Visual NetLogo-Based Simulation of Anti-SARS Immune System and Low-to-High Resolution Reconstruction of Sequence Medical CT Images

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***Abstract*—In the immune responses against the SARS (Severe Acute Respiratory Syndromes), human immune systems are complex intelligent systems, which show good properties such as the self-organizing and adaptivity. Modeling the immune systems has important significance in both immunology and artificial immune system. In order to improve the visualization and readability of the anti-SARS immune system model, the visual tri-tier computational model of the anti-SARS immune system was simulated with NetLogo, which is a multi-agent-based tool. On the other hand, to fight against the SARS disease, the low-resolution medical CT (Computed Tomography) images should be transformed into the high-resolution ones for better SARS analysis. In order to obtain the high-resolution image from some low-resolution chest CT sequence images of a SARS patient, the low-to-high resolution reconstruction was designed and tested in this paper. First, the low-resolution medical images were preprocessed. Then the pretreated low-resolution medical images were registered with the sub-pixel-level image registration techniques. Finally, the POCS (Projections onto Convex Sets) image reconstruction algorithm was designed and tested. We obtained higher entropy and more detail information of the medical images with our approach than the Marcel method, especially for the rotated medical images in our experiments. Multiple-user browser-based experimental results show that the visual NetLogo-based simulation of the immune system is better to understand than the traditional mathematic equation model of the immune system.**

Keywords—visual immunization model; NetLogo; super-resolution; medical image reconstruction; image registration

I. INTRODUCTION

In the long history of mankind, human beings are always searching for the essence of life. In recent years, with the rapid development in medicine and physiology, some features of the immune system cause the attentions of researchers in other fields, and they begin to focus on the research and simulation of immune system. The research of immune mechanism has always been the focus point of studies home and abroad.

Inspired from the mechanism of the human immune system, new information processing system (i.e. the artificial immune system, AIS) can be established. Since 1997, an increasing number of international conferences have been organized on the AIS. Therefore, it is important to investigate the principle of the biological immune system and propose some mathematical models or engineering models of the immune system. First of all, according to the biological views, the development of the computer-based model of the immune system provides new way to test the theory of immunology, thus the model will help the immunologists to better understand and develop biological immunology. Besides, the visual simulation of the immune system has an important guiding significance in studying complex intelligent systems and proposing new intelligent methods. So an increasing number of researchers from different fields start to simulate the immune system with new techniques on computers.

In the real industry procedure, when some visual images are obtained with the imaging system, the recording equipment, the transmission medium and some processing methods, the images are possibly blurred and deformed [1]. In these cases, these low-resolution images should be transformed into the high-resolution images. This problem becomes a hot issue of medical image processing. Though these single images have low resolutions, we can use the super-resolution reconstruction approach to break through the resolution limits of the medical images [2], in order to generate the high-resolution image for better disease analysis.

SARS patients' lungs show different degree of flake or patchy ground glass density shadow. The shadow shows a trend of progress, because in some cases a small shadow may quickly grows into a large shadow. The super-resolution reconstruction can help us to detect more shadows, so we can use this method for decrease early lesions.

Why human beings can live healthy in this world with dangers and diseases? An important reason is that the nature has granted the mankind a natural defense system, i.e. immune system. With this system, human beings are able to survive

against the dangers and diseases. In medicine, the immunity refers to a physiological response when the body is exposed to the foreign substances named antigens [3]. The modern definition of the immunity is the reaction of the body against some exogenous substances. And the immulogical function is to identify the antigens and exclude the nonselfs from the body. Generally speaking, the reaction that maintains a stable state of the body is beneficial to the body, but it is also harmful under some certain conditions.

There are great differences between the model of the natural immune system and the artificial immune system. These differences not only reflect in the application objects of the models, but also in the modeling approaches. So it's difficult to establish an appropriate mapping between these two models. In order to investigate the immune system from the perspective of natural computing, the tri-tier visual model of the natural immune system includes the innate immune tier, the adaptive immune tier and the immune cell tier in this paper.

II. VISUAL IMMUNE MODEL AND SUPER-RESOLUTION RECONSTRUCTION OF MEDICAL CT IMAGES

The mapping relationship between the natural immune system and the computer- based artificial immune system is shown in Table I.

TABLE I. IMMUNE MAPPING FROM NATURE TO COMPUTERS

Biological immune system	Artificial immune system
Non-self antigen	Computer virus, faults
Self antigen	Normal component
Phagocyte	Object eliminator
Antibody	Immune Agent (IA)
Memory cell	Memory
Feature matching	Database query
Pattern recognition	Learning and reasoning
B cells, T cells etc.	Parallel computer

When the antigen enters body, the body is protected by the immune system. First of all, the system detect antigen by means of self/non-self identification mechanism, and then recognize the antigen by feature matching. When the antigen is identified as known antigen, it will be eliminated by phagocytes immediately; but if the antigen can't be identified by innate immune tier, it will be handed to adaptive immune tier. Subsequently, a large number of immune cells begin to produce antibodies. Finally, the unknown antigen will be eliminated through pattern recognition and learning. After the antigen is identified by the antibody, the antigen becomes known antigen and be eliminated by phagocytes. Phagocytes are double-edged, and this is precisely the key of biological immune system [4]. When phagocytes work normally, they can combine with hazardous antigen and then elimination them; when phagocytes work anomaly, they may be combined with normal cells or molecules, and kill normal cells.

NetLogo is a programmable modeling environment, which is written with Java independent of the platforms such as Windows, Linux, Mac, etc. It is often used to simulate natural and social phenomena, and especially suited for modeling the complex systems, which evolved over time [5-6]. Researchers from different fields can create the relevant models according to their needs. Besides, a model library can be built to contain a number of simulation models. So the researchers can not only use them directly, but also use them after some modifications. These models cover many areas of nature and social science such as biology, medicine, physics, chemistry, computing mathematics, and computer science, etc [7]. There are two ways to view the simulation model with NetLogo: in the NetLogo client; in a remote web browser after the model is saved as Java Applet and embedded into a web page.

Because of the complexity of biological systems and the limitations of technology, we are unable to simulate the immune system completely. Thus, we select an important immune mechanism named cellular immunity to simulate. The cellular immune mechanism is designed with the immune D-cells. The D cells have tree-root shapes under a microscope [8], and the D cells exist in the body's first line of defense (e.g. skin, mucous membranes). They are important for the innate immune system and the strongest professional antigen-presenting cells (pAPC) in the body. In addition, they are the main bearer of T cell activation. When the body encounters the invasion of pathogenic microorganisms, the D cells are activated through combining with pathogen, thus the antigen information is attained quickly. The immature D cells have a strong ability of migration. They can present the antigen information to the inferior immune system, also namely the adaptive immune system. The D cells that obtain sufficient antigen information move to the nearest lymph nodes through the lymphatic and blood circulation. These D cells get mature gradually, and then move to the T cell zones of the lymphoid organs with the function of chemokines. Mature D cells present information of the antigen to the T cells after they reach the T cell area. And then the T cells become into the effector T cells after the proliferation and differentiation. Meanwhile, a small portion of T cells become into the memory T cells. When the same kind of antigens intrude into body, the memory cells will proliferate and differentiate rapidly, the immune system can generate a large number of effector T cells, which could make stronger specific immune response. Thus, the mature D cells can stimulate the proliferation of the naive T cells effectively, which is the most prominent feature of the D cells. In fact, the D cells are the first link of the immune response. Whether the antigen presentation is effective or not, it is directly related to immune activation or induction of immune tolerance. Therefore, the D cells have a special status in immune response. And this is also one of important reasons for choosing the cellular immunity for the simulation.

As shown in Fig. 1, the super-resolution medical image reconstruction has 5 steps: image preprocessing, image registration, image transformation, image reconstruction and inverse transformation. The medical image registration and the motion estimation model are both important for the super-resolution reconstruction of the medical images.

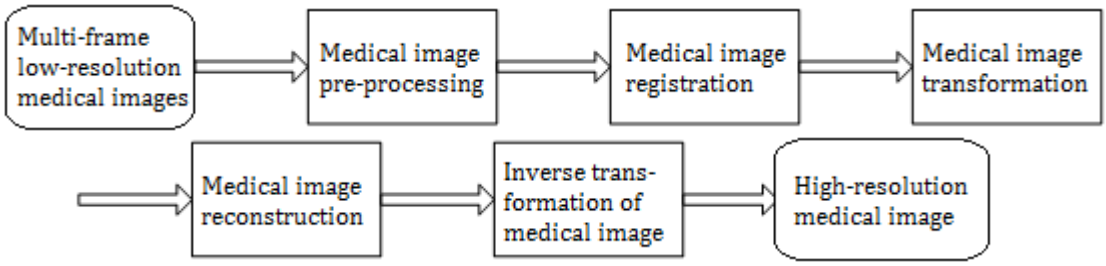


Fig. 1. Super-resolution reconstruction of the medical images.

In addition, the higher are the accuracies of the image registration and the motion estimation, the better effect of the image reconstruction is made [8]. At first, the multi-frame low-resolution medical images should be made through the micro-displacement with each other, in order to get a high-resolution image. The accuracy of the medical image registration is one of the main factors for the super-resolution image reconstruction, and this factor often affects the resolution of the reconstructed medical image [9]. After the image registration and the image recovery, the uniform sampling of the super-resolution image can be made. We register the medical image with the micro-displacement method, and the pre-processing of the medical images, the medical image registration, and the medical image reconstruction are based on the POCS super-resolution image reconstruction algorithm.

III. Medical Image Registration with Improved Keren Sub-pixel-based Registration Algorithm

The medical image registration is the seeking process of the one-to-one mapping between an image and another one, which is used to make the two images mapped to the coordinate position [11]. We designed the medical image registration with the Keren-pixel-based image registration method. The medical image registration can be roughly divided into four categories: multi-modal medical image registration, medical image template registration, medical image observation point registration and medical image time sequence registration. We used the time sequence registration method [12].

For example, if we use two medical images in the image registration, then the reference image of the two images is represented by $I_1(x, y)$, and the observed image of the two ones is represented by $I_2(x, y)$. Then the medical image registration is mathematically defined below.

$$I_2(x,y) = g(I_1(f(x,y))) \tag{1}$$

Here, $f(x, y)$ is the coordinate transformation function, and $g(\cdot)$ denotes the 1-dimension gray-scale/radiation transformation function.

For this reason, it is very crucial for the medical image registration to find the best space or geometric transformation [13]. This transformation can be made by the single-valued function $I_1(\cdot)$ with the two variables f_x and f_y.

$$I_2(x,y) = I_1(f_x(x,y), f_y(x,y)) \tag{2}$$

In the past few decades, an increasing number of scholars from different fields had investigated the problem of image registration from different angles and in different application backgrounds [14]. However, most of these methods are of the pixel-level accuracy, and this accuracy level is not enough for advanced processing of the medical images. For example, the remote sensing and the high-precision reconstruction of the medical image need the more accurate registration of the medical images, and the sub-pixel level registration of the medical images can make higher accuracy. Usually, in the medical image processing, only the sub-pixel level image registration can provide the possibility to detect the small differences between the sequence medical images. So the sub-pixel level registration method is a necessary foundation for this image reconstruction, and the Keren sub-pixel-based image registration method is used to process the medical sequence images.

The Keren sub-pixel-based image registration algorithm uses the three-layered Gaussian pyramid to increase the speed, accuracy, and stability. After the Gaussian filtering and sampling, the original $N \times N$ images are transformed into the new two images, which have the $N/2 \times N/2$ resolutions. When we repeat the above procedures, the final two $N/4 \times N/4$ images are generated. This algorithm utilizes a coarse-to-fine resolution image pyramid, from the first coarse layer to strike X. According to X, the second layer is rotated and transformed, and then we get a new second layer with the interpolation. Then the new X is calculated again, and so we get the high accuracy registration parameters.

However, the Keren sub-pixel-based image registration algorithm has the major drawback that this algorithm depends on the small angle Taylor series expansion. For the small angles (less than 6°), this algorithm is useful for the high registration accuracy. But the rotation angle of the medical sequence images sometimes causes relatively big errors by this Keren algorithm. To avoid these big errors, the following formula is used to improve this Keren algorithm with the successive approximation.

$$\mathrm{X}_{k+1} = C_k^{-1}\mathrm{V}_k + \mathrm{X}_k \tag{3}$$

Here, k is the iteration sum of this Keren iterative algorithm.

In order to overcome the errors from the Taylor series, our improved medical image registration method embeds the rigid transformation model of the medical image into the simplified four-parameter affine transformation model.

$$\left.\begin{aligned} x' &= x + a_1 x + a_2 y + a_3 \\ y' &= y + a_1 y - a_2 x + a_4 \end{aligned}\right\} \tag{4}$$

$$\mathrm{X} = \begin{bmatrix} a \\ b \\ \theta \end{bmatrix} \tag{5}$$

$$\mathrm{C} = \begin{bmatrix} \sum\left(\frac{\partial f}{\partial x}\right)^2 & \sum\frac{\partial f}{\partial x}\frac{\partial f}{\partial y} & \sum R\frac{\partial f}{\partial x} \\ \sum\frac{\partial f}{\partial x}\frac{\partial f}{\partial y} & \sum\left(\frac{\partial f}{\partial y}\right)^2 & \sum R\frac{\partial f}{\partial y} \\ \sum R\frac{\partial f}{\partial x} & \sum R\frac{\partial f}{\partial y} & \sum R^2 \end{bmatrix} \tag{6}$$

We design the improved medical image registration algorithm below.

Step 1: Decompose the target image into three-layered Gaussian pyramid.

Step 2: Initial the iteration sum k, the rotation angle □ and the horizontal/vertical displacement all with zero.

Step 3: Calculate C_k^n *and* K_k^n*, and calculate* X_k^N *according to equation (3).*

Step 4: If K=k, then go to step 7.

Step 5: According to X_k^N*, resample* $g(x, y)$.

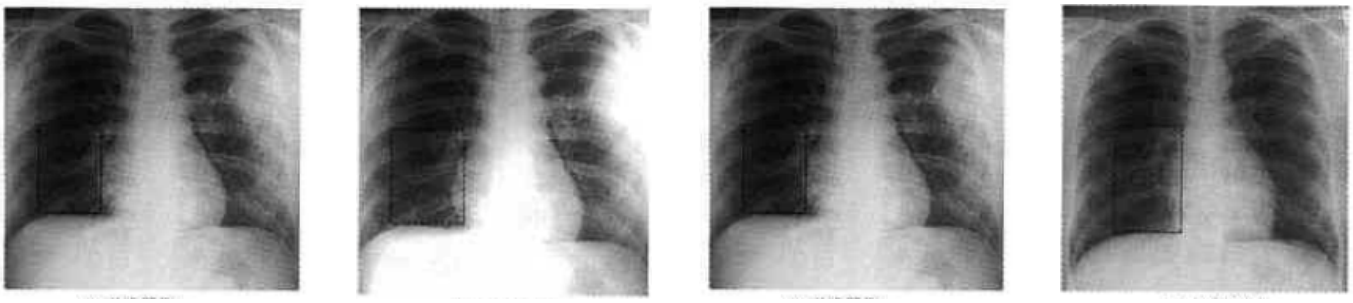
Step 6: k=k+1, and return to step3.

Step 7: If n<3, then calculate X_0^{n+1}*, n=n+1, and go to step 2 or end.*

Here, n is the number of image, and K is the maximum iteration sum.

With the above-improved algorithm, some experiments are made with some selected samples (as shown in Fig. 2) from the chest CT sequence images of a SARS patient. We use the first image of the samples as the benchmark image, and the displacements of the images are made in the X-direction and Y-direction at the sub-pixel level.

Afterward, the traditional Marcel algorithm and the improved Keren sub-pixel-based image registration algorithm are tested with the above medical images, and then we compare the results of the two algorithms. The experimental result in Fig. 3 of the traditional Marcel algorithm shows that this traditional algorithm cannot calculate the rotation values. In addition, the experimental result in Fig. 4 of the improved Keren sub-pixel-based image registration algorithm shows higher accuracy than that of the Marcel algorithm in Fig. 3. In the following figures, the parameters Rotations are the rotation angles of the medical images, the parameter Shifts x is the horizontal displacement, and the parameter Shifts y is the vertical displacement. The four original medical images are all 128×128 pixels.



(1) Reference image (2) 2nd image (3) 3rd image (4) 4th image

Fig. 2. Four medical images for the registration.

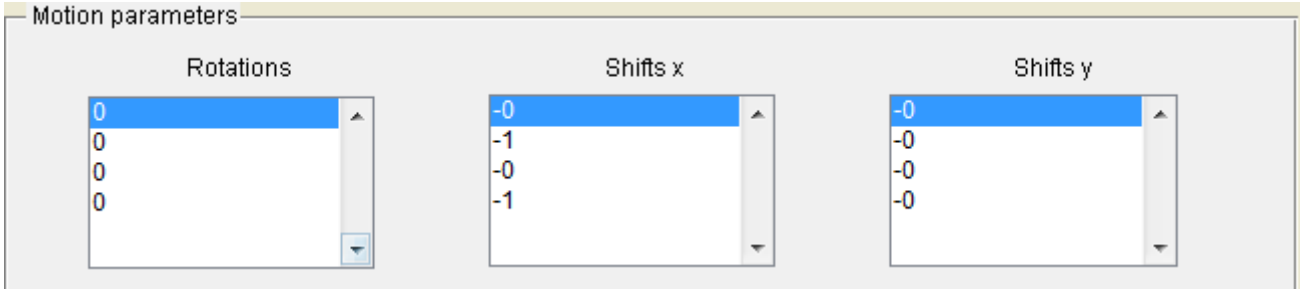


Fig. 3. Experimental result of the traditional Marcel algorithm.

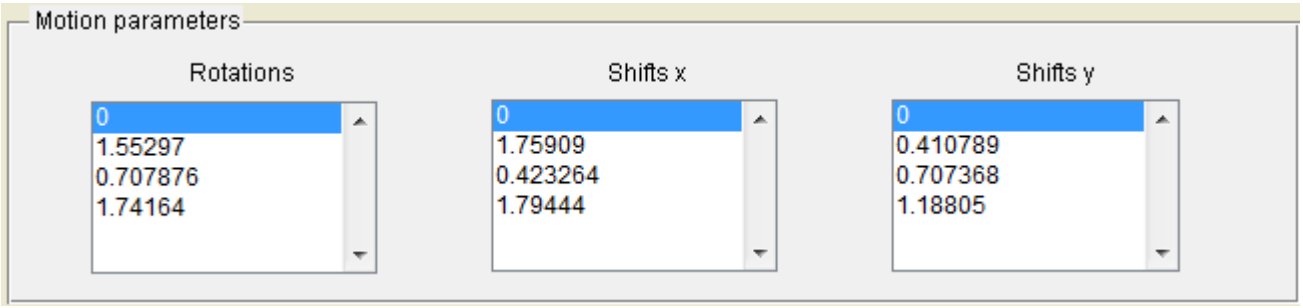


Fig. 4. Experimental result of the improved Keren sub-pixel-based image registration algorithm.

IV. SUPER-RESOLUTION RECONSTRUCTION OF MEDICAL CT IMAGES

The super-resolution reconstruction is used to reconstitute a high-resolution medical image from multi-frame low-resolution medical CT images. This medical image reconstruction is required to merge the reiterated low-resolution CT images into a high-resolution image [15]. The super-resolution reconstruction of the medical images can take full advantage of the valid correlated data on the time and space of the sequences images [16]. The POCS method was called the algebraic reconstruction when Vandewalle et al used this method for the image reconstruction [17].

We process the medical images with the POCS method according to the following steps.

Step 1: With the initial estimation of the high-resolution primarily through the interpolation operation to the low-resolution medical images, attain the expected resolution.

Step 2: Estimate the motion parameters for each pixel by the sequence of low-resolution medical images, and then find the pixel for the mapping to the pixel position in the high-resolution image of the initial estimation within the motion vector field.

Step 3: According to the image degradation processing model, calculate the estimated value of the pixel. Then calculate the residuals. If the residue exceeds a set limit, then correct the pixel value of the current high-resolution estimation until the residue meets the requirements.

Step 4: Constantly revise the pixel values within the estimated scope of the current high-resolution, until we accept the suitable results.

V. EXPERIMENTAL RESULTS

After building the simulation system of the immune system, the parameters settings can be changed. For example, the initial infection amount is set with 2 and the amount of the D cells is also set with 2. After the button **[setup]** was clicked, the amounts of the infections, the D cells and the lymph nodes were calculated, as shown in Fig. 5. The meaning of each pattern that appears in this scene is represented, as shown in Table II. After the button **[go]** was clicked, this scene (ticks = 1) was displayed, as shown in Fig. 6. As shown in the above figure, the mature D cells moved to the lymph nodes gradually, after the infection was detected.

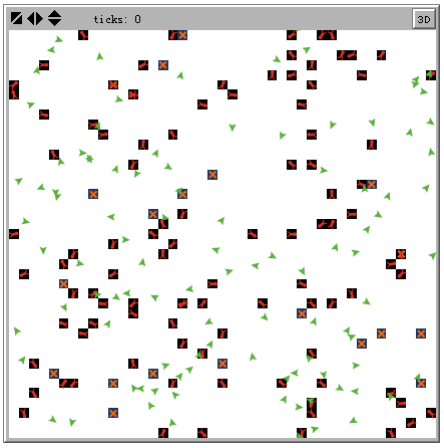


Fig. 5. Initialization scene of the simulation

TABLE II. MEANING OF EACH PATTERN

Pattern	Meaning
	infection-count
	scouting-dendritic-cell/d-cell-count
	reporting-dendritic-cell
	lymph-node-count
	effector-t-cell
	after infection
	lymphokines released by lymph nodes

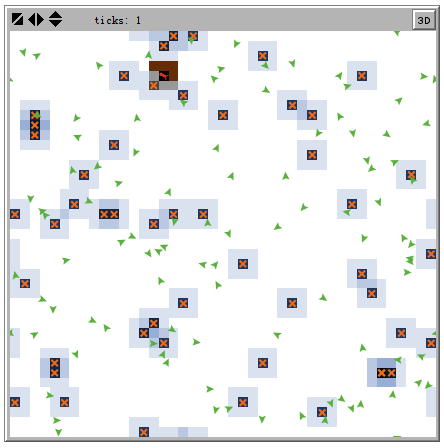


Fig. 6. Initial scene when ticks = 1.

After the button [go] was clicked until ticks = 27, the lymph nodes began to stimulate the release of T cells after the D cells moved to the lymph nodes. Then the T cells moved to the infection site under the role of cytokine, and the target cells were killed directly. Eventually, the intracellular antigens were killed because of the loss of the hideouts, as shown in the left side of Fig. 7. Similarly, after the button [go] button was clicked until ticks = 58, the infection was basically cleared, as shown in the right side of Fig. 7. Fig. 8 shows the dynamic curve for the number of the T cells, the number of the infections and the number of the D cells. The infection-site was represented by the gray line gradually. However, the effector T cells that are represented by the blue line roughly showed an increasing trend at first. Then the curve gradually decreased accompanied by the decrease of the infection-site. All these show that the dynamic nature of immune response is reproduced. In the web-based simulation, the B/S structure was adopted. Besides, a PC was used as the server, with a laptop as the client. Then, the result was shown on the browser, as shown in Fig. 9.

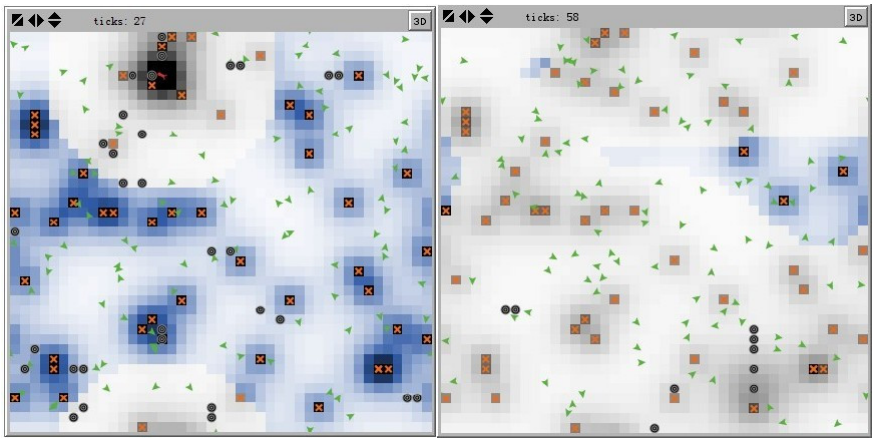


Fig. 7. Simulation scenes when ticks = 27 and ticks = 58.

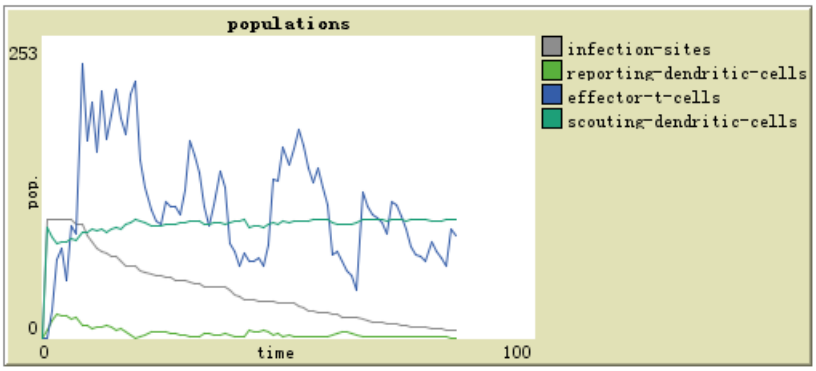


Fig. 8. Curve graph of the model.

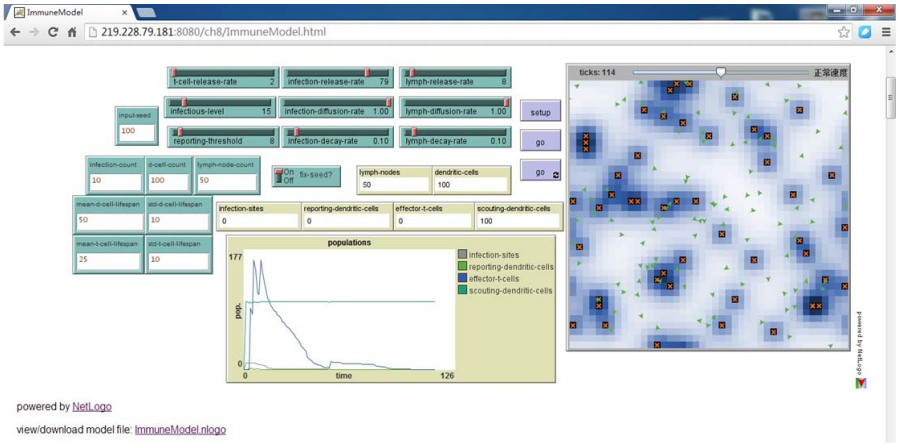


Fig. 9. Simulation interface of the visual immune model in the client browser.

We use the chest CT sequence images of the SARS patient for the reconstruction experiments, and the experiments are simulated in Matlab. The high-resolution image of the experiment result with our approach is shown in Fig. 10.

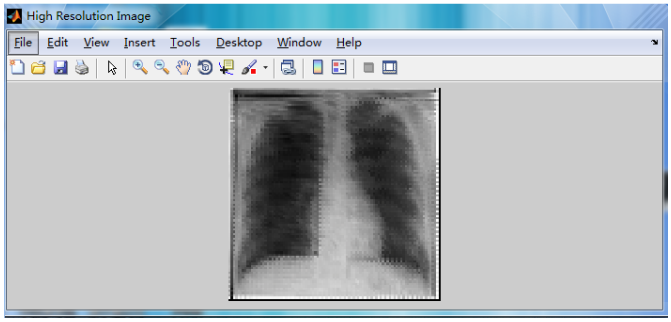
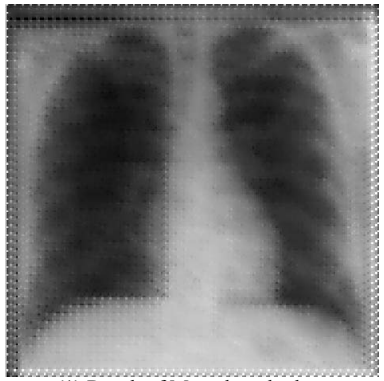
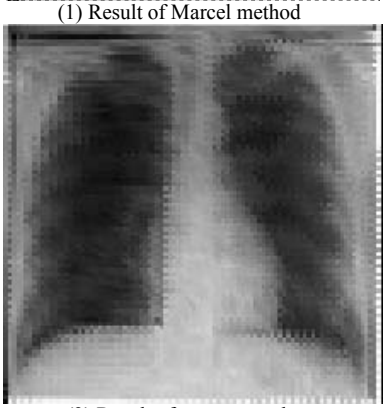


Fig. 10. Reconstruction result of the medical image with our approach.

The above result is compared with the super-resolution reconstruction result of the Marcel method as shown in Fig. 11. The original medical images are all 128×128 pixels, and the results of the reconstruction images are 256×256 pixels. In the right picture of Fig. 11, the iterated back projection algorithm is used to reconstruct the medical images, and the right image contains more detail than the left one as we can see. Also, the information entropies of the two pictures can be calculated to compare the qualities of the two results below, and this comparison shows the advantage of our approach. The entropy of the left image is 7.5924, and the entropy of the right image is 7.6477, which is higher than that of the left one.



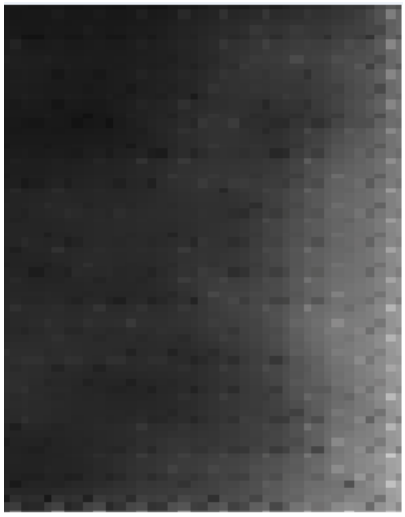
(1) Result of Marcel method



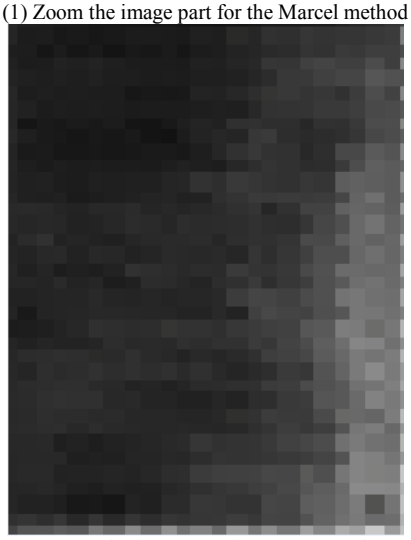
(2) Result of our approach

Fig. 11. Comparison made between the result of Marcel method and that of our approach on the medical images.

We select the bottom right part of the left lung to enlarge the images in Fig. 11, as shown in Fig. 12. We can see that the result of our approach has more detail information than that of the Marcel method. This is more beneficial for the further disease analysis.



(1) Zoom the image part for the Marcel method



(2) Zoom the image part for our approach

Fig. 12. Zoom the image parts for the Marcel method our approach for further comparison.

The rotation perhaps causes noise to decrease the enhancement effect of the medical image, and the small rotation angle (<2 degree) cause no apparent decrease of the image enhancement effects for the two methods. In this case, our approach can get more detail information than the Marcel method, similarly as shown in Fig. 11 and Fig. 12. When we use the large-rotation-angle (>6 degree) images to do this comparison experiments, the four images are used in Fig. 13.

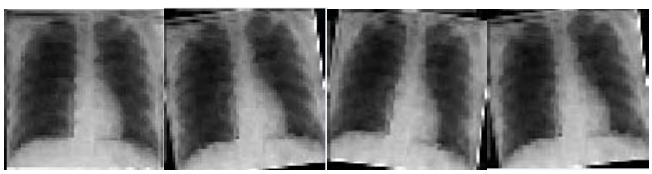
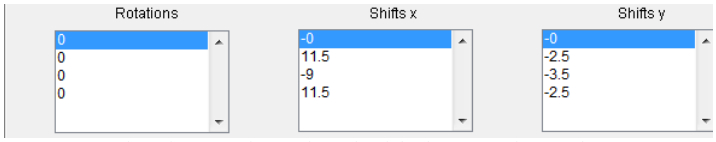
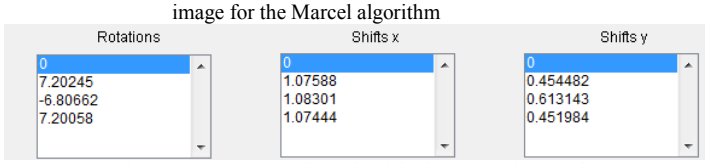


Fig. 13. Four large-rotation-angle images.

The registration experiment results of the large-rotation-angle images are shown in Fig. 14. The first result is the traditional Marcel, and the second one is our method. We can see that, when the rotation angle is large than 6 degree, the traditional method has a large error. The reconstruction result is shown in Fig. 15. We can see from the result that when the rotation angles are larger than 6 degree, the traditional method reconstruction result has a lot of noise and that is bad for disease detection.

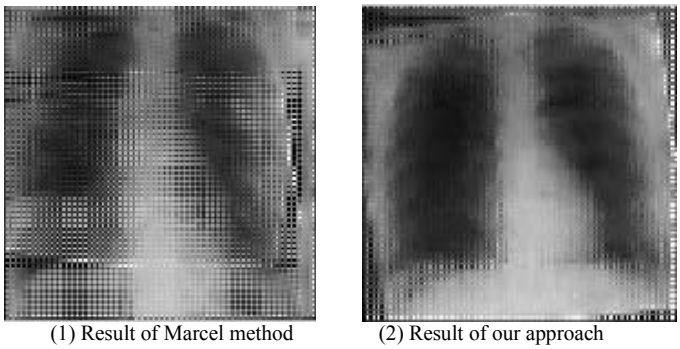


(1) Registration experimental result of the large-rotation-angle image for the Marcel algorithm



(2) Registration experimental result of the large-rotation-angle image for our approach

Fig. 14. Registration results of the large-rotation-angle medical images.



(1) Result of Marcel method (2) Result of our approach

Fig. 15. Comparison made between the reconstruction results of the large-rotation-angle images.

VI. CONCLUSIONS

In this paper, after the biological basis of immune system was analyzed, a new visual tri-tier computational model of the immune system was proposed. Then, the NetLogo tool and the cellular immunity were introduced. The simulation system of the immune system was constructed, and the visual simulation of cellular immunity was displayed by the means of the simulation system. When the simulation was completed, the simulation model was viewed on both the NetLogo client and the remote web browser, after the model was saved as the Java Applet and embedded into the web pages.

In addition, we presented a super-resolution reconstruction algorithm, which enables a fast and detailed reconstruction of the sequence chest CT images. Through the super-resolution reconstruction experiments, we can see that this algorithm is useful to solve the problem of the insufficient resolution. This algorithm will help us to make better edge detection or measurement of the medical images, and enhance our ability to fight against with the diseases such as SARS.

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