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Intelligent Multi-Tier Modeling of Immune System against SARS Viruses

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Immune system is a complex defending system for the health of a body, and the modeling of this immune system is as complex as that of the brain. In fact, immunologists know no enough knowledge about this immune system, and the traditional modeling of this immune system is the mathematic formulas such as ordinary differential equations (ODEs). But these mathematic tools are difficult to understand and use due to the strict conditions, which are often far away from the real data. To improve the research on this immune system, computing techniques are applied in the modeling of this immune system, and the immunology is generating a new computing-based branch, named computational immunology. In this paper, a visual intelligent modeling approach with advanced computing techniques is used to represent a kind of immune system and its different states against the viruses such as SARS viruses. This immune system is comprised of immune cells and immune molecules, and we establish an intelligent multi-tier immune model. The immune tiers include innate immune tier, adaptive immune tier and immune cell tier. Thus, this intelligent visual model of the immune system was seamless and coherent with the architecture of the artificial immune system, so that the research on the natural immune system and the artificial one could be improved together. To validate the new approach to visualize and explore this immune system, many simulations were tested on the intelligent multi-tier artificial immune system. The visual results show that this intelligent multi-tier modeling approach can provide an effective and better way of understanding this immune system.

Key words: Immune system; modeling; computational immunology; intelligence; SARS.

Immune system is a complex defending system for the health of a body, and the modeling of this immune system is as complex as that of the brain (Perelson, Hightower, & Forrest, 1996). This immune system is of natural parallel nonlinear recognition ability, and it can discriminate selfs and nonselfs in normal immune responses. This immune system is based on some complex pattern recognition mechanism in its models and functions. So inspired from this immune system, the artificial immune system can be applied to pattern recognition and is currently regarded as a subset of computational intelligence, which is a subset of artificial intelligence. The neural network of the body has about 10^{10} neurons, while this immune system of the body also has about 10^{12} lymphocytes (Kim, Spelta, & Sim *et al*, 2001).

Both the two most important systems of the body have memory and uncertainty features. Inspired from them, the artificial neural network and the artificial immune system have close ties with each other, and they can be integrated in an application system. One major function of this immune system is to provide the body a powerful defense mechanism, which can identify dangerous antigens (non-self, e.g. viruses) and eliminate them.

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Thus, understanding the immune system is important for human beings, because of its role against complex diseases such as AIDS and its inspiring applications to computational problems on machines (Fauci, 2003; Balthrop, Forrest, & Newman, *et al*., 2004). But, the mechanisms of the immune system are so complex and poorly understood, even by immunologists (Chao, Davenport, & Forrest, *et al*., 2004). One of the difficult problems in understanding this immune system is how to generate the simulation results in biological shapes, which are similar to cells and molecules. Recently, the information visualization is becoming a new and important technique to investigate and simulate the immune system and the artificial immune system (Timmis, 2001). And the Java-based visualization technique provides a useful tool to design visual cells and molecules and simulate this immune system on computers (Gong, Li, & Du, 2011). In this paper, an intelligent multi-tier model is proposed for this immune system against the viruses such as SARS viruses, and then simulated with Java.

Intelligent Immune Model against Viruses

In the traditional modeling of immune system, the differential equations are often used (Ho, Neumann, & Perelson, *et al*., 1995; Nowak & Bangham, 1996). In these models, populations of antigens and immune cell types are continuous variables in systems of ordinary differential equations (ODEs). Analytical techniques allow modellers to define system behaviours, associated parameters and initial conditions, but these equations need too strict conditions and the result data are not easy to understand. Data on the behaviour of individual cells is difficult to incorporate directly, and these data must generally be recast as population-level phenomena. The mathematic models of the immune system are not in a united frame of immunology, and some conditions of these models are not practical in real medical cases. To improve the understanding of this immune system and create a united frame of immunology, an intelligent multi-tier model of this immune system against the SARS viruses is proposed, which is seamless and suitable for the visual simulations on computers, and this new model is within a new branch of immunology, named as computational immunology. As shown in Figure 1, the visual tri-tier model against the SARS viruses of this immune system includes three tiers, i.e. the innate immune tier, the adaptive immune tier and the immune cell tier. Figure 1 shows the structure of this immune system and the relationships between one component and another of this system. According to the hierarchical computing idea, this immune system is divided into three tiers in functions and mechanisms. In fact, the immune response is a kind of dynamic balance process, and the balance state of this system is maintained by the generation and elimination of all the components. This immune response can be visualized by Figure 2, according to some terms of immunology. The innate immune tier is represented with IIT; the adaptive immune tier is denoted with AIT; the immune cell tier is named as ICT; the first immune response is called FIR; the secondary immune response is denoted with SIR; the antigen such as the SARS virus is named *Ag*; *Ab* represents the antibody; the generator of normal cells (i.e. selfs) is called M_1; the generator of infected cells is called M_2; the generator of damaged cells is called M_3, and the damaged cells include the repairable cells and the cancer cells etc.; the generator of immune memory cells is called M_4; the generator of antibodies is called M_5. In Figure 2, the innate immune tier does two procedures: one is the self/non-self detection and the other is the recognition of known non-self. The objects include normal cells, antigen, infected cells, damaged cells and immune memory cells.

Visual Simulations of Immune System

With the visualization tool, it is necessary to simulate all the states of this immune system and then analyze the principles. The typical states include the normal metabolism (before the SARS viruses infect the body or the genes have pathology), the damaged state due to the viruses or the pathology, the innate immune response, the adaptive immune response, the self- repairing of the damaged body (Gong & Cai, 2011). Before the SARS viruses infect the body or the genes have pathology, the body maintains the dynamic balance of this immune system by itself. In this system, some older cells are dying, and some new cells are generated to make up the physical loss of cells, as shown in Figure 3. This immune system can detect the dying cells and the physical loss, and the regenerating tissues of cells can generate new cells responding to the loss change of this body, in

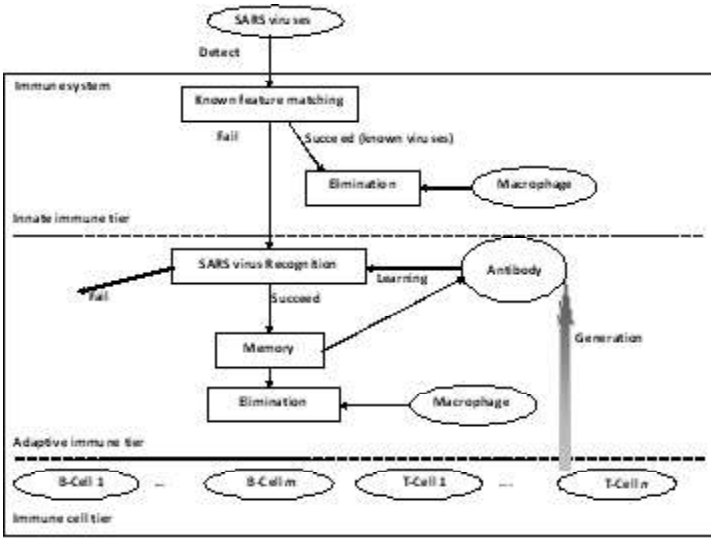

Fig. 1. Intelligent multi-tier model of this immune system against SARS viruses

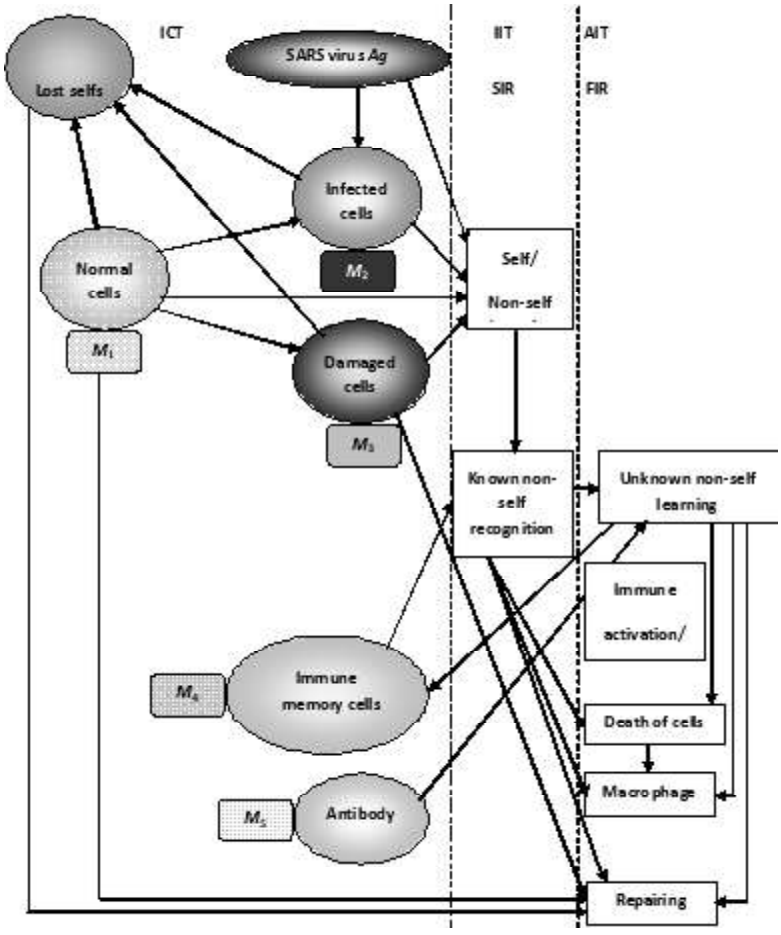

Fig. 2. Immune response frame of this immune system against SARS viruses

order to take place of the dying cells and the lost cells with the new cells.

In Figure 3, cell 1 represents the dying cell; tissue 2 denotes a regenerating tissue of cells; cell 3 represents the new cell to take place of the dying cell (No. 1) through the generation of regenerating tissue; cell 4 represents the new cell to make up the lost cell (No. 5) through the generation of regenerating tissue; cell 5 represents the lost cell due to the physical loss; cell 6 denotes the normal cell; cell 7 denotes a macrophage. After cell 1 dies, the macrophage eliminates the trash from the dying cell (No. 1). The body takes place of cell 1 with the new cell (No. 3), and the new cell has the same effectiveness as the dying cell. After cell 5 is lost, the body takes place of the lost cell (No. 5) with the new cell (No. 4), and the new cell can also maintain the normal state of this system. The regenerating tissues of cells transform the nutrition into new normal cells through the digestive system, blood and marrow, in order to maintain the metabolism of the normal body. When the body is growing, the regenerating tissues of cells are very active and powerful, and the body really develops from a single zygote through the regenerating tissues.

When the SARS viruses infect the body, some cells are infected by the viruses. Afterwards the infected cells gradually lose their normal functions and continue to spread the viruses, as shown in Figure 4.

In Figure 4, cell 1 represents an invading SARS virus; cell 2 represents the cell, which is infected by cell 1; cell 3 represents the dying cell; tissue 4 represents the regenerating tissue of cells;

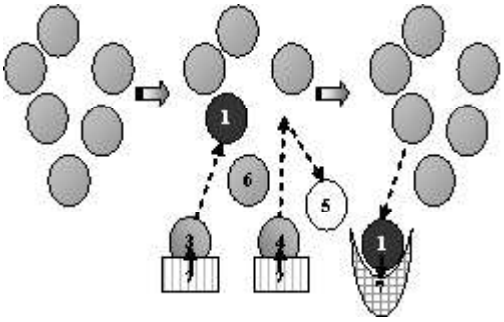

Fig. 3. Normal metabolism before the SARS viruses infect the body or the genes have pathology

cell 5 represents the new cell to repair the infected cell, which is damaged by cell 2; cell 6 represents the new cell to make up the dying cell (No. 1); cell 7 represents the abnormal cell, which has gene pathology; cell 8 represents the new cell, which is

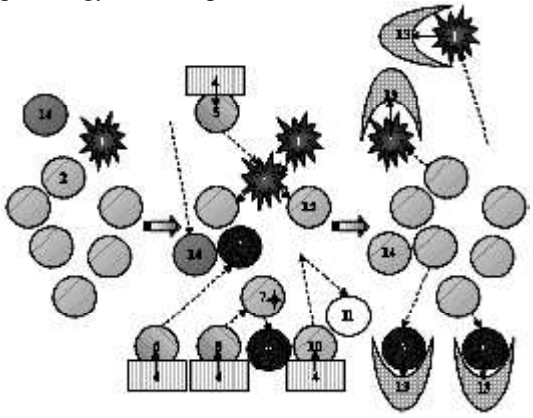

Fig. 4. Damage of the SARS viruses and the gene pathology to the body

generated by the regenerating tissue (No. 4) to repair cell 7; cell 9 represents the dying cell, which was cell 7; cell 10 represents the new cell, which is generated by the regenerating tissue (No. 4) to repair the lost cell (No. 11); cell 12 represents the normal cell; cell 13 represents a macrophage; antigen 14 denotes a new self. After cell 2 is infected by SARS virus 1, the cell (No. 2) becomes an infective cell and begins to spread SARS virus to another normal cell (No. 12). This immune system recognizes the infected cell (No. 2) and generate new cell (No. 5) with the regenerating tissue to repair the infective cell (No. 2).

Nowadays, the immune tests get some samples from the biological cells, and do some biomedical tests on these samples to detect the special nonselfs in the samples. In fact, these immune tests change the compositions of the immune cells and the environment of cells. Besides, these tests only measure the results of immune responses and cannot measure the real processes of the immune responses. It's impossible to accurately measure when and which antibody recognizes which virus, which we call the uncertainty feature of this immune system. This uncertainty feature shows the complexity, which is similar to that of the quantum system, and the limits of the current measure techniques. Besides, this inspires immunologists not to emphasize on

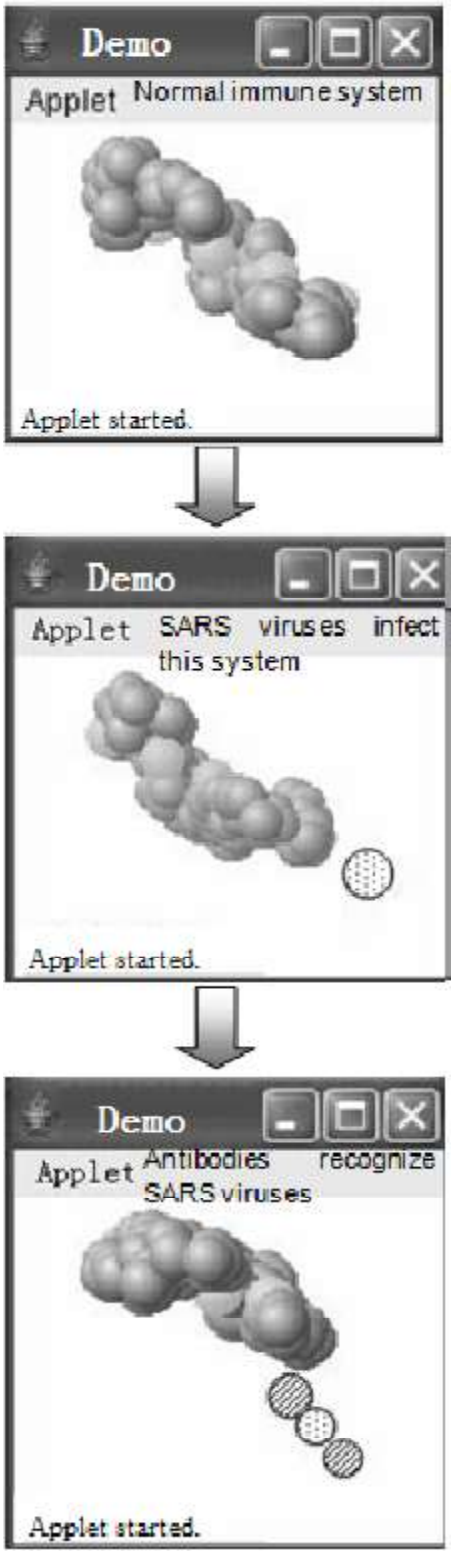

Fig. 5. Visual 3D simulation of this immune system

measuring the immediate states of the antibodies and the immune cells, and to do more researches on measure the results of the immune response and control the immune processing to keep the robustness of the body.

Suppose the example of immune sub-system has 100 immune cells, and three antigens attack the immune sub-system. The example of this immune system is visualized with Java in Figure 5. The gray balls without any point represent the normal cells of this immune system; the dotted ball denotes the SARS virus; the balls with slashes denote the antibodies, and the antibodies are generated by the immune cells.

The immune response is used to detect the selfs and the nonselfs, and then recognize the SARS viruses. For the unknown SARS viruses, the second immune response is quicker than the first one. When a large number of SARS viruses infect the body, this immune system will make a kind of unbalanced immune response, which will do harm to the immune system and the body. Because at that time this immune system has faults in detecting the selfs and the nonselfs, and this system may regard the normal cells as the nonselfs and eliminate some normal cells.

CONCLUSIONS

Collaborations between many computer scientists and biologists have produced spectacular results, and the most important example is the sequencing of the human genome. Recently, these scientists are creating a new branch of immunology, named computational immunology. Modeling of this immune system is an important task of computational immunology. As we know, the intelligent simulation of the model is better as it is more visual. We propose an intelligent multi-tier immune model, which is a kind of logic proposal and need biomedical verification. With the intelligent multi-tier immune model of this immune system against the SARS viruses, the doctors, immunologists and patients will have a chance to understand this immune system more easily, though there are still many mysteries in the computational immunology, which may produce a great power to improve many sciences such as immunology, mathematics, medicine, biology, computer science etc.

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