New Computational Trends in Modeling and Evaluating Immune System Function against Pathogen Agents

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Abstract: The immune system is a complex system with multiple interacting, which full understanding the function and predict its behavior is vital in finding effective and safer treatments for diseases. This paper aimed to investigate and evaluates the immune system dynamics simulation models. Researches on modeling immune system interactions have been carried out over the past three decades and received noticeable results. The earliest immune system models that stand-alone were based on differential equation. Lately, different facets of artificial intelligence, fuzzy logic, cellular automata and agent based models are used in simulating immune cell that its outcomes is very strong compared to the known classic results. Two rules-base models, cellular automaton and agent based model can satisfy immune system simulation well due to their unique characteristics.
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1. Introduction

A healthy immune system is essential to survive of whole body; it is made up millions of cells, tissues and collection of organs that interact to make a protective defense system. When foreign invaders include bacteria, viruses or parasites entered the body, immune system launches a huge planned attack. The importance of the immune system is stressed by individuals who have been born with, or acquired immunodeficiency. Knowing the complete function of the immune system provides a comprehensive understanding of various immune cells' ability to fight foreign invaders or its defense mechanism against invaders; it may also be useful in finding new ways to cure disease caused by harmful invaders.

Although, most important studies have been carried out for realizing molecular and cellular occurrences of immune system, accurate principles that manage all facets of an immune response are still vague.

Research scientists have used several tools to explain and evaluate complete function of different parts of body. Numerous behavior of body parts as a complex networks can be expressed by computational modeling using mathematics, physics and computer science. Computational modeling has helped to produce simulations in order to explain behavior of body parts well. Several mathematical modeling have recently been applied to simulating various aspects of immunology [1]. Mathematical relationships in biological quantities are full of physical meaning; mathematics and physics are both parts of Theoretical Biology; physics often tries to fix problems by combining different tools: separation of scales and coarse-grained modelling [2].

The number of surveys has been done to diagnose diseases and evaluate function of body parts; these researches have applied fuzzy logic, artificial intelligence, cellular automaton and agent based model. In the present paper we have discussed these tools and extended them in the different aspects of immune system.

2. Trends in evaluating immune system

Immune system is, compared to the central nervous system, the second most complex physiological system in the body [3]. Yet, it is difficult to comprehend immune system function and the way of its planning to respond specifically to strange pathogens. In another word, this system is an unpredictable organism, because complex interactions of the immune system with a target population of bacteria, viruses, antigens, or tumor cells are ruled by nonlinear dynamical laws [4]. Lots of trends using new technologies have been introduced to finding and solving unclear problems related to immune system function; where new area called computational immunology or immunoinformatics created; applying their techniques would be able to simulate immune system with multi-scaling nature. In this regard in the following part we would have evaluate some models:

2.1 Mathematical Modeling

Biomathematics which integrates mathematics and biology aims at treatment and modeling biological processes, using mathematical tools. Unclear immune cells interactions can be simulated by precise mathematical models. One of mathematical areas is differential equation which is now being applied in modeling immune cell function.

Mathematical models based on Ordinary Differential Equations systems have been used for cancer immunology [5], primary and secondary immune cell responses [4] and T cell response [6]. Delay Differential Equation is used to model the development of neutrophils from stem cells [7]; another example is devising a mathematical model to study the regulation of the T cell response by naturally occurring Tregs (CD4+ T) [8]. Using Partial Differential Equation to model neutrophil migration toward a site of infection was applies as well [9]. Stochastic Differential Equations has been applied to simulate immune response model. The model accounts for the depletion of immunoglobulin by natural degradation and antigenic consumption and its periodic replenishment [10].

Various autoimmune responses can be modeled using differential equations to predict immune cells behavior and their effect on autoimmunity. A mathematical framework, an Ordinary Differential Equation, is developed for type I diabetes (an autoimmune process in the body). This model integrates metabolism and the immune system responses in early stages of diabetes disease process and typically describe B cell death [11] moreover autoimmunity in a regulatory T cell is modeled by Ordinary Differential Equation; the model shows T cells quantitative effects on reducing autoimmune responses [12]. Immune system function may be simulated in other autoimmune disease like Parkinson using Delay Differential Equation.

Ordinary Differential Equations are the most efficient method for modeling biological complexity without a substantial increase in the computational work and any networks that do not rely on delayed feedback and probabilistic events. Delay Differential Equations are suitable to model networks depending on delayed feedback [13].

Some mathematical models have been developed to evaluate drugs, modulating with immune response or invaders interaction with immune cells; or totally to model the kinetics of the immune response [14]. Modeling with coupled differential equations has been proposed to analyze the dynamics of malaria parasite (Malaria is one of the world's deadliest disease [15]), with respect to interaction between antimalarial drug and immune response [16, 17]. The interaction of the NK and CD8+ T cells with various tumor cell lines has modeled with coupled of differential equations too [18]; likewise the interaction of the NK and CD8+ T cells with Toxoplasma gondii (Toxoplasmosis: a cat born disease [19]) may be simulated using coupled differential equations.

The simulation results by differential equations describe clinical and nonclinical behaviors well and introduce it as an effective method in evaluation function of immune cell against invaders.

2.2 Physicist's Approach

Physics Laws can explain Theoretical Immunology in a quantitative way; Problems in Theoretical Immunology include Natural selection, Antigen recognition, Stability and statistical populations can be considered in physics point of view. For example, three different aspects (operating at different scales of energy, length and time) of antigen presentation have been calculated by some physics tools [2].

Statistical Physics in Biology is a survey of problems at the interface of statistical physics, biological elements and networks [20]; statistical mechanical models simply can be used to make clear various aspects of the immune response and predict immune system interactions.

Kosmrlj *et al*, discuss how key components of the adaptive immune system, T cells, develop to enable pathogen-specific responses against various pathogens by employing methods from statistical physics, such as extreme value distributions (EVDs) and Hamiltonian minimization [21]. Other aspects of physics as quantum mechanics may highly be used in describing immune systems behavior in near future.

2.3 Artificial Intelligence

Artificial intelligence (AI), as a branch of computer science, has affected clinical and medical fields in different ways. However AI is still in the early stages of its development, but its methods are designing more effective cancer drugs with fewer side effects. Moreover we can see its application in Clinical Decision Making, medical education, automated reasoning and Meta reasoning with significant results. Some other application of AI has been used in evaluating immune system that we would described them as follows:

2.3.1 Machine Learning

Machine learning is a field of AI, with wide range of application in bioinformatics. Different aspect of machine learning such as Support Vector Machines, Hidden Markov Models, and Probably Approximately Correct (PAC) learning are usable to describe bio phenomena.

Support Vector Machines can build predictive models when the data is high in dimension and the number of observation is limited; therefore it has been used in improving accuracy in T-cell epitope prediction [22]. Using of machine learning aspects in immune system has not extended yet; while applying immune system as a model for machine learning has been grown.

In machine learning, Artificial Neural Networks (ANNs) are computational models inspired by biological neural network or brain system which is able to do data mining tasks such as categorization as well as pattern recognition. However, neural network algorithms are appropriate in modeling non-linear dynamical systems as immune systems.

Immune cell differentiation and subset classification are two immunological processes that have not completely described. For the first time, two neural network models for modeling CD4+ T cell differentiation and immune cell subset classification has been proposed in a study; which resulted high accuracy in both models [23]; vice versa immune system functions can be used to model novel neural networks [24].

2.3.2 Genetic Algorithms

Genetic algorithms (GA), a subfield of artificial intelligence is effective in solving certain optimization problems and has been used in many application areas, including pattern recognition; immune system does pattern recognition tasks to distinguish self-cells from antigens; therefore genetic algorithm can offer models for studying its behavior.

However, scientists consider immune system as a model for the design of pattern recognition systems and novel genetic algorithms [25, 26]. Genetic algorithm as a search heuristic which mimics the process of natural selection may be used in Epitope selection.

2.4 Fuzzy Logic

Fuzzy logic has widely used in different science; and nowadays we can see its usage in biological systems. Uncertainty and imprecision are two aspects of medical science likewise fuzzy logic addresses different forms of uncertainty thus, this feature of fuzzy logic is able to support medical diagnosis as well.

Prediction the response to treatments, analyze of disease behavior in body, determining appropriate dosage of drugs, improving decision making in medicine and genetic in bioinformatics field are some other application of fuzzy logic [27].

Many biological organisms are naturally fuzzy rather than deterministic; The immune repertoire is able to recognize self and non-self-antigen in a fuzzy manner and the T cells and antibodies can recognize given cells to a certain degree, although deterministically. Such a fuzzy characteristic of the immune system may make clear mechanism of auto immune disease [28]. *Fuzzy Biology* term is created by Afshari and RezaeeNezhad to define “application of fuzzy logic and fuzzy set theory to biological problems”; they show how fuzzy logic modeling might be appropriated in biological problems [29].

2.5 Cellular Automaton

A cellular automaton (CA) is a fully discrete dimensional model, consists of grid of cells with specific values, driven by updatable rules which are subjected to the states of the neighbors. It is used in theoretical biology modeling and other branch of sciences. Cellular automaton can describe cellular structural biology, morphogenesis and growth, reproduction, competition as well as evolution of biological processes well; thus, it is applicable in simulating immune system.

It has been proved that Cellular Automata is an appropriate and simple model to simulate complex machines as immune system over space and time but the challenge is about the difficulty of obtaining analytical results in comparison to numerical ones.

Simple cellular automata model of the immune cell dynamics was proposed from 1990‘s decade to the extent that currently its progressive models is used to simulate humoral and cell-mediated immune responses against invaders and modeling behavior of invaders, which will lead to designing vaccines. Simulating interaction between the immune system and the HIV has been done in some study using CA model [30, 31, 32 and 33]. Cellular automata model for interaction of tumor growth or cancer with immune system have been consider for years too.

2.6 Agent-Based Modeling

Generalized cellular automaton can simulate the immune system in a better way; Agent-based model (ABM) can be a generalization of cellular automata. It has been applied recently in variety of biological research areas; it is a proper tool to simulate and predict the dynamics of complex systems like immune system at cellular level virtually. In ABM approach, three elements detect, model and program: agents (It is defined as computational entities which makes decisions using predefined rules), agent interactions and agent environments. Entities in immune system would be immune cells like Tregs, B cells etc.

The successful application of agent-based model in modeling the immune system responses have been explored in some researches [34, 35 and 36]. ABM is a bottom-up model similar to CA, which simulate agents in the microscopic level. The immune system function may be studied using agent-based modeling linked cellular automata; it would call An Agent-based Cellular Automata (ABCA).

2.7 Applications of Artificial immune system

Different part of human body system may benefit from engineering models; vice versa natural models can be used to solve engineering problems. Immune systems characteristics like negative selection and clonal selection induce scientist to create Artificial Immune Systems.

Artificial Immune Systems (AIS) are computational prototypes that belong to the computational intelligence group and take inspiration from biological immune system; during the past decade, they have used to develop immune-based models and methods to solve intricate computational or engineering difficulties [37]. At the moment Artificial Immune Systems are being used from industrial application to medical diagnosis.

Scientists have combined Artificial Immune Systems with other computational models, creating the hybrid techniques, in order to improve capability of individual algorithms without losing their advantages: developing hybrid classification method based on a combination of Artificial Immune Systems and Genetic Algorithms [38, 39]; fuzzy artificial immune system has been proposed to take advantage of the strengths of fuzzy and AIS [40]. Some models can work with each other to improve processing results with good accuracy: as some aspects of AIS have direct parallels with Swarm Intelligence (SI), AIS and SI are complementary tools and can be work together [41] using Artificial Neural Network to explore features, together with Artificial Immune System for rules extraction was successful as well [42]; although ANNs are widely used, but AISs have been partly abandoned.

3 Conclusion

The immune system is a complex system with integration of many different components and multiple interacting, which understanding the function and predict its behavior is vital to human health especially in finding new treatments for disease as well as modelling of vaccination. Several applicable methods has introduced in this paper in simulating dynamic interaction between immune cells and foreigner invaders. The earliest models of the immune system were based on differential equation that stand-alone. In recent years, artificial intelligence, fuzzy logic, cellular automata and agent based models are broadly used in simulating immune cell for which their results are very strong compared to the known results of differential equation that stand-alone. Immune responses process has two scale of time and space so cellular automaton and agent based model, as discrete dimensional models, can satisfy immune system simulation; However, these two rules-base models are applied in discrete systems with bottom-up approach in microscopic level; features of immune system are inspired in problem-solving techniques, namely, Artificial Immune System (AIS).

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References

1. Molina-Paris C. Mathematical Models and Immune Cell Biology. 1st ed. Lythe G, editor. Leeds: Springer; 2011.
2. Castro M. A Physicist's Approach to Immunology. Mathematical Models and Immune Cell Biology. Leeds: Springer; 2011. p. 339–50.
3. Northrop RB. The human immune system seen from a biomedical engineering veiw point. Endogenous and Exogenous Regulation and Control of Physiological Systems. Florida: Chapman & Hall/CRC; 2000.
4. Mayer H, Zaenker KS, An Der Heiden U. A basic mathematical model of the immune response. Chaos An Interdiscip J Nonlinear Sci [Internet]. 1995 Mar;5(1):155–61.
5. De phills LG, Radunskaya AE, Wiseman CL. A validated mathematical model of cell-mediated immune response to tumor growth. Cancer Res [Internet]. 2005 Sep 1;65(17):7950–8.
6. Wodarz D, Thomsen AR. Effect of the CTL proliferation program on virus dynamics. Int Immunol [Internet]. 2005 Sep;17(9):1269–76.
7. Colijn C, Mackey MC. A mathematical model of hematopoiesis: II. Cyclical neutropenia. J Theor Biol [Internet]. 2005 Nov 21 [cited 2014 Aug 16];237(2):133–46.
8. Castro M. A Physicist's Approach to Immunology. Mathematical Models and Immune Cell Biology. Leeds: Springer; 2011. p. 339–50.
9. Onsum M, Rao C V. A mathematical model for neutrophil gradient sensing and polarization. PLoS Comput Biol [Internet]. 2007 Mar 16;3(3):e36

10. Figge MT. Optimization of immunoglobulin substitution therapy by a stochastic immune response model. PLoS One [Internet]. 2009 Jan;4(5):e5685.
11. Marinković T, Sysi-Aho M, Orešič M. Integrated model of metabolism and autoimmune response in β-cell death and progression to type I diabetes. PLoS One [Internet]. 2012 Jan;7(12):e51909.
12. Alexander HK, Wahl LM. Self-tolerance and autoimmunity in a regulatory T cell model. Bull Math Biol [Internet]. 2011 Jan;73(1):33–71.
13. Kim PS, Lee PP, Levy D. Modeling regulation mechanisms in the immune system. J Theor Biol [Internet]. 2007 May 7 [cited 2014 Aug 16];246(1):33–69.
14. Radunskaya A, Hook S. Modeling the Kinetics of the Immune Response. New Challenges for Cancer Systems Biomedicine. Springer Milan; 2012. p. 267–82.
15. Otarigho B. Malaria Vaccine: Hope in the Future. Nat Sci. 2012;10(11):87–95.
16. Gurarie D, McKenzie FE. Dynamics of immune response and drug resistance in malaria infection. Malar J [Internet]. 2006 Jan [cited 2014 Aug 19];5(1):86–101.
17. Mason DP, McKenzie FE. Blood-stage dynamics and clinical implications of mixed Plasmodium vivax-Plasmodium falciparum infections. Am J Trop Med Hyg [Internet]. 1999 Sep;61(3):367–74.
18. De phills LG, Radunskaya AE. A mathematical model of immune response to tumor invasion. Proceedings of the Second MIT Conference on Computational Fluid and Solid Mechanics. 2003. p. 1661–8.
19. Al-Olayan EM, Metwally DM, Alabooshkh F. Sero-Epidemiological Studies of Toxoplasmosis among Pregnant Women in Hail region Saudi Arabia. J Am Sci. 2013;9(12):619–25.
20. Kardar M, Leonid M. Statistical Physics in Biology [Internet]. MIT OpenCourseWare: Massachusetts Institute of Technology. 2011 [cited 2014 Aug 17]. Available from: http://ocw.mit.edu/courses/physics/8-592j-statistical-physics-in-biology-spring-2011.
21. Kosmrlj A, Kardar M, Chakraborty AK. Statistical Physics of T-Cell Development and Pathogen Specificity. Condens MATTER Phys. 2013;4(1):339–60.
22. Zhao Y, Sung M-H, Simon R. Artificial intelligence methods for predicting T-cell epitopes. Methods Mol Biol [Internet]. 2007 Jan;409:217–25.
23. Mei Y, Hontecillas R, Zhang X, Carbo A, Bassaganya-Riera J. Neural network models for classifying immune cell subsets. 2013 IEEE International Conference on Bioinformatics and Biomedicine [Internet]. Shanghai: Ieee; 2013. p. 5–11.
24. Younis A, Ibrahim M, Kabuka M, John N. An artificial immune-activated neural network applied to brain 3D MRI segmentation. J Digit Imaging [Internet]. 2008 Oct;21(Suppl 1):69–88.
25. Carter JH. The immune system as a model for pattern recognition and classification. J Am Med Informatics Assoc [Internet]. 2000;7(1):28–41.
26. Jiao L, Member S, Wang L. A Novel Genetic Algorithm Based on Immunity. IEEE Trans Syst Man Cybern. Ieee; 2000;30(5):552–61.
27. Torres A, Nieto JJ. Fuzzy logic in medicine and bioinformatics. J Biomed Biotechnol [Internet]. 2006 Jan [cited 2014 Aug 8];2006(2):1–7.
28. Xu D, Keller JM, Popescu M, Bondugula R. Introduction to fuzzy set theory and fuzzy Logic. Applications of fuzzy logic in bioinformatics. Imperial College Press; 2008. p. 19–20.
29. Afshari A, Rezaeenezhad H. Fuzzy Biology. International Conference on Biotechnology and Nanotechnology. 2009.
30. Mostafa K, Khalid H, Noura Y. Modeling the Adaptive Immune Response in HIV Infection Using a Cellular Automata. Int J Eng Comput Sci. 2014;3(3):5040–5.
31. Kougias CF, Schulte J. Simulating the immune response to the HIV-1 virus with cellular automata. J Stat Phys [Internet]. 1990 Jul;60(1-2):263–73.
32. Zorzenon dos Santos R, Coutinho S. Dynamics of HIV Infection: A Cellular Automata Approach. Phys Rev Lett [Internet]. 2001 Sep [cited 2014 Aug 26];87(16):ID:168102.
33. Precharattana M, Triampo W. Modeling dynamics of HIV infected cells using stochastic cellular automaton. Phys A Stat Mech its Appl [Internet]. 2014 Aug [cited 2014 Aug 26];407:303–11.
34. An G. In silico experiments of existing and hypothetical cytokine-directed clinical trials using agent-based modeling. Crit Care Med [Internet]. 2004 Oct;32(10):2050–60.
35. Baldazzi V, Castiglione F, Bernaschi M. An enhanced agent based model of the immune system response. Cell Immunol [Internet]. 2006 Dec [cited 2014 Aug 26];244(2):77–9.
36. Chiacchio F, Pennisi M, Russo G, Motta S, Pappalardo F. Agent-based modeling of the immune system: NetLogo, a promising framework. Biomed Res Int [Internet]. 2014 Jan;2014:ID: 907171.
37. Al-Enezi J., Abbod M., Alsharhan S. Artificial Immune Systems – Models , Algorithms And Applications. IJRRAS. 2010;3(2):118–31.

38. Sotiropoulos D, Athioudakis D, Tsihrintzis GA. Genetic-AIRS A hybrid classification method based on Genetic Algorithms and Artificial Immune Syste. The 5th International Conference on Information, Intelligence, Systems and Applications, IISA 2014. Chania, Crete, Greece; 2014. p. 1–5.
39. Ali M o, Koh SP, Chong KH, Yap DFW. Hybrid Artificial Immune System-Genetic Algorithm optimization based on mathematical test functions. 2010 IEEE Student Conference on Research and Development (SCOReD) [Internet]. Putrajaya: Ieee; 2010. p. 256–61.
40. Xu L, Chow M-Y. Distribution fault diagnosis using a hybrid algorithm of fuzzy classification and artificial immune systems. 2008 IEEE Power and Energy Society General Meeting - Conversion and Delivery of Electrical Energy in the 21st Century [Internet]. Pittsburgh, PA: Ieee; 2008. p. 1–6.
41. Timmis J, Andrews P, Hart E. On Artificial Immune Systems and Swarm Intelligence. Swarm Intell. 2010;4(4):247–73.
42. Javanmard R, Jeddisaravi K, Alinejad-Rokny H. Proposed a New Method for Rules Extraction Using Artificial Neura. J Bionanoscience. American Scientific Publishers; 2013;7(6):665–72.

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