IMMUNOREGULATION

Summer & Autumn 2023. Vol 6. No. 1

Review Paper

Modeling the Immune System Through Agent-based Modeling: A Mini-review

Yousef Jamali[1]

1. Biomathematics Laboratory, Department of Applied Mathematics, School of Mathematical Science, Tarbiat Modares University, Tehran, Iran.

Use your device to scan and read the article online

Citation Jamali Y. Modeling the Immune System Through Agent-based Modeling: A Mini-review. Immunoregulation. 2023; 6(1):3-12. http://dx.doi.org/10.32598/Immunoregulation.6.1.7

http://dx.doi.org/10.32598/Immunoregulation.6.1.7

Article info:
Received: 18 Mar 2023
Accepted: 25 May 2023
Available Online: 01 Jul 2023

Keywords:
Immune system modeling, Agent-based modeling, Multi-scale modeling, Complex system, Computational immunology

ABSTRACT

The immune system plays a critical role in protecting the human body against various pathogens and diseases. Understanding the complexity and dynamics of the immune system is essential for developing effective therapies and interventions. Agent-based modeling (ABM) has emerged as a powerful tool for simulating and studying the behavior of complex systems, including the immune system. This review examines the advantages, challenges, and applications of ABM in immune system modeling. ABM captures the complexity of immune cell behavior, spatial effects and stochasticity. It has been applied to study immune cell dynamics, immune responses to pathogens, immune cell migration, immunotherapies and immune system disorders. Challenges include parameterization, validation, and computational resource requirements. Future directions involve integrating multi-omics and single-cell data, incorporating machine learning, exploring multi-scale modeling, and developing user-friendly interfaces. ABM holds promise for enhancing our understanding of immune system dynamics and advancing diagnostics and treatments in immunology.

*** Corresponding Author:**
Yousef Jamalia, Associate Professor.
Address: *Biomathematics Laboratory, Department of Applied Mathematics, School of Mathematical Science, Tarbiat Modares University, Tehran, Iran.*
Phone: *+98 (21) 82884762*
E-mail: *y.jamali@gmail.com*

Introduction

The immune system is a remarkable defense mechanism that safeguards the human body against a wide range of pathogens, including viruses, bacteria and parasites [1]. Comprising an intricate network of cells, molecules, and organs, the immune system plays a pivotal role in maintaining health and combating diseases [2]. Understanding the complex dynamics and functionality of the immune system is crucial for developing effective therapies, interventions, and preventive strategies [3].

Modeling the immune system provides a means to gain insights into its intricate workings, uncover the underlying principles governing immune responses and predict the outcomes of various perturbations. Agent-based modeling (ABM) has emerged as a powerful computational tool for simulating and studying the behavior of complex systems, including the immune system [4-8]. ABM allows for the representation of individual entities, referred to as agents and their interactions, enabling the exploration of emergent behaviors that arise from the collective actions of these agents [4, 8-11].

This review provides a mini-review of ABM and its applications in modeling the immune system. By simulating the behavior of immune cells, signaling molecules, and other components, ABM can shed light on the intricate dynamics of immune responses and offer valuable insights into the development and progression of diseases [12]. ABM captures the heterogeneity observed within the immune cell population, accounting for variations in behavior, functional properties, and response to stimuli. Additionally, ABM enables the integration of spatial effects, simulating immune cell trafficking and interactions within tissues [13].

Below, this study explores the advantages and challenges of using ABM for immune system modeling, discusses key applications of ABM in this field and highlights potential future directions for research. By harnessing the power of ABM, we can enhance our understanding of the immune system's intricacies and pave the way for the development of more targeted and effective interventions in the battle against diseases.

Agent-based modeling (ABM)

ABM is a computational modeling technique that has gained popularity in various scientific disciplines for studying complex systems. ABM provides a flexible and intuitive framework for simulating the behavior and interactions of autonomous entities, known as agents, to understand emergent phenomena that arise from their collective actions. In the context of the immune system, ABM allows for the simulation and analysis of the behavior of individual immune cells, signaling molecules, and other components, providing insights into the dynamics of immune responses [4, 14].

ABM operates on the principle that the collective behavior of a system can be understood by modeling the interactions and behaviors of its agents. Each agent in an ABM represents an autonomous entity with its set of rules and characteristics. Agents can exhibit adaptive behavior, respond to stimuli and interact with other agents and their environment based on predefined rules. These interactions can be spatially explicit, allowing for the simulation of cell movement and localization within tissues [8, 9].

One of the key advantages of ABM is its ability to capture heterogeneity within the immune cell population. Immune cells exhibit diverse phenotypes, functional properties, and response patterns. ABM allows for the representation of this heterogeneity, enabling the modeling of individual immune cells with distinct characteristics and behaviors [14]. By incorporating this variation into the model, ABM can simulate a more realistic immune response, providing a deeper understanding of the system's dynamics.

Spatial effects play a crucial role in immune system function, as immune cells navigate through tissues to locate and eliminate pathogens or infected cells. ABM provides a spatially explicit framework for modeling immune cell trafficking and interactions within specific tissue compartments [14]. By considering the spatial organization of cells and their movement rules, ABM can simulate the migration of immune cells, their encounters with pathogens or antigen-presenting cells and the subsequent immune response.

Another important aspect of immune system modeling is the stochastic nature of immune cell behavior and immune responses. ABM allows for the incorporation of stochasticity, capturing the inherent randomness and variability observed in immune system dynamics [5, 11]. This stochasticity can arise from various factors, such as receptor-ligand interactions, cytokine production, and cell fate decisions. By integrating stochasticity into the model, ABM can generate probabilistic outcomes that more accurately reflect the variability observed in experimental data [11, 14].

ABM also provides a flexible framework for incorporating various biological components and processes into the model [15-17]. It can capture the interactions between immune cells and signaling molecules, such as cytokines, antibodies, and chemokines. ABM can simulate the impact of immunomodulatory factors, such as immune checkpoints or regulatory T cells, on immune responses. By integrating these components, ABM enables the exploration of complex regulatory mechanisms and the investigation of the effects of perturbations on the immune system.

Accordingly, ABM offers a powerful approach for modeling the immune system, allowing for the simulation and analysis of the behavior and interactions of individual immune cells, signaling molecules, and other components [15-19]. ABM's ability to capture heterogeneity, incorporate spatial effects, and integrate stochasticity provides valuable insights into immune system dynamics. By harnessing the potential of ABM, researchers can gain a deeper understanding of immune responses, infection dynamics and the development of immunotherapies. For instance, ABM has been used to simulate the interactions between tumor cells and the immune system in the melanoma model [18]. ABM has also been applied to study the emergent behaviors of immune system cells and their interactions [16]. Moreover, ABM has been used to develop an interactive reference framework for modeling a dynamic immune system [19]. Additionally, ABM has been used to compute the information transferred by viral proteins in the immune system, which can help identify the biological processes susceptible to dysregulation [17]. These studies demonstrate the potential of ABM in modeling the immune system and its applications in various areas of immunology research.

Advantages of agent-base modelling for modeling the immune system

ABM offers several advantages for modeling the immune system, providing a valuable tool for studying the complex behavior and dynamics of immune responses. The following section outlines the key advantages of ABM in the context of immune system modeling.

Representation of heterogeneity

The immune system consists of diverse cell types, each with distinct functions, phenotypes, and response patterns. ABM allows for the representation of this heterogeneity within the immune cell population. By modeling individual immune cells with their specific characteristics and behaviors, ABM can capture the variations observed in immune responses. This ability to account for heterogeneity enhances the realism and accuracy of the immune system model [20-22].

Simulation of spatial effects

Spatial organization and cell movement are critical factors in immune system function. Immune cells navigate through tissues, interacting with pathogens, antigen-presenting cells, and other immune cells. ABM provides a spatially explicit framework, allowing researchers to simulate immune cell trafficking and interactions within specific tissue compartments. By considering the spatial aspects of immune responses, ABM enables the investigation of cell migration, localization and the impact of tissue microenvironments on immune cell behavior [20, 21].

Incorporation of stochasticity

The behavior of immune cells and immune responses is inherently stochastic. Numerous factors, such as receptor-ligand interactions, cytokine production, and cell fate decisions, exhibit inherent randomness and variability. ABM can incorporate stochasticity into the model, capturing this natural variation in immune system dynamics. By integrating stochastic elements, ABM simulations generate probabilistic outcomes that closely resemble the variability observed in experimental data. This stochastic modeling approach provides insights into the probabilistic nature of immune responses and aids in understanding the range of potential outcomes [16, 18].

Flexible integration of biological components

The immune system comprises a complex network of interactions between immune cells, signaling molecules, and other components. ABM offers a flexible framework for integrating various biological components into the model. This includes representing the interactions between immune cells and cytokines, antibodies, chemokines, and other immune mediators. ABM can also incorporate immunomodulatory factors, such as immune checkpoints or regulatory T cells, allowing researchers to explore the effects of these factors on immune responses. The ability to integrate diverse biological components enhances the model's comprehensiveness and facilitates the investigation of complex regulatory mechanisms [15].

Exploration of intervention strategies

ABM can be instrumental in studying the effects of interventions and therapeutic strategies on the immune system. By incorporating immunotherapies, such as immune checkpoint inhibitors or adoptive T-cell therapies, into the model, ABM enables researchers to simulate the impact of these interventions on immune responses. This can aid in the design and optimization of therapeutic approaches, contributing to the development of personalized medicine and precision immunotherapy [23].

By harnessing these advantages, ABM facilitates a deeper understanding of immune responses, infection dynamics and the development of immunotherapies, contributing to advancements in the field of immunology.

Challenges of agent-based modelling in modeling the immune system

While ABM offers significant advantages for modeling the immune system, it also presents several challenges that researchers must address to ensure the accuracy and reliability of their simulations. The following section discusses the key challenges associated with ABM in the context of immune system modeling.

Parameterization and data availability

Developing an ABM for the immune system requires accurate parameterization of the model. Gathering experimental data to determine appropriate parameter values for the agents and their interactions can be challenging [23]. The availability of comprehensive and quantitative data on immune cell behavior, signaling pathways and immune responses is crucial for accurately representing the dynamics of the immune system [16]. Bridging the gap between experimental data and model parameters requires extensive research efforts and collaborations between experimentalists and computational modelers [15].

Validation against experimental data

Validating ABM simulations against experimental data is a critical step in ensuring the reliability and accuracy of the model. However, validating complex and dynamic biological processes, such as immune responses, can be challenging [16]. Experimental measurements often provide aggregate or incomplete information, making direct comparisons with ABM outputs difficult. Furthermore, the high dimensionality and stochastic nature of immune system dynamics pose additional challenges for validation. Developing robust validation frameworks and methodologies that capture the complexity and variability of immune responses is an ongoing research area [20, 23].

Computational resource requirements

ABM simulations of the immune system can involve large-scale and computationally demanding simulations [24]. Modeling the interactions and behaviors of numerous immune cells and their interactions with spatial and molecular components can require substantial computational resources [18, 25]. Running large-scale simulations on high-performance computing clusters or distributed computing platforms may be necessary to handle the computational load. However, access to these resources may not be readily available, limiting the scalability and scope of ABM studies [18].

Complexity and model complexity management

The immune system is a highly complex biological system with intricate interactions and regulatory mechanisms. Developing a comprehensive ABM that captures this complexity can be challenging [21]. Determining which components and interactions to include in the model and identifying the appropriate level of abstraction are critical decisions that impact the model's accuracy and computational feasibility. Balancing model complexity and computational tractability is an ongoing challenge in ABM for the immune system [21, 26].

Addressing these challenges requires interdisciplinary collaborations between immunologists, computational scientists, and mathematicians. These collaborations can foster the exchange of expertise and knowledge, enabling the refinement of ABM techniques, improving the parameterization and validation of models and enhancing the integration of experimental data. Additionally, advancements in data acquisition techniques, such as high-throughput technologies, can aid in obtaining quantitative data for parameterization and validation, addressing some of the challenges associated with ABM in immune system modeling.

Despite these challenges, ABM remains a powerful and promising approach for modeling the immune system. Overcoming these obstacles will contribute to the development of more accurate and comprehensive models, leading to a deeper understanding of immune responses, disease dynamics and the design of effective immunotherapies.

Applications of agent-based modelling in modeling the immune system

ABM has been extensively used in various aspects of immune system modeling, providing valuable insights into immune cell dynamics, immune response to pathogens, immune cell migration and the development of immunotherapies. Here are some examples of studies that have utilized ABM in the following areas.

Immune cell dynamics

ABM has been employed to simulate the behavior and interactions of immune cells, providing insights into their spatiotemporal dynamics. For example, a study [18] used ABM to investigate the migration of immune cells in lymphoid organs and the recruitment of immune cells to inflamed tissues. These studies have shed light on the mechanisms underlying cell movement, the role of chemokines and adhesion molecules, and the spatial distribution of immune cells within tissues.

Immune response to pathogens

ABM has been instrumental in simulating immune responses to various pathogens, including viruses, bacteria, and parasites. A review article [16] discussed how ABM can be used to investigate the dynamics of infection, the activation of immune cells and the subsequent immune response. These simulations have provided insights into the role of different immune cell subsets, the importance of spatial organization in pathogen control, and the impact of immune evasion strategies employed by pathogens.

Immune cell migration and homing

ABM has enabled the simulation of immune cell migration and homing, providing a deeper understanding of these processes. A study [15] used ABM to simulate the movement of immune cells toward specific chemokine gradients or extracellular matrix components. These simulations have revealed the importance of chemokine signaling, receptor-ligand interactions, and cell adhesion molecules in immune cell migration and homing.

Immunotherapies and cancer immunology

ABM has found applications in the field of cancer immunology and the study of immunotherapies. A review article [23] discussed how ABM can be used to investigate the dynamics of tumor growth, immune evasion mechanisms and the efficacy of immunotherapeutic interventions. These simulations have provided insights into the interplay between tumor cells and the immune system, aiding in the development of personalized and combination immunotherapies.

Immune system disorders

ABM has been applied to study immune system disorders, including autoimmune diseases and hypersensitivity reactions. A study [21] used ABM to simulate the dysregulation of immune responses, exploring the dynamics of these disorders and potential therapeutic interventions. These simulations have provided insights into the mechanisms underlying the development and progression of autoimmune diseases, such as rheumatoid arthritis and multiple sclerosis.

Host-pathogen interactions

ABM has been employed to model the interactions between host immune responses and pathogens, facilitating the study of host-pathogen dynamics. A study [20] used ABM to simulate the outcomes of these interactions, including pathogen clearance, chronic infections, or the establishment of host tolerance. These simulations have provided insights into the factors influencing host susceptibility to infection, the impact of immune evasion strategies employed by pathogens and the effectiveness of therapeutic interventions.

Therefore, ABM has been successfully utilized in various applications related to immune system modeling. By capturing the complexity of immune cell behavior, spatial dynamics, and interactions, ABM has contributed to our understanding of immune responses, infection dynamics, immunotherapies, and immune system disorders. The versatility and flexibility of ABM make it a valuable tool for studying the immune system and exploring the effects of interventions, providing a platform for the development of targeted and personalized immunotherapeutic strategies.

Examples of ABM in scientific research

In this section, we review several new studies that utilize ABM to address critical issues in these fields. By examining the methodologies and results of these studies, we provide insights into the diverse applications of ABM and its significance in advancing scientific understanding and informing evidence-based decision-making. Through these examples, we underscore the versatility and effectiveness of ABM in modeling various immune system phenomena, guiding policy interventions and facilitating interdisciplinary collaboration.

Example 1: Covasim model

Kerr et al. [27] introduced Covasim, an agent-based model specifically designed to simulate COVID-19 dynamics and evaluate the effectiveness of various interventions. The model's strength lies in its integration of country-specific demographic data, realistic transmission networks, age-specific disease outcomes, and intrahost viral dynamics. This comprehensive approach allows Covasim to accurately represent epidemic trends and guide policy decisions.

One notable aspect of Covasim is its versatility in supporting a wide range of interventions, including non-pharmaceutical measures, such as physical distancing, and pharmaceutical interventions like vaccination. By implementing these interventions within the model, researchers can simulate different scenarios and assess their impact on disease transmission and healthcare resource utilization.

The results of Covasim simulations have been instrumental in informing evidence-based policy decisions worldwide. Through collaborations with local health agencies and policymakers, Covasim has provided valuable insights into epidemic dynamics and the effectiveness of various intervention strategies. For example, by simulating different vaccination rollout strategies, Covasim has helped policymakers optimize vaccination campaigns to achieve maximum population immunity.

Example 2: ABM in cancer research

In their paper, West et al. [28] discuss the pivotal role of ABM in advancing integrative cancer research. ABM involves developing mathematical models that track individual agents, such as cancer cells, and their interactions within complex biological systems. By representing the intricate biological processes underlying cancer progression, therapeutic resistance, and metastasis, ABM offers a powerful framework for collaborative scientific inquiry.

One key advantage of ABM is its ability to incorporate diverse aspects of cancer biology, including cellular interactions, signaling pathways and the tumor microenvironment. By calibrating these models using experimental data, researchers can generate testable hypotheses and explore novel intervention strategies. For instance, ABM simulations can predict how changes in tumor microenvironmental factors influence cancer cell behavior and response to therapy, guiding the development of more effective treatment approaches.

The quantitative insights provided by ABM complement experimental research by facilitating parameterization, extrapolation of data, and the design of targeted experiments to validate model-generated predictions. This synergistic approach enhances our understanding of cancer biology across different scales and lays the foundation for more personalized and effective cancer therapies.

Example 3: Interferon beta (IFNβ) production dynamics

Gregg et al. [10] utilized ABM to investigate the dynamics of IFNβ production in response to viral infection within the cGAS pathway of the innate immune system. By representing individual cells and their heterogeneous and stochastic responses to DNA stimuli, their ABM framework offers a nuanced perspective on immune system dynamics.

Their simulations demonstrate that a heterogeneous cell population exhibits improved IFNβ production, leading to better protection against cell death and reduced viral load during infection. This highlights the significance of cellular diversity in mounting effective immune responses. Furthermore, their study identifies the optimal range of cellular stochasticity required for optimal immune potency and viral control, providing insights into the finely tuned regulation of immune responses.

The observed stochasticity and heterogeneity in IFNβ signaling suggest an evolved mechanism aimed at balancing immune potency while mitigating potential detrimental effects. By elucidating the roles of cellular variability and stochasticity in immune modulation, their findings contribute to a deeper understanding of immune system dynamics and have implications for the development of immunomodulatory therapies.

Example 4: ABM in tuberculosis research

Petrucciani et al. [29] introduced a novel application of ABM to analyze various in vitro tuberculosis (TB) infection models. By explicitly representing individual cells, including macrophages and Mycobacterium tuberculosis (Mtb) bacteria and their interactions within the in vitro system, their ABM framework captures the complex dynamics and heterogeneity observed in TB infection.

Their simulations successfully recapitulate key dynamics observed in multiple in vitro TB infection models, including Mtb growth kinetics, cytokine production, and interactions between cells and bacteria. Insights gleaned

from the ABM shed light on specific factors influencing infection dynamics, such as the initial Mtb inoculum and the presence of T cells. These detailed insights complement experimental observations and guide future research directions in TB pathogenesis and drug screening efforts.

Example 5: Immunity agent-based model

The immunity ABM (IABM), introduced by Gonzaga et al. [30], offers a comprehensive approach to understanding disease dynamics by integrating immune system dynamics, pathogen behavior and social interactions within epidemiological systems. By simulating interactions between the immune system, pathogens, and social factors, the IABM provides insights into how different variables impact disease transmission, progression, and control strategies.

For example, simulations using the IABM elucidate how variations in immune responses and viral load dynamics influence disease transmission rates, guiding the development of public health strategies for controlling infectious diseases. By incorporating the physiological characteristics of individuals and complex immune responses, the IABM provides a platform for exploring different scenarios and informing targeted interventions to mitigate disease spread.

Future directions

ABM has already made significant contributions to our understanding of the immune system. However, several exciting directions and opportunities lie ahead that can further enhance the application of ABM in immune system modeling. The following section discusses some future directions for ABM in this field.

Integration of multi-omics data

With the advancements in high-throughput technologies, the availability of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, has increased [14]. Integrating these multi-omics data into ABM can provide a more comprehensive and accurate representation of immune cell behavior and immune system dynamics. By incorporating this wealth of data, ABM can capture the intricate regulatory networks and molecular interactions within the immune system, facilitating the exploration of personalized immune responses and the identification of novel therapeutic targets.

Incorporation of single-cell data

Single-cell technologies have revolutionized our understanding of immune cell heterogeneity and functional diversity [23]. Integrating single-cell data, such as single-cell ribonucleic acid sequencing, into ABM can enable the modeling of individual immune cells with greater resolution and accuracy. This integration can capture the phenotypic and functional variations within immune cell populations and their impact on immune responses. ABM can also simulate the transitions between different cellular states, such as differentiation and activation, and explore the dynamics of cell fate decisions.

Integration with machine learning and artificial intelligence

ABM can benefit from the integration of machine learning and artificial intelligence techniques [31]. Machine learning algorithms can assist in parameter estimation, model calibration and validation, enabling more efficient and accurate model development. Additionally, machine learning algorithms can be used to extract patterns and insights from large-scale ABM simulations and experimental datasets, aiding in the identification of key regulatory mechanisms and the prediction of immune system behavior under different conditions.

Integration of multi-scale modeling approaches

The immune system operates at multiple scales, from molecular interactions to cellular behavior and tissue-level dynamics [23]. Integrating ABM with other modeling approaches, such as differential equation-based models or agent-based continuum models, can facilitate multi-scale modeling of immune system processes. These integrated models can capture both the microscale and macroscale aspects of immune responses, providing a more comprehensive understanding of immune system dynamics.

Visualization and user-friendly interfaces

Developing user-friendly interfaces and visualization tools for ABM can enhance the accessibility and usability of immune system models [23]. Interactive visualizations can aid researchers in exploring and interpreting model outputs, facilitating hypothesis generation and experimental design. Furthermore, user-friendly interfaces can encourage collaborations between immunologists and computational scientists, fostering knowledge exchange and advancing the field [16].

Experimental validation and model-driven experiments

The integration of ABM with experimental validation is crucial for the advancement of the field [4]. Experimental data can be used to refine and validate ABM simulations, ensuring their accuracy and reliability. Additionally, ABM can guide the design of experiments by suggesting key parameters and conditions to test in the laboratory. Model-driven experiments can provide insights into the mechanisms underlying immune system dynamics and generate new hypotheses for further investigation.

The future of ABM in immune system modeling holds tremendous potential. Integrating multi-omics data, single-cell data, and machine learning techniques, as well as exploring multi-scale modeling approaches, can further enhance the accuracy and predictive power of ABM simulations. Additionally, user-friendly interfaces, visualization tools and collaborations between experimentalists and computational modelers can accelerate the translation of ABM findings into experimental validation and contribute to a deeper understanding of immune system dynamics and the development of novel immunotherapies [32].

Conclusion

ABM offers a powerful and flexible approach for modeling the complex behavior and dynamics of the immune system. It provides a valuable tool for studying immune cell interactions, immune responses to pathogens, immune cell migration and the development of immunotherapies. ABM captures the heterogeneity of immune cells, incorporates spatial effects and integrates stochasticity, enhancing the realism and accuracy of the models. Furthermore, ABM allows for the exploration of intervention strategies and the investigation of immune system disorders.

While ABM has already made significant contributions to immune system modeling, some challenges need to be addressed, such as parameterization, validation and computational resource requirements. Collaborations between immunologists, computational scientists, and mathematicians are essential to overcome these challenges and refine ABM techniques.

Future directions for ABM in immune system modeling include the integration of multi-omics and single-cell data, the incorporation of machine learning and artificial intelligence, the integration of multi-scale modeling approaches, the development of user-friendly interfaces and visualization tools, and the close collaboration between computational modelers and experimentalists.

Overall, ABM holds great promise in advancing our understanding of immune system dynamics, infection dynamics, and the development of immunotherapies. By harnessing the advantages of ABM and addressing the associated challenges, we can unlock new insights into the complex workings of the immune system and pave the way for improved diagnostics, treatments and personalized medicine in the field of immunology.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Acknowledgements

The author would like to thank Tahereh Jamali for her thorough revision and insightful comments, which significantly improved the quality of this manuscript.

References

[1] Nicholson LB. The immune system. Essays in Biochemistry. 2016; 60(3):275-301. [DOI:10.1042/EBC20160017] [PMID] [PMCID]

[2] Janeway C, Travers P, Walport M, Shlomchik M. Immunobiology: The immune system in health and disease . New York: Garland Pub; 2001. [Link]

[3] Parham P. The immune system. New York: Garland Science, Taylor & Francis Group; 2015. [Link]

[4] Pappalardo F, Russo G, Reche PA. Toward computational modelling on immune system function. BMC Bioinformatics. 2020; 21(Suppl 17):546. [DOI:10.1186/s12859-020-03897-5] [PMID] [PMCID]

[5] Handel A, La Gruta NL, Thomas PG. Simulation modelling for immunologists. Nature Reviews. Immunology. 2020; 20(3):186-95. [DOI:10.1038/s41577-019-0235-3] [PMID]

[6] Celada F, Seiden PE. A computer model of cellular interactions in the immune system. Immunology Today. 1992; 13(2):56-62. [DOI:10.1016/0167-5699(92)90135-T] [PMID]

[7] An G. Agent-based computer simulation and sirs: Building a bridge between basic science and clinical trials. Shock. 2001; 16(4):266-73. [DOI:10.1097/00024382-200116040-00006] [PMID]

[8] Thorne BC, Bailey AM, Peirce SM. Combining experiments with multi-cell agent-based modeling to study biological tissue patterning. Briefings in Bioinformatics. 2007; 8(4):245-57. [DOI:10.1093/bib/bbm024] [PMID]

[9] Bonabeau E. Agent-based modeling: Methods and techniques for simulating human systems. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99(Suppl 3):7280-7. [DOI:10.1073/pnas.082080899] [PMID] [PMCID]

[10] Gregg RW, Shabnam F, Shoemaker JE. Agent-based modeling reveals benefits of heterogeneous and stochastic cell populations during cGAS-mediated IFNβ production. Bioinformatics. 2021; 37(10):1428-34. [DOI:10.1093/bioinformatics/btaa969] [PMID]

[11] Chiacchio F, Pennisi M, Russo G, Motta S, Pappalardo F. Agent-based modeling of the immune system: NetLogo, a promising framework. BioMed Research International. 2014; 2014:907171. [DOI:10.1155/2014/907171] [PMID] [PMCID]

[12] Bauer AL, Beauchemin CA, Perelson AS. Agent-based modeling of host-pathogen systems: The successes and challenges. Information Sciences. 2009; 179(10):1379-89. [DOI:10.1016/j.ins.2008.11.012] [PMID] [PMCID]

[13] Sabzian H, Shafia MA, Bonyadi Naeini A, Jandaghi G, Sheikh MJ. A review of agent-based modeling (ABM) concepts and some of its main applications in management science. Interdisciplinary Journal of Management Studies (Formerly known as Iranian Journal of Management Studies). 2018; 11(4):659-92. [DOI:10.22059/IJMS.2018.261178.673190]

[14] Verma M, Bassaganya-Riera J, Leber A, Tubau-Juni N, Hoops S, Abedi V, et al. High-resolution computational modeling of immune responses in the gut. Gigascience. 2019; 8(6):giz062. [DOI:10.1093/gigascience/giz062] [PMID] [PMCID]

[15] Amparore EG, Beccuti M, Castagno P, Franceschinis G, Pennisi M, Pernice S, et al. Multiformalism modeling and simulation of immune system mechanisms. Paper presented at: 2021 IEEE International Conference on Bioinformatics and Biomedicine; 12 December 2021; Houston, USA. [DOI:10.1109/BIBM52615.2021.9669796]

[16] Oryani M. Applying agent-based modeling to studying emergent behaviors of the immune system cells [MA Degree Project]. Stockholm; 2014. [Link]

[17] Sarkar S. Communication network model of the immune system identifies the impact of interactions with SARS-CoV-2 proteins. arXiv. 2022; [Unpublished]. [Link]

[18] Rahbar S, Shafiekhani S, Allahverdi A, Jamali A, Kheshtchin N, Ajami M, et al. Agent-based modeling of tumor and immune system interactions in combinational therapy with low-dose 5-fluorouracil and dendritic cell vaccine in melanoma B16F10. Iranian Journal of Allergy, Asthma, and Immunology. 2022; 21(2):151-66. [DOI:10.18502/ijaai.v21i2.9223] [PMID]

[19] Spitzer MH, Gherardini PF, Fragiadakis GK, Bhattacharya N, Yuan RT, Hotson AN, et al. IMMUNOLOGY. An interactive reference framework for modeling a dynamic immune system. Science. 2015; 349(6244):1259425. [DOI:10.1126/science.1259425] [PMID] [PMCID]

[20] Romao OC, de Souza LE, Ferreira RS, de Araujo Possi M, Paiva Oliveira A. Multiagent systems modeling using GPUs--A case study of the human immune system. Paper presented at: 2012 13th Symposium on Computer Systems; 19 October 2012; Petropolis, Brazil. [DOI:10.1109/WSCAD-SSC.2012.31]

[21] Özköse F, Yılmaz S, Yavuz M, Öztürk İ, Şenel MT, Bağcı BŞ, et al. A fractional modeling of tumor-immune system interaction related to Lung cancer with real data. The European Physical Journal Plus. 2022; 137:1-28. [DOI:10.1140/epjp/s13360-021-02254-6]

[22] Yu JS, Bagheri N. Agent-based models predict emergent behavior of heterogeneous cell populations in dynamic microenvironments. Frontiers in Bioengineering and Biotechnology. 2020; 8:249. [DOI:10.3389/fbioe.2020.00249] [PMID] [PMCID]

[23] Tong X, Chen J, Miao H, Li T, Zhang L. Development of an agent-based model (ABM) to simulate the immune system and integration of a regression method to estimate the key ABM parameters by fitting the experimental data. Plos One. 2015; 10(11):e0141295. [DOI:10.1371/journal.pone.0141295] [PMID] [PMCID]

[24] Montañola-Sales C, Casanovas-Garcia J, Onggo BS, Li Z. A user interface for large-scale demographic simulation. Paper presented at: 2014 IEEE 6th International Conference on Cloud Computing Technology and Science; 12 February 2015; Singapore; Singapore. [DOI:10.1109/CloudCom.2014.46]

[25] Kabiri Chimeh M, Heywood P, Pennisi M, Pappalardo F, Richmond P. Parallelisation strategies for agent based simulation of immune systems. BMC Bioinformatics. 2019; 20(Suppl 6):579. [DOI:10.1186/s12859-019-3181-y] [PMID] [PMCID]

[26] Husáková M. The usage of the agent modeling language for modeling complexity of the immune system. New Trends in Intelligent Information and Database Systems; 2015; 598:323-32. [DOI:10.1007/978-3-319-16211-9_33]

[27] Kerr CC, Stuart RM, Mistry D, Abeysuriya RG, Rosenfeld K, Hart GR, et al. Covasim: An agent-based model of COVID-19 dynamics and interventions. Plos Computational Biology. 2021; 17(7):e1009149. [DOI:10.1371/journal.pcbi.1009149] [PMID] [PMCID]

[28] West J, Robertson-Tessi M, Anderson ARA. Agent-based methods facilitate integrative science in cancer. Trends in Cell Biology. 2023; 33(4):300-311. [DOI:10.1016/j.tcb.2022.10.006] [PMID] [PMCID]

[29] Petrucciani A, Hoerter A, Kotze L, Du Plessis N, Pienaar E. In silico agent-based modeling approach to characterize multiple in vitro tuberculosis infection models. Plos One. 2024; 19(3):e0299107. [DOI:10.1371/journal.pone.0299107] [PMID] [PMCID]

[30] Gonzaga M, de Oliveira M, Atman A. Immunity agent-based model (IABM) for epidemiological systems. Chaos, Solitons & Fractals. 2023; 176:114108. [DOI:10.1016/j.chaos.2023.114108]

[31] Pennisi M. Multi-scale agent-based models in immunology. A short review. CEUR Workshop Proceedings; 2021. [Link]

[32] Montealegre N, Rammig FJ, editors. Agent-based modeling and simulation of artificial immune systems. Paper presented at: 2012 IEEE 15th International Symposium on Object/Component/Service-Oriented Real-Time Distributed Computing Workshops. 11 April 2012; Washington, United States. [DOI:10.1109/ISORCW.2012.43]