LA SALUD Y LA CALIDAD DE VIDA

TÍTULO: SIMULACIÓN BASADA EN AGENTES DEL SISTEMA INMUNOLÓGICO EN UN MARCO CIBER FÍSICO

TITLE: AGENT-BASED SIMULATED CYBER-PHYSICAL FRAMEWORK OF THE IMMUNE SYSTEM

Armando de Jesús Plasencia Salgueiro[1], Dasha Fuentes Morales[2], Ileana Suárez Blanco[3]

1- Departamento de Control del Instituto de Cibernética, Matemática y Física, Cuba. Jefe de Departamento, Dr.C., Investigador Auxiliar, E-mail: armando@icimaf.cu
2- Centro Nacional de Animales de Laboratorio. CENPALAB, Cuba. Dr.C., Investigador Titular, E-mail: dasha.fuentes@cenpalab.cu
3 - Departamento de Control del Instituto de Cibernética, Matemática y Física, Cuba. Especialista para la Ciencia, E-mail: ileanasb@icimaf.cu

Resumen: El sistema inmunológico nos protege de virus y enfermedades y produce anticuerpos para matar patógenos. El SARS-CoV-2 es un patógeno emergente de importancia crítica para la salud pública internacional. El conocimiento acerca de la interacción entre las interacciones virus-receptor a escala molecular, la replicación viral unicelular, el transporte viral a escala intracelular y la propagación viral emergente a escala tisular aún es limitado. Los métodos de investigación tradicionales siempre se basan en escenarios de la vida real, pero a medida que el número de células crece exponencialmente y la complejidad de las interacciones, el proceso de investigación consume demasiado tiempo. Dada la complejidad del problema y la gran necesidad de un modelo procesable para guiar el descubrimiento y la optimización de la terapia, presentamos en este artículo la propuesta de un sistema inmunológico en un marco ciber físico mediante el modelado y la simulación basados en agentes con el empleo de NetLogo.

Palabras claves: Simulación basada en agentes; Sistema Inmunológico; Marco Ciber Físico.

Abstract: *The immune system protects us from viruses and diseases, and it produces antibodies to kill pathogens. SARS-CoV-2 is an emerging pathogen of critical significance to international public health. Knowledge of the interplay between molecular-scale virus-receptor interactions, single-cell viral replication, intracellular-scale viral transport, and emergent tissue-scale viral propagation is limited. Traditional research methods are always based on real-life scenarios, but as the number of cells grows exponentially, and the complexity of interactions, the research process is too time-consuming. Given the complexity of the problem and the acute need for an actionable model to guide therapy discovery and optimization, we introduce in this paper a Cyber-Physical Framework of the Immune System using Agent-Based Modeling and Simulation with NetLogo.*

Keywords: Agent-Based Simulation; Immune System; Cyber-Physical Framework

1. Introduction

The adaptive immunity of vertebrates is a complex adaptive system. The system constantly adapts to intruding pathogens by orchestrating the populations and responses of diverse immune cells, each type of which can have distinct roles. For example, effector cells (innate cells, T killer cells, a part of innate lymphoid cells, B cells, etc.) are responsible for executing intrinsic pathogen-specific responses, whereas T helper (Th) cells mainly control and bias the activities of these effector cells. The diversity and activity of immune cells are modulated over the organisms' lifetimes through inter-cellular communications via hundreds of chemical messengers and subsequent adaptive changes in the population sizes or phenotypic states. Even though young children are susceptible to infections, they may develop higher resistance to infections through modulation. As evidenced by the vaccination and immunization, such modulation may be achieved as an adaptive response to previous infections, which can be regarded as a type of learning from experience [1].

Despite the availability of the latest experimental technologies, revealing the principles of such complex learning dynamics is still intricate because the immunological dynamics are shaped and organized by the collective interactions of the entire immune cell

population, which prevents us from simply reducing the problem down to the mere existence of specific cell types or molecules. To comprehend a complex learning system, the importance of characterizing the system may be divided at three levels: the goal of the system (the computational level), the process and computation to realize the goal (the algorithmic level), and the physical implementation of the process (the implementation level).

The reductionist approach to science will continue to play an important role in scientific inquiry and progress. However, there is increasing interest across disciplines in studying the multiple interacting components of a given system simultaneously. This stems from the realization that it is often the complex interactions among these components that determine the outcome. While complexity in immunology is readily acknowledged, in many cases the ability to measure the contribution of each component is challenging. Even where this can be achieved, it can be difficult to interpret the results by looking at individual components independently. Mathematical and computational modeling can provide valuable information on the relative importance of different immunological components, how they are influenced by other components and how these relationships may vary across conditions. Models can provide informed hypotheses for experimental testing, generate a comprehensive map of the integrated performance of the immune system and identify potential targets for clinical manipulation of the immune response [2].

Viral respiratory infections, such as influenza, result in over 1 million deaths worldwide each year, mostly due to severe acute respiratory infection (SARI) brought on by influenza infection and/or secondary infections. To date, there are few therapeutic interventions able to affect the course of the disease once acquired, a deficit with stark consequences that were readily evident in the current COVID-19 pandemic [3].

A major component of the challenge presented by SARI and viral pneumonia is the fact that there is a relative paucity of effective anti-viral agents; post-infection therapy is primarily limited to supportive care, such as supplemental oxygen and ventilation, as the infection runs its course. In addition to the persistent difficulty of developing anti-viral

agents, the fact that disease severity can be attributed to the systemic response to infection presents another challenging aspect to the search for effective treatments. Characterizing the detailed underlying immune dynamics of these viral infections could facilitate the development of new therapies that modulate these dynamics to positively affect the course of the disease. While there is promising data to suggest that immune manipulation in COVID-19, be it through steroids or anti-mediator therapy, may be effective, there are also contradictory findings that other plausible anti-cytokine therapies may not be effective. This pattern of promise and disappointment has marked the historical failure of attempts to modulate the immune system during an acute infection, where nearly 50 years of research have provided no currently approved pharmacological agents able to affect the underlying biology of disordered systemic inflammation (i.e. sepsis). The heterogeneity of clinical populations, and the sepsis population, in particular, manifesting both among different individuals and within an individual's course of the disease, points to the need to develop precise, multi-modal therapeutic regimens personalized to individual disease trajectories with the aid of mathematical/computational modeling. The scope of interventions required to affect effective control of sepsis may be using a combination of mechanism-based multi-scale models (specifically agent-based models or ABMs) with evolutionary computing (genetic algorithms) [4] and model-based artificial intelligence [5]. The complex and heterogeneous nature of the clinical immune response is an example of a perspective that notes the limits of current biomedical experimental approaches for adequately exploring underlying functional relationships in human systems; the dynamic mathematical and computational model can provide an adjunct to traditional experimental and data analysis methods to increase this understanding.

In terms of viral respiratory infections, mathematical/computational modeling has been successfully used to examine multiple aspects of influenza: replicating flu dynamics by predicting viral load, response to antivirals, and immune dynamics, among other insights. These models, which primarily use deterministic differential equations, are well suited for characterizing system-level dynamics and showing how the changes in basic system characteristics, such as virulence, viral load, and host resistance, can affect disease outcomes. However, differential equation models are limited in their ability to represent the component-level stochasticity, behavioral heterogeneity, and spatial effects that

generate the variations in individual disease trajectories. With the development of technologies able to characterize cellular behavior at a much more detailed level, down to the behavior of single cells, effectively utilizing this knowledge calls for modeling approaches able to represent such granular information [3].

The organization of the article is the following, in the Background is related all theories fundamental for the development of a Cyber-Physical Framework of the Immune System using Agent-Based Modeling and Simulation, in Methods, the selected methodological conceptions for the development of the ABM, in Discussion, how implemented both in a practical case.

Background

Agent-based models (ABMs) (discussed next) are a good and flexible approach for explicitly modeling spatial features in immunology. ABMs allow for great potential detail and realism in the model. ABM represents a critical application of AI, providing a strong approach in analyzing and understanding emergent behavior of complex systems (that represent the majority when dealing with biological systems) [6]. ABM represents one of the best-suited techniques to model the behavior and dynamics of the immune system and falls within the definition of 'distributed artificial intelligence.' Their capability to reproduce unexpected emergent behaviors of complex systems may be beneficial for testing the acquisition of immunity elicited by candidate vaccines to challenge the acquired protection even in the presence of comorbidities (i.e., HIV), and to optimize dosage and timing.

ABMs are a powerful alternative to differential equation-based models. Although differential equation-based models excel in providing precise predictions for systems in which mechanisms are well understood and uncertainty is low, ABMs facilitate exploring the behavior space for complex stochastic systems in which mechanisms are poorly understood and uncertainty is high. ABMs can also be highly modularized [5], affording the ability to easily explore the space of new mechanisms and control strategies. ABMs have proved to be useful tools for biological applications, including immune system modeling.

Agent-based models (ABMs) are discrete event, rule-based, spatially explicit computational models that have been used for decades to explore and quantify aspects of dynamic and complex systems. ABMs treat systems as aggregates of multiple components ("agents") where system-level behavior arises from their interactions. The ready mapping of computational agents to biological entities (such as cells) and the ability of an ABM to represent physical processes like diffusion or force applications facilitate the use of ABMs to model various biological systems, such as the immune response. ABMs have been used to investigate acutely disordered systemic inflammation, otherwise known as sepsis. Sepsis is known to involve a hyper-inflammatory response, or 'cytokine storm', on top of systematic viral or bacterial infection, and as such prior ABMs of sepsis may be relevant in the search for effective treatments for SARS-CoV-2 infection, which is also theorized to have cytokine storm as a leading cause of mortality. In the previous models investigating sepsis [5] primarily represented bacterial infections and the innate immune system, the response to viral infections typically requires the adaptive immune response to completely clear an infection. As such is necessary to extend these original innate immune ABMs to include aspects of adaptive immunity.

2. Methods

2.1. Cellular Immunity Agent-Based Model.

Cellular Immunity Agent-Based Model (CIABM), is an extension of the previously validated Innate Immune Response ABM (IIRABM) from Cockrell and An [4]. The CIABM was implemented in C++; the code for the CIABM is available at https://github.com/An-Cockrell/CIABM_release. For the CIABM to represent viral infections, the following new agents were added: myeloid dendritic cells (mDCs), naive CD8+ T-cells (Naive T), cytotoxic CD8+ T cells (Cyto T), T Effector Memory cells (TEM), T Central Memory cells (TCM), and **T**erminally differentiated **E**ffector **M**emory T cells **R**e-expressing CD45**A** (TEMRA) [3].

The CIABM is a two-dimensional abstract representation of the human endothelial-blood-tissue interface. This abstraction is designed to model these interfaces during infection and does so by representing these interfaces as the unwrapped internal vascular surface of a 2D projection of the capillary vascular network. The closed surfaces can be represented as a torus, and these two-dimensional surfaces define the interaction space

simulated by the model. Organ interfaces are represented via several compartments which are separated by either fully distinct 2D surfaces or by tags within the model.

The CIABM is divided into two interfacing tori. The first torus represents the surface of the circulatory system with 3 segments in series each representing a particular functional compartment: the vascular capillary network of endothelial cells, the primary lymphatic bed, and the secondary lymphatic bed (see Figure 1). This torus interfaces with a second torus, representing tissue or epithelial cells, that maps onto the capillary/endothelial segment of the circulatory torus; circulating immune cells can migrate "through" the endothelial surface and into the tissue/epithelial torus.

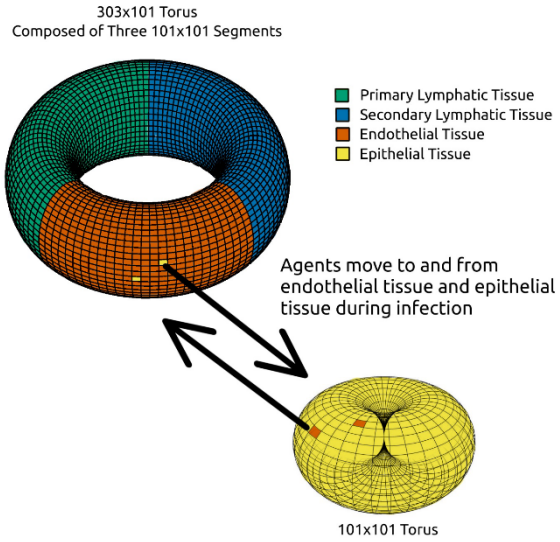

Figure 1. Diagram of tissue surfaces folded into tori and transfer of agents between those tori [3]

3. Discussion

Research on bacterial and viral dynamics has progressed greatly due to mathematical and computational modeling efforts, elucidating immune system mechanisms for pathogen clearance, and quantifying important parameters in the viral life cycle. Mathematical research of the effects of aging on the immune system, coinfections, and the use of vaccinations could improve the treatment of influenza. Complex mechanisms such as activation of different phenotypes of immune cells like macrophages should [6] be studied further, as well as the positive and negative feedback loops that, when dysregulated, can exacerbate inflammation or contribute to the reappearance of infection. ABMs, data,

systems-based approaches, and high-performance computing have been suggested for future modeling efficacy.

For the future development of Agent-based modeling for the simulation of the immunological was proposed the use, in the first order, of the software NetLogo [7]

NetLogo is a functional programming language with "turtles" that represent the agents and "patches" that represent a given point into the simulation space. Both of these may have multiple properties that can be defined by the user such as age, color, and position.

In practice, the fact that NetLogo uses a functional programming language means that many language statements are almost read as sentences, and this enables even unskilled and untrained users to understand and learn it through the examples.

NetLogo can be slower than other tools, but it is very easy to use, it supports the automatic drawing of agents in 2D or 3D, it gives the possibility to simply build user interfaces, and it is supplied with a lot of examples and HOWTOs, making it a suitable platform for beginner programmers. Moreover, NetLogo models can be effortlessly shared as Java applets, which is very important for the ensemble with another platform, and this means that such models can be run on almost all (if not all) computer platforms. It is also possible to perform better statistical analysis of results thanks to a plug-in that allows communication between NetLogo and R. NetLogo has been released under the GNU General Public License, meaning that it is free and open-source. NetLogo thus represents a good choice to realize multiagents models, networks, and complex dynamical systems. NetLogo exist actually in version 6.1.1. (http://ccl.northwestern.edu/netlogo/6.1.1)

4. Results

Was make and research work to find the best solution with NetLogo that models the immunity system. Between found platforms were NetLogo Rhemuatoid Arthritis, which demonstrates how T-regulatory (Treg) effectiveness correlates with inflammation in Rheumatoid Arthritis (RA) [8], Netlogo blood-borne inflammatory cell, that is a model of the interface between the endothelial cells that line capillaries [8], and blood-borne inflammatory cells (white blood cell species (WBCs)) and mediators, designed to simulate the processes of the innate inflammatory response (IIR) [8], and finally the Adaptive Immunity 1.0. that is a teaching model demonstrating adaptive immunity as

generated by clonal selection of antibodies in the immune system. Is all of these models were selected the last [9].

Using NetLogo for modeling adaptive immunity is shown in their Immune Public model (https://github.com/klemensj/Immune). Its intended use is as a classroom teaching model for demonstrating adaptive immunity as generated by clonal selection of antibodies in the immune system. The Immune.nlogo file contains background readings and a lesson plan for teaching with this model within the info tab. The LESSON_PLAN.md file contains [9] a self-contained lesson plan that overlaps with the info tab of the model file but is organized as a step-by-step guide to using the model in a classroom setting. A deployed HTML version of the model is located here in [9] and will eventually be relocated to the Netlogo modeling.

This model is designed to demonstrate the process by which adaptive immunity arises as a result of clonal selection. The model also includes functions for simulating the dynamics of vaccination and the loss of adaptive immunity provoked by measles infection. It is intended to be used as an active learning activity in a college or high-school biology course.

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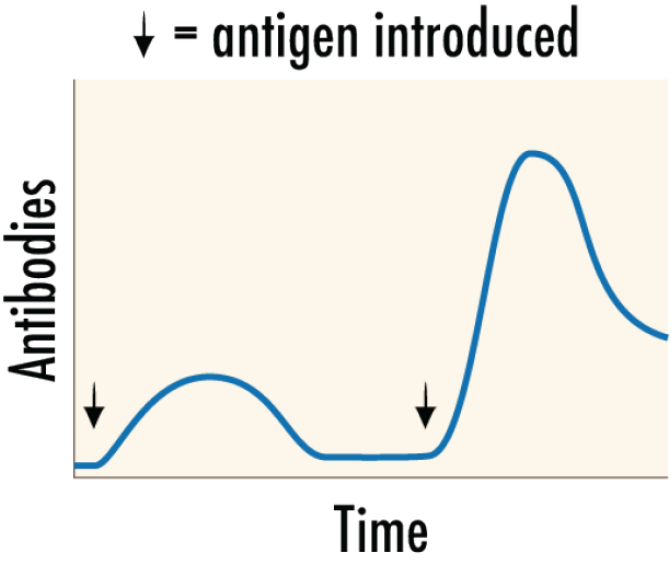

Figure 2. Is a static version of the Antibody Population graphs that will be generated dynamically during this simulation [9].

5. Conclusion

In summary, we introduce in this paper an Agent-Based Modeling and Simulation for Immunological system. The growing developments of artificial intelligence technologies made the cyber-physical systems an integrating component of most critical applications where the environment is diverse in nature. The goal of the selected Internet Framework in NetLogo is to build a biomimetic environment for a better comprehension of molecular and virus interactions.

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