Multi-scale agent-based models in immunology. A short review

Marzio Pennisi[1]

[1]Computer Science Institute, Dipartimento di Scienze e Innovazione Tecnologica, Università degli Studi del Piemonte Orientale "Amedeo Avogadro", Viale T. Michel 11, 15121 Alessandria, Italy

Abstract

In the drug discovery pipeline, the lack of multi-scale modeling approaches able of taking into account the observation of an immunological phenomenon from the molecular to the tissue/organism levels represents a big issue. In this scenario, agent-based models can partially make up for this issue allowing them to accurately describe all the interactions that occur at the cellular level and showing the phenomenon at the tissue/organ level thanks to their capability of producing emergent global behaviors. This short review will present some of these agent-based approaches developed for the simulation of diseases and the relative immune system response that also try to explicitly include molecular-level aspects such as internal cell behavior or receptor binding, for a more real and complete representation of the immunological phenomena under examination.

Keywords

immune system, Agent-based models, simulation, computational biology, multi-scale model, systems biology

1. Introduction

One of the biggest unsolved issues in the drug discovery pipeline is given by the lack of multi-scale modeling approaches able of taking into account the observation of an immunological phenomenon from different points of view, i.e. from the molecular to the tissue/organism level.

This aspect is particularly critical for the development of new vaccines, where researchers make use of bioinformatics approaches only on a limited number of aspects of the phenomenon (as existing tools are usually designed to tackle specific questions, such as immunogenicity and so on) to detect possible candidate drugs or to design possible vaccines. Such compounds have to be then tested at later stages to verify their safety and efficacy. So, further studies possibly carried on expensive in vitro/in vivo setups are then needed, but the results are not always capable of supporting the previous findings.

For example, it is well known that developing a universal influenza/A has been challenging [1], and various attempts have fallen short during in vitro and/or in vivo verification.

To this end, simulation approaches that can be used to substitute in vivo/in vitro experiments may reduce both the time-to-market and the development costs. These approaches, referred to as in-silico approaches, must be capable of reproducing the target disease and the involved entities first; then the possibly relevant immune system entities (cells and molecules) and their behavior in absence of any external perturbation (i.e., the treatment); finally the expected direct (against the disease) and/or indirect (i.e., to instruct the immune system) effects of the candidate treatment under investigation.

There are at least 3 possible different levels for such in-silico approaches that it is worth considering. These levels, that refer to different levels of magnification of the natural phenomenon under study, are:

- The molecular-level scale, in which interactions at the molecular level are taken into account
- the cellular-level scale that mostly considers cell-cell (and eventually cell-molecule) interactions
- The tissue/organ scale, in which the system is seen as a whole.

For the molecular-level scale, we can consider both intracellular and extracellular molecular processes. For what regards the intracellular point of view, we can have gene co-expression networks, protein-protein interaction networks, metabolic and signal transduction pathways that drive the behavior of cells. Such processes are usually represented by systems of differential equations and modeled using specific software such as COPASI [2] or mathematical formalisms such as Petri nets [3, 4].

At the extracellular level, we can consider all the processes involved in recognizing non-self antigens, such as their binding to major histocompatibility complex (MHC) class molecules in antigen-presenting cells, and B and T cell epitope recognition processes. Many recent methodologies for solving these tasks are nowadays based on structural and machine learning algorithms [5, 6].

Workshop on Multi-Omics Data Integration for Modelling Biological Systems, in conjunction with ACM CIKM 2021

marzio.pennisi@uniupo.it (M. Pennisi)

0000-0003-0231-7653 (M. Pennisi)

For the cellular level scale, in which cell-cell interactions hold, the use of agent-based models (ABMs) represents the most natural choice. ABMs allow to accurately describe all the interactions that occur at the cellular level naturally and simply, making also easier the communication between the modeler and the domain expert (i.e., the immunologist, biologist, pharmaceutical scientist, or medical doctor). Furthermore, their capability of producing emergent global behaviors at a higher level as the sum of the actions of their agents makes ABMs an exceptional tool to describe immunological phenomena at the cellular level, obtaining a representation at the tissue/organ level. In this sense, ABMs can be already considered multi-scale models in immunology and can be used in substitution of continuous approaches based on ODE/PDE systems that are instead frequently used for tissue scale representation, provided that sufficient computational resources are available [7].

Many agent models have been developed for reproducing the immune system behavior, however few of them try to explicitly include also molecular-level aspects. These models are either developed to tackle specific pathologies, or presented as general-purpose platforms and then specialized each time on given diseases. The goal of this short review is to present some of these models and approaches. To this end, we will first recall some crucial aspects of agent-based models for the immune system and how to build them, then we summarize some of the models and approaches based on ABMs that include molecular aspects (either intracellular o extracellular) in these cellular to tissue level approaches.

2. Building immune system enabled ABMs

Although the development of an ABM does not strictly require the same mathematical knowledge as for differential equations-based models, it is mandatory to possess minimal knowledge of computer science and some programming skills.

We would like to distinguish between two different aspects in the implementation of an ABM of IS and that may influence the required degree of computer science knowledge. The first aspect is the modeling aspect, which regards the implementation of the biological knowledge, including the description of which entities are involved, and how they act and interact. The second aspect is instead the simulation aspect, which takes instead care of the underlying infrastructure that executes the simulation, performs the movement and the evolution of the entities, manages memory allocation for the entities and the physical space, and governs all the accessory activities like the storage and visualization of the results.

To build from scratch an ABM, a substantial effort is needed since both the modeling and the simulation aspects must be considered and developed. This entitles, besides the longer developing times, the risk to have implementation errors that may be present not only in the modeling part (i.e., biological conceptual errors), but also in the simulation part (i.e., programming bugs). However, there are some advantages to implement an ABM from scratch. Since both simulation and modeling parts are in general partially merged, it is possible to include and describe in depth any biological aspect without any limitation, having as a result also better simulation speeds.

It is of course possible to implement an ABM by using some of the general frameworks devoted to the simulation of ABMs. In such cases, less programming knowledge is required, as such frameworks typically require specific ABM-oriented programming languages that are easier to understand and learn. The use of a pre-built ABM simulation framework allows focusing on the modeling part of the problem, as the underlying simulator part is provided by the framework itself. This speeds up the development of the model and lowers the risk of programming bugs and errors. On the other hand, such models are usually slower than custom models, and the possibility of defining custom agent behaviors, properties and functions, as well as the capacity to allow large-scale simulations, are strictly connected to the flexibility and capabilities of the chosen simulation platform. Some ABM frameworks have been used quite fruitfully in the modeling of IS. Among these we recall Netlogo [8], Swarm[9], Repast[10], Flame and FlameGPU[11].

3. Multi-scale ABMs of the immune system

While there is a broad historical literature about differential equations (DE) based approaches in immunology, ABM literature on this topic is far more recent, particularly when we concentrate on multi-scale ABM approaches that include molecular aspects. Here we review the most relevant ABM models and simulators that deal, to some extent, with the immune system behavior, privileging the most recent approaches, the approaches that are still under development, or those that have given birth to descending projects that are still alive.

One of the first ABM approaches for the modeling of the immune system function is represented by IMMSIM, a computer model presented by Franco Celada and Philip Seiden in the early 90' [12, 13]. In their work, the authors present what they call a "generalized cellular automaton" (the term agent-based model was not so common at that time), which was able to mimic both the cognate recognition and response of the immune system system to general pathogens. In this approach, the space representation is discretized by means of a hexagonal grid

called lattice. At each time-step, all the entities in the same lattice point can act and interact with each other according to pre-defined rules that drive the entities' behavior. Entities may also diffuse from a lattice point to another in the neighborhood. Agents are used to either represent cellular immune system entities of the innate and adaptive response, or pathogens such as viruses and bacteria. Moreover, this approach includes many molecular entities such as chemokines and cytokines, which are represented by their concentration per lattice-point. The model does not explicitly include extracellular receptors but tries instead to mimic receptor diversity by using binary strings, and hamming distance between strings to measure receptor affinity. More specifically, a piece-wise function calculates an interaction probability according to the hamming distance of two strings representing the cells' receptors. Under a given threshold of mismatching bits, the function will return no affinity, so the entities will have zero probability to interact. Over such a threshold, the function will return a probability that is proportional to the number of mismatching bits. While this approach may appear quite simplistic, it allows to execute many cell-cell and cell-molecules interactions rapidly, and its adoption indeed allows to reproduce some important hallmarks of the adaptive immune system response: specificity, memory and discrimination between self and non-self. From their effort many other models originated and, while some of them were lost on the road, others are still actively developed and represent the state-of-the-art immune system models at the cellular scale.

Among these models we recall two frameworks named UISS and C-IMMSIM, defined as general-purpose immune system simulators and specialized each time for the disease under investigation. These two frameworks are written in C, and include both the simulation and the modeling aspects into one single code.

UISS has been successfully used for optimizing, in silico, the vaccination schedule of a prophylactic vaccine named Triplex against mammary carcinoma [14, 15]. Then it has been used, under the name Metastasim, with a similar goal (i.e., optimizing an administration schedule) but in a different experimental setup, in which the same vaccine was used as a therapeutic agent against lung metastases derived by mammary carcinoma [16]. Then, UISS has been recently used inside the H2020 Project STriTuVaD to predict the effects of combined immunization strategies against tuberculosis [17], and also specialized to suggest the best therapeutic options in patients with Multiple Sclerosis [18]. Finally, UISS-COVID was used for predicting SARS-CoV-2 dynamics and related immune system host response [19]. C-IMMSIM, used instead for simulating HIV alone or under HAART therapy administration [20] and Epstein-Barr virus [21].

While being considered polyclonal models, in the sense that such models may include various immune system cells and pathogens with different receptors, these approaches lack the possibility to include real antigenic sequences, and this limits their applicability to specific cases. Furthermore, cells' internal dynamics are based on rules derived from immunology rather than driven by intracellular pathways. So it is not possible to predict cell behaviors outside the actions established by such predefined rules.

However, when the binding-affinity is known a priori it is possible to translate it into a pair of binary strings, one representing a given antigenic sequence of the entity that will challenge the immune system (i.e., a pathogen, a drug or a vaccine), and the other one representing a specific receptor of the IS family that will be challenged, in such a way that their interaction will entitle an interaction probability that is proportional to the in-vivo binding affinity.

This approach has been used in [22], where the authors predicted the efficacy of some candidate citrus-derived adjuvants (to be used instead of Aluminum salts) for influenza-A vaccines. The methodology applied some virtual-screening techniques to calculate the interaction scores of the candidate adjuvants and aluminum salts (used as a reference value). Then, such scores were used to build-up a translation function that converts a given score into a required number of mismatching bits to reproduce the adjuvants capability to stimulate the immune system. The in-silico experiment predicted Beta-Sitosterol as the best potential candidate, and this result was then confirmed by in vitro experiments.

Another UISS extension to reproduce avascular tumor growth and the involved immune system response was presented in [23]. A lattice Boltzmann (LB) method (a computational fluid dynamics technique that avoids solving the Navier–Stokes equations directly by using instead a discrete lattice mesh [24]), was used for nutrient distribution and propagation, while the ABM infrastructure was used to describe the immune system reaction against the tumor at the cellular level.

Various studies extended the C-IMMSIM framework by including more features at the molecular level for better describing either intracellular or extracellular behaviors. A first extension (called VaccImm) was presented to reproduce in-silico peptide vaccination in cancer therapy. The ABM infrastructure, that was already capable of reproducing the involved cells (immune system and cancer) behavior as well as molecules (antibodies, antigens and semiochemicals), was extended by substituting part of the machinery based on binary strings for receptors' interactions with real amino acid sequences to represent molecular binding sites of immune cells [25].

Another C-IMMSIM version deals instead with intracellular aspects. Specifically, C-IMMSIM was extended to include, at the intracellular level, a Boolean network

with the aim to describe the activation dynamics of a gene regulatory network driving Th1 and Th2 polarization [26]. The model has been further extended [27] to also include T helper cell polarization towards Th17 and Treg, with a boolean network composed by 40 nodes.

A similar approach was used by Beyer and Meyer-Hermann[28], with an ABM that includes a set of ODEs for chemokine receptor internalization. The ABM was specifically developed to study the formation of cell aggregates and consequent tissue instability in rheumatoid arthritis.

Dutta-Moscato et al. [29] developed a multiscale agent-based in silico Model of Liver Fibrosis Progression. The liver fibrosis ABM (LFABM) includes five types of agents (parenchymal cells, inflammatory cells, collagen-producing cells, and structural elements that define lobules). Agents can release various factors, such as tumor necrosis factor alpha, transforming growth factor beta 1, high mobility group box protein 1, that can influence the agent behavior. LFABM made use of literature-derived rules to the inflammation and fibrosis in a portion of a chemically injured liver.

Using Netlogo as a starting point [8], Gary An developed the epithelial barrier agent-based model (EBABM), an ABM that includes the enterocytes of the gut and their response to inflammatory mediators such as nitric oxide (NO) and to pro-inflammatory cytokines, including tumor necrosis factor, interleukin-1 and interferon-gamma. To this end, tight junction protein metabolism and pro-inflammatory signaling cascades were included in the model as considered responsible for gut epithelial barrier function [30].

ENISI-MSM is instead a multi-scale platform that makes use of an agent-based framework for cell-cell interaction and movement based on Repast. This framework is connected to a module that uses the COPASI [2] ODE/SDE (ordinary/stochastic differential equation) solver for representing intracellular pathways, and an integrated PDE (partial differential equation) simulator for molecule gradient and diffusion. The model has been used to obtain the immune response in the gut at a high resolution [31] thanks to the use of the REPAST-HPC library [32].

4. Conclusions

The development of multi-scale ABMs of the immune system may help to address various immunological questions on how diseases happen and evolve, on what is the role of the immune system in developing and contrasting such diseases, and on if and how candidate treatments act. However, there are still some major issues that need to be solved. Models from the molecular scale are commonly developed exploiting methodologies that are usually far from the concepts and approaches for ABMs. To this end, it would be important to establish a common language for the communication of the models at different scales. On the other hand, the molecular and cellular scales can be in general developed independently, and put together at later times, making easier the development of these multi-scale hybrid models.

Another problem with multi-scale modeling in immunology is correlated to the different spatiotemporal dimensions of the processes that happen at different levels. Usually, the phenomena at a lower scale have reduced dimensions, but they happen and are repeated many times during one single instance of the phenomena at a higher level. For example, the development of Tuberculosis may require years, but the involved cells' interactions may happen billions of times in that period. However, simulation of these processes usually does not require less time as the modeling scale goes down, and this makes difficult the development of comprehensive models. In this case, it would be (in principle) possible to make use of pre-calculated results using look-up tables for a given subset of results referring to the molecular-level models and use interpolation (if the low-level solutions are smooth enough) or lazy-evaluation for obtaining, when needed, the missing points.

Furthermore, the accuracy of the low-level molecular models may negatively influence the results of the model at a higher scale. For example, the accuracy of B cell epitope prediction tools is generally rather poor, having AUC values ranging from 0.6 to 0.7 [6]. In such a case, it is important to execute extensive robustness and sensitivity analyses on the multi-scale models to estimate how and in what measure these inaccuracies influence the global behavior of the model.

Finally, to reach a real tissue/organ scale, beyond a more accurate anatomical description that should be taken into account for the involved organs (such as lymph-nodes), it is important to have the capability of reproducing the behavior of (at least) millions of agents, and it is well known that this aspect represents the Achille's heel of any ABM approach. In this case specific HPC [32] and/or GPU [11] enabled ABM infrastructures may come to the aid to mitigate this issue.

In conclusion, despite the existing challenges and issues, we expect in the coming years that the contribution of these multi-scale models will become even more important and substantial, helping all the researchers from the immunology and life-science fields in general in better understanding disease mechanisms and thus in developing faster more effective treatments.

References

[1] A. Madsen, R. J. Cox, Prospects and Challenges in the Development of Universal Influenza Vaccines, Vaccines (Basel) 8 (2020).

[2] S. Hoops, S. Sahle, R. Gauges, C. Lee, J. Pahle, N. Simus, M. Singhal, L. Xu, P. Mendes, U. Kummer, COPASI–a COmplex PAthway SImulator, Bioinformatics 22 (2006) 3067–3074. URL: https://doi.org/10.1093/bioinformatics/btl485. doi:10.1093/bioinformatics/btl485.

[3] A. Sackmann, M. Heiner, I. Koch, Application of petri net based analysis techniques to signal transduction pathways, BMC Bioinformatics 7 (2006). URL: https://doi.org/10.1186/1471-2105-7-482. doi:10.1186/1471-2105-7-482.

[4] P. Simone, F. Laura, B. Gianfranco, M. Luciano, S. Giulia, T. Niccoló, L. Pietro, M. Ivan, C. Francesca, B. Marco, Integrating petri nets and flux balance methods in computational biology models: a methodological and computational practice, Fundamenta Informaticae 171 (2019) 367–392. URL: https://doi.org/10.3233/FI-2020-1888. doi:10.3233/FI-2020-1888.

[5] D. V. Desai, U. Kulkarni-Kale, T-cell epitope prediction methods: An overview, in: Methods in Molecular Biology, Springer New York, 2014, pp. 333–364. URL: https://doi.org/10.1007/978-1-4939-1115-8_19. doi:10.1007/978-1-4939-1115-8_19.

[6] W. Fleri, S. Paul, S. K. Dhanda, S. Mahajan, X. Xu, B. Peters, A. Sette, The immune epitope database and analysis resource in epitope discovery and synthetic vaccine design, Frontiers in Immunology 8 (2017). URL: https://doi.org/10.3389/fimmu.2017.00278. doi:10.3389/fimmu.2017.00278.

[7] C. Bianca, M. Pennisi, Immune System Modelling by Top-Down and Bottom-Up Approaches, International Mathematical Forum 7 (2012) 109–128.

[8] F. Chiacchio, M. Pennisi, G. Russo, S. Motta, F. Pappalardo, Agent-based modeling of the immune system: NetLogo, a promising framework, Biomed Res. Int. 2014 (2014). doi:10.1155/2014/907171.

[9] M. Askenazi, R. Burkhart, C. Langton, N. Minar, The Swarm Simulation System : A Toolkit for Building Multi-agent Simulations, Simulation (1996) 1–11. URL: http://cobweb.cs.uga.edu/{~}maria/pads/papers/swarm-MinarEtAl96.pdf.

[10] M. J. North, N. T. Collier, J. Ozik, E. R. Tatara, C. M. Macal, M. Bragen, P. Sydelko, Complex adaptive systems modeling with Repast Simphony, Complex Adapt. Syst. Model. 1 (2013) 3. URL: http://casmodeling.springeropen.com/articles/10.1186/2194-3206-1-3. doi:10.1186/2194-3206-1-3.

[11] P. Richmond, M. K. Chimeh, Flame GPU: Complex system simulation framework, Proc. - 2017 Int. Conf. High Perform. Comput. Simulation, HPCS 2017 (2017) 11–17. doi:10.1109/HPCS.2017.12.

[12] F. Celada, P. E. Seiden, A computer model of cellular interactions in the immune system., Immunol. Today 13 (1992) 56–62. URL: http://www.sciencedirect.com/science/article/pii/016756999290135T. doi:10.1016/0167-5699(92)90135-T.

[13] P. E. Seiden, F. Celada, A model for simulating cognate recognition and response in the immune system, J. Theor. Biol. 158 (1992) 329–357. doi:10.1016/S0022-5193(05)80737-4.

[14] M. Pennisi, F. Pappalardo, P. Zhang, S. Motta, Searching of Optimal Vaccination Schedules, IEEE Engineering In Medicine and Biology Magazine (2009) 67–72.

[15] M. Pennisi, G. Russo, F. Pappalardo, Combining Parallel Genetic Algorithms and Machine Learning to Improve the Research of Optimal Vaccination Protocols, in: Proceedings - 26th Euromicro International Conference on Parallel, Distributed, and Network-Based Processing, PDP 2018, 2018, pp. 399–405. doi:10.1109/PDP2018.2018.00070.

[16] M. Pennisi, F. Pappalardo, A. Palladini, G. Nicoletti, P. Nanni, P.-L. Lollini, S. Motta, Modeling the competition between lung metastases and the immune system using agents., BMC bioinformatics 11 Suppl 7 (2010) S13. URL: http://www.biomedcentral.com/1471-2105/11/S7/S13. doi:10.1186/1471-2105-11-S7-S13.

[17] M. Pennisi, G. Russo, G. Sgroi, A. Bonaccorso, G. Parasiliti Palumbo, E. Fichera, D. Mitra, K. Walker, P.-J. Cardona, M. Amat, M. Viceconti, F. Pappalardo, Predicting the artificial immunity induced by RUTI® vaccine against tuberculosis using universal immune system simulator (UISS), BMC Bioinformatics 20 (2019). doi:10.1186/s12859-019-3045-5.

[18] F. Pappalardo, G. Russo, M. Pennisi, G. A. Parasiliti Palumbo, G. Sgroi, S. Motta, D. Maimone, The Potential of Computational Modeling to Predict Disease Course and Treatment Response in Patients with Relapsing Multiple Sclerosis, Cells 9 (2020).

[19] G. Russo, M. Pennisi, E. Fichera, S. Motta, G. Raciti, M. Viceconti, F. Pappalardo, In silico trial to test COVID-19 candidate vaccines: a case study with UISS platform, BMC Bioinformatics 21 (2020). URL: https://doi.org/10.1186/s12859-020-03872-0. doi:10.1186/s12859-020-03872-0.

[20] E. Mancini, R. Quax, A. D. Luca, S. Fidler, W. Stohr, P. M. A. Sloot, A study on the dynamics of temporary HIV treatment to assess the controversial outcomes of clinical trials: An in-silico approach, PLOS ONE 13 (2018) e0200892. URL: https://doi.org/10.1371/journal.pone.0200892. doi:10.1371/journal.

pone.0200892.

[21] F. Castiglione, K. Duca, A. Jarrah, R. Laubenbacher, D. Hochberg, D. Thorley-Lawson, Simulating epstein-barr virus infection with c-ImmSim, Bioinformatics 23 (2007) 1371–1377. URL: https://doi.org/10.1093/bioinformatics/btm044. doi:10.1093/bioinformatics/btm044.

[22] F. Pappalardo, E. Fichera, N. Paparone, A. Lombardo, M. Pennisi, G. Russo, M. Leotta, F. Pappalardo, A. Pedretti, F. De Fiore, S. Motta, A computational model to predict the immune system activation by citrus-derived vaccine adjuvants, Bioinformatics 32 (2016) 2672–2680. URL: http://bioinformatics.oxfordjournals.org/content/early/2016/05/08/bioinformatics.btw293.abstract%5Cnhttp://bioinformatics.oxfordjournals.org/lookup/doi/10.1093/bioinformatics/btw293. doi:10.1093/bioinformatics/btw293.

[23] D. Alemani, F. Pappalardo, M. Pennisi, S. Motta, V. Brusic, Combining cellular automata and lattice Boltzmann method to model multiscale avascular tumor growth coupled with nutrient diffusion and immune competition, Journal of Immunological Methods 376 (2012) 55–68. URL: http://linkinghub.elsevier.com/retrieve/pii/S0022175911003152. doi:10.1016/j.jim.2011.11.009.

[24] S. Chen, G. D. Doolen, LATTICE BOLTZMANN METHOD FOR FLUID FLOWS, Annual Review of Fluid Mechanics 30 (1998) 329–364. URL: https://doi.org/10.1146/annurev.fluid.30.1.329. doi:10.1146/annurev.fluid.30.1.329.

[25] J. von Eichborn, A. L. Woelke, F. Castiglione, R. Preissner, VaccImm: simulating peptide vaccination in cancer therapy, BMC Bioinformatics 14 (2013). URL: https://doi.org/10.1186/1471-2105-14-127. doi:10.1186/1471-2105-14-127.

[26] D. Santoni, M. Pedicini, F. Castiglione, Implementation of a regulatory gene network to simulate the TH1/2 differentiation in an agent-based model of hypersensitivity reactions, Bioinformatics 24 (2008) 1374–1380. URL: https://doi.org/10.1093/bioinformatics/btn135. doi:10.1093/bioinformatics/btn135.

[27] P. Tieri, V. Prana, T. Colombo, D. Santoni, F. Castiglione, Multi-scale simulation of t helper lymphocyte differentiation, in: Advances in Bioinformatics and Computational Biology, Springer International Publishing, 2014, pp. 123–134. URL: https://doi.org/10.1007/978-3-319-12418-6_16. doi:10.1007/978-3-319-12418-6_16.

[28] T. Beyer, M. Meyer-Hermann, Cell transmembrane receptors determine tissue pattern stability, Phys. Rev. Lett. 101 (2008) 148102. URL: https://link.aps.org/doi/10.1103/PhysRevLett.101.148102. doi:10.1103/PhysRevLett.101.148102.

[29] J. Dutta-Moscato, A. Solovyev, Q. Mi, T. Nishikawa, A. Soto-Gutierrez, I. J. Fox, Y. Vodovotz, A Multiscale Agent-Based in silico Model of Liver Fibrosis Progression, Front Bioeng Biotechnol 2 (2014) 18.

[30] G. An, Introduction of an agent-based multi-scale modular architecture for dynamic knowledge representation of acute inflammation, Theoretical Biology and Medical Modelling 5 (2008). URL: https://doi.org/10.1186/1742-4682-5-11. doi:10.1186/1742-4682-5-11.

[31] M. Verma, J. Bassaganya-Riera, A. Leber, N. Tubau-Juni, S. Hoops, V. Abedi, X. Chen, R. Hontecillas, High-resolution computational modeling of immune responses in the gut, Gigascience 8 (2019).

[32] N. Collier, M. North, Repast HPC: A Platform for Large-Scale Agent-Based Modeling, John Wiley & Sons, Inc., 2012, pp. 81–109. URL: http://dx.doi.org/10.1002/9781118130506.ch5. doi:10.1002/9781118130506.ch5.