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Innate immune memory and its application to artificial immune systems

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Abstract

The study of innate immune-based algorithms is an important research domain in Artificial Immune System (AIS), such as Dendritic Cell Algorithm (DCA), Toll-Like Receptor algorithm (TLRA). The parameters in these algorithms usually require either manually pre-defined usually provided by the immunologists, or empirically derived from the training dataset, and result in poor self-adaptation and self-learning. The fundamental reason is that the original innate immune mechanisms lack adaptive biological theory. To solve this problem, a theory called â€˜Trained Immunity™ or Innate Immune Memory (IIM)™ that thinks innate immunity can also build immunological memory to enhance the immune system™s learning and adaptive reactions to the second stimulus is introduced into AIS to improve the innate immune algorithms™ adaptability. In this study, we present an overview of IIM with particular emphasis on analogies in the AIS world, and a modified DCA with an effective automated tuning mechanism based on IIM (IIM-DCA) to optimize migration threshold of DCA. The migration threshold of Dendritic Cells (DCs) determines the lifespan of the antigen collected by DCs, and directly affect the detection speed and accuracy of DCA. Experiments on real datasets show that our proposed IIM-DCA which integrates Innate Immune Memory mechanism delivers more accurate results.

Keywords Innate immune memory · Artificial immune systems · Danger theory · Dendritic cell algorithm · Classification

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1 Introduction

Artificial immune system(AIS) is a type of computational intelligence. It mainly simulates the biology immune system, more accurately, it simulates the human immune system to solve real-world problems, such as abnormal pattern detection, fault detection and cyber-physical system solution selection[1–3]. The human immune system is developed to protect the body against the invasion of foreign or harmful pathogens. The human immune system consists of innate immune subsystem and adaptive immune subsystem. Many immunologists study these two encompass and develop some theories or mechanisms such as Clonal Selection theory, Immune Network theory, Self-nonself discrimination theory, and Danger theory. Then, the computer scientists abstract the model, algorithm, or technique of the theory or mechanism to apply in solving engineering and Scientific problems, thus AIS is gradually established.

When AIS was first established, it concerns more about adaptive immune system. In adaptive immune system, *B* and *T* cell are the major cell populations. *B* cells, also known as *B* lymphocytes, present antigens and secret antibodies which bind a specific antigen, respectively. What™s more, once *B* cells are activated by binding their target antigens, some *B* cells differentiate into high-affinity *memory B* cells for persistent protection. When the host was invaded by the target antigen again, *memory B* cells can be activated immediately and secrete numerous antibodies to eliminate antigens faster. This is the so-called immune memory. *T* cells are also a type of lymphocyte, undergo two critical mechanisms called maturation and tolerance. The self-tolerance mechanism of *T* cells makes the immune cells have the ability of distinguishing invading cells from self™ and prevent the formation of self-reactive *T* cells that are capable of inducing autoimmune diseases in the host. This theory is termed negative selection.™ Based on these theories of the adaptive immune system, three major research directions in AIS have been developed, including clonal selection algorithm that mimics the process of antibodies generation[4], negative selection algorithm that simulates the process of *T* cells maturation and tolerance[5], and Immune Network model that abstracts the interaction of *T* and *B* cells[6].

In contrast, the studies of innate immune-based algorithms in AIS are slightly thin. The innate immune-based algorithms mainly focus on the research of DCs, and a few researchers have made some initial attempts in natural killer (NK) cell model but have not formed a complete theory [7–9]. The algorithms based on DCs include DCA and TLRA. But TLRA is proposed by hybriding the DCs with adaptive immune cells to improve its capabilities of learning and memory. So far, the only one algorithm that is inspired by innate immune system is DCA. But in fact, for many organisms without an adaptive immune system, they can still resist most of the antigens and maintain the balance of the body. What they rely on is the innate immune system.

Greensmith et al. [10] used the biological mechanism of DCs to simulate the antigen processing and presentation process and proposed the DCA. DCA has been applied to binary classification, intrusion detection and many other fields.

DCA mainly consists of four phases, including data pre-processing, signal selection, signal processing and classification. Through the data pre-processing phase, DCA processes the dataset as numerical value and maps the data to antigens. During the signal selection phase, DCA selects the most important attributes and categories them into its specific signal category(either as PAMP, DS or SS). In signal processing phase, three cumulative output context values termed *csm*, *smDC* and *mDC* are generated, and then, DCs™ states are assigned according to these values. The specific process and pseudocode of each phase is detailed in 3.2.

The DCA classifier was successfully applied to a wide range of real-world applications, including cyber-attack detection, classification and anomaly detetion[11–13], but DCA still suffers from low accuracy and detection rate due to the fact that the lack of regulating, learning and memory mechanisms of innate immune system which results in DCA™s large number of random parameters are set according to expert knowledge. Over the past few years, many researchers have developed different works to extend the standard DCA version. For the large number of random parameters in DCA(the classic DCA has more than 10 parameters), [14] proposes a main DCA-based version called deterministic DCA (dDCA). The dDCA removed or replaced most stochastic components and simplified the signal processing calculation. Although the dDCA alleviated the learning dilemma of DCA to a certain extent, it did not cure the root cause, since even relatively few parameters still require expert experiences.

To solve this problem, a new theory called Innate Immune Memory can be introduced to improve the innate immune-based algorithms™ learning ability and adaptability. Most studies about immunological memory have only focused on that the adaptive immunity can build immunological memory and have not realized that the innate immunity can also build memory. It is termed Innate Immune Memory, and its chief advocate is Mihai G. Netea [15–20]. Innate Immune Memory reveals that the innate immune system also has learning and memory mechanism.

A number of advantages are claimed for this theory. Recently, the emergence of the new coronavirus (COVID-19) has attracted the attention of bats™ special immune system. Gralinski et al. [21] suggests that COVID-19 originated from bat coronavirus. Xia et al. [22] reveals that MERS-CoV is also from bat. Why bats can be hosts to so many viruses? Zhou et al. [23] reports that bats have a higher lever of constitutive expressed *IFN-α* mRNA. And *IFN-α* plays an important role in innate immune memory, which can enhance inflammatory and antimicrobial properties in innate immune cells. Many immunologists infer that it is the high level of innate immune memory of bats keep them safe from the kinds of viruses [24].

It is beyond the scope of this study to examine the details of Innate Immune Memory theory, e.g., how it actually works and changes the reaction, due to the theory is not complete now, and what we value more is the guidance inspired from the theory to the AISs. The innate immune memory theory contains enough potentially interesting ideas to make it worth assessing its relevance to AISs. One of the new ideas that can instruct algorithms™ optimization is that the parameters in algorithms vary with environmental change in the process of execution. As the environment changes, the parameters in the algorithm are not static, but when the indicators for detecting environmental changes reach the threshold, some parameters are

reversible and re-adjustable. This is the memory updating or evolution process. It is very necessary to update the algorithm™s ability in time to describe the current environment more precisely, especially in the era of big data that the data are growing and huge increasing abnormal pattern of data.

We propose a modified dendritic cell algorithm with an effective automated tuning mechanism based on Innate Immune Memory, called IIM-DCA, to optimize migration threshold of DCA. The migration threshold of DCs determined the lifespan of the antigen collected by DCs and directly affects the detection speed and accuracy of DCA [25]. And we use some classical classification dataset including KDD99 intrusion detection dataset, UCI™s Epileptic Seizure Recognition dataset, Breast Cancer Wisconsin(Original) dataset and Diabetes dataset for experiments. In this paper, the proposed method has been compared with well-known machine learning algorithms, such as Dendritic Cell Algorithm (DCA)[10], dDCA[14], random forest[26], Support Vector Machine (SVM)[27], K-Nearest Neighbor (KNN) [28] and Recurrent Neural Network (RNN)[29]. Moreover, some representative papers™ methods are also selected to compare with our proposed method.

Few other AIS practitioners are conversant with the innate immune memory theory. Hence, this is the first paper that deals with the innate immune memory theory.

The remaining part of the paper proceeds as follows: In Sec. 2, we provide an overview of the innate immune memory theory. In Sec. 3, we point out some analogies in current AIS models where appropriate, and we present a modified DCA model with an effective automated tuning mechanism based on IIM (IIM-DCA). In Sec. 4 and 5, we introduce the experiments and report the experimental evaluation. Finally, our conclusions about the potential of the IIM concept are given in Sec. 6.

2 The innate immune memory

Host immune responses consist of innate immune responses and adaptive immune responses. The adaptive immune responses were previously considered the most important and complex level because of its pattern matching mechanism between antibodies and antigens, but adaptive immune responses are slower to develop and are specific. In addition, many studies show that in organisms(including mammals) lacking adaptive immunity, the innate immune system can mount resistance to reinfection and live healthily in their lifetime [15–30], which reminds us that the importance and working principles of innate immune system should be re-considered.

Netea et al. [15] found that the innate immune system can mount resistance to secondary stimulus. In other words, the innate immune system also has memory in some form. Netea termed the de facto phenomenon as Innate Immune Memory™ or Trained immunity.™ The comparison between classical immunological memory and innate immune memory is shown in Fig. 1. Figure 1 (A) shows that adaptive immunological memory involves gene recombination in B and T lymphocytes, which has high specificity and often long-term, pathogen-specific protection. And Fig. 1 (B) shows innate immune memory, which induces enhanced inflammation and antimicrobial properties in innate immune cells, leading to an increased non-specific response to secondary infections and improved survival of

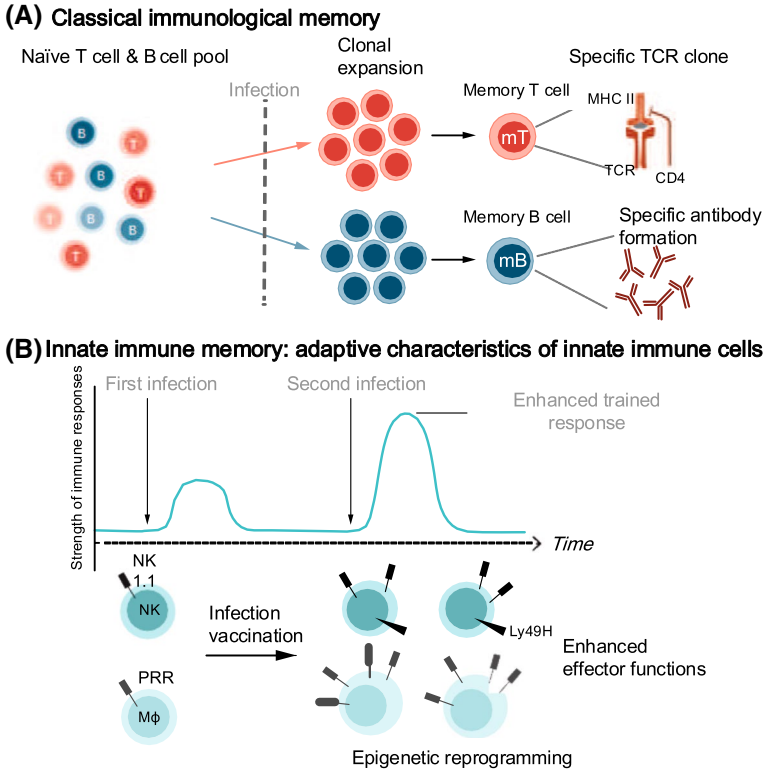


Fig. 1 Classical adaptive immunological memory versus Innate Immune Memory

the host. Innate immune memory is mainly based on epigenetic reprogramming without involving permanent changes, such as gene mutations and recombination. It is just this rapid and non-specific innate immune memory responses that lies at the core of the immune system defences and then triggers the adaptive immune responses.

Natoli et al. [31] gave the explanation of innate immune memory, who believe that cells, tissues and organisms can rapidly and reversibly modify their characteristics to maximize fitness in a constantly changing environment. This explanation explained several characteristics of innate immune memory: fast, complex, reversible, adjustment, plastic, training, change, and huge environment. These characteristics are exactly what we need in solving computer security problems, so innate immune memory mechanism is worth learning and reference.

Since the underlying molecular frameworks of innate immune memory are usually incompletely understood, we list the main discriminative characteristics of innate immune memory and adaptive immune memory in the immune system (Table 1) to help understand.

Firstly, the reversibility of innate immune memory(IIM) state is different from the adaptive immune memory(AIM). The IIM™s mechanisms are driven by

Table 1 Discriminative properties of Innate Immune Memory and Adaptive Immune Memory in the immune system

	Innate immune memory	Adaptive immune memory
Reversibility	Yes	No
Persistence	Short-term or long-term	Long-term
Specificity	No	Yes
Mechanisms	Receptor signaling/recycling; Metabolic reprogramming; Chromatin/histone modification; Transcription factor occupancy/distribution	DNA sequence alterations; Epigenetic modifications (DNA methylation); Self-sustaining feedback loops; Induction of long-lived mediators
Target cells	Innate, adaptive immune cells; Non-immune cells	Adaptive immune cells

molecular changes which can be rapidly removed,™ whereas AIM is based on DNA which will last for life. Moreover, the persisted time window of the IIM phenotypes and related molecular changes are variable – from a few hours to several weeks or even months, where AIM can build long-term memory. Therefore, the persistence can be seen as a feature of innate immune memory [15].

Secondly, specificity is a key property that distinguishes IIM and AIM. Traditionally, we believe that IIM is non-specific to pathogens, while AIM can identify different pathogens with high affinity using gene recombination and mutation processes [32].

The last property of discriminating IIM and AIM is the mechanisms which are summarized in Table 1. IIM is controlled by molecular mechanisms involving reversible biochemical, metabolic or chromatin changes. These changes are often weakened throughout cell division. On the contrary, the mechanism of adaptive immune memory depends more on stable genetic/epigenetic changes and self-sustaining loops.

The IIM is not without its limitations. As mentioned earlier, the exact nature of the memory process is still unclear, including the alert/priming condition, the memory time and strength, the way of memory mediates. In addition, there are sometimes alert signals that should not react too severely or build the IIM. For instance, in the case of transplantation and autoimmune diseases, it is usually necessary to remove some innate immune cells from the transplanted organ or host.

3 The innate immune memory and some analogies to artificial immune system

3.1 The considerations of innate immune memory to artificial immune system

Innate Immune Memory(IIM) has many aspects and complexity, and we only touch a few of them. It may be helpful to list some considerations for practitioners of Artificial Immune System regarding the suitability of the IIM model for their application. The basic consideration is to identify the importance of IIM.

Firstly, IIM is the original form of immune memory that exists in all living organisms, while adaptive immune memory is an advanced form of immune memory, representing the evolutionary innovation of vertebrates. In other words, IIM is the basis of adaptive immune memory. In AIS, Negative Selection Algorithm [33], Clonal Selection Algorithm [34], etc., are all inspired by the adaptive immune system and its memory mechanisms.

Secondly, adaptive immune memory is highly specific, slow and relies on the first recognition, which means it is incapable for unknown pathogens, while IIM is on the contrary. Last but not least, pathogens change over time. Therefore, one can expect problems with fixed adaptive immune memory cells, which later proved to be inaccurate or even auto-reactive.

If these points are sufficient for practitioner to consider incorporating the IIM into their model, the following considerations may be instructive:

1) An IIM model requires an alert™ cell, which can sense the micro-changes in the environment/system. Dendritic cell and macrophages cell can play this role.
2) Change™ includes the concentration/dose variation in pathogens/signals/cytokines and the type of materials in system such as PAMP, Heme, β-glucan, etc. In the works describing change,™ Zhou et al. [35] proposes a numerical differentiation method that processes the signals and perceive danger can be borrowed.
3) Not all changes are danger. If necessary, changes of changes™ can be used. For instance, the second-derivative equation(Eq. 2) in mathematics which can describe the change of first-derivative equation(Eq. 1) can be introduced.

$$f^{'}(x_i) = \frac{f(x_{i+1}) - f(x_i)}{h} \tag{1}$$

$$f^{''}(x_i) = \frac{f^{'}(x_{i+1}) - f^{'}(x_i)}{h} = \frac{f(x_{i+2}) - 2f(x_{i+1}) + f(x_i)}{h^2} \tag{2}$$

where x is the independent variable, i is serial number, h is the difference between two adjacent independent variable, f is the function.

4) The host does not intend to eliminate all pathogens / changes, rather to achieve a balance between pathogens and the body. It is the better way to build the IIM based on balance theory.™ In Artificial Immune System applications, some other definition of balance (for instance entropy) may be used. Yang et al. [36] proposes a method for presenting danger signals based on system balance.
5) IIM of innate immune cells is orchestrated by epigenetic reprogramming and changes of chemical medians, which leads to an increased non-specific response to subsequent infections and improved survival of the innate immune cells. How to make analogies between biological phenomenons and computer model is a challenging task.
6) Since IIM can rapidly and reversibly modify their characteristics to maximize fitness in a constantly changing environment, the influence and feedback of sub-environment must be designed.

Table 2 Comparison between biological mechanisms and abstract components in computer

Biological mechanisms	Abstract components in computer
Pathogens \ Antigens	Abnormal signals in data observation
Alert cell	Change preceptor & Dose preceptor
Histone modification	Feedback and model adjustment
Receptor signaling	Positive feedback regulator
Receptor recycling	Negative feedback regulator
Pro-inflammatory \ Inhibitory	Speed

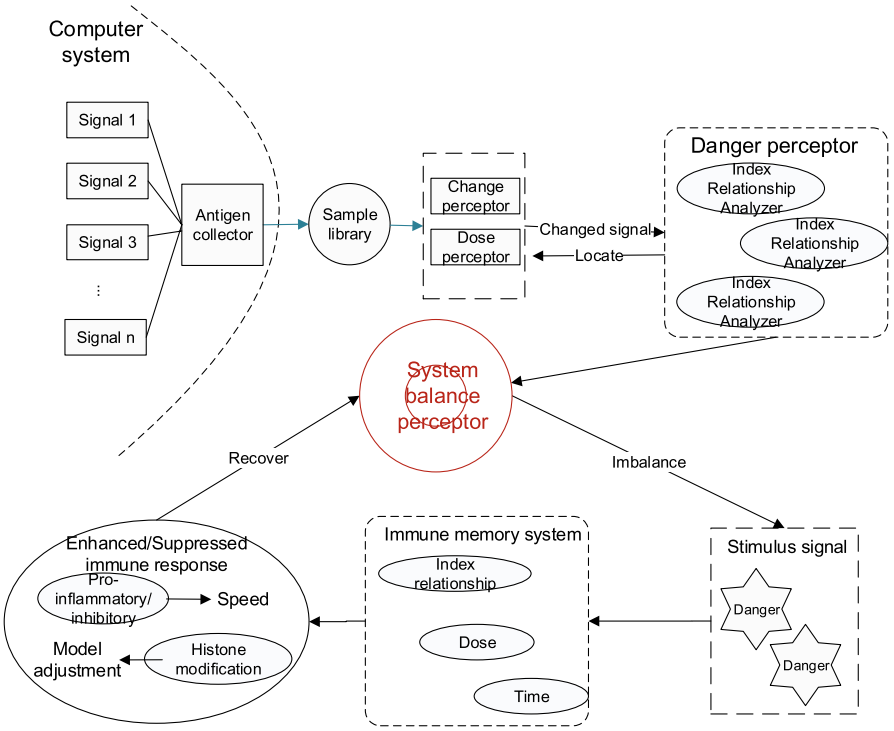


Fig. 2 Computer model-based IIM

In order to introduce the IIM mechanism into the computer field to solve real-world problems, we give a form of comparison chart between biological mechanisms and abstract components in computer in Table 2. And we proposed a computer model based on IIM and these abstract components, as in 2. System balance preceptor is the center of the model, which determines whether the model needs to be adjusted. Assume that we have collected many signals in computer system, map them into antigens, and construct a sample library. Then, the change preceptor and dose preceptor preliminary process the sample and send the changed signals to danger

preceptor for deeper analysis, e.g., analyzing the index relationships between the changed signals, and if possible, locate the danger position. If the danger preceptor makes the system into imbalance, stimulus signals will activate the innate immune memory system, resulting in an enhanced or suppressed immune responses. It is worth noting that the pro-inflammatory and inhibitory influence the model™s processing speed, and histone modification determines how to adjust the model.

There are a couple of points that may attract practitioners to alter the IIM model introduced here. For example, the IIM model has quite a number of elements. Assuming that the alert cell monitors the changing elements, we might be able to simplify the model-for example, we can ignore many other specific cells and their interaction. In addition, there are some changes that might in some sense be reasonable and thus should not trigger an immune response. In such cases, a method for avoiding the IIM pathway must be found. A biological example is transplanted organs, where some alert cells are removed.

Then, we will take the DCA for example to show how the IIM works in AIS. DCs are natural alert cells in innate immune system that always collect signals in hosts and present danger antigens to other cells, and DCA is just inspired from DCs.

3.2 DCA overview

As an algorithm, the DCA was first proposed in 2005 [37], it is an anomaly detector in a population-based style. The DCA is based on an abstract model of dendritic cell behavior. DCs are antigen-presenting cells whose purpose is to collect, process and present antigens to T-cells. In addition to antigen processing, DCs also express receptors necessary to collect four signals from their environment: pathogen-associated molecular pattern (PAMP), safe signal (SS), danger signal (DS), and inflammatory cytokines (IC). After signals collection, the DCs will migrate to lymphocytes and differentiate into three different maturity states: immature DCs(iDCs), semi-mature DCs(smDCs) and mature DCs(mDCs), according to the outputs. Eventually, the abnormal value of the antigen is determined through a voting mechanism by the status of all DCs presenting the antigen. DCA mainly includes four phases: pre-processing and initialization phase, detection phase, context assessment phase and classification phase.

In the pre-processing and initialization phase, DCA selects the appropriate attributes as the input signals, including PAMPs, DSs, SSs and ICs.

In the detection phase, DCA generates a signal matrix that combines input signals with the antigens and then generates three interim outputs: costimulatory molecules (CSMs), semi-mature DCs (smDCs), and mature DCs (mDCs) by Eq. (3). These two output signals, smDC and mDC, are used to determine whether the antigen is abnormal or not, while CSM limits the data sampling lifespan.

$$\begin{aligned} C_{[CSM,smDC,mDC]} = ((W_P * C_P) + (W_S * C_S) + \\ (W_D * C_D)) * 2(1 + IC)/(|W_P| + |W_S| + |W_D|) \end{aligned} \tag{3}$$

where W_P, W_S, W_D are the weights between PAMP, SS, DS signals and the output signals, and a set of biological empirical weights or user-defined values as in [10]. C_P, C_S, C_D are the antigen™s PAMP, SS, DS values.

In the context assessment phase, the contexts of DCs whose CSM exceeds the migration threshold can be determined. The DCs in the migrated pool can process and collect signals and antigens. The algorithm uses (4) to calculate the median value of the migration threshold, and the DCs™ migration threshold is randomly generated within ± 50% of the median value. Through the generation of interim output signals, smDC and mDC, DC obtains a cell context that are the greatest value of smDC and mDC.

$$t_{median} > 0.5 * ((max_p * \omega_{p,c}) + (max_d * \omega_{d,c}) + (max_s * \omega_{s,c})) \tag{4}$$

where max_p, max_d, max_s are the maximum value of PAMP, DS, SS signals, $\omega_{p,c}, \omega_{d,c}, \omega_{s,c}$ are the weights between CSM output and PAMP, DS, SS signals.

In the last phase, all antigens are analyzed and a parameter that measures the abnormality level of antigens called Mature Context Antigen Value(MCAV) is derived. The closer the value is to 1, the more anomalous the antigen.

DCA is currently considered a no-training algorithm, and learning mechanisms are absent in the original DCA. IIM theory shows that DCs have trained™ properties and memory mechanism. Its trained™ properties are reflected in the secondary stimulation of DCs, which can stimulate their epigenetic reprogramming and enhance capacity to resist reinfection. In the computer field, IIM means self-adaptively learn and adjust the models™ instructions and parameters as the environmental changes or time goes by. Assume the output of the system S be $y$and the parameters adjusted be θ, and y feeds $\nabla\theta$ to the system S through the regulator R, then

$$\nabla\theta = Ry \tag{5}$$

where R is an operator representing the adjustment function.

$$y = S(\theta + \nabla\theta) \tag{6}$$

where S is an operator representing system function. There is

$$\theta_{(t+1)} = \theta_t + SR(\theta_t - \theta_{(t-1)}) \tag{7}$$

If $SR > 0$, then it is a positive feedback. If $SR < 0$, then it is a negative feedback. If $SR = 0$, it means no feedback from previous time window.

Greensmith [25] explores the sensitivity of the migration threshold parameter in the Deterministic Dendritic Cell Algorithm (dDCA), the results indicate that tuning the maximum migration threshold determines the results of the signal processing within the algorithm. The migration threshold of DCs determines the lifespan of the antigen collected by DCs. Adjusting the migration threshold can control the speed of DC maturation. The size setting will directly affect the detection speed and accuracy of the algorithm. Therefore, the IIM-DCA will choose the migration threshold to train an innate memory and make it to be learned over time.

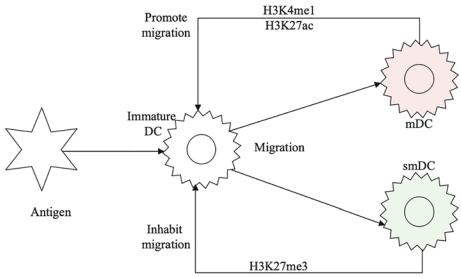


Fig. 3 Bio-feedback adjustment of histones in DCs

3.3 The IIM-based DCA model

Although the migration threshold in classic DCA has a certain randomness in setting, DCs™ migration threshold is randomly generated within ± 50% of the median value, once the median is determined in the subsequent detection process, it cannot be changed, so that the migration threshold set by the method cannot reflect the change of data characteristics in the dynamic environment and lacks adaptability.

In innate immune memory, histones are highly basic proteins providing structural support to a chromosome. Histone modification can predict the type of chromatin, determine whether cells are active or inhibited, and play an important role in regulating cell generation and growth, tissue repair, and immune processes effect. Histone modification is divided into two categories according to the function– H3K4me1 and H3K27ac modifications are mostly used to activate gene expression, while H3K27me2 and H3K27me3 were associated with gene suppression.

DCA and its artificial model only simulate the process of DCs™ antigen presentation to T cells without considering the adjustment of histone modification to DCs. In fact, DCs that have never seen a first encounter/stimulation are in immature state, and so are their histone modification enhancers. Upon a first stimulation, enhancers are within few hours rapidly marked with H3K4me1 often together with H3K27ac to promote DCs™ migration. After the first stimuli was waned, the promoters will decrease and H3K27me3 will increase to express the gene suppression and inhabit the DCs™ migration. Figure 3 shows the process of bio-feedback adjustment of histones in DCs. The adjustment of the DC migration capability is exactly the adjustment of the DC lifespan, so that the DC can accelerate or slow down the maturity, which is mapped to adjust the DC migration threshold in the artificial DC model.

In order to achieve the purpose of constant adjustment of DCs™ migration threshold with time and environment, we will divide the antigen environment along the time axis. And to achieve dynamic monitoring and adjustment, the antigens must be processed in each antigen environment divided in the first step, and output the antigens™ contexts in real time.

The IIM-DCA model is shown in Fig. 4, where k is the sliding window size, and the value of k depends on how long the antigen or how many antigens are suitable as an antigen environment (mostly related to the application field). Let

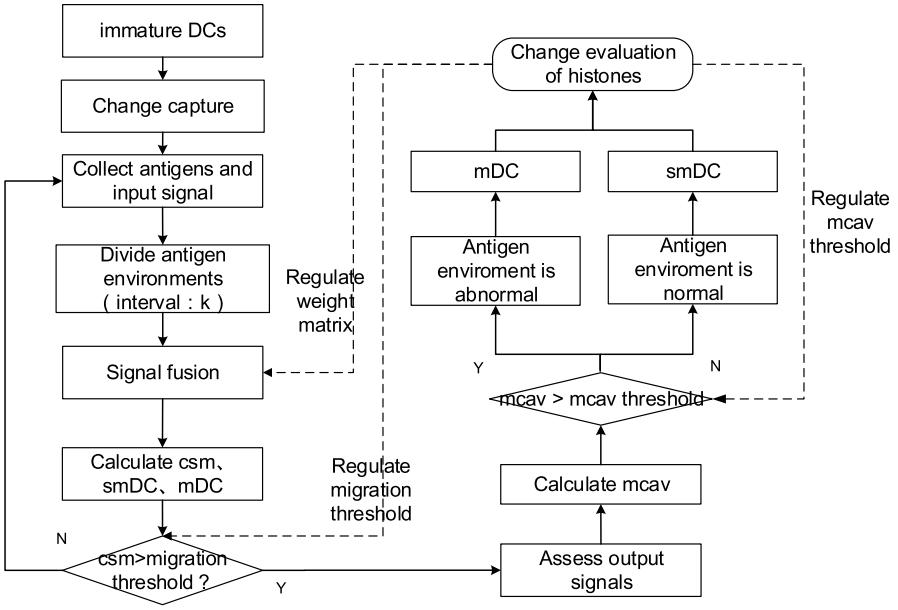


Fig. 4 Artificial immune model of IIM-DCA

the concentration change of histones be *SR* in (7) (as shown in (8)), and (9) defines the concentration of *histones*.

$$SR = \nabla histones \tag{8}$$

$$histones = \frac{1}{1 + e^{-(FP-FN)}} \tag{9}$$

where *FP* is False Positive, *FN* is False Negative(see Table 4 for detail).

We add a change capture model at the beginning to sense danger and add a feedback regulation phase after classification phase to adjust the model. When the accuracy is lower than the accuracy threshold, the concentration of histones is calculated. When *histones* increase, it means that *FP* increases, and *FN* decreases, that is, there are more false positives than false negatives, indicating that the number of normal antigen is determined to be abnormal is too large, too many DCs mature prematurely and the migration threshold should be increased at this time. On the contrary, when the concentration of *histones* is decreased, it indicates that the abnormal antigen is missed more frequently, and at this time, it is necessary to reduce the migration threshold to make it lower that the DCs can mature faster. When the accuracy exceeds the accuracy threshold, we need not adjustment. This can improve the accuracy of the classification, obtain a lower false positive rate, false negative rate, and accelerate the convergence of the algorithm.

4 Experiments of IIM-DCA

4.1 Used benchmarks

In order to test the IIM-DCA™s performance, our experiment uses KDD99 intrusion detection dataset, UCI™s Epileptic Seizure Recognition dataset, Breast Cancer Wisconsin(Original) dataset and Diabetes dataset. They are all classification datasets evaluating and classifying the data into normal or abnormal. The detailed descriptions of these datasets are as follows:

1) KDD99 is an intursion detection dataset whose goal is to label the network connections as normal or abnormal attack. We used 10% of the KDD99 dataset considering the computational efficiency, which was practiced in a series of works, such as [38, 39]. KDD99 sub-dataset consists of 494,021 records, 97,277(19.69%) of which are normal and the rest are abnormal. Each connection records was composed of 41 features including basic features that are extracted from a TCP/IP connection, time-based traffic features such as the number of connecitons to the same host over the 2 second interval, host-based traffic features, and content features.
2) UCI™s Epileptic Seizure Recognition is an epileptic seizure detection dataset, the goal of which is to classify the EEG(Electroencephalogram) data of patients into seizure condition or healthy condition. The raw data for UCI™s Epileptic Seizure Recognition dataset contain five different folders, each containing 100 files, each representing a person, which records the individual™s 23.6 seconds of brain activity, i.e., the dataset contains 500 recordings of 23.6s from 500 different patients. The sampling frequency is 173.61 Hz, so each time series contains $23.6\times 173.6 = 4097$ data points. Each data point is an EEG value at different points in time. The 4097 data points are divided into 23 blocks, each of which contains 178 pieces of data as a one-second data record. The dataset contains $23\times500=11500$ data (rows), each row has 179 columns of data, the first 178 is a one-second EEG time series data point, the last column is the classification flag, 1 represents epileptic seizure, and the other numbers represent normal EEG signals in different states. In the dataset, there were 2,300 epileptic data, and the remaining 9200 were healthy data under normal conditions.
3) Breast Cancer Wisconsin(Original) dataset is a breast cancer diagnosis dataset, which has 699 instances, and each instance consists of 10 attributes. There are 458(65.52%) records in dataset are benign, the other 241(34.48%) records are malignant.
4) Diabetes dataset consists of 768 data points, each with 9 features. Out of 768 data points, 500(65.10%) are marked as 0 which means no diabetes, and 268(34.90%) are marked as 1 which means diabetes.

4.2 Data pre-processing

This phase is specified for UCI™s Epileptic Seizure Recognition, since the first 178 columns of data in the original dataset represent EEG values at different time, in order to define the three input signals of the DCA, some features related to the onset of epileptic need to be abstracted from these raw data[40]. The features extracted include:

1) In 3.1, changes capture are the first step to sense danger. To describe the EEG data™s change, we use the numerical differentiation between the EEGs of the adjacent two columns, i.e., the EEG fluctuation range. This forms a total of 177 feature columns;
2) Epileptic signals are often judged clinically by the presence or absence of sharp waves and spike waves [41, 42]. Therefore, The number of the sharp waves and spike waves is two features related to seizure.
3) For sharp waves, we used the number of amplitude values above 100μV as one of the seizure features of EEG. And the number of amplitude values greater than 200 μV and the duration greater than 80 ms is a feature that represents a more severe seizure.
4) For spike waves, we used the number of amplitude values ranging from 100μV to 200μV and the duration greater than 20 ms as one of the EEG seizure features.

Finally, the dataset consists of a total of 182 attributes. There are other good feature selection strategies can be used in our next study, e.g., Manifold learning[43], wavelet transforms[44].

4.3 Parameters description

In the paper, an antigen is mapped to a data item. The parameter settings are presented in Table 3. A control experiment is performed with the IIM-DCA using the standard parameters that population size is set to 1000 and random sample antigen vector each cycle is set to 100 DCs. The MCAV threshold and the weight matrix are set according to [10]. Other settings such as antigen environment and accuracy threshold which

Table 3 Parameter setting table

Parameter	Set
Weighted matrix	$\begin{bmatrix} 2 & 1 & 2 \\ 0 & 0 & 3 \\ 2 & 1 & -2 \end{bmatrix}$
DC population	1000
Random sample number	100
Antigen environment window	Application-based
MCAV threshold	Application-based
Accuracy threshold	90%

determine whether the parameters need to be adjusted are application-based. Taking the Epileptic Seizure Recognition dataset as example, the value of antigen environment and accuracy threshold are chosen on a logarithmic scale to examine the link between the dataset and antigen environment set at {5, 10, 20, 50, 100, 500, 1000, 11500(size of dataset)}, while accuracy threshold is set at {0.5, 0.6, 0.7, 0.8, 0.9}. The experimental results on Epileptic Seizure Recognition dataset are shown in Fig. 5, and Fig. 5a shows the line graph of accuracy and antigen environment window value, Fig. 5b shows the line graph of accuracy and accuracy threshold. From Fig. 5, we can see that antigen environment window size is set at 10 and the accuracy threshold set at 90% can reach a better result on Epileptic Seizure Recognition dataset.

4.4 Used metrics

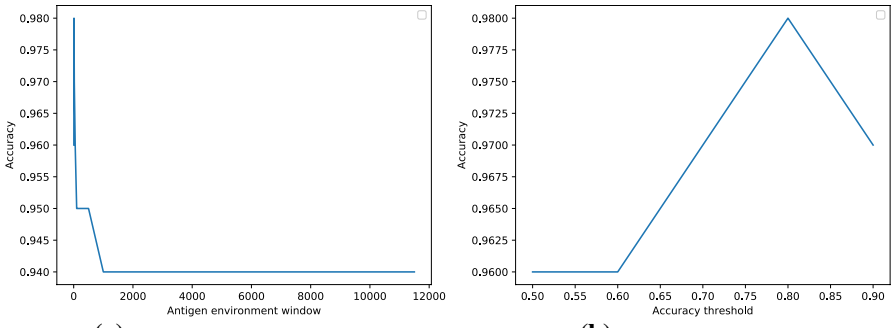
The metrics we evaluate the performance of the IIM-DCA in this paper are Accuracy, Recall, Specificity, FAR, AUC and running time.(see Chapter 4.5 for detail). All experiment is run on Huawei Matebook 13 (Intel(R) Core(TM) i7-8565U CPU @ 1.8GHz 1.99GHz). We have developed our program in JetBrains PyCharm 2018.3.2 x64.

4.5 Detection verification

In this paper, prediction accuracies obtained from the five different algorithms are compared using some statistical evaluation method: Accuracy, Recall, Specificity, false acceptance rate (FAR), area under curve (AUC) and running time(RT). The calculation method of the statistical indicators is shown as Eqs. 10 - 13. These are based on four possible classification outcomes–True Positive (TP), True Negative (TN), False Positive (FP), and False Negative (FN) as presented in Table 4.

$$Accuracy = (TP + TN)/(TP + TN + FP + FN) \tag{10}$$

$$Recall = TP/(TP + FN) \tag{11}$$



(a) Antigen environment window variation **(b)** Accuracy threshold variation

Fig. 5 Results of parameters variation in antigen environment window and accuracy threshold

Table 4 Classification outcomes

Acronym	Detection type	Real-world scenario
TP	True Positive	If the record is labeled as abnormal™ and also correctly detected as an abnormal™
TN	True Negative	The record is actually normal and the classifier also detected as a normal™
FP	False Positive	Incorrect detection, when the classifier detects the normal record as an abnormal™ case
FN	False Negative	Incorrect detection, when the classifier detects the record with abnormal™ as a normal case. This is a severe problem in health informatics research and intrusion detection

$$Specificity = TN/(TN + FP) \tag{12}$$

$$FAR = FN/(FN + TN) \tag{13}$$

5 Experimental results and analysis

We compare our proposed IIM-DCA with classic DCA[10], dDCA[14], random forest(RF)[26], Support Vector Machine (SVM)[27], K-Nearest Neighbor (KNN) [28] and Recurrent Neural Network (RNN)[29]. The DCA used PCA as signal acquisition method. In our experiments, we create 1000 DCs for the pool and select 100 DCs at random to sample each antigen according to [37]. RF consists of 100 trees. KNN uses standard Euclidean distance and binary-tree search for neighbors, and all points in each neighborhood are weighted equally. SVM uses the rbf kernel and gamma is set to 0.01. RNN uses relu™ as the activation function and has eight hidden layers. The batch size is set to 16, the learning rate indicator is set to 0.001, and the number of training epochs is set to 30 epochs. The weights in the multi-layer perception have been set to use A Method for Stochastic Optimization (Adam) to learn.

Tables 5, 6, 7 and 8 refers to the results for the UCI™s Epileptic Seizure Recognition dataset, Breast Cancer Wisconsin dataset, Diabetes dataset and KDD99 dataset, respectively, that were analyzed in this work. And the best performances are also highlighted in bold.

First, for Epileptic Seizure Recognition dataset, the IIM-DCA led to higher total classification accuracy (98.88%) compared to the classic DCA (80.21%) and dDCA(90.66%). Also, comparing with other five machine learning methods™ results, IIM-DCA provides better results in terms of all the evaluation indicators except RT. DCA is relatively slow, cause that the algorithm uses an antigen multiplier (m) for classification. Each data instance (x_i) is copied (m) times generating $\lfloor x_i \rfloor m$ antigens. When the size of the dataset is N, DCA will generate a total of $\lfloor x_i \rfloor mN$ antigens for the whole input dataset.

Table 5 Experimental results of the Epileptic Seizure Recognition dataset(%)

Value	Accuracy	FAR	Specificity	Recall	AUC	RT(s)
DCA	80.21	1.73	80.55	6.71	50.64	15.45
dDCA	90.66	3.25	95.33	44.82	70.58	22.18
IIM-DCA	**98.88**	**1.01**	**99.12**	**98.02**	**98.68**	10.07
RF	97.36	2.12	98.21	94.55	96.32	10.55
SVM	97.85	2.01	98.31	94.22	95.58	**6.2**
KNN	96.88	1.05	97.02	96.38	94.87	7.11
RNN	96.96	4.58	99.09	85.47	96.66	11.01

Table 6 Experimental results of the Breast Cancer Wisconsin(Original) dataset(%)

Value	Accuracy	FAR	Specificity	Recall	AUC	RT(s)
DCA	95.71	3.66	97.17	92.92	95.05	0.56
dDCA	95.14	**0.23**	92.83	**99.58**	96.20	10.17
IIM-DCA	**97.86**	0.67	97.39	98.75	98.07	15.70
RF	96.57	3.48	98.23	96.67	99.16	0.11
SVM	97.14	3.48	99.11	98.33	98.38	0.06
KNN	97.71	2.61	**99.12**	98.33	97.73	**0.05**
RNN	95.43	2.61	95.73	91.67	**99.35**	2.94

Table 7 Experimental results of the Diabetes dataset(%)

Value	Accuracy	FAR	Specificity	Recall	AUC	RT(s)
DCA	55.60	32.21	60.60	46.27	46.57	0.18
dDCA	52.21	34.05	55.00	47.01	51.01	24.66
IIM-DCA	**79.39**	31.53	71.60	68.67	82.75	0.20
RF	78.65	32.84	70.31	**82.81**	**86.16**	0.16
SVM	77.08	44.78	**72.55**	55.22	82.57	0.08
KNN	77.60	34.33	68.75	65.67	81.75	**0.05**
RNN	79.17	**31.34**	70.77	68.66	84.72	7.14

Table 8 Experimental results of the KDD99 dataset(%)

Value	Accuracy	FAR	Specificity	Recall	AUC	RT(s)
DCA	51.12	46.32	86.01	7.80	47.02	2.64
dDCA	73.94	29.45	90.90	53.59	71.92	83.83
IIM-DCA	96.82	1.53	98.02	94.22	95.53	11.58
RF	**99.84**	**0.00**	**99.71**	**99.64**	**99.99**	**0.25**
SVM	96.00	**0.00**	93.26	91.04	98.06	0.58
KNN	98.72	1.01	98.70	98.39	99.78	6.70
RNN	99.60	0.14	99.42	99.28	99.81	2.97

Second, for Breast Cancer Wisconsin dataset, IIM-DCA also achieves a better performance in terms of Accuracy. DCA has a slightly higher FAR and a slightly lower Recall value than dDCA, but are better than other five algorithms. KNN achieves the best performances in specificity and running time.

For the Diabetes dataset, IIM-DCA also obtains the best performance in Accuracy, and KNN has the shortest execution time, the same as the results of Breast Cancer dataset. RF achieves the highest Recall and AUC value, while SVM achieves the best Specificity. In this experiment, RNN™s FAR is the lowest, that is, the best.

For KDD99 dataset, the experimental results are very different from the previous three datasets. RF achieves the best performances in all metrics, and SVM obtains a same value of FAR(0.00%) as RF. Even so, IIM-DCA™s performances are better than other two DCA-based algorithms, and basically the same level as other machine learning methods. In fact, DCA-based algorithms are incapable of solving large datasets[45].

Figure 6 shows the comparison of classifiers™ average accuracy performance on the four Datasets. From Fig. 6, we can notice that our proposed IIM-DCA that based on the innate immune memory mechanism outperforms the mentioned classifiers including the classic DCA, dDCA, SVM, Random Forest, KNN and RNN in terms of overall accuracy.

From a joint analysis of the tables, a conclusion can be easily concluded. Since the many indicators such as Accuracy, Specificity and AUC values for IIM-DCA are better than other two DCA-based algorithms and is basically equal to other machine learning methods, it can be concluded that IIM-DCA™s improvements to DCA are effective. In other words, the addition of innate immune memory mechanism can make DCA achieve a better performance.

It is the first time to introduce the IIM mechanisms of DCs into DCA as far as I know. IIM mechanism™ means we can consider how to construct dynamic memory

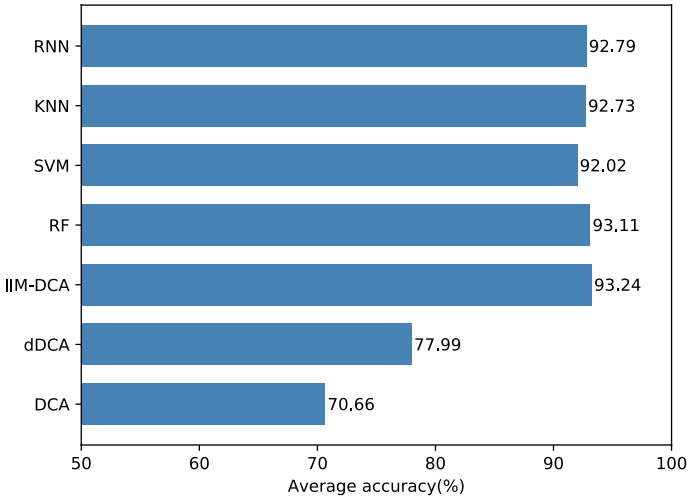


Fig. 6 Comparison of classifiers™ Average performance on the four Datasets

mechanism and learn from data more adaptive and flexible. The parameters and structures of DCA do not require manually pre-defined and fixed anymore. This paper uses a relatively simple approach to implement the IIM mechanism, the experimental results prove that the method is efficient for time series data anomaly detection, and we will consider more suitable methods to implement the IIM to achieve a better and robust model.

6 Conclusions

In this paper, we review the theory of IIM and point out some analogies in current AIS models. IIM thinks innate immunity can also build immunological memory to enhance the immune system™s learning and adaptive reactions to the second stimulus, which can be introduced into AIS to improve the innate immune algorithms™ adaptability. The main characteristics of IIM include reversibility, non-specificity to pathogens, short persistence and molecular mechanisms. And we list some considerations for practitioners of AIS regarding the suitability of the IIM model for their application. What™s more, we abstract the computer components and propose a computer model based on IIM. Then, we present a detailed modified DCA based on IIM to show how the IIM works in AIS. The modified DCA, named IIM-DCA, which integrates Innate Immune Memory mechanism to adaptively adjust the migration threshold of DCA. The experimental result shows that the proposed algorithm, reducing the false positive rate effectively, delivers more accurate results and is more automatic. Although we applied the IIM mechanism to DCA, this is a simplified version and has not been formalized yet. Few other AIS practitioners are conversant with the innate immune memory theory. Hence, this is the first paper that deals with the innate immunememory theory. We hope this paper can attract more and more researchers to study Innate Immune Memory theory. The further research direction will be exploring the IIM mechanism deeper and closer to biological nature to display the diversity, fuzzy and robust properties, and making it formalized to apply easily in AIS, including defining a suitable definition form of alert signals, strength, time, change, etc. And apply it to intrusion detection, anomaly detection, fault diagnosis and more fields. Nevertheless, if these challenges are met, then future Artificial Immune System applications might derive considerable benefit, and new insights, from the IIM.

References

1. Sharmila L, Sakthi U (2020) An artificial immune system-based algorithm for abnormal pattern in medical domain. J Supercomput 76(6):4272–4286
2. Silva GC, Carvalho EE, Caminhas WM (2020) An artificial immune systems approach to case-based Reasoning applied to fault detection and diagnosis. Expert Syst Appl 140:112906
3. Semwal T, Nair SB (2020) A decentralized artificial immune system for solution selection in cyber-physical systems. Appl Soft Comput 86:105920
4. Hatata AY, Osman MG, Aladl MM (2017) A review of the clonal selection algorithm as an optimization method. Leonardo J Sci 16(30):1–14

5. Ramdane C, Chikhi S (2017) Negative selection algorithm: recent improvements and its application in intrusion detection system. Int J Comput Acad Res (IJCAR) 6(2):20–30
6. Khan F, Kanwal S, Alamri S, Mumtaz B (2020) Hyper-parameter optimization of classifiers, using an artificial immune network and its application to software bug prediction. IEEE Access 8:20954–20964
7. Fu J, Yang H, Liang Y, Tan C (2012 August) Bait a trap: introducing natural killer cells to artificial immune system for spyware detection. In: Proceedings of the International Conference on Artificial Immune Systems. Springer, Berlin, Heidelberg. pp 125–138
8. Laurentys CA, Palhares RM, Caminhas WM (2011) A novel artificial immune system for fault behavior detection. Expert Syst Appl 38(6):6957–6966
9. Bejoy BJ, Janakiraman S (2018 May) An intrusion detection and prevention system using AIS-An NK cell-based approach. In: proceedings of the International Conference on Ismac in Computational Vision and Bio-engineering. Springer, Cham. pp 883–893
10. Greensmith J (2007) The dendritic cell algorithm (Doctoral dissertation, University of Nottingham, UK)
11. Igbe O, Darwish I, Saadawi T (2017 June) Deterministic dendritic cell algorithm application to smart grid cyber-attack detection. In: Proceedings of the 2017 IEEE 4th International Conference on Cyber Security and Cloud Computing (CSCloud). IEEE pp 199–204
12. Zhou W, Liang Y (2021) A new version of the deterministic dendritic cell algorithm based on numerical differential and immune response. Appl Soft Comput 102:107055
13. Elisa N, Yang L, Qu Y, Chao F (2018 June) A revised dendritic cell algorithm using k-means clustering. In 2018 IEEE 20th International Conference on High Performance Computing and Communications; IEEE 16th International Conference on Smart City; IEEE 4th International Conference on Data Science and Systems (HPCC/SmartCity/DSS). IEEE pp 1547–1554
14. Greensmith J, Aickelin U (2008 August) The deterministic dendritic cell algorithm. In: proceedings of the International Conference on Artificial Immune Systems. Springer, Berlin, Heidelberg. pp 291–302
15. Netea M. G., Joosten L. A. B., Latz E, Mills K. H. G, Natoli G, Stunnenberg H. G et al (2016) IIM: a program of trained immunity in health and disease. Science 352(6284):aaf1098–aaf1098
16. Netea MG, van der Meer JW (2017) IIM: an ancient way of remembering. Cell Host Microbe 21(3):297–300
17. Netea MG, Joosten LA (2018) IIM and local trained immunity in the lung. Cell 175(6):1463–1465
18. Netea MG, Schlitzer A, Placek K, Joosten LA, Schultze JL (2019) Innate and adaptive immune memory: an evolutionary continuum in the host's response to pathogens. Cell Host Microbe 25(1):13–26
19. Khader SA, Divangahi M, Hanekom W, Hill PC, Maeurer M, Makar KW, Netea MG (2020) Targeting innate immunity for tuberculosis vaccination. J Clin Investig 129(9):3482–3491
20. Mantovani A, Netea MG (2020) Trained innate immunity, epigenetics, and Covid-19. N Engl J Med 383(11):1078–1080
21. Gralinski LE, Menachery VD (2020) Return of the coronavirus: 2019-nCoV. Viruses 12(2):135
22. Xia S, Lan Q, Pu J, Wang C, Liu Z, Xu W, Lu L (2019) Potent MERS-CoV fusion inhibitory peptides identified from HR2 domain in spike protein of bat coronavirus HKU4. Viruses 11(1):56
23. Zhou P, Tachedjian M, Wynne JW, Boyd V, Cui J, Smith I, Mendenhall IH (2016) Contraction of the type I IFN locus and unusual constitutive expression of IFN-α in bats. Proc Natl Acad Sci 113(10):2696–2701
24. Ahn M, Anderson DE, Zhang Q, Tan CW, Lim BL, Luko K, Ng JHJ (2019) Dampened NLRP3-mediated inflammation in bats and implications for a special viral reservoir host. Nat Microbiol 4(5):789–799
25. Greensmith J (2019) Migration Threshold Tuning in the Deterministic Dendritic Cell Algorithm. In: proceedings of the International Conference on Theory and Practice of Natural Computing. Springer, Cham. pp 122–133
26. Breiman L (2001) Random forests. Mach Learn 45(1):5–32
27. Chang CC (2001) LIBSVM: a library for support vector machines, 2001. http://www.csie.ntu.edu.tw/cjlin/libsvm
28. Franco-Lopez H, Ek AR, Bauer ME (2001) Estimation and mapping of forest stand density, volume, and cover type using the k-nearest neighbors method. Remote Sens Environ 77(3):251–274
29. Medsker LR, Jain LC (2001) Recurrent neural networks. Design and Applications, 5

30. Farber DL, Netea MG, Radbruch A, Rajewsky K, Zinkernagel RM (2016) Immunological memory: lessons from the past and a look to the future. Nat Rev Immunol 16(2):124
31. Natoli G, Ostuni R (2019) Adaptation and memory in immune responses. Nat Immunol 20(7):783–792
32. Danilova N (2012) The evolution of adaptive immunity. Self and Nonself. Springer, New York, NY, pp 218–235
33. Forrest S, Perelson AS, Allen L, Cherukuri R (1994 May) Self-nonself discrimination in a computer. In: Proceedings of the 1994 IEEE Computer Society Symposium on Research in Security and Privacy. Ieee pp 202–212
34. De Castro LN, Von Zuben FJ (2000) The clonal selection algorithm with engineering applications. In: Proceedings of the GECCO (Vol. 2000, pp. 36-39)
35. Zhou W, Liang Y, Dong H, Tan C, Xiao Z, Liu W (2017 November) A Numerical Differentiation Based Dendritic Cell Model. In: proceedings of the 2017 IEEE 29th International Conference on Tools with Artificial Intelligence (ICTAI). IEEE pp 1092–1098
36. Yang H, Xiong S (2015) Method for Presenting Danger Signals Based on System Balance. In International Conference on Advances in Mechanical Engineering and Industrial Informatics. Atlantis Press
37. Greensmith J, Aickelin U, Cayzer S (2005) Introducing dendritic cells as a novel immune-inspired algorithm for anomaly detection. In: proceedings of the International Conference on Artificial Immune Systems. Springer, Berlin, Heidelberg. pp 153–167
38. Elisa N, Yang L, Naik N (2018) Dendritic cell algorithm with optimised parameters using genetic algorithm. In: proceedings of the 2018 IEEE Congress on Evolutionary Computation (CEC). IEEE pp 1–8
39. Santanelli JL, de Lima Neto FB (2016) Network intrusion detection using danger theory and genetic algorithms. In: proceedings of the International Conference on Intelligent Systems Design and Applications. Springer, Cham. pp 394–405
40. Oliva JT, Rosa JLG (2017) How an epileptic EEG segment, used as reference, can influence a cross-correlation classifier? Appl Intell 47(1):178–196
41. Sobieszek A (2014) [In search of the sharp wave of epileptic nature]. przegl lek, 690-693
42. Hamandi K, Laufs H, Naey U, Carmichael DW, Duncan JS, Lemieux L (2008) Bold and perfusion changes during epileptic generalised spike wave activity. Neuroimage 39(2):608–618
43. Dornaika F (2020) Multi-layer manifold learning with feature selection. Applied Intelligence, 1-13
44. Sharma M, Patel S, Acharya U R (2020) Automated detection of abnormal EEG signals using localized wavelet filter banks. Pattern Recognition Letters
45. Chelly Z, Elouedi Z (2016) A survey of the dendritic cell algorithm. Knowl Inf Syst 48(3):505–535

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