER	94.520	95.374	96.513	**100.000**
BCWD	**93.849**	90.510	88.928	93.670
BCWP	64.141	56.566	74.242	**79.290**
LCDS	53.125	56.250	46.875	**68.750**
MMDS	63.372	74.298	70.031	**78.980**
BCDS	67.483	73.427	67.133	**73.776**
HSDS	63.726	56.810	73.203	**76.471**
TSDS	69.787	72.979	81.064	**85.319**

When comparing the classifiers based on immune systems, we used the Wilcoxon signed rank test. This comparison is presented in Table 5. The p-Values in all cases were lower than the significant value $\alpha = 0.1$, which means that significant differences existed among the performances of AISAC and the compared algorithms within a 90% of confidence, and the null hypothesis H0 was rejected. Considering the wins, losses, and ties obtained, we can state that AISAC outperforms the other compared immune-based algorithms.

Table 5. Wilcoxon test for of the immune-based algorithms.

AISAC versus	Wins	Losses	Ties	*p*	Decision
AIRS1	7	1	2	0.035	Reject H0
CLONALG	10	0	0	0.005	Reject H0
Immunos1	10	0	0	0.005	Reject H0

These results confirm that our proposal obtained a significantly better performance in cancer classification than all other tested immune-based learning classification systems.

4.4.2. Comparison of AISAC versus Well-Known Learning Algorithms

Table 6 shows the performance of the AISAC and other well-known learning algorithms over the 10 cancer-related datasets. The best results are highlighted in bold.

Table 6. Average performances obtained by the well-known learning algorithms. The best results are highlighted in bold.

Dataset	SVM	MLP	NN	RIPPER	C4.5	Naïve Bayes	Random Forest	AISAC
BCDR	80.111	79.006	72.928	75.414	74.862	72.652	**81.491**	64.360
BCWO	96.996	95.422	95.279	95.565	95.136	95.994	96.852	**97.420**
BCSEER	**100.00**	**100.00**	98.363	**100.00**	**100.00**	97.153	**100.00**	**100.00**
BCWD	**97.715**	96.661	95.958	95.606	93.146	92.970	96.836	93.670
BCWP	76.263	76.263	70.707	77.778	72.727	66.667	**80.303**	79.290
LCDS	56.250	53.125	53.125	50.000	46.875	59.375	43.75	**68.750**
MMDS	79.501	81.166	75.234	**82.934**	82.310	77.836	79.708	78.980
BCDS	69.930	66.783	68.182	70.280	**74.126**	72.727	71.328	73.776
HSDS	72.876	72.222	66.013	73.856	70.261	74.837	67.647	**76.471**
TSDS	84.468	81.489	75.957	84.681	84.468	74.468	84.893	**85.319**

Again, we used the Wilcoxon test to compare the algorithms, and results are presented in Table 7.

Table 7. Wilcoxon test for of the state of the art classification algorithms.

AISAC versus	Wins	Losses	Ties	*p*	Decision
SVM	5	3	2	0.673	Do not reject H0
MLP	6	3	1	0.259	Do not reject H0
NN	8	2	0	0.066	Reject H0
RIPPER	5	3	2	0.779	Do not reject H0
C4.5	6	2	2	0.326	Do not reject H0
Naïve Bayes	9	1	0	0.034	Reject H0
Random Forest	3	4	3	0.799	Do not reject H0

These values showed significant differences for two algorithms (nearest neighbor and naïve Bayes), while there were no significant differences for the remaining five algorithms.

It is important to emphasize the breast cancer detection ability of the new model, which was significantly better than both nearest neighbor and naïve Bayes, models considered among the top 10 best algorithms in data mining. In addition, it obtained a comparable performance to the remaining ones. Although no significant differences were found, it obtained more wins than losses, and it was the best for 5 out of 10 datasets.

In 2019 [52] a preliminary work was carried out using the first version of an algorithm based on the immune system. Good results were obtained, however in this new study, analysis with a larger number of datasets and a comparison with more classification algorithms was considered. In addition, we refined the adjustment of the immune response, as well as the selection of antibodies.

Having a low computational cost while being competitive and highly configurable, this algorithm stands out as a more than adequate and novel pattern classifier.

5. Discussion

Unlike other classification algorithms, our proposal is based on a biological process, which turns our algorithm into a bio-inspired algorithm which, as presented in the results, obtains good performances compared to the rest of the classifiers.

Most datasets are imbalanced, in addition to containing missing values. The proposed algorithm is able to work with these characteristics and obtain results without significant differences against some classical classification algorithms. On the other hand, it obtained significant differences when compared to other algorithms based on the same principle; that is, our proposal surpasses those algorithms based on the same principle.

According to the statistical tests, the proposed model obtained better results compared to other algorithms, and no differences with respect to others. In no case was our proposal significantly worse than other classifiers. This opens an interesting knowledge gap about this area and its possible exploration in the use of bioinspired algorithms for classification.

The main contribution lies in the proposal of a new classification model based on the immune system obtaining good results compared to literature classification algorithms. In a similar way, the AISAC algorithm obtains good results compared to algorithms based on the same principle. The results presented reveal the possibility of using the proposed algorithm as an alternative for the classification of unbalanced datasets as well as big datasets due to their guided stochastic behavior, which allows these datasets to be classified.

To deal with the adjustment of parameters, we opted to carry out empirical studies for each dataset, obtaining the appropriate parameters for our proposed algorithm in order to make it more powerful. The analysis results presented in this work can help to explain why those parameters work well. Using these parameter values guarantees the good classification of the iterative process and it makes it possible to obtain competitive results, comparing our proposal with other classification algorithms.

We found that 100 antibodies and 90 iterations were enough to obtain accurate classification results.

Finally, in the evaluation of the running time of the algorithm it is relevant to emphasize that our algorithm does not exceed 40 s in performing the training and classification of a dataset.

6. Conclusions and Future Work

The classification model presented in this work exhibits a performance equivalent to the classic algorithms for classification, which was proven using Wilcoxon tests.

This new model is a contribution to evolutionary methods as classifiers and opens a gap for future research and developments in the area of bio-inspired classification algorithms based on the human immune system.

AISAC is not a definitive solution for classification, since there was no classifier that had the best performance for all datasets. However, notable contributions are provided to the fields of evolutionary computation, and specifically to algorithms for classification based on artificial immune systems.

The use of distributed computation can make it possible to reduce the time and computational cost of the algorithm proposed in this work; in the same way, it can allow the use of more robust algorithms for the adjustment of antibodies if the algorithm runs in parallel. However, as stated before, the computational cost of AISAC is low.

In future work we want to test with other cloning strategies, so the cloning and competition between generations can be a more extensive work that allows the development of a more robust algorithm capable of classifying imbalanced datasets with a better performance.

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